Clinical trial results:
Efficacy and safety of Hemangiol solution in the treatment of high risk infantile hemangioma

Summary

EudraCT number	2014-005555-80
Trial protocol	ES
Global end of trial date	21 February 2017

Results information

Result version number	v1 (current)
This version publication date	03 September 2017
First version publication date	03 September 2017
Summary attachment (see zip file)	CSR Synopsis (CSR_V00400SB302_Final v1.1 - 10AUG2017_Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	V00400 SB 3 02

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-Billancourt, France, 92100
Public contact	Clinical Trial Information Desk, PIERRE FABRE DERMATOLOGIE, 34 931850200, contact_essais_cliniques@pierre-fabre.com
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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	21 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 February 2017
Global end of trial reached?	Yes
Global end of trial date	21 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To document the efficacy of Hemangiol administered during at least 6 months and upto a maximum of 12 months of age in infants with high risk infantile haemangioma (IH)

Protection of trial subjects:

The study was conducted in compliance with GCP (CPMP/ICH/135/95), ethical principles that have the origins in the amended version of the Declaration of Helsinki, and all SOPs interne to Pierre Fabre. Trial subjects were infants aged 35 to 142 days (corrected age) at inclusion. The informed consents were obtained from parents prior to screening. The information consent form, in the local language of the 2 participating countries (Spanish in Spain and Polish in Poland), detailled the procedures involved, the aims, methodology, constraints, potential risks to the study subject and the rights of the parents to withdraw consent at any stage or time of the study. The investigators exposed in detail to the parents, in a layman language the what, the why and the how of the study.

Background therapy:

No other therapies, (other than the subject's usual treatments which do not fall in the non-inclusion criteria defined in the protocol), were administered in the framework of the study.

Evidence for comparator:

This is a single arm, non comparative study carried out in real clinical situation.

Actual start date of recruitment	29 June 2015
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	Poland: 24
Country: Number of subjects enrolled	Spain: 21
Worldwide total number of subjects	45
EEA total number of subjects	45

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)	45
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:

Subjects were recruited within the medical consultations of physicians who are familiar with the management of IH (4 centres in Poland, 6 in Spain): infants with severe IH in proliferative phase, in the age group 25 to 142days (corrected age). The included subjects had to be able to complete the initial treatment period (6 months) before age 1 year

Pre-assignment

Screening details:

46 subjects aged, 35 - 150 days (corrected age for premature infants), with high risk IH and, in accordance with Hemangiol SmPC were screened and 45 patients were included in the study. The one patient excluded did not meet the 35 - 150 days age criteria.

Pre-assignment period milestones

Number of subjects started	46[1]
Number of subjects completed	45

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Age criteria not met: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 46 patients were screened for enrolment and 45 patients were definitely enrolled in the study as an inclusion criterion was not met for one patient

Period 1

Period 1 title	Initial Treatment Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Hemangiol

Arm description: -

Arm type	Experimental
Investigational medicinal product name	HEMANGIOL
Investigational medicinal product code	V00400SB
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Dose titration:
1mg/kg/day from Day 1 - 7
2mg/kg/day from Day 8 - 14
3mg/kg/day up to the end of the initial treatment period.
Orally, twice daily (morning and late afternoon) during or straight after a feed.

Number of subjects in period 1	Hemangiol
Started	45
Basic 6 month treatment	44
Completed	43
Not completed	2
Consent withdrawn by subject	1
Lack of efficacy	1

Period 2

Period 2 title	Follow-up Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Hemangiol FU

Arm description:

Patients in success at the end of the initial treatment period

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2[2]	Hemangiol FU
Started	34
Completed	34

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 43 patients completed the initial treatment period but only the patients in success at the end of this period (n=34) entered the follow-up period as per protcocol.

Period 3

Period 3 title	Retreatment period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Retreatment

Arm description:

Patients in success at the end of the initial treatment period and who had success regression during the follow-up period

Arm type	Experimental
Investigational medicinal product name	HEMANGIOL
Investigational medicinal product code	V00400SB
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Dose titration:
1mg/kg/day from Day 1 - 7 (re-treatment period)
2mg/kg/day from Day 8 - 14 (re-treatment period)
3mg/kg/day up to the end of the re-treatment period.
Orally, twice daily (morning and late afternoon) during or straight after a feed.

Number of subjects in period 3[3]	Retreatment
Started	8
Completed	8

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only 8 of the 34 patients who were in success at the end of the initial treatment period needed to be re-treated in the Investigator's opinion during the follow-up period (success regression) and entered the re-tretreatment period as per protocol.

