Clinical trial results:
A Phase III Double-Blind, Randomised, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of Idebenone in 10 – 18 Year Old Patients with Duchenne Muscular Dystrophy

Summary

EudraCT number	2009-012037-30
Trial protocol	BE DE FR NL SE AT ES IT
Global end of trial date	24 April 2014

Results information

Result version number	v2 (current)
This version publication date	30 October 2019
First version publication date	07 June 2015
Version creation reason	• Correction of full data set Reposting needed due to reassignement of results owner in EudrCT + updating of short name of study
Summary attachment (see zip file)	Clinical Study Report Synopsis (EudraCT_Synopsis from DELOS_CSR_Final V 1_Apr 24_2015.pdf) Efficacy of idebenone on respiratory function in patients with Duchenne muscular dystrophy not using glucocorticoids (DELOS): a double-blind randomised placebo-controlled phase 3 trial (Buyse et al., 2015.pdf)

Trial information

Trial identification

Sponsor protocol code	SNT-III-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01027884
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Santhera Pharmaceuticals (Switzerland) Ltd
Sponsor organisation address	Hammerstrasse 49, Liestal, Switzerland, CH-4410
Public contact	Dr. Gunnar Buyse, University Hospital Leuven-Children Hospital, +32 016343845,
Scientific contact	Dr. Gunnar Buyse, University Hospital Leuven-Children Hospital, +41 09068950,

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	24 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 January 2014
Global end of trial reached?	Yes
Global end of trial date	24 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

•To assess the efficacy of idebenone, compared to placebo, in improving respiratory function or delaying the loss of respiratory function in patients with DMD

Protection of trial subjects:

This study was completed and archived according to the guidelines of Good Clinical Practice (GCP), ICH E3 (CPMP/ICH/135/95) and conducted in compliance with the World Medical Assembly Declaration of Helsinki and its most recent amendments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 April 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Sweden: 2
Worldwide total number of subjects	66
EEA total number of subjects	58

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)	16
Adolescents (12-17 years)	43
Adults (18-64 years)	7
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 23 centers in 10 countries (Belgium, Germany, The Netherlands, Switzerland, France, Sweden, Austria, United States, Italy and Spain) participated in this study. Seventeen centers in 10 countries enrolled patients.
Study Period: 27 July 2009 (first subject screened) to 14 January 2014 (last subject completed).

Pre-assignment

Screening details:

96 patients were screened. Inclusion criteria required:
- patients to be able to provide reliable and reproducible repeat PEF measurements (within 15% of the first assessment, i.e. Baseline vs. Screening)
- no previous use of idebenone, CoQ10 or vitamin E
- no glucocorticoid steroids use

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Idebenone

Arm description:

Treatment

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

Dosage and administration details:

Idebenone was formulated as film-coated 150 mg tablets. Patients took 2 x 150 mg tablets orally 3 times daily with meals (total dose 900 mg daily).

Arm title	Placebo

Arm description:

no Treatment

Arm type	Placebo
Investigational medicinal product name	matching placebo tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two matching placebo tablets were taken three times a day with meals.

Number of subjects in period 1	Idebenone	Placebo
Started	32	34
Completed	25	30
Not completed	7	4
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	2
spinal fixation surgery	3	-
Lost to follow-up	1	-
non-compliance	1	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Idebenone
Reporting group description: Treatment	
Reporting group title	Placebo
Reporting group description: no Treatment	

Reporting group values	Idebenone	Placebo	Total
Number of subjects	32	34	66
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Idebenone arm: 13.5 (2.7) mean age Placebo arm: 15.0 (2.5) mean age			
Units: years			
arithmetic mean	13.5	15	
standard deviation	± 2.7	± 2.5	-
Gender categorical			
Young males (10 to 18 years old)			
Units: Subjects			
Male	32	34	66

End points

End points reporting groups	
Reporting group title	Idebenone
Reporting group description: Treatment	
Reporting group title	Placebo
Reporting group description: no Treatment	

Primary: Peak Expiratory Flow (PEF)	
End point title	Peak Expiratory Flow (PEF)
End point description:	
End point type	Primary
End point timeframe: 52 weeks	

End point values	Idebenone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	27		
Units: percentage				
number (confidence interval 95%)	-3.05 (-7.08 to 0.97)	-9.01 (-13.18 to -4.84)		

Statistical analyses

Statistical analysis title	Mixed Model for Repeated Measurements (MMRM)
Comparison groups	Placebo v Idebenone
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	5.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	11.76

Secondary: Peak Expiratory Flow (PEF), Forced Vital Capacity (FVC), Peak Cough Flow (PCF)

End point title	Peak Expiratory Flow (PEF), Forced Vital Capacity (FVC), Peak Cough Flow (PCF)

End point description:

To assess the efficacy of idebenone, compared to placebo, in improving respiratory function or delaying the loss of respiratory function using measures other than those used for the primary endpoint.

End point type	Secondary

End point timeframe:

Respiratory function measurements were performed periodically over the entire study duration.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Entire study duration	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	14
Reporting groups	
Reporting group title	Idebenone
Reporting group description: Treatment	
Reporting group title	Placebo
Reporting group description: no Treatment	

Serious adverse events	Idebenone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 32 (6.25%)	5 / 34 (14.71%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal			

disorders			
Acute Respiratory Failure			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary microemboli			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Sleep apnoea syndrome			
subjects affected / exposed	1 / 32 (3.13%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Tendinous contracture			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 34 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			

subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 32 (0.00%)	1 / 34 (2.94%)	
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: 0 %

Non-serious adverse events	Idebenone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 32 (93.75%)	32 / 34 (94.12%)	
Cardiac disorders			
Left ventricular failure			
subjects affected / exposed	3 / 32 (9.38%)	1 / 34 (2.94%)	
occurrences (all)	3	1	
Electrocardiogram abnormal			
subjects affected / exposed	2 / 32 (6.25%)	1 / 34 (2.94%)	
occurrences (all)	3	1	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 32 (18.75%)	7 / 34 (20.59%)	
occurrences (all)	13	15	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 32 (15.63%)	3 / 34 (8.82%)	
occurrences (all)	6	4	
Influenza like illness			
subjects affected / exposed	2 / 32 (6.25%)	1 / 34 (2.94%)	
occurrences (all)	2	2	
Blood and lymphatic system disorders			
Blood phosphorus increased			
subjects affected / exposed	1 / 32 (3.13%)	3 / 34 (8.82%)	
occurrences (all)	1	4	

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 32 (25.00%)	4 / 34 (11.76%)	
occurrences (all)	10	6	
Constipation			
subjects affected / exposed	3 / 32 (9.38%)	6 / 34 (17.65%)	
occurrences (all)	4	6	
Abdominal pain			
subjects affected / exposed	3 / 32 (9.38%)	3 / 34 (8.82%)	
occurrences (all)	4	5	
Nausea			
subjects affected / exposed	1 / 32 (3.13%)	2 / 34 (5.88%)	
occurrences (all)	2	2	
Vomiting			
subjects affected / exposed	1 / 32 (3.13%)	2 / 34 (5.88%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	4 / 32 (12.50%)	6 / 34 (17.65%)	
occurrences (all)	5	7	
Rhinorrhoea			
subjects affected / exposed	3 / 32 (9.38%)	2 / 34 (5.88%)	
occurrences (all)	3	2	
Nasal congestion			
subjects affected / exposed	2 / 32 (6.25%)	1 / 34 (2.94%)	
occurrences (all)	2	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 32 (6.25%)	1 / 34 (2.94%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 32 (3.13%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Renal and urinary disorders			
Chromaturia			

subjects affected / exposed	3 / 32 (9.38%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 32 (6.25%)	4 / 34 (11.76%)	
occurrences (all)	2	6	
Scoliosis			
subjects affected / exposed	2 / 32 (6.25%)	1 / 34 (2.94%)	
occurrences (all)	2	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 32 (25.00%)	9 / 34 (26.47%)	
occurrences (all)	12	11	
Upper respiratory tract infection			
subjects affected / exposed	2 / 32 (6.25%)	6 / 34 (17.65%)	
occurrences (all)	2	10	
Gastroenteritis			
subjects affected / exposed	5 / 32 (15.63%)	1 / 34 (2.94%)	
occurrences (all)	6	1	
Rhinitis			
subjects affected / exposed	1 / 32 (3.13%)	6 / 34 (17.65%)	
occurrences (all)	1	8	
Otitis media			
subjects affected / exposed	3 / 32 (9.38%)	0 / 34 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2009	Introduction of Group Sequential Design (of already pre-specified subgroups; cohort 1: glucocorticoid non-users; cohort 2: glucocorticoid users) Introduction of definitions for "Glucocorticoid non-users" Introduction of regular (weekly) assessment of PEF by the patient at home (in addition to assessment s during study site visits) Discontinuation of handgrip strength assessment (handheld myometry upper limb unchanged) Removal of cough frequency assessment as study endpoint Introduction of muscle strength and motor function testing at the Screening Visit
22 February 2010	Allow enrolment of siblings of randomized patients
18 August 2010	Introduction of second PEF assessment at every study visit
05 July 2011	Increase sample size of glucocorticoid non users
05 December 2012	Amendment of sample size required for prespecified futility analysis
19 June 2013	Amendment of time point for starting recruitment of glucocorticoid using patients
24 April 2014	Termination of the study following planned analysis of glucocorticoid non-user subgroup. Amendment of Type I error rate. Introduction of secondary endpoint: annual rate of change in PEF measured by ASMA-1 device.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25907158