Clinical trial results:
Systemic and local diffusion of ethanol after administration of ethanol 96% formulated in a gel (L0122 Gel) and ethanol 98% solution (absolute ethanol) by the percutaneous route, in patients with congenital venous malformations (CVM): pharmacokinetic, pharmacodynamic and clinical study.

Summary

EudraCT number	2009-011276-29
Trial protocol	FR
Global end of trial date	30 June 2010

Results information

Result version number	v1 (current)
This version publication date	11 August 2016
First version publication date	11 August 2016

Trial information

Trial identification

Sponsor protocol code	L00122 GI 201 (ORF)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00462462
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Orfagen
Sponsor organisation address	3, avenue Hubert Curien, Toulouse CEDEX 1, France, 31035
Public contact	Clinical project manager, Orfagen, info@orfagen.com
Scientific contact	Clinical project manager, Orfagen, info@orfagen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000414-PIP02-11
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 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 January 2010
Global end of trial reached?	Yes
Global end of trial date	30 June 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the systemic exposure to ethanol with the two test products.

Protection of trial subjects:

- Storage of blood samples for ethanolemia dosage up to clinical study report finalisation, in case of need.
- Limitation of CVM lesion volume to treat
- Analyse of coagulation parameters before treatment administration
- For better handling of the L0122 gel product by the American Investigator who has never experimented it before this study, the following step-by-step procedure was carried out in the US center:
* The first set of 4 patients to be included were adult patients with CVM lesion, providing that the treated malformation volume had to be between 12 cm3 and 100 cm3, as assessed by MRI, and lesion located in areas other than the neck.
* In the absence of SAE related to the gel, the second set of 4 patients were patients of any age (≥ 12 years old) with a treated CVM volume between 12 cm3 and 100 cm3, as assessed by MRI, and a lesion located in areas other than the neck.
* The third set of patients with the treated malformation volume was of at least 12 cm3, but requiring no more than 0.6 mL/Kg b.w. and 15 mL of L0122 gel.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 January 2008
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: 15
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	31
EEA total number of subjects	15

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)	7
Adults (18-64 years)	22
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

- Confirmation of CVM diagnosis (clinically and radiologically)
- Assessment of the lesion size
- Assessment of the coagulation parameters

Pre-assignment period milestones

Number of subjects started	34[1]
Number of subjects completed	31

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failure: 2
Reason: Number of subjects	Diagnosis mistake: 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: Patients who started the pre-assignment period are called "selected patients". Enrolled patients are patients who completed the pre-assignement period and who were randomised in a study treatment group.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	L0122 Gel Group

Arm description: -

Arm type	Experimental
Investigational medicinal product name	L0122 gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel for injection
Routes of administration	Intralesional use

Dosage and administration details:

The dosage schedule depended on the size and the venous drainage of the test lesion. In the case of few or no connections to normal local veins at the venogram performed just before product infusion, the amount to inject was defined as 40 to 60% of the amount of previously injected contrast medium. In case the draining veins opacification was displaced during the infusion under the fluoroscopic control or resistance to injection occurs, test product administration was stopped. Maximum amount of the test product to deliver was 0.6 mL/Kg b.w., including 0.1 mL/kg as a pilot dose per injection site and no more than 15 mL per session.

Arm title	Absolute ethanol Group

Arm description: -

Arm type	Active comparator

Investigational medicinal product name	Absolute ethanol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intralesional use

Dosage and administration details:

The dosage schedule depended on the outflow of the opacifying product into the draining veins. The amount of absolute ethanol to infuse was reached when the draining veins opacification was displaced during the infusion under fluoroscopic control, or when resistance to injection was encountered.
The amount to inject was estimated as 80 to 100% of the amount of previously injected contrast medium. In case the draining veins opacification was displaced during the infusion under the fluoroscopic control or resistance to injection occurs, test product administration was stopped. Maximum amount of the test product to deliver was 1 mL/Kg b.w. in USA and 0.5 mL/Kg b.w. in France (upon French Authorities request), including 0.1ml/kg as a pilot dose per injection site, and no more than 30 mL per session.

Number of subjects in period 1	L0122 Gel Group	Absolute ethanol Group
Started	17	14
Completed	17	13
Not completed	0	1
Physician decision	-	1

Baseline characteristics

Reporting groups	
Reporting group title	L0122 Gel Group
Reporting group description: -	
Reporting group title	Absolute ethanol Group
Reporting group description: -	

Reporting group values	L0122 Gel Group	Absolute ethanol Group	Total
Number of subjects	17	14	31
Age categorical Units: Subjects			
Adolescents (12-17 years)	5	2	7
Adults (18-64 years)	11	11	22
From 65-84 years	1	1	2
Gender categorical Units: Subjects			
Female	11	8	19
Male	6	6	12

End points

End points reporting groups

Reporting group title	L0122 Gel Group
Reporting group description: -	
Reporting group title	Absolute ethanol Group
Reporting group description: -	

Primary: Plasma level determination of ethanol

End point title	Plasma level determination of ethanol[1]
End point description:	
End point type	Primary

End point timeframe:

Blood samples were performed, just before infusion, then 5 min, 10 min, 20 min, 40 min, 60 min, 90 min, and 120 min after infusion at the first site, then every 60 min onwards until ethanol levels are found under the detection limit.

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: Absolute ethanol Group: Cmax: mean: 0.202g/L; [0.05 - 0.940]
L0122 Gel Group: Cmax: mean: 0.0604g/L; [0.015 - 0.4]

End point values	L0122 Gel Group	Absolute ethanol Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	13[2]		
Units: g/L				
number (not applicable)	17	13		

Notes:

[2] - Withdraw by the investigators due to difficulties to access the lesion. Blood sampling not performed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From test product administration to study end.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	L0122 Gel Group
Reporting group description:	
Treatment emergent AE for patients having received L0122 Gel	
Reporting group title	Absolute ethanol Group
Reporting group description:	
Treatment emergent AE for patients having received Absolute ethanol	

Serious adverse events	L0122 Gel Group	Absolute ethanol Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 17 (11.76%)	4 / 14 (28.57%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Blood ethanol increased			
subjects affected / exposed	0 / 17 (0.00%)	3 / 14 (21.43%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Arteriovenous malformation			
subjects affected / exposed	2 / 17 (11.76%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 2	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	L0122 Gel Group	Absolute ethanol Group	
Total subjects affected by non-serious adverse events subjects affected / exposed	12 / 17 (70.59%)	10 / 14 (71.43%)	
Vascular disorders Deep vein thrombosis subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions Injection site paraesthesia subjects affected / exposed	3 / 17 (17.65%)	0 / 14 (0.00%)	
occurrences (all)	3	0	
Pain subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Chest pain subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Injection site discolouration subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Injection site extravasation subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Injection site thrombosis subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Complication of device insertion subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Injection site haematoma subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Injection site pain subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Injection site ulcer			

subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Investigations			
Fibrin degradation products increased			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Procedural hypotension			
subjects affected / exposed	2 / 17 (11.76%)	4 / 14 (28.57%)	
occurrences (all)	2	4	
Delayed recovery from anaesthesia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Procedural hypertension			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Airway complication of anaesthesia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Arteriovenous malformation			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	2 / 17 (11.76%)	4 / 14 (28.57%)	
occurrences (all)	2	4	
Coagulopathy			

subjects affected / exposed	1 / 17 (5.88%)	5 / 14 (35.71%)	
occurrences (all)	1	5	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Skin irritation			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Haemoglobinuria			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Pharyngitis streptococcal			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2007	- increase of the lesion size (or part of the lesion size) allowed to be treated for the 1st set of included patients, - allowance to perform intermediate visits by phone, - new JHU IRB template of consent form, - study prolongation.
28 July 2008	Study prolongation
14 January 2009	- update of the Helsinki declaration, - precision on infusion procedure, - consent form modifications following the JHU IRB proposal.
20 April 2009	- addition of a French centre (Tours), - study prolongation

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported