Clinical trial results:
Taste and palatability of Orfadin suspension. An open, non-controlled 3-day study in pediatric patients with hereditary tyrosinemia type 1 treated with Orfadin.

Summary

EudraCT number	2012-002286-36
Trial protocol	DE GB
Global end of trial date	01 March 2013

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	Sobi.NTBC-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01734889
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Swedish Orphan Biovitrum AB
Sponsor organisation address	Tomtebodavägen 23, Stockholm, Sweden, 11276
Public contact	Medical Director, Swedish Orphan Biovitrum AB, 0046 86970000, anders.broijersen@sobi.com
Scientific contact	Medical Director, Swedish Orphan Biovitrum AB, 0046 86970000, anders.broijersen@sobi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000784-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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 March 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2013
Global end of trial reached?	Yes
Global end of trial date	01 March 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the acceptability of the suspension in the pediatric population.

Protection of trial subjects:

Monitoring procedures performed prior to, during, and upon completion of the study have verified that this study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 November 2012
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	United Kingdom: 12
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	6
Children (2-11 years)	6
Adolescents (12-17 years)	6
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients less than 18 years old with HT-1 currently managed on Orfadin (nitisinone) capsules.

Period 1

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

Blinding implementation details:

The objective of this study was to demonstrate that taste and palatability of the suspension are acceptable to the patients, especially those who are too young to swallow capsules. The objective was not to compare the taste of the suspension with that of the capsules,nor to evaluate different flavors of the suspension. Therefore, an open, non-randomized designwas used.

Arms

Arm title	Overall study

Arm description:

All subjects receive the same study treatment

Arm type	Experimental
Investigational medicinal product name	Orfadin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Orfadin suspension 4 mg/mL.
Twice daily for three days, dose as current with Orfadin capsules

Number of subjects in period 1	Overall study
Started	18
Completed	18

Baseline characteristics

Reporting groups

Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	18	18	
Age categorical Units: Subjects			
<5	6	6	
5-<18	12	12	
Gender categorical Units: Subjects			
Female	9	9	
Male	9	9	

Subject analysis sets

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who received at least one dose of IMP

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who received at least one dose of IMP and had at least one taste or acceptability assessment

Subject analysis set title	Per protocol analysis set (PPAS)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects who had completed the questionnaire at all occasions

Subject analysis set title	< 5 years (FAS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Analyses of the data were made using subgroups <5 years and 5 to <18 years considered more appropriate for evaluation of taste and palatability and also related to the children's ability to swallow capsules, as described in the clinical study report Sections 6.7.3.3 and 6.7.3.4

Subject analysis set title	5 - <18 years (FAS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Analyses of the data were made using subgroups <5 years and 5 to <18 years considered more appropriate for evaluation of taste and palatability and also related to the children's ability to swallow capsules, as described in the clinical study report Sections 6.7.3.3 and 6.7.3.4

Reporting group values	Safety analysis set	Full analysis set (FAS)	Per protocol analysis set (PPAS)
Number of subjects	18	18	18
Age categorical Units: Subjects			
<5	6	6	6

5-<18	12	12	12

Gender categorical Units: Subjects			
Female	9	9	9
Male	9	9	9

Reporting group values	< 5 years (FAS)	5 - <18 years (FAS)	
Number of subjects	6	12	
Age categorical Units: Subjects			
<5	6	6	
5-<18	12	12	
Gender categorical Units: Subjects			
Female	3	6	
Male	3	6	

End points

End points reporting groups

Reporting group title	Overall study
Reporting group description:	
All subjects receive the same study treatment	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least one dose of IMP	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects who received at least one dose of IMP and had at least one taste or acceptability assessment	
Subject analysis set title	Per protocol analysis set (PPAS)
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects who had completed the questionnaire at all occasions	
Subject analysis set title	< 5 years (FAS)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Analyses of the data were made using subgroups <5 years and 5 to <18 years considered more appropriate for evaluation of taste and palatability and also related to the children's ability to swallow capsules, as described in the clinical study report Sections 6.7.3.3 and 6.7.3.4	
Subject analysis set title	5 - <18 years (FAS)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Analyses of the data were made using subgroups <5 years and 5 to <18 years considered more appropriate for evaluation of taste and palatability and also related to the children's ability to swallow capsules, as described in the clinical study report Sections 6.7.3.3 and 6.7.3.4	

Primary: Taste score on Day 3 for subjects aged 5 - <18 years (Median)

End point title	Taste score on Day 3 for subjects aged 5 - <18 years
End point description:	
Subjects who were 5 to < 18 years of age were asked to rate the taste of the suspension on 5-graded verbal/numerical scales	
End point type	Primary
End point timeframe:	
Taste score at the last dose of the suspension on Day 3	

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: No statistical analyses was performed.

