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 study

END OF STUDY REPORT

1. Details of Chief Investigator

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2. Details of study

Full title of study:	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 study
REC reference number:	09/H1102/113
Sponsors:	King's College Hospital NHS Foundation Trust and King's College London
EudraCT Number:	2009-016873-13
Number of Centres	1
Number of Patients	48 – randomised (2 withdrew consent at randomisation and were not exposed to IMP/placebo)

3. Commencement and completion dates in the UK

First Patient First Visit	11/Aug/2010
Last Patient Last Visit	30/Oct/2013

4. Primary Objective

The main objective of this study was to investigate a novel intervention in Charcot osteoarthropathy and to examine whether recombinant human parathyroid hormone (rh PTH 1-84) can enhance fracture healing and arrest bone and joint destruction in the acute diabetic Charcot foot.

5. Background and Rationale

The Charcot foot is a major diabetic complication and results in considerable morbidity and reduction in quality of life. It is characterised by pathological fracture, leading to bone fragmentation and joint disruption. The Charcot foot is also associated with severe foot deformity, ulceration, sepsis and long hospital admissions.

There is a growing body of evidence to show that parathyroid hormone is an effective anabolic therapy for the enhancement of bone repair, following fracture. Furthermore, healing of fractures can be monitored with markers of bone turnover. We hypothesise that treatment with rh 1-84 PTH could enhance the rate of fracture repair and accelerate resolution of the acute Charcot osteoarthropathy, and thereby prevent deformity and ulceration. Currently, studies have shown that the median duration of casting for acute Charcot osteoarthropathy is 10 months. Enhanced fracture repair and healing would also reduce the length of time that patients would be in a plaster cast. Thus, the risk of complications related to prolonged cast immobilisation would be reduced, including limb disuse, muscle atrophy and bone demineralisation. Overall, such rapid healing would be of great economic benefit.

The main objective of this study was to propose a novel intervention in Charcot osteoarthropathy and to investigate whether recombinant human parathyroid hormone (rh PTH 1-84) can enhance fracture healing and arrest bone and joint destruction in the acute diabetic Charcot foot.

We carried out a double blind randomised placebo controlled trial in patients with acute Charcot osteoarthropathy and compared the median time to resolution of the osteoarthropathy between active treatment and placebo. We treated patients with rh PTH 1-84 or placebo until clinical resolution of the osteoarthropathy or up to a period of 12 months.

6. IMP

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 Marketing Authorisation Number is - EU/1/06/339/001-002

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.

The IMP and placebo were supplied by Nycomed, who also provided QP release certificates. During the course of the study Nycomed was taken over by Takeda.

7. Inclusion Criteria

A patient was eligible for study participation if he or she met the following criteria:

1. Aged 18 to 75 years inclusive
2. Has diabetes mellitus either Type 1 or Type 2
3. Has acute Charcot osteoarthropathy defined as recent onset of a unilateral hot swollen foot with foot skin temperature 2°C greater than the contralateral foot. Patients should either have bone fracture and joint subluxation on standard foot and ankle x-rays or bone marrow oedema and bone microfracture on MRI.

4. If female, is nonpregnant (negative pregnancy tests at the baseline visit) and nonlactating.
5. If female, is either not of childbearing potential (defined as postmenopausal for ≥ 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy or hysterectomy]) or practising one of the following medically-acceptable methods of birth control and agrees to continue with the regimen throughout the duration of the study:
    a. Oral, implantable or injectable contraceptives for 3 consecutive months before the baseline visit.
    b. Total abstinence from sexual intercourse (≥ 1 complete menstrual cycle before the baseline visit).
    c. Intrauterine device
    d. Double barrier method (condoms, sponge, diaphragm or vaginal ring with spermicidal jellies or cream)
6. Meets the following laboratory criteria:
    a. Aspartate aminotransferase (AST) within 3x the upper limit of normal.
    b. Glycated Haemoglobin A1C (HbA1C) < 12%
    c. Patients with eGFR> 30 ml/min and/or Creatinine clearance above 30 ml/min.
7. Must be able to fluently speak and understand English and be able to provide meaningful written informed consent for the study.

8. Exclusion Criteria

A patient was excluded from the study if he or she met the following exclusion criteria:

1. Has active foot ulceration and infection
2. Patients taking drugs that may affect calcium metabolism, patients on immuno-suppression, inhaled corticosteroids, anabolic steroids, other treatment for osteoporosis, rheumatoid arthritis.
3. Patients with previous radiation therapy to skeleton, pre-existing hypercalcaemia, metabolic bone disease (including Paget's and hyperparathyroidism)
4. Has any uncontrolled illness that, in the opinion of the Investigator, would interfere with interpreting the results of the study.
5. Has unexplained elevations of bone-specific alkaline phosphatase
6. Has severe renal impairment defined as eGFR< 30 ml/min
7. Has severe hepatic impairment defined as aspartate aminotransferase (AST) greater than 3x the upper limit of normal
8. Has pre-existing hypercalcemia and other disturbances in the phosphocalcic metabolism.

9. Treatment Plan

Patients received 100µg of parathyroid hormone/ placebo administered once-daily as a subcutaneous injection into the abdomen. Patients were trained in the Diabetic Foot Clinic to use the proper injection techniques.
All patients received supplemental Calcium and vitamin D daily including 2 tablets daily of Calceos. Each tablet Calceos contains Calcium carbonate 1.25g equivalent to 500 mg elemental calcium or Ca^{2+} 12.5 mmol and 10 micrograms cholecalciferol (vitamin D_3) equivalent to 400 units). The trial flow chart is presented below.

Table 1Trial Flow chart

	SCREENING	RANDOMSATION	TREATMENT PHASE												POST TREATMENT PHASE
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Activity	Screen Visit	Randomi-sation visi	1month	2month	3month	4month	5month	6month	7month	8month	9 month	10 mo n t h	11 month	Final treatment visit (resolution of Charcot foot or at 12 months)	30 DAYS AFTER CLINICAL RESOLUTION
Patient information and informed consent	X														
Blood sample Biochemistry, Calcium, Phosphate, vitamin D, Parathyroid hormone Glycated Hb Bone turnover markers (CTX and P1NP)	X		X	X	X			X			X			X	
Pregnancy test (blood)	X													X	
Full physical examination	X													X	
Vital signs (temperature, pulse, blood pressure, breathing rate)	X		X	X	X			X			X			X	

Skin foot temperature (monthly until clinical resolution	X		X	X	X	X	X	X	X	X	X	X	X	X	
Foot and ankle radiograph	X				X			X			X			X	
MRI scan of Charcot foot		X												X	
SF-36		X												X	
EQ-5D		X	X		X			X						X	X
Dispense study drug (monthly or until clinical resolution)		X	X	X	X	X	X	X	X	X	X	X	X		
Drug accountability			X	X	X	X	X	X	X	X	X	X	X	X	
Adherence to treatment Monthly until clinical resolution			X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event monitoring			X	X	X	X	X	X	X	X	X	X	X	X	X

10. Protocol Deviations

No major protocol deviations that would have an impact on the outcome of the trial were made.

11. Study Results

We carried out a double blind randomised placebo controlled trial in patients with acute Charcot osteoarthropathy and compared the median time to resolution of the osteoarthropathy between active treatment and placebo. We screened a total of 72 patients of whom 48 were randomised to rhPTH 1-84 or placebo in 1:1 ratio as per study protocol. Two patients withdrew consent at randomisation and therefore were not exposed to IMP/ placebo.
We treated the patients with rhPTH 1-84/placebo until clinical resolution of the osteoarthropathy or up to a period of 12 months.
During the study period a total of 36 resolutions were observed, which fulfilled the requirements for sample size for which a total of 30 resolutions were required to guarantee a power of 80% to detect this difference at the 5% significance level.

Statistical analysis was performed on an intention-to-treat basis.

The study objectives were to determine whether there was a difference between active treatment with rh PTH 1-84 and standard treatment alone in terms of seven criteria which are listed below.

1. 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

There was no statistically significant difference between the survival (non-resolution) patterns of the two groups. The log-rank (Mantel-Cox) statistic was 0.11 yielding a p-value of 0.74 and the estimated hazard (for resolution) ratio was 1.1 (95% ci 0.57 to 2.1; P=0.78).

2. Percentage of patients with a clinical outcome of Charcot foot resolution by 6 months. This was 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).

Logistic regression analysis indicated that there was no statistical difference in the percentage of patients with clinical resolution at 6 months between the active and placebo group (Odds ratio=0.94; 95% ci 0.30 to 3; P=0.92).

3. Percentage of patients with a clinical outcome of Charcot foot resolution by 12 months. This was 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).

Logistic regression analysis indicated that there was no statistical difference in the percentage of patients with clinical resolution at 12 months between the active and placebo group, (Odds ratio=2.3; 95% ci 0.68 to 7.7; P=0.18).

4. Rate of change in the total bone marrow oedema (BMO) score assessed on non-contrast foot MRI scans carried out at presentation and at follow up (at the time of clinical resolution or at 12 months)

The total BMO score significantly decreased between presentation and follow up ($p<0.001$). However, the rate of change in the total BMO score was not significantly different between the active and placebo groups ($p=0.95$).

5. Rate of change in the total fracture score assessed on non-contrast foot MRI scans carried out at presentation and at follow up (at the time of clinical resolution or at 12 months)

The total fracture score significantly decreased between presentation and follow up ($p=0.001$). However, the rate of change in the total fracture score was not significantly different between the active and placebo groups ($p=0.55$).

6. Rate of change of bone turnover markers from baseline and up to clinical resolution of the Charcot foot

There was a significant reduction in the serum concentration of the bone marker amino-terminal propeptide of type I procollagen (P1NP), ($P=0.004$). However, the rate of change in P1NP was not significantly different between the active and placebo groups ($P=0.13$).

The serum concentration of the bone marker carboxyterminal telopeptide of type 1 collagen (CTX) remained unchanged from presentation to follow up ($P=0.92$). There was no significant difference in the longitudinal change of this marker between the two groups. ($P=0.25$).

7. Rate of change of score in quality of life from baseline up to clinical resolution using the SF-36 and EQ-5D

No significant differences between the two groups were found for any of the dimensions of these two QOL instruments.

12. Safety Evaluation

A total of 48 subjects were enrolled into this trial (2 of whom withdrew at randomisation stage). A total of 6 SAEs have been reported but no SARs or SUSARs.

The reported SAEs have been considered unlikely or not related to the IMP.

3 of these SAEs resulted in IMP being discontinued (1 of which only temporarily):

1. Subject was admitted to hospital with an infected foot ulcer, IMP was discontinued.

2. Subject was admitted to hospital with left buttock pain - diagnosis confirmed as left L3 nerve impingement and left trochanteric bursitis. IMP was discontinued.

3. Subject was admitted to hospital with acute on chronic rise in Liver Function Tests. IMP was discontinued temporarily.

Appendix I presents a cumulative table of the number of serious adverse events (SAEs) that have been reported during the trial; It is arranged by **System Organ Classification** (SOC).

APPENDIX I

Cumulative Summary Tabulation of Serious Adverse Events (SAEs)

System Organ Classification	Serious Adverse Event Details	Related to IMP/Placebo?	Outcome
Endocrine/Metabolic	Infected Diabetic Foot Ulcer	Unlikely	Recovered
Cardiovascular / Respiratory	Respiratory depression caused by fentanyl patch	Unlikely	Recovered
Neurological	L3 nerve impingement and left throchanteric bursitis	Unlikely	Recovered
Hepatobiliary disorders	Acute on chronic rise in Liver Function Tests	Unlikely	Recovered
Gastrointestinal disorders	Vomiting caused by mild active chronic gastritis	Unlikely	Recovered
Cardiac disorders	Suddenly became unresponsive and unconscious at home – Death due to Diabetes Mellitus and Ischaemic Heart Disease	Not related	Resulted in Death

12. Declaration

Signature of Chief Investigator:	Michael Edmonds
Print name:	Professor Michael Edmonds
Date of signature:	24/03/2016