



Clinical trial results:

An Open Label, Longitudinal Study of the Effects of Subcutaneous Acute and Chronic Pasireotide (SOM230) Therapy on Adrenocorticotrophic Hormone and Tumour Volume in Patients with Nelson's Syndrome.

Summary

EudraCT number	2009-014457-33
Trial protocol	GB
Global end of trial date	21 May 2014

Results information

Result version number	v1 (current)
This version publication date	06 June 2019
First version publication date	06 June 2019
Summary attachment (see zip file)	Study Report (2016 4 19 Clinical Study Report - Nelson's STH 15164 docx.pdf)

Trial information

Trial identification

Sponsor protocol code	STH 15164
-----------------------	-----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01617733
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sheffield Teaching Hospitals NHS Foundation Trust
Sponsor organisation address	Royal Hallamshire Hospital, Glossop Road, Sheffield, United Kingdom, S10 2JF
Public contact	Dr Sharon Caunt, Sheffield Teaching Hospitals NHS FT, sharon.caunt@sth.nhs.uk
Scientific contact	Prof John Newell-Price, Sheffield Teaching Hospitals NHS FT, j.newellprice@sheffield.ac.uk

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	23 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 May 2014
Global end of trial reached?	Yes
Global end of trial date	21 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Does pasireotide lower on the level of level of the circulating hormone ACTH in patients with Nelson's Syndrome?

Protection of trial subjects:

Investigators could reduce the dose of the IMP if the participant had tolerability issues.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 November 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from four UK tertiary endocrine centres.

First Patient First Visit = 24-Nov-2010

Last Patient First Visit = 20-Nov-2013

Pre-assignment

Screening details:

Screening confirmed biochemistry consistent with Nelsons syndrome.

Period 1

Period 1 title	First blinded test dose
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Test doses were not blind to the investigator, only to subject for the purposes of adverse event monitoring

Arms

Arm title	First blinded test dose
-----------	-------------------------

Arm description:

First blinded test dose

Arm type	Placebo
Investigational medicinal product name	Saline solution (0.9% NaCl)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

subcutaneous injection, volume identical to active product

Number of subjects in period 1	First blinded test dose
Started	8
Completed	8

Period 2

Period 2 title	Second Blinded Test Dose
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Test doses were not blind to the investigator, only to subject for the purposes of adverse event monitoring

Arms

Arm title	Active
------------------	--------

Arm description:

Pasireotide s.c. test dose

Arm type	Experimental
Investigational medicinal product name	Pasireotide subcutaneous
Investigational medicinal product code	
Other name	SOM230, Signifor
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

600 microgram single dose s.c.

Number of subjects in period 2	Active
Started	8
Completed	8

Period 3

Period 3 title	Subcutaneous
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Arm title	Pasireotide s.c.
------------------	------------------

Arm description:

Pasireotide s.c.

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Pasireotide subcutaneous
Investigational medicinal product code	
Other name	SOM230, Signifor
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

4 weeks of 600 micrograms of pasireotide s.c twice daily, reduced to 300 micrograms in cases of tolerability issues.

Number of subjects in period 3	Pasireotide s.c.
Started	8
Completed	6
Not completed	2
Adverse event, non-fatal	2

Period 4

Period 4 title	Long Acting Release
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Long Acting Release
------------------	---------------------

Arm description:

LAR pasireotide

Arm type	Experimental
Investigational medicinal product name	Pasireotide long acting release (LAR) and vehicle
Investigational medicinal product code	
Other name	SOM230
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Long-term pasireotide LAR 60mg (or 40mg if reduced for tolerability when on s.c dosing) every 28 days treatment (24 weeks).

Number of subjects in period 4 ^[1]	Long Acting Release
Started	5
Completed	4
Not completed	1
Adverse event, non-fatal	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 1 patient completed the subcut period but did not want to commence the long acting release period due to patient choice

Baseline characteristics

Reporting groups

Reporting group title	First blinded test dose
-----------------------	-------------------------

Reporting group description: -

Reporting group values	First blinded test dose	Total	
Number of subjects	8	8	
Age categorical Units: Subjects			
Adults (18-64 years)	8	8	
From 65-84 years	0	0	
Age continuous Units: years			
arithmetic mean	52.5		
full range (min-max)	43 to 62	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	0	0	

End points

End points reporting groups

Reporting group title	First blinded test dose
Reporting group description: First blinded test dose	
Reporting group title	Active
Reporting group description: Pasireotide s.c. test dose	
Reporting group title	Pasireotide s.c.
Reporting group description: Pasireotide s.c.	
Reporting group title	Long Acting Release
Reporting group description: LAR pasireotide	

Primary: Plasma ACTH levels

End point title	Plasma ACTH levels ^[1]
End point description: ACTH levels at 0h prior to the morning hydrocortisone dose at baseline compared to ACTH 0h pre-HC levels during s.c. phase and LAR phase.	
End point type	Primary
End point timeframe: 28 weeks	

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: Number of subjects was too small to warrant statistical analysis

End point values	Pasireotide s.c.	Long Acting Release		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: nanograms/litre				
arithmetic mean (standard deviation)	888 (± 812.8)	829 (± 1171)		

Attachments (see zip file)	Mean plasma ACTH at 0 hours/Figure - Mean plasma ACTH.pdf
-----------------------------------	---

Statistical analyses

No statistical analyses for this end point

Secondary: Acute response to test dose

End point title	Acute response to test dose
End point description: Positive acute response defined as the mean relative decrease in plasma ACTH levels >25% No response defined as the mean relative decrease in plasma ACTH levels <25%	

End point type	Secondary
End point timeframe:	
6 hours	

End point values	Active			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Percentage				
Positive acute response	5			
No response	1			
Partial response	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in tumour volume

End point title	Change in tumour volume
End point description:	
Change in adenoma tumour volume before and after pasireotide treatment (s.c. and LAR).	
End point type	Secondary
End point timeframe:	
28 weeks	

End point values	Long Acting Release			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: cm3				
arithmetic mean (standard deviation)	1.3 (± 1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After baseline to 4 weeks post final treatment

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	20
--------------------	----

Reporting groups

Reporting group title	All subjects
-----------------------	--------------

Reporting group description: -

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Renal and urinary disorders			
Raised creatinine	Additional description: MEDRA 10062237		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia	Additional description: MEDRA 10020635		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)		
Vascular disorders			
Hot flush	Additional description: MedDRA code: 10060800		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	5		

Hypotensive subjects affected / exposed occurrences (all)	Additional description: MedDRA code: 10021107		
	1 / 8 (12.50%)		
	2		
General disorders and administration site conditions			
	Additional description: MedDRA code: 10008479		
	1 / 8 (12.50%)		
	1		
	Additional description: MedDRA code: 10015608		
	2 / 8 (25.00%)		
	2		
	Additional description: MedDRA code: 10016256		
	1 / 8 (12.50%)		
	1		
	Additional description: 10016334		
	1 / 8 (12.50%)		
	1		
	Additional description: MedDRA code: 10016797		
	3 / 8 (37.50%)		
	4		
	Additional description: 10022052		
	2 / 8 (25.00%)		
	2		
	Additional description: MedDRA code: 10022086		
	1 / 8 (12.50%)		
	1		
	Additional description: MedDRA code: 10022095		
	1 / 8 (12.50%)		
	1		
	Additional description: MedDRA code: 10042693		
	1 / 8 (12.50%)		
	2		
Respiratory, thoracic and mediastinal disorders			
	Additional description: MedDRA code: 10011224		
	1 / 8 (12.50%)		
	1		
Nose bleed			
	Additional description: MedDRA code: 10029792		

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Sore throat	Additional description: MedDRA code: 10041367		
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Psychiatric disorders			
Disorientation	Additional description: MedDRA code: 10013394		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Investigations			
High cholesterol	Additional description: MedDRA code: 10020049		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Bruising of leg	Additional description: MedDRA code: 10006510		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness	Additional description: MedDRA code: 10013573		
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	9		
Headache	Additional description: MedDRA code: 10019211		
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	7		
Lethargic	Additional description: MedDRA code: 10024262		
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Light-headed	Additional description: MedDRA code: 10024490		
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	3		
Migraine	Additional description: MedDRA code: 10027599		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Numbness of face	Additional description: MedDRA code: 10029836		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

Sleepy subjects affected / exposed occurrences (all)	Additional description: MedDRA code: 10041018		
	1 / 8 (12.50%) 2		
Taste metallic subjects affected / exposed occurrences (all)	Additional description: MedDRA code: 10043135		
	1 / 8 (12.50%) 4		
Ear and labyrinth disorders Motion sickness subjects affected / exposed occurrences (all)	Additional description: MedDRA code: 10027990		
	1 / 8 (12.50%) 1		
Eye disorders Diplopia subjects affected / exposed occurrences (all) Visual disturbance subjects affected / exposed occurrences (all)	Additional description: MedDRA code: 10013036		
	1 / 8 (12.50%) 2		
	Additional description: MedDRA code: 10047543		
	1 / 8 (12.50%) 1		
Gastrointestinal disorders Abdominal cramps subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Loose stools subjects affected / exposed occurrences (all) Nausea	Additional description: MedDRA code: 10000057		
	3 / 8 (37.50%) 12		
	Additional description: MedDRA code: 10000081		
	1 / 8 (12.50%) 1		
	Additional description: MedDRA code: 10010774		
	1 / 8 (12.50%) 1		
	Additional description: MedDRA code: 10012735		
	7 / 8 (87.50%) 15		
	Additional description: MedDRA code: 10013781		
	2 / 8 (25.00%) 3		
	Additional description: MedDRA code: 10024840		
	1 / 8 (12.50%) 1		
	Additional description: MedDRA code: 10028813		

subjects affected / exposed	6 / 8 (75.00%)		
occurrences (all)	19		
Steatorrhea	Additional description: MedDRA code: 10041968		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Stomach cramps	Additional description: MedDRA code: 10049901		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vomiting	Additional description: MedDRA code: 10047700		
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Swelling of face	Additional description: MedDRA code:		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Back Pain	Additional description: MedDRA code: 10003988		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Leg cramps	Additional description: MedDRA code: 10024125		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Muscle fatigue	Additional description: MedDRA code: 10049565		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Muscle tightness	Additional description: MedDRA code: 10049816		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Neck pain	Additional description: MedDRA code: 10028836		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Swelling of knees	Additional description: MedDRA code: 10042697		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Infections and infestations			

Common cold subjects affected / exposed occurrences (all)	Additional description: MedDRA code: 10010106	
	1 / 8 (12.50%)	
	1	
Eye infection subjects affected / exposed occurrences (all)	Additional description: MedDRA code: 10015929	
	1 / 8 (12.50%)	
	1	
Gastroenteritis norovirus subjects affected / exposed occurrences (all)	Additional description: MedDRA code: 10068189	
	1 / 8 (12.50%)	
	1	
Urinary tract infection subjects affected / exposed occurrences (all)	Additional description: MedDRA code: 10046571	
	2 / 8 (25.00%)	
	2	
Metabolism and nutrition disorders		
	Additional description: MedDRA code: 10002646	
	1 / 8 (12.50%)	
	1	
	Additional description: MedDRA code: 10003028	
	1 / 8 (12.50%)	
	1	
	Additional description: MedDRA code: 10016803	
	1 / 8 (12.50%)	
	1	
	Additional description: MedDRA code: 10020635	
	4 / 8 (50.00%)	
	4	
	Additional description: MedDRA code: 10020947	
	1 / 8 (12.50%)	
	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2010	<p>To enhance the safety of the study protocol the following points were added:</p> <ol style="list-style-type: none">1) Patients with symptomatic cholelithiasis (active gallstones) will not be included in the study - gallbladder ultrasound imaging will be performed at visit 1 and end of study.2) Glycaemic control will be assessed by fasting venous blood glucose measures taken at each visit. Development of diabetes will prompt referral to a diabetologist (defined as a fasting plasma glucose of >7 mmol/L on two consecutive occasions) and managed appropriately. Patients with pre-existing diabetes mellitus or impaired fasting glucose will be monitored for any deterioration in glycaemic control and advised to regularly monitor their blood sugars by finger prick during the initiation of the study drug and to continue monitoring weekly. They will be referred to a diabetologist if necessary as indicated by a deterioration in glycaemic control.3) Patients with prolonged QTcF as measured by ECG at baseline >480msec will be excluded from the study. Patients with a confirmed QTc >500 ms or >60ms from baseline will be withdrawn from the study.4) Sexually active males recruited to the study will be advised to use condoms for the duration of the study and for 3 months after the final injection of the study drug.5) Patients will be given a drug treatment diary to record administration of IMP injections.6) Patients will be given a card detailing the potential side effects of the study drug.
23 December 2010	<p>Additional pharmacy labels were produced following the receipt of 1mL ampoules of placebo and IMP solutions for injection. The pharmacy labels previously approved were for 2mL ampoules of placebo and IMP solutions for injection.</p>
02 August 2011	<ol style="list-style-type: none">1) The Principal Investigators at two Participating Sites changed.2) Activities and documents to assist with the patient recruitment process were added.
16 November 2011	<p>Addition of new research site.</p>
03 August 2012	<ol style="list-style-type: none">1) Removal of an exclusion criterion relating to prior or current treatment with a pasireotide or other somatostatin analogue.2) Introduction of dose reduction for tolerability issues.3) Altered timelines to take into account slow recruitment into study.4) Definitions of AEs, SAEs and SUSARs added to protocol for completeness.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
03 August 2012	Recruitment and study activity was paused while a protocol amendment was reviewed by REC and MHRA to allow a dose reduction of treatment when a participant experienced tolerability issues e.g. gastrointestinal effects.	11 September 2012

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Only 8 patients were recruited to this study, which was not enough to detect a clinically significant change of ACTH with a power of 80%; the recruitment target was 17 patients.

Notes: