# 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<br>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