End point values	5 - <18 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: N/A				
median (full range (min-max))	4 (2 to 5)			

Statistical analyses

No statistical analyses for this end point

Primary: Taste score on Day 3 for subjects 5 to < 18 years (Categories)

End point title	Taste score on Day 3 for subjects 5 to < 18 years

End point description:

Subjects who were 5 to < 18 years of age were asked to rate the taste of the suspension on 5-graded verbal/numerical scales

End point type	Primary

End point timeframe:

Taste score for the last dose on Day 3

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: No statistical analyses was performed.

End point values	5 - <18 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Number of subjects				
Very bad taste (1)	0			
Bad taste (2)	1			
Neither good nor bad taste (3)	3			
Good taste (4)	4			
Very good taste (5)	4			

Statistical analyses

No statistical analyses for this end point

Primary: Acceptability score on Day 3 for subjects < 5 years (Median)

End point title	Acceptability score on Day 3 for subjects < 5 years (Median)[3]

End point description:

For subjects younger than 5 years of age, one of the parents rated the child's acceptability of the suspension on a verbal/numerical scale.

End point type	Primary

End point timeframe:

Acceptability score at the last dose of the suspension on Day 3

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: No statistical analyses was performed.

End point values	< 5 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: N/A				
median (full range (min-max))	5 (4 to 5)			

Statistical analyses

No statistical analyses for this end point

Primary: Acceptability score on Day 3 for subjects < 5 years (Categories)

End point title	Acceptability score on Day 3 for subjects < 5 years (Categories)[4]

End point description:

For subjects younger than 5 years of age, one of the parents rated the child's acceptability of the suspension on a verbal/numerical scale.

End point type	Primary

End point timeframe:

Acceptability score at the last dose of the suspension on Day 3

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: No statistical analyses was performed.

End point values	< 5 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Number of subjects				
Very badly (1)	0			
Badly (2)	0			
Neither well nor badly (3)	0			
Well (4)	2			
Very well (5)	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Taste score on Day 1 for subjects aged 5 - <18 years (Median)

End point title	Taste score on Day 1 for subjects aged 5 - <18 years (Median)

End point description:

Subjects who were 5 to < 18 years of age were asked to rate the taste of the suspension on 5-graded verbal/numerical scales

End point type	Secondary

End point timeframe:

Day 1

End point values	5 - <18 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: N/A				
median (full range (min-max))	4 (3 to 5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Taste score on Day 1 for subjects aged 5 - <18 years (Categories)

End point title	Taste score on Day 1 for subjects aged 5 - <18 years (Categories)

End point description:

Subjects who were 5 to < 18 years of age were asked to rate the taste of the suspension on 5-graded verbal/numerical scales

End point type	Secondary

End point timeframe:

Day 1

End point values	5 - <18 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Number of subjects				
Very bad taste (1)	0			
Bad taste (2)	0			
Neither good nor bad taste (3)	1			
Good taste (4)	6			
Very good taste (5)	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Taste score on Day 2 for subjects aged 5 - <18 years (Median)

End point title	Taste score on Day 2 for subjects aged 5 - <18 years (Median)

End point description:

Subjects who were 5 to < 18 years of age were asked to rate the taste of the suspension on 5-graded verbal/numerical scales

End point type	Secondary

End point timeframe:

Day 2

End point values	5 - <18 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: N/A				
median (full range (min-max))	4 (3 to 5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Taste score on Day 2 for subjects aged 5 - <18 years (Categories)

End point title	Taste score on Day 2 for subjects aged 5 - <18 years (Categories)

End point description:

Subjects who were 5 to < 18 years of age were asked to rate the taste of the suspension on 5-graded verbal/numerical scales

End point type	Secondary

End point timeframe:

Day 2

End point values	5 - <18 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Number of subjects				
Very bad taste (1)	0			
Bad taste (2)	0			
Neither good nor bad taste (3)	3			
Good taste (4)	6			
Very good taste (5)	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Acceptability score Day 1 for subjects < 5 years (Median)

End point title	Acceptability score Day 1 for subjects < 5 years (Median)

End point description:

For subjects younger than 5 years of age, one of the parents rated the child’s acceptability of the suspension on a verbal/numerical scale.

End point type	Secondary

End point timeframe:

Day 1

End point values	< 5 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: N/A				
median (full range (min-max))	4.5 (4 to 5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Acceptability score Day 1 for subjects < 5 years (Categories)

End point title	Acceptability score Day 1 for subjects < 5 years (Categories)

End point description:

For subjects younger than 5 years of age, one of the parents rated the child’s acceptability of the suspension on a verbal/numerical scale.

End point type	Secondary

End point timeframe:

Day 1

End point values	< 5 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Number of subjects				
Very badly (1)	0			
Badly (2)	0			
Neither well nor badly (3)	0			
Well (4)	3			
Very well (5)	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Acceptability score Day 2 for subjects < 5 years (Median)

End point title	Acceptability score Day 2 for subjects < 5 years (Median)

End point description:

For subjects younger than 5 years of age, one of the parents rated the child’s acceptability of the suspension on a verbal/numerical scale.

End point type	Secondary

End point timeframe:

Day 2

End point values	< 5 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: N/A				
median (full range (min-max))	5 (4 to 5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Acceptability score on Day 2 for subjects < 5 years (Categories)

End point title	Acceptability score on Day 2 for subjects < 5 years (Categories)

End point description:

For subjects younger than 5 years of age, one of the parents rated the child’s acceptability of the suspension on a verbal/numerical scale.

End point type	Secondary

End point timeframe:

Day 2

End point values	< 5 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Number of subjects				
Very badly (1)	0			
Badly (2)	0			
Neither well nor badly (3)	0			
Well (4)	1			
Very well (5)	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability score on Day 1 for subjects aged 5 - <18 years (Median)

End point title	Palatability score on Day 1 for subjects aged 5 - <18 years (Median)

End point description:

Subjects who were 5 to < 18 years of age were asked to rate the palatability of the suspension on 5-graded verbal/numerical scales

End point type	Secondary

End point timeframe:

Day 1

End point values	5 - <18 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: N/A				
median (full range (min-max))	4 (3 to 5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability score on Day 1 for subjects aged 5 - <18 years (Categories)

End point title	Palatability score on Day 1 for subjects aged 5 - <18 years (Categories)

End point description:

Subjects who were 5 to < 18 years of age were asked to rate the palatability of the suspension on 5-graded verbal/numerical scales

End point type	Secondary

End point timeframe:

Day 1

End point values	5 - <18 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Number of subjects				
Very bad (1)	0			
Bad (2)	0			
Neither good nor bad (3)	3			
Good (4)	4			
Very good (5)	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability score on Day 2 for subjects aged 5 - <18 years (Median)

End point title	Palatability score on Day 2 for subjects aged 5 - <18 years (Median)

End point description:

Subjects who were 5 to < 18 years of age were asked to rate the palatability of the suspension on 5-graded verbal/numerical scales

End point type	Secondary

End point timeframe:

Day 2

End point values	5 - <18 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: N/A				
median (full range (min-max))	4 (2 to 5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability score on Day 2 for subjects aged 5 - <18 years (Categories)

End point title	Palatability score on Day 2 for subjects aged 5 - <18 years (Categories)

End point description:

Subjects who were 5 to < 18 years of age were asked to rate the palatability of the suspension on 5-graded verbal/numerical scales

End point type	Secondary

End point timeframe:

Day 2

End point values	5 - <18 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Number of subjects				
Very bad (1)	0			
Bad (2)	1			
Neither good nor bad (3)	4			
Good (4)	3			
Very good (5)	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability score on Day 3 for subjects aged 5 - <18 years (Median)

End point title	Palatability score on Day 3 for subjects aged 5 - <18 years (Median)

End point description:

Subjects who were 5 to < 18 years of age were asked to rate the palatability of the suspension on 5-graded verbal/numerical scales

End point type	Secondary

End point timeframe:

Day 3

End point values	5 - <18 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: N/A				
median (full range (min-max))	4 (2 to 5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability score on Day 3 for subjects aged 5 - <18 years (Categories)

End point title	Palatability score on Day 3 for subjects aged 5 - <18 years (Categories)

End point description:

Subjects who were 5 to < 18 years of age were asked to rate the palatability of the suspension on 5-graded verbal/numerical scales

End point type	Secondary

End point timeframe:

Day 3

End point values	5 - <18 years (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Number of subjects				
Very bad (1)	0			
Bad (2)	1			
Neither good nor bad (3)	2			
Good (4)	4			
Very good (5)	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall acceptability

End point title	Overall acceptability

End point description:

At the end of the treatment period (last dose on Day 3), an overall question was filled out by the subject if possible, otherwise by the parent: “Would you/your child accept taking the new medicine again?”. The response alternatives were “Yes” or “No”.

End point type	Secondary

End point timeframe:

After last dose on Day 3

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Number of subjects				
Yes	14			
No	4			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE reporting period began on administration of the first dose of IMP and ended at the last study visit (1 w after last dose of IMP).The SAE reporting period began when the subject had signed the informed consent until 28 days past the last dose of IMP

Adverse event reporting additional description:

All directly observed AEs, and all AEs spontaneously reported by the subject, were recorded in the CRF. In addition, each subject was questioned about AEs during the follow-up telephone contact. The question asked was "Since you/your child began taking the Orfadin suspension, have you/has your child had any health problems?"

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	<5 years
Reporting group description: -	
Reporting group title	5-<18 years
Reporting group description: -	
Reporting group title	Safety analysis set

Reporting group description: -

Serious adverse events	<5 years	5-<18 years	Safety analysis set
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 12 (0.00%)	0 / 18 (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: 0 %

Non-serious adverse events	<5 years	5-<18 years	Safety analysis set
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	2 / 12 (16.67%)	4 / 18 (22.22%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			

Diarrhea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Mouth hemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 12 (8.33%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Regurgitation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 12 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	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