Clinical trial results:
Investigation of the intra-tumoural concentration and activity of sorafenib in cutaneous schwannomas

Summary

EudraCT number	2011-001789-16
Trial protocol	GB
Global end of trial date	05 April 2017

Results information

Result version number	v1 (current)
This version publication date	03 May 2021
First version publication date	03 May 2021
Summary attachment (see zip file)	Letter to JNNP (jnnp-2018-319713.full.pdf)

Trial information

Trial identification

Sponsor protocol code	PenCTU/2011/CTIMP-005

Additional study identifiers

ISRCTN number	ISRCTN49989464
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC Reference: 11/LO/0771, Local R&D No: 11/P/014

Notes:

Sponsors

Sponsor organisation name	University Hospitals Plymouth NHS Trust (previously known as Plymouth Hospitals NHS Trust)
Sponsor organisation address	Research Office, L2 MSCP, Bircham Park Offices, 1 Roscoff Rise, Derriford, Plymouth, United Kingdom, PL6 5FP
Public contact	Dr Chris Rollinson, Research Governance Manager, Research Development and Innovation, University Hospitals Plymouth NHS Trust (formerly Plymouth Hospitals NHS Trust), 01752 431045, crollinson@nhs.net
Scientific contact	Prof. C. Oliver Hanemann, Consultant in Neurology, Faculty of Medicine and Dentistry, University of Plymouth, 01752 437418, oliver.hanemann@plymouth.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	31 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 March 2017
Global end of trial reached?	Yes
Global end of trial date	05 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study are: To measure steady-state plasma concentrations and intra-tumoural concentrations of sorafenib in cutaneous schwannomas after 11 days of oral dosing with sorafenib To investigate indices of molecular activity of sorafenib in tumour and blood, before and after treatment with sorafenib.

Protection of trial subjects:

Study was approved by the MHRA and a Research Ethics Committee. The study was monitored by the Peninsula Clinical Trials Unit (PenCTU) and an Independent Trial steering Committee was set up for the study oversight.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 February 2012
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: 5
Worldwide total number of subjects	5
EEA total number of subjects	5

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)	4
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients will be identified and recruited into the trial via two routes: (i) from existing clinic patient databases held by the two Investigators, and (ii) from patients who contact the Investigators in response to information about the trial posted on the Neuro Foundation UK and Advocure NF2 websites. Recruitment is limited to two sites in the UK.

Pre-assignment

Screening details:

Screening procedures will be undertaken after informed consent: Medical history; Serum pregnancy test ; Physical examination (inc neurological examination); Blood pressure; 12 lead Electrocardiograph; Blood sample for haematology, chemistry, coagulation, target inhibition analysis; CS biopsy; Concomitant medication; Adverse events.

Pre-assignment period milestones

Number of subjects started	5
Number of subjects completed	5

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Sorafenib

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

800mg per day (400mg bd): orally on Days 1-10 inclusive , 400mg od on Day 11 (morning)

Number of subjects in period 1	Sorafenib
Started	5
Completed	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	5	5	
Age categorical			
Diagnosis of NF2, over 18 years in age and with cutaneous schwannoma(s) accessible for two biopsies >1cm3 in area			
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)	4	4	
From 65-84 years	1	1	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	1	1	
Male	4	4	

End points

End points reporting groups

Reporting group title	Sorafenib

Reporting group description: -

Primary: Steady-state plasma and intra-tumoural concentrations

End point title	Steady-state plasma and intra-tumoural concentrations[1]

End point description:

Primary objective: measure steady-state plasma concentrations and intra-tumoural concentrations of sorafenib in cutaneous schwannomas after 11 days of oral dosing with sorafenib. At day 11 participation will undergo: Post-dose CS biopsy, Physical examination, Blood pressure, ECG, Blood sample for Haematology, chemistry and coagulation and Blood sample for plasma concentration of sorafenib.

End point type	Primary

End point timeframe:

Baseline vs Day 11

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: Descriptive analysis only, see linked publication.

End point values	Sorafenib			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: ng/mg				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs will be reported to the Sponsor and PenCTU by telephone/fax within 24 hours. Fatal or life threatening SUSARs reported to NCA within 7 days. Non-fatal or non-life threatening SUSARs reported to NCA within 15 days.

Adverse event reporting additional description:

The sponsor and PenCTU must be made aware of any AEs by the CI or a member of the research in the appropriate time frame. The Sponsor will then inform the NCA where applicable.

Assessment type	Systematic

Dictionary used

Dictionary name	None
Dictionary version	0

Reporting groups

Reporting group title	Sorafenib

Reporting group description: -

Serious adverse events	Sorafenib		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Skin and subcutaneous tissue disorders			
Rash	Additional description: Severe rash face, leg, arms, rash whole body worse knees.		
subjects affected / exposed	1 / 5 (20.00%)		
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	Sorafenib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
General disorders and administration site conditions			
Nausea			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Headache			

subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Hypersensitivity	Additional description: Sensitive scalp, lips, tongue		
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	3		
Hot flush			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Abdominal discomfort	Additional description: Abdominal soreness		
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Hunger	Additional description: Lack of appetite		
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Lethargy			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Immune system disorders			
Rhinitis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Menstruation irregular	Additional description: Worsened menstrual bleeding		
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Breathlessness		
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Psychiatric disorders			

Insomnia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Investigations			
Liver function test	Additional description: ALT (alanine aminotransferase), ALP (Alkaline phosphatase), AST (Aspartate aminotransferase)		
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	5		
Amylase			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Prothrombin time prolonged			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Nervous system disorders			
Tremor			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Pain	Additional description: Neuropathic pain		
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Hearing disability	Additional description: Reduced hearing in right ear.		
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		

Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	6		
Urticaria chronic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Skin exfoliation	Additional description: Left thumb palmar side		
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Cystitis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Limb discomfort	Additional description: Leg pain		
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Back pain			

subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Pain	Additional description: Joint pain		
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	3		
Infections and infestations			
Throat irritation	Additional description: Sore throat		
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Oral bacterial infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2011	Protocol Version 2.0: Amendment made primarily to add section describing recruitment of participants via Neuro Foundation UK and Advocure NF2 websites.
23 July 2012	Protocol Version 6.0: Substantial amendment to the statistical section to reduce the sample size required for the study. Wording added to utilise further sites / PICs as required to improve recruitment.
02 July 2013	Protocol Version 8.0: Substantial amendment to section 16.1 'Side effects of Sorafenib' and removal of appendix I, to ensure the current SmPC is the main point of reference for side effects.

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/30718294