Baseline characteristics

Reporting groups

Reporting group title	Initial Treatment Period

Reporting group description: -

Reporting group values	Initial Treatment Period	Total	
Number of subjects	45	45	
Age categorical Units: Subjects			
Infants 35 - 150 days	45	45	
Age continuous Units: days			
median	44		
inter-quartile range (Q1-Q3)	44 to 50	-	
Gender categorical Units: Subjects			
Female	33	33	
Male	12	12	
Gender	0	0	

End points

End points reporting groups

Reporting group title	Hemangiol
Reporting group description: -	
Reporting group title	Hemangiol FU
Reporting group description:	
Patients in success at the end of the initial treatment period	
Reporting group title	Retreatment
Reporting group description:	
Patients in success at the end of the initial treatment period and who had success regression during the follow-up period	
Subject analysis set title	PP set
Subject analysis set type	Per protocol
Subject analysis set description:	
FAS patients without major deviations or any bias for primary criterion assessment	

Primary: Primary Criterion - Success rate at the end of the initial treatment period (FAS)

End point title	Primary Criterion - Success rate at the end of the initial treatment period (FAS)[1]
End point description:	
The primary outcome measure was treatment success at the end of the initial treatment period. Success was determined by the Investigator and was defined as the resolution of the target IH and the absence of functional impact linked to the target IH.	
End point type	Primary
End point timeframe:	
11 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: The statistical analysis was purely descriptive with no p value provided as the trial was non comparative for ethical reasons: the primary endpoint was the success rate at the end of the initial treatment period with Hemangiol(R) (after 6 months or until success before one year of age) and this rate was 34/45=75.6% 95% CI [61.7;86.3]. Of note the number of patients in success ("34") is specified in the field labelled "Count". The same has been done for the other efficacy endpoints.

End point values	Hemangiol			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: yes / no	34			

Statistical analyses

No statistical analyses for this end point

Secondary: Success rate at 6 months (FAS)

End point title	Success rate at 6 months (FAS)
End point description:	

End point type	Secondary

End point timeframe:

6 months

End point values	Hemangiol			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: yes / no	21			

Statistical analyses

No statistical analyses for this end point

Secondary: Success rate after re-Initiation of treatment (retreated FAS subset)

End point title	Success rate after re-Initiation of treatment (retreated FAS subset)

End point description:

The number (%) of patients in success after re-initiation of treatment in the subset of patients who were in success at the end of the initial treatment period and had a success regression during the follow-up period.

End point type	Secondary

End point timeframe:

6 months

End point values	Retreatment			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: yes / no	7			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Primary criterion (PP)

End point title	Primary criterion (PP)

End point description:

Number of PP patients in success at the end of the initial treatment period

End point type	Other pre-specified

End point timeframe:

11 months

End point values	PP set			
Subject group type	Subject analysis set			
Number of subjects analysed	40			
Units: yes / no	31			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Whole study period after first administration (initial treatment period + Follow-up + retreatment)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19

Reporting groups	
Reporting group title	Full analysis set
Reporting group description:	
All patients treated	

Serious adverse events	Full analysis set		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 45 (17.78%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ulcerated haemangioma			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemangioma			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Somnolence			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Choking			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis rotavirus	Additional description: TESAE; Moderate; No causuality		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Full analysis set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 45 (80.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Infantile haemangioma			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	14		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 45 (22.22%)		
occurrences (all)	19		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Gastrointestinal disorders			
Teething			
subjects affected / exposed	7 / 45 (15.56%)		
occurrences (all)	12		
Vomiting			

subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	13		
Abdominal pain			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	8		
Rhinorrhoea			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Nightmare			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Sleep disorder			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Infections and infestations			
Bronchitis			
subjects affected / exposed	10 / 45 (22.22%)		
occurrences (all)	13		

Conjunctivitis subjects affected / exposed occurrences (all)	9 / 45 (20.00%) 9		
Nasopharyngitis subjects affected / exposed occurrences (all)	9 / 45 (20.00%) 21		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	8 / 45 (17.78%) 12		
Pharyngitis subjects affected / exposed occurrences (all)	6 / 45 (13.33%) 6		
Bronchiolitis subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 6		
Ear infection subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2		
Laryngitis subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2		
Respiratory tract infection subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2		
Tonsillitis subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 3		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2015	Replacement of "relapse" by "success regression" throughout protocol. Success regression, based on the Investigator's opinion could lead to 3 options: re-initiation, follow-up without re-initiation, withdrawal. Visits: renumbering of visits as D1, D8 and D15 (instead of D0, D7 and D14). Instructions to patients: clarification that syringes included in study treatment should be returned to the study centre. Note: as these above points were mentioned in the information leaflet, an additional information leaflet and corresponding ICF was prepared for signature by all patients' parents at the time of amendment approval. Number of patients: clarification that the number of ulcerated IHs (as main severity reason) limited to 2 patients per centre. Recruitment per centre capped to 8 patients maximum to avoid excessive influence of any given centre. Note: these two criteria were met by the previous 41 patients enrolled under the initial protocol. Precisions to procedures in case of safety issues at titration and/or in case of lower respiratory tract infection (LRTI): In case of safety issue at dose increase, the dose could be postponed 2 times/dose (1 week between 2 attempts). If after the third attempt (i.e. 1 initial attempt + 2 additional) the safety issue remains, treatment was definitively stopped and patient withdrawn. In case of bronchitis or LRTI, treatment was stopped immediately until full recovery. Re-administration did not necessitate an up-titration (i.e. full maintenance dose can be given directly). BP and HR limits modified to take into account chronological age instead of corrected age. As chronological age may be greater than corrected age, BP and HR limits for age > 150 days were added to the exclusion criteria. Note: as recruitment was nearing completion at the time of the amendment, this change was implemented at statistical analysis. The BP and HR limit modification was with regard to 2 patients born prematurely (chronological age of 191 and 211

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.

None

Notes: