



## Clinical trial results:

### The beta-2-agonist terbutaline for the treatment of painful polyneuropathy. A randomised, active- and placebo-controlled trial Summary

EudraCT number	2015-002984-40
Trial protocol	DK
Global end of trial date	29 April 2019

#### Results information

Result version number	v1 (current)
This version publication date	20 June 2021
First version publication date	20 June 2021
Summary attachment (see zip file)	BETA2summary (BETA2summary.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	beta2
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Odense University Hospital
Sponsor organisation address	J.B. Winløvsvej 4, Odense, Denmark, 5000
Public contact	Neuromuscular Team, Odense University Hospital, 45 65412471, soeren.sindrup@rsyd.dk
Scientific contact	Neuromuscular Team, Odense University Hospital, 45 65412471, soeren.sindrup@rsyd.dk

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:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	31 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 April 2019
Global end of trial reached?	Yes
Global end of trial date	29 April 2019
Was the trial ended prematurely?	Yes

Notes:

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**General information about the trial**

Main objective of the trial:

The objective of the trial is to determine if terbutaline relieves pain in polyneuropathy.

Protection of trial subjects:

Escape medication paracetamol

Background therapy:

None

Evidence for comparator:

Comparator imipramine (TCA) evidenced in several RCTs.

Actual start date of recruitment	01 October 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Denmark: 141
Worldwide total number of subjects	141
EEA total number of subjects	141

Notes:

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**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)	0
Adults (18-64 years)	75
From 65 to 84 years	66
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The patients were recruited from neurology out patient clinics at Odense and Aarhus University Hospitals in Denmark,

### Pre-assignment

Screening details:

Screening period for confirmation of diagnosis of peripheral neuropathic pain, as well as in- and exclusion criteria.

### Pre-assignment period milestones

Number of subjects started	141
Number of subjects completed	141

### Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Baseline to terbutaline

Arm description:

Baseline period with no treatment before terbutaline

Arm type	Baseline no treatment
Investigational medicinal product name	no treatment
Investigational medicinal product code	None
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

No treatment

<b>Arm title</b>	Baseline to imipramine
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Arm description:

Baseline period with no treatment before imipramine

Arm type	No intervention
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	Baseline to placebo

Arm description:

Baseline period with no treatment before placebo

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Baseline to terbutaline	Baseline to imipramine	Baseline to placebo
Started	48	50	43
Completed	46	48	41
Not completed	2	2	2
low pain score (<4 NRS)	2	2	2

## Period 2

Period 2 title	Treatment periods summary
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Placebo capsules identical to terbutaline and imipramine capsules. Double-dummy technique.

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Terbutaline

Arm description:

Treatment with terbutaline 5 mg to 15 mg daily

Arm type	Experimental
Investigational medicinal product name	Terbutaline capsule 5 mg
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Age <70years 5-15 mg/day

Age ≥ 70 years 5 mg/day

<b>Arm title</b>	Imipramine
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Arm description:

Double-blinded treatment with imipramine 30 mg to 150 mg

Arm type	Active comparator
Investigational medicinal product name	Imipramine 30 mg capsule
Investigational medicinal product code	PR2
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Age < 70 years, fast metabolizer 30-150 mg/day

Age < 70 years, poor metabolizer 30 mg/day

Age ≥ 70 years 30 mg/day

<b>Arm title</b>	Placebo
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Arm description:

Treatment with placebo capsules

Arm type	Placebo
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Investigational medicinal product name	Placebo capsule
Investigational medicinal product code	PL
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dosage (number of capsules) corresponding to number of capsules with active substances

<b>Number of subjects in period 2</b>	Terbutaline	Imipramine	Placebo
Started	46	48	41
Completed	41	44	38
Not completed	5	4	3
Physician decision	1	-	-
Adverse event, non-fatal	3	3	-
Other disease	1	1	2
Lack of efficacy	-	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Baseline
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Reporting group description:

Subjects countet for each baseline period

Reporting group values	Baseline	Total	
Number of subjects	141	141	
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)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	111	111	
From 65-84 years	30	30	
85 years and over	0	0	
Age continuous			
Age at baseline period 1			
Units: years			
median	59		
full range (min-max)	20 to 76	-	
Gender categorical			
Units: Subjects			
Female	66	66	
Male	75	75	

### Subject analysis sets

Subject analysis set title	Intention to treat popultion
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

Modified intention to treat analysis set, subjects with data from 1 or to treatment periods

Reporting group values	Intention to treat popultion		
Number of subjects	135		
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)	109		
From 65-84 years	26		
85 years and over	0		
Age continuous			
Age at baseline period 1			
Units: years			
median	59		
full range (min-max)	20 to 76		
Gender categorical			
Units: Subjects			
Female	63		
Male	72		

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## End points

### End points reporting groups

Reporting group title	Baseline to terbutaline
Reporting group description: Baseline period with no treatment before terbutaline	
Reporting group title	Baseline to imipramine
Reporting group description: Baseline period with no treatment before imipramine	
Reporting group title	Baseline to placebo
Reporting group description: Baseline period with no treatment before placebo	
Reporting group title	Terbutaline
Reporting group description: Treatment with terbutaline 5 mg to 15 mg daily	
Reporting group title	Imipramine
Reporting group description: Double-blinded treatment with imipramine 30 mg to 150 mg	
Reporting group title	Placebo
Reporting group description: Treatment with placebo capsules	
Subject analysis set title	Intention to treat population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Modified intention to treat analysis set, subjects with data from 1 or to treatment periods	

### Primary: Numeric Rating of average daily pain (NRS), weekly median

End point title	Numeric Rating of average daily pain (NRS), weekly median
End point description: Average daily pain NRS score 0-10, 0 = no pain and 10 = worst possible pain.	
End point type	Primary
End point timeframe: Weekly median of the average daily pain from the each of the 5 weeks in each treatment period and the 3 baseline periods were included in the analysis.	

End point values	Baseline to terbutaline	Terbutaline	Imipramine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	41	44	38
Units: NRS 0-10 points				
median (standard deviation)	6.44 (± 1.83)	6.13 (± 2.34)	4.77 (± 2.43)	5.66 (± 1.91)

End point values	Baseline to imipramine	Baseline to placebo	Intention to treat population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	44	38	41	



Units: NRS 0-10 points				
median (standard deviation)	6.58 ( $\pm$ 1.91)	6.27 ( $\pm$ 1.74)	6.13 ( $\pm$ 2.34)	

## Statistical analyses

<b>Statistical analysis title</b>	Primary outcome in general linear model
Statistical analysis description: General linear model Including terbutaline treatment weeks 1-5 and corresponding baseline period compared to placebo treatment weeks 1-5 and corresponding baseline period,	
Comparison groups	Terbutaline v Placebo v Baseline to terbutaline v Baseline to placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.032 <sup>[1]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.123
upper limit	0.379
Variability estimate	Standard error of the mean
Dispersion value	0.126

Notes:

[1] - 2 comparisons: Terbutaline vs placebo and Terbutaline vs Imipramine

The second comparison, i.e. Tebutaline vs Imipramine, showed lower pain scores on imipramine (week 5: 4.77 NRS) than on Terbutaline (week 5: 6.13),  $p < 0.001$

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

End of terbutaline, imipramine and placebo treatment periods.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.03
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### Reporting groups

Reporting group title	Terbutaline
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Reporting group description:

End of treatment with terbutaline

Reporting group title	Imipramine
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Reporting group description:

End of imipramine treatment period

Reporting group title	Placebo
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Reporting group description:

End of placebo treatment period.

Serious adverse events	Terbutaline	Imipramine	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 46 (0.00%)	1 / 48 (2.08%)	1 / 41 (2.44%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Chest pain			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection after planned knee surgery			
subjects affected / exposed	0 / 46 (0.00%)	1 / 48 (2.08%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

<b>Non-serious adverse events</b>	Terbutaline	Imipramine	Placebo
Total subjects affected by non-serious adverse events subjects affected / exposed	27 / 46 (58.70%)	38 / 48 (79.17%)	17 / 41 (41.46%)
Cardiac disorders palpitations subjects affected / exposed occurrences (all)	27 / 46 (58.70%) 6	38 / 48 (79.17%) 0	17 / 41 (41.46%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)  Leg Cramps subjects affected / exposed occurrences (all)  Tremor subjects affected / exposed occurrences (all)  Dizziness subjects affected / exposed occurrences (all)	27 / 46 (58.70%) 10  27 / 46 (58.70%) 8  27 / 46 (58.70%) 7  27 / 46 (58.70%) 5	38 / 48 (79.17%) 8  38 / 48 (79.17%) 0  38 / 48 (79.17%) 0  38 / 48 (79.17%) 12	17 / 41 (41.46%) 3  17 / 41 (41.46%) 0  17 / 41 (41.46%) 0  17 / 41 (41.46%) 0
General disorders and administration site conditions Tiredness subjects affected / exposed occurrences (all)  Vivid dreams subjects affected / exposed occurrences (all)  Sweating subjects affected / exposed occurrences (all)	27 / 46 (58.70%) 1  27 / 46 (58.70%) 1  27 / 46 (58.70%) 0	38 / 48 (79.17%) 9  38 / 48 (79.17%) 0  38 / 48 (79.17%) 8	17 / 41 (41.46%) 5  17 / 41 (41.46%) 0  17 / 41 (41.46%) 0
Gastrointestinal disorders Dry mouth subjects affected / exposed occurrences (all)  Constipation subjects affected / exposed occurrences (all)	27 / 46 (58.70%) 5  27 / 46 (58.70%) 1	38 / 48 (79.17%) 21  38 / 48 (79.17%) 0	17 / 41 (41.46%) 3  17 / 41 (41.46%) 0

Nausea subjects affected / exposed occurrences (all)	27 / 46 (58.70%) 0	38 / 48 (79.17%) 8	17 / 41 (41.46%) 3
Endocrine disorders High blood sugar subjects affected / exposed occurrences (all)	27 / 46 (58.70%) 1	38 / 48 (79.17%) 0	17 / 41 (41.46%) 0

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported