



Clinical trial results:

A novel therapy using recombinant human PTH 1-84 to stimulate bone repair and enhance fracture healing in the acute Charcot foot: a double blind placebo controlled phase IV trial

Summary

EudraCT number	2009-016873-13
Trial protocol	GB
Global end of trial date	25 July 2014

Results information

Result version number	v1 (current)
This version publication date	20 December 2018
First version publication date	20 December 2018
Summary attachment (see zip file)	FINAL STUDY REPORT (End-of-study-report-PTH-signed.pdf)

Trial information

Trial identification

Sponsor protocol code	PTHinCharcotfoot
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	King's College Hospital NHS Foundation Trust
Sponsor organisation address	Denmark Hill, London, United Kingdom, SE5 9RS
Public contact	Investigator's Trial Team, Kings College Hospital NHS Foundation Trust, 0044 203299 5124, nina.petrova@nhs.net
Scientific contact	Investigator's Trial Team, Kings College Hospital NHS Foundation Trust, 0044 203299 5124, nina.petrova@nhs.net

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	30 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 October 2013
Global end of trial reached?	Yes
Global end of trial date	25 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Can recombinant human parathyroid hormone (rh PTH 1-84) accelerate clinical resolution of the acute Charcot foot by enhancing bone repair and fracture healing. This will be assessed in terms of:

- Time to resolution of the acute Charcot foot
- Percentage of patients with a clinical outcome of Charcot foot resolution by 6 months
- Percentage of patients with a clinical outcome of Charcot foot resolution by 12 months

Protection of trial subjects:

We will also undertake a safety evaluation monthly for the first 3 months and then at three monthly intervals until termination of treatment. This will include physical examinations, vital signs (sitting systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature) and assessment of adverse events (AEs) and serious adverse events (SAEs), and laboratory measurement of serum calcium, phosphate and creatinine. We will also record adherence to medications.

Background therapy:

All patients will receive standard treatment which includes treatment with cast immobilisation and Calcium and Vitamin D supplementation (1000 mg Ca++/ daily and 800IU of Vitamin D3). This will include 2 tablets daily of Calceos. Each tablet Calceos contains Calcium carbonate 1.25g equivalent to 500 mg elemental calcium or Ca2+ 12.5 mmol and 10 micrograms colecalciferol (vitamin D3) equivalent to 400 units).

Evidence for comparator: -

Actual start date of recruitment	01 October 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	United Kingdom: 46
Worldwide total number of subjects	46
EEA total number of subjects	46

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	46
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from one clinical site in London UK between 2010 and 2013.

Pre-assignment

Screening details:

Inclusion Criteria

Aged 18 to 75 years inclusive

Has diabetes mellitus either Type 1 or Type 2

Has acute Charcot osteoarthropathy defined as recent onset of a unilateral hot swollen foot with foot skin temperature 2oC greater than the contralateral foot. Patients should either have bone fracture and joint subluxation on standard

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

Blinding implementation details:

The placebo has the same composition as the active drug except without the PTH 1-84. The powder in the placebo is composed of mannitol, citric acid monohydrate, sodium chloride 0.4%, dilute hydrochloric acid (for pH adjustment) and sodium hydroxide 1N (for pH) adjustment; the solvent is metacresol and water

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A - Active

Arm description:

Treatment A: active treatment will be 100µg rhPTH 1-84 (Preotact) administered subcutaneously (s.c.) daily

Arm type	Experimental
Investigational medicinal product name	Preotact
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection in cartridge
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients will receive 100µg of parathyroid hormone administered once-daily as a subcutaneous injection into the abdomen.

Arm title	Group B - Placebo
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Arm description:

Treatment B: Placebo treatment will be 100µg placebo administered subcutaneously (s.c.) daily

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The investigational product is Preotact. Nycomed UK Ltd is the MAH for Preotact 100 micrograms powder and solvent for solution for injection, which is supplied as the Preotact pen device which is a dual-chamber cartridge. The first chamber contains 1.61 mg parathyroid hormone. Each dose of 71.4

microliter contains 100 micrograms parathyroid hormone.

The placebo has the same composition as the active drug except without the PTH 1- 84. The powder in the placebo is composed of mannitol, citric acid monohydrate, sodium chloride 0.4%, dilute hydrochloric acid (for pH adjustment) and sodium hydroxide 1 N (for pH) adjustment; the solvent is metacresol and water.

Patients will receive 100µg of parathyroid hormone/ placebo administered once-daily as a subcutaneous injection into the abdomen for 12 months.

Number of subjects in period 1	Group A - Active	Group B - Placebo
Started	26	20
Completed	23	20
Not completed	3	0
Adverse event, serious fatal	1	-
Adverse event, non-fatal	2	-

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial
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Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	46	46	
Age categorical			
Units: Subjects			
85 years and over	0	0	
Aged 18 to 75 years	46	46	
Gender categorical			
Units: Subjects			
Female	10	10	
Male	36	36	

End points

End points reporting groups

Reporting group title	Group A - Active
Reporting group description:	
Treatment A: active treatment will be 100µg rhPTH 1-84 (Preotact) administered subcutaneously (s.c.) daily	
Reporting group title	Group B - Placebo
Reporting group description:	
Treatment B: Placebo treatment will be 100µg placebo administered subcutaneously (s.c.) daily	

Primary: Primary Endpoint

End point title	Primary Endpoint ^[1]
End point description:	
The primary objective is to determine whether there is a difference between active treatment with rh PTH 1-84 and standard treatment alone in terms of Time to resolution of the Charcot foot in relation to the adverse event of a skin foot temperature difference of greater than 2°C between the Charcot and the contralateral foot. Percentage of patients with a clinical outcome of Charcot foot resolution by 6 months. This will be expressed as a binary indicator for resolution of the acute Charcot foot (in relation to the adverse event of a difference of greater than 2°C between the Charcot and the contralateral foot). Percentage of patients with a clinical outcome of Charcot foot resolution by 12 months. This will be expressed as a binary indicator for resolution of the acute Charcot foot (in relation to the adverse event of a difference of greater than 2°C between the Charcot and the contralateral foot).	
End point type	Primary
End point timeframe:	
12 months	
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: See attached document for results.	

End point values	Group A - Active	Group B - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	20		
Units: whole	26	20		

Attachments (see zip file)	Results/12747076_985.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint

End point title	Secondary Endpoint
End point description:	
The secondary objectives will be to determine whether there is a difference between active treatment with rh PTH 1-84 and standard treatment alone in terms of: Percentage of patients with healed fractures	

at clinical resolution on foot and ankle radiographs Percentage of patients with bony union and healing of fractures at the time of clinical resolution on MRI scans Rate of change of bone turnover markers from baseline and up to clinical resolution of the Charcot foot Rate of change of score in quality of life from baseline up to clinical resolution using the SF-36 Rate of change of score in quality of life from baseline and up to clinical resolution using the EQ-5D;

End point type	Secondary
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End point timeframe:

12 months

End point values	Group A - Active	Group B - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	20		
Units: whole	26	20		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Adverse Events reported throughout the trial and for a period of 30 days after the last treatment visit or early termination visit

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Active
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: See document

Serious adverse events	Active	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 26 (11.54%)	3 / 20 (15.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Cardiac disorders			
Unresponsive & unconscious at home			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
L3 nerve impingement and left throchanteric bursitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting caused by mild active chronic gastritis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	
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			

Respiratory depression caused by fentanyl patch			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute on chronic rise in liver function tests			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Infected diabetic foot ulcer			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (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: 0 %

Non-serious adverse events	Active	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2010	Change to IMP label.
12 July 2011	To amend the duration of treatment phase. To amend the study protocol to clarify that the renal function will be assessed by estimated glomerular filtration rate (eGFR) AND/OR creatinine clearance To amend the inclusion and exclusion criteria. To amend the visit for the measurement of skin foot temperatures. To amend the protocol to cancel the home visit by the nurse 2 weeks post randomisation. To update the manufacturer site due to change of address
11 July 2014	To reduce the subject recruitment sample size from 92 to 46. This reduction is due to a slow recruitment process and expiry of available IMP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported