Clinical trial results:
An open-label, non-randomized, sequential, multicenter study to evaluate the pharmacokinetics, efficacy and safety of once daily dosing compared to twice daily dosing of Orfadin in patients diagnosed with hereditary tyrosinemia type 1

Summary

EudraCT number	2013-004132-29
Trial protocol	SE DK BE
Global end of trial date	21 September 2015

Results information

Result version number	v1 (current)
This version publication date	07 April 2016
First version publication date	07 April 2016

Trial information

Trial identification

Sponsor protocol code	Sobi.NTBC-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02323529
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Swedish Orphan Biovitrum AB
Sponsor organisation address	Tomtebodavägen 23a, Stockholm, Sweden, 112 76
Public contact	Medical Information, Swedish Orphan Biovitrum AB, +46 86972000, info@sobi.com
Scientific contact	Medical Information, Swedish Orphan Biovitrum AB, +46 86972000, info@sobi.com

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 September 2015
Global end of trial reached?	Yes
Global end of trial date	21 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the steady-state exposure to nitisinone during once and twice daily dosing of Orfadin

Protection of trial subjects:

This study was conducted in compliance with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), applicable regulatory requirements, and in accordance with the latest revision of the Ethical Principles for Medical Research Involving Human Patients (the Declaration of Helsinki).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 December 2014
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	Sweden: 1
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 6
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	2
Children (2-11 years)	5
Adolescents (12-17 years)	5
Adults (18-64 years)	7

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

6 study centers in 5 European countries participated in the trial. The first patient was enrolled 22 December 2014 and the last patient was enrolled 3 June 2015.

Pre-assignment

Screening details:

Male and female patients of all ages diagnosed with HT-1, currently well controlled, on twice-daily (or more frequent) dosing with Orfadin.

Pre-assignment period milestones

Number of subjects started	19
Number of subjects completed	18

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1

Period 1

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

Arms

Arm title	Nitisinone

Arm description:

All patients in the study was first put on twice daily dosing of nitisinone for 4 weeks. This was then followed by once daily dosing of nitisinone for 4 weeks

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

Dosage and administration details:

Orfadin (nitisinone) capsules are swallowed whole or emptied and mixed with food or drink. The dose of Orfadin in the study was the same as the one prescribed at the completion of the Screening period.

Number of subjects in period 1[1]	Nitisinone
Started	18
Completed	18

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 18 patients received drug in this study. The 19th patient withdraw consent before any intervention had occured. All patients were on their normal prescription of nitisinone before study start.

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			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	2	2	
Children (2-11 years)	5	5	
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	6	6	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	9	9	
Male	9	9	

Subject analysis sets	
Subject analysis set title	Twice daily - Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

Enrolled patients who received at least one dose of IMP

Subject analysis set title	Twice daily - Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

Enrolled patients who had SA assessment after the 4-weeks twice daily treatment period.

Subject analysis set title	Twice daily - Per protocol set
Subject analysis set type	Per protocol

Subject analysis set description:

Enrolled patients who had PK data from the twice daily treatment period and who had no protocol violations potentially affecting the analysis of PK.

Subject analysis set title	Once daily - Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects who received at least one dose of IMP during the Once daily period

Subject analysis set title	Once daily - Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

Enrolled patients who had SA assessment after the 4-weeks once-daily treatment period.

Subject analysis set title	Once daily - Per protocol set

Subject analysis set type	Per protocol

Subject analysis set description:

Enrolled patients who had PK data from the once daily period and who had no protocol violations potentially affecting the analysis of PK.

Reporting group values	Twice daily - Safety Set	Twice daily - Full analysis set	Twice daily - Per protocol set
Number of subjects	18	18	17
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)	2	2	2
Children (2-11 years)	5	5	5
Adolescents (12-17 years)	5	5	4
Adults (18-64 years)	6	6	6
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	9	9	8
Male	9	9	9

Reporting group values	Once daily - Safety set	Once daily - Full analysis set	Once daily - Per protocol set
Number of subjects	18	18	17
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)	2	2	2
Children (2-11 years)	5	5	5
Adolescents (12-17 years)	5	5	4
Adults (18-64 years)	6	6	6
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	9	9	8
Male	9	9	9

End points

End points reporting groups

Reporting group title	Nitisinone
Reporting group description:	
All patients in the study was first put on twice daily dosing of nitisinone for 4 weeks. This was then followed by once daily dosing of nitisinone for 4 weeks	
Subject analysis set title	Twice daily - Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Enrolled patients who received at least one dose of IMP	
Subject analysis set title	Twice daily - Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Enrolled patients who had SA assessment after the 4-weeks twice daily treatment period.	
Subject analysis set title	Twice daily - Per protocol set
Subject analysis set type	Per protocol
Subject analysis set description:	
Enrolled patients who had PK data from the twice daily treatment period and who had no protocol violations potentially affecting the analysis of PK.	
Subject analysis set title	Once daily - Safety set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who received at least one dose of IMP during the Once daily period	
Subject analysis set title	Once daily - Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Enrolled patients who had SA assessment after the 4-weeks once-daily treatment period.	
Subject analysis set title	Once daily - Per protocol set
Subject analysis set type	Per protocol
Subject analysis set description:	
Enrolled patients who had PK data from the once daily period and who had no protocol violations potentially affecting the analysis of PK.	

Primary: C(min) of nitisinone after at least 4 weeks of treatment on each dosing regimen

End point title	C(min) of nitisinone after at least 4 weeks of treatment on each dosing regimen[1]
End point description:	
End point type	Primary
End point timeframe:	
C(min) was measured immidiately before taking a dose of nitisinone after at least 4 weeks of treatment on once- or twice-daily dosing of nitisinone.	

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 protocol did not stipulate statistical testing for differences rather only the 95% confidence intervals were to be calculated.

End point values	Twice daily - Per protocol set	Once daily - Per protocol set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	17		
Units: micromole(s)/litre				
geometric mean (confidence interval 95%)	24.68 (20.351 to 29.93)	18.943 (14.586 to 24.602)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum succinylacetone (s-SA) after at least 4 weeks of treatment

End point title	Serum succinylacetone (s-SA) after at least 4 weeks of treatment

End point description:

Efficacy was assessed by the proportion of patients who had SA above the LLOQ after at least 4 weeks of Orfadin once-daily treatment.

End point type	Secondary

End point timeframe:

s-SA was measured at the end of each treatment period.

End point values	Twice daily - Full analysis set	Once daily - Full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: patients	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentration of nitisinone, Cmin at possible occurrence of s-SA above lower limit of quantification (LLOQ).

End point title	Serum concentration of nitisinone, Cmin at possible occurrence of s-SA above lower limit of quantification (LLOQ).

End point description:

This endpoint was never assesed as no patients had measurable SA levels above LLOQ.

End point type	Secondary

End point timeframe:

C(min) was measured immidiately before taking a dose of nitisinone after at least 4 weeks of treatment on once- or twice-daily dosing of nitisinone.

End point values	Twice daily - Full analysis set	Once daily - Full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[2]	0[3]		
Units: micromole(s)/litre				
number (not applicable)				

Notes:

[2] - No subjects had SA above LLOQ

[3] - No subjects had SA above LLOQ

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and tolerability assessments

End point title	Safety and tolerability assessments

End point description:

Safety and tolerability assessments; including adverse events (AEs), routine clinical chemistry tests including serum alpha fetoprotein (s-AFP), hepatic and renal function, coagulation, and serum tyrosine.

End point type	Secondary

End point timeframe:

From start of treatment (Visit 2) until 2 weeks after end of treatment (Visit 6)

End point values	Twice daily - Safety Set	Once daily - Safety set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18[4]	18[5]		
Units: patients	0	0		

Notes:

[4] - No patient had any clinically significant change in any laboratory parameter during the study.

[5] - No patient had any clinically significant change in any laboratory parameter during the study.

Statistical analyses

No statistical analyses for this end point

Secondary: C(max) of nitisinone after at least 4 weeks of treatment on each dosing regimen

End point title	C(max) of nitisinone after at least 4 weeks of treatment on each dosing regimen

End point description:

Secondary endpoint related to primary objective.

End point type	Secondary

End point timeframe:

C(max) was measured 3 to 4 hours after taking a dose of nitisinone after at least 4 weeks of treatment on once- or twice-daily dosing of nitisinone.

End point values	Twice daily - Per protocol set	Once daily - Per protocol set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	17		
Units: micromole(s)/litre				
geometric mean (confidence interval 95%)	28.107 (22.09 to 35.763)	27.187 (22.16 to 33.354)		

Statistical analyses

No statistical analyses for this end point

Secondary: C(max)/C(min) ratio after at least 4 weeks of treatment on each dosing regimen

End point title	C(max)/C(min) ratio after at least 4 weeks of treatment on each dosing regimen

End point description:

Secondary endpoint related to primary objective.

End point type	Secondary

End point timeframe:

C(min) was measured immidiately before taking a dose of nitisinone after at least 4 weeks of treatment and C(max) was measured 3-4 hours after taking a dose after at least 4 weeks of treatment on once- or twice-daily dosing of nitisinone.

End point values	Twice daily - Per protocol set	Once daily - Per protocol set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	17		
Units: ratio				
geometric mean (confidence interval 95%)	1.138 (0.998 to 1.299)	1.436 (1.307 to 1.576)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From start of treatment (Visit 2) until 2 weeks after end of treatment (Visit 6)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Twice daily - safety set
Reporting group description: -	
Reporting group title	Once daily - safety set
Reporting group description: -	

Serious adverse events	Twice daily - safety set	Once daily - safety set	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Twice daily - safety set	Once daily - safety set	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 18 (72.22%)	11 / 18 (61.11%)	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Ligament sprain			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Dizziness			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 18 (11.11%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
Fatigue			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Influenza like illness			
subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Asthenia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal tenderness			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Skin irritation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 18 (16.67%)	2 / 18 (11.11%)	
occurrences (all)	3	2	
Acute tonsillitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Diarrhoea infectious			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pyelonephritis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			

Vitamin D deficiency subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	2 / 18 (11.11%) 2	
Decreased appetite subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 18 (5.56%) 1	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

According to the study protocol a minimum of 20 patients were to be enrolled. Due to the absence of eligible patients in the youngest age group it was decided that the study should be terminated with 19 enrolled patients.

Notes: