



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 | <ul style="list-style-type: none">• Correction of full data set Reposting needed due to reassignment 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 occurrences (all) | 3 / 32 (9.38%) 3 | 0 / 34 (0.00%) 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 assessments 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>