Clinical trial results:
An early phase trial of topical tropomyosin kinase (TRK) inhibitor as a treatment for inherited CYLD defective skin tumours

Summary

EudraCT number	2014-001342-21
Trial protocol	GB
Global end of trial date	19 September 2016

Results information

Result version number	v1 (current)
This version publication date	22 August 2018
First version publication date	22 August 2018
Summary attachment (see zip file)	TRAC Cohort 1 Summary attachment (TRAC_Summary attachment_Cohort 1.pdf)

Trial information

Trial identification

Sponsor protocol code	NCTUTRK1(6840)

Additional study identifiers

ISRCTN number	ISRCTN75715723
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Level 1, Regent Point, Regent Point Road, Newcastle upon Tyne, United Kingdom, NE3 3HD
Public contact	Neil Rajan, Newcastle University, 0191 2418813, neil.rajan@ncl.ac.uk
Scientific contact	Neil Rajan, Newcastle University, 0191 2418813, neil.rajan@ncl.ac.uk
Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Level 1 Regent Point, Regent Point Road, Newcastle upon Tyne, United Kingdom, NE3 3HD
Public contact	Dr Neil Rajan, Newcastle University, 0191 241 8813,
Scientific contact	Dr Neil Rajan, Newcastle University, 0191 241 8813, neil.rajan@newcastle.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 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 September 2016
Global end of trial reached?	Yes
Global end of trial date	19 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal research objective for Cohort 1 was to find out whether CT327 (an ointment with a drug called a TRK inhibitor in it) is a safe treatment for patients with CYLD defective tumours (lumps). The results for Cohort 1 are in the summary attachment.

The principal research objective for Cohort 2 was to investigate whether CYLD defective tumours (lumps) respond to CT327.

Protection of trial subjects:

The trial involved an independent data monitoring committee to provide overall supervision for the trial on behalf of the Trial Sponsor and Trial Funder and to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial.

Background therapy:

No Background therapy used by all subjects.

Evidence for comparator:

There are no known effective medical alternatives to treat this condition.

Actual start date of recruitment	09 March 2015
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: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	11
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

CYLD mutation carrier patients known to the clinical genetics and dermatology department in Newcastle will be reviewed by the clinical team to verify that they meet the trial inclusion criteria. Patients were either approached during a routine outpatient appointment or written to and invited to attend a clinical appointment to discuss the trial.

Pre-assignment

Screening details:

Inclusion criteria was checked and patients were assessed to ensure they had an appropriate tumour scheduled for routine excision, which was not ulcerated. Once written informed consent was obtained patients would undergo the trial specific screening which was a urine based pregnancy test for Female patients of child bearing age.

Period 1

Period 1 title	Cohort 2 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Randomisation was at the per patient level randomising active and placebo treatments to left or right sided application. Patients and investigators were blinded to the treatment allocation. Those responsible for tumour volume measurements, histology assessments and molecular analysis were also blinded. Participants randomised to arm A received active treatment on the 5 tumours on the left hand side of the body whereas participants randomised to Arm B received active treatment on the right side.

Arms

Arm title	Cohort 2: Arm A and Arm B

Arm description:

In cohort 2, active and placebo trial medication was provided at baseline and visit 4 to supply enough ointment for the 12 week period. Active medication contained CT327 at 0.5%w/w. Each participant pack of active medication or placebo was presented as a 20g glass jar. Tumours on one half of the body with active CT327 and the other half of the body with placebo according to the randomisation allocation for a 12 week period.

Participants randomised to arm A received active treatment on the 5 tumours located on the left hand side. The 5 tumours on the right hand side received placebo treatment.

Participants randomised to Arm B received active treatment on the 5 tumours located on the right hand side of the body.

The 5 tumours on the left hand side received placebo treatment. The Investigator, study team and trial management team were blinded to which side the participants received active treatment vs placebo treatment.

Arm type	Experimental
Investigational medicinal product name	Pegcantratinib 0.5% w/v
Investigational medicinal product code	CT327 (0.5%w/v)
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Epicutaneous use

Dosage and administration details:

Patients were allocated both active and placebo treatments to be applied randomly to tumours on their left or right side (Group1: L=active; R=placebo, Group 2: L=placebo; R=active). In cohort 2 active and placebo trial medication were provided at baseline and visit 4 to supply enough ointment for the 12 week period. Active medication contained CT327 at 0.5%w/w. Each participant pack of active medication or placebo was presented as a 20g glass jar. The dose consisted of one application (1

standardised spatula) in the evening to each tumour as directed at the first visit by the research nurse/doctor. Patients recorded the application of treatment in a patient diary. All participants were treating tumours on one half of the body with active CT327 and the other half of the body with placebo according to the randomisation allocation for a 12 week period.

Number of subjects in period 1	Cohort 2: Arm A and Arm B
Started	15
Completed	14
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups

Reporting group title	Cohort 2

Reporting group description:

The trial is split into two phases namely a phase 1b (cohort 1) which aims to determine the safety profile of CT327, and a phase 2a (cohort 2) that will investigate if CYLD defective tumours respond to CT327. Cohort 2 is a Phase 2a is a randomised double blind single site trial where the primary objective is to establish if CYLD defective tumours respond to CT327. The primary outcome will be the proportion of tumours responding to treatment by 12 weeks in both actively treated lesions and placebo treated lesions.
Secondary outcome measures will be change in tumour volume, adverse events, compliance, confirmation of the definition of response, patient reported quality of life according to EQ5D and DLQI, acceptability of treatment and a trial specific pain measure.
To achieve the 150 tumours required 15 were recruited into Phase 2a.

Reporting group values	Cohort 2	Total	
Number of subjects	15	15	
Age categorical			
8 participants were first randomised to cohort 1 to determine the safety of CT327 application before moving onto cohort 2 assessing the efficacy of CT327 application versus placebo.			
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)	11	11	
From 65-84 years	4	4	
85 years and over	0	0	
Age continuous			
Participants enrolled in cohort 2.			
Units: years			
median	51		
inter-quartile range (Q1-Q3)	46 to 69	-	
Gender categorical			
Participants enrolled in cohort 2.			
Units: Subjects			
Female	13	13	
Male	2	2	
Ethnicity			
Participants in cohort 2			
Units: Subjects			
White	15	15	
Other	0	0	

End points

End points reporting groups

Reporting group title	Cohort 2: Arm A and Arm B

Reporting group description:

In cohort 2, active and placebo trial medication was provided at baseline and visit 4 to supply enough ointment for the 12 week period. Active medication contained CT327 at 0.5%w/w. Each participant pack of active medication or placebo was presented as a 20g glass jar. Tumours on one half of the body with active CT327 and the other half of the body with placebo according to the randomisation allocation for a 12 week period.

Participants randomised to arm A received active treatment on the 5 tumours located on the left hand side. The 5 tumours on the right hand side received placebo treatment.

Participants randomised to Arm B received active treatment on the 5 tumours located on the right hand side of the body.

The 5 tumours on the left hand side received placebo treatment. The Investigator, study team and trial management team were blinded to which side the participants received active treatment vs placebo treatment.

Primary: Proportion of tumours responding to treatment

End point title	Proportion of tumours responding to treatment[1]

End point description:

Cohort 2- Participants randomised to Arm A receiving active treatment on the 5 tumours located on the left hand side of the body. The 5 tumours on the right hand side of the body received placebo treatment.

Please note the number reported in the endpoint table below is a percentage value.

End point type	Primary

End point timeframe:

12 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: No additional statistical analysis performed

End point values	Cohort 2: Arm A and Arm B			
Subject group type	Reporting group			
Number of subjects analysed	14[2]			
Units: number				
number (confidence interval 95%)				
Complete response (Active)	1.4 (0.19 to 9.88)			
Complete response (Placebo)	1.4 (0.19 to 9.88)			
Partial response (Active)	1.4 (0.19 to 9.88)			
Partial response (Placebo)	7.1 (2.93 to 16.35)			
Stable disease (Active)	82.9 (71.88 to 90.14)			

Stable disease (placebo)	75.7 (64.04 to 84.52)			
Progressive disease (Active)	14.3 (7.74 to 24.87)			
Progressive disease (Placebo)	15.7 (8.79 to 26.51)			

Notes:

[2] - 10 tumours from each participant were used for this trial. Therefore 140 tumours from 14 patients.

Attachments (see zip file)	Table 1-4 Tumour size at baseline/Table 1-4 Tumour size at Table 6 Tumour response according to WHO RECIST/Table 6-

Statistical analyses

No statistical analyses for this end point

Primary: Sensitivity analysis of response

End point title	Sensitivity analysis of response[3]

End point description:

The primary analysis has been repeated without the inclusion of 1007, who was found to have applied treatment ointment to the wrong tumours.

Please note the number reported in the endpoint table below is a percentage value.

End point type	Primary

End point timeframe:

Tumour response at 12 weeks

Notes:

[3] - 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: No additional statistical analysis performed

End point values	Cohort 2: Arm A and Arm B			
Subject group type	Reporting group			
Number of subjects analysed	13[4]			
Units: number				
number (confidence interval 95%)				
Complete Response (Active)	1.5 (0.21 to 10.62)			
Complete Response (Placebo)	1.5 (0.21 to 10.62)			
Partial response (Active)	1.5 (0.21 to 10.62)			
Partial response (Placebo)	7.7 (3.16 to 17.54)			
Stable disease (Active)	83.1 (71.61 to 90.53)			
Stable disease (placebo)	76.9 (64.82 to 85.77)			
Progressive disease (Active)	13.8 (7.24 to 24.88)			
Progressive disease (Placebo)	13.8 (7.24 to 24.88)			

Notes:

[4] - 130 tumours from 13 participants were analysed.

Attachments (see zip file)	Table 7 WHO RECIST excluding 1007/Table 7 WHO RECIST Table 13 Sensitivity analysis of response endpoint/Table 13

Statistical analyses

No statistical analyses for this end point

Primary: Tumour-level change

End point title	Tumour-level change[5]

End point description:

Tumour measurements have been reported descriptively as mean (standard deviation), median and IQR at baseline, 4 weeks and 12 weeks by treatment received and overall.

End point type	Primary

End point timeframe:

Tumour level change from baseline to 12 week tumour measurement.

Notes:

[5] - 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: No additional statistical analysis performed

End point values	Cohort 2: Arm A and Arm B			
Subject group type	Reporting group			
Number of subjects analysed	14[6]			
Units: number				
arithmetic mean (confidence interval 95%)				
Active	1.03 (0.97 to 1.10)			
Placebo	1.00 (0.94 to 1.07)			
Overall	1.02 (0.98 to 1.06)			

Notes:

[6] - 140 tumours were measured from 14 participants.

Attachments (see zip file)	Table 5 Tumour level change endpoint/Table 5 Tumour level

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of acceptability of trial treatment

End point title	Assessment of acceptability of trial treatment

End point description:

Patients completed questions 1-5 of the patient treatment questionnaire. This was used to determine

the acceptability of the treatment. The questionnaire was completed at the final visit, at the end of treatment by 14 participants.
The Patient Treatment Questionnaire has been analysed descriptively reporting the number of patients answering each response level in each question. Question 5 is reported as the percentage of patients who were able to correctly identify which side had been allocated the treatment ointment. Comments left in the text box are listed.

End point type	Secondary

End point timeframe:

End of treatment (EOT) visit

End point values	Cohort 2: Arm A and Arm B			
Subject group type	Reporting group			
Number of subjects analysed	14[7]			
Units: number				
Application of ointment - Easy	12			
Application of ointment -neither easy or difficult	2			
Application of ointment- difficult	0			
Duration taken to apply treatment- less than 1 min	2			
Duration taken to apply treatment 1-4 mins	7			
Duration taken to apply treatment- 5-9 mins	5			
Duration taken to apply treatment- 10+ mins	0			
Overall satisfaction score- very satisfied	7			
Overall satisfaction score- satisfied	3			
Overall satisfaction score- neither	1			
Overall satisfaction score- Dissatisfied	3			
Overall satisfaction score- very dissatisfied	0			
If ointment was available, would you use it- yes	10			
If ointment was available, would you use it- No	4			

Notes:

[7] - 14 participants answered 5 questions using the patient treatment questionnaire.

Attachments (see zip file)	Table 8 & 9 Treatment questionnaire and compliance/Table 8-

Statistical analyses

No statistical analyses for this end point

Secondary: Patient reported Quality of Life - EQ-5D-5L

End point title	Patient reported Quality of Life - EQ-5D-5L

End point description:

EQ-5D-3L was collected at the baseline visit. The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no Descriptive problems, some problems, extreme problems. A variable is derived to describe the unique health of each participant this state is defined by combining 1 level from each of the

5 dimensions. Detailed descriptions regarding calculation of scores can be found in the user guide found at http://www.euroqol.org.

Health states determined by the EQ-5D are reported as numbers of patients responding to each dimension.

End point type	Secondary

End point timeframe:

EQ-5D-3L was collected at the baseline visit.

End point values	Cohort 2: Arm A and Arm B			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: number				
11111	8			
11121	5			
12133	1			
21223	1			

Attachments (see zip file)	Table 10 EQ-5D-5L at baseline visit/Table 10 Patient QOL EQ-

Statistical analyses

No statistical analyses for this end point

Secondary: Patient reported quality of life - DLQI

End point title	Patient reported quality of life - DLQI

End point description:

The Dermatology Life Quality Index (DLQI) questionnaire is designed for use in adults, i.e. patients over the age of 16 and is a patient reported questionnaire. It is collected at the baseline visit. The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. The DLQI can also be expressed as a percentage of the maximum possible score of 30. Detailed description of the calculation of the DLQI can be found in the instructions for use on the Cardiff University website.
http://www.cardiff.ac.uk/dermatology/quality-of-life.

To obtain a total DLQI score the responses are scored as follows with a total score being a maximum of 30:
Very much scored 3
A lot scored 2
A little scored 1
Not at all scored 0
Not relevant scored 0
Question unanswered scored 0
Question 7: "prevented work or studying" scored 3

End point type	Secondary

End point timeframe:

Dermatology Life Quality Index (DLQI) was completed at the baseline visit.

End point values	Cohort 2: Arm A and Arm B			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: number				
no effect at all on patient's life (0-1)	3			
small effect on patient's life (2-5)	6			
moderate effect on patient's life (6-10)	4			
very large effect on patient's life (11-20)	2			
extremely large effect on patient's life (21-30)	0			

Attachments (see zip file)	Table 11 & 12 DLQI scores/Table 11-12 Patient reported QOL

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

In cohort 2 adverse events were reported for 16 weeks. AE Reporting commenced from the start date participant received CT327 and placebo treatment at baseline to 4 weeks after end of treatment.

Adverse event reporting additional description:

14 adverse events were reported in 8 participants, all were reported as mild.

Assessment type	Systematic

Dictionary used

Dictionary name	verbatim
Dictionary version	1

Reporting groups

Reporting group title	Cohort 2

Reporting group description:

Adverse events were recorded by clinical staff on a three-point scale of severity (mild, moderate or severe) and also by causality (relationship to treatment as categorised on a six point scale), as described in the protocol.

Serious adverse events	Cohort 2		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort 2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 15 (53.33%)		
Ear and labyrinth disorders			
Tinnitus	Additional description: Right side of participant's ear.		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cold			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Allergic rhinitis			

subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Sore throat			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cough and sputum	Additional description: In addition to cough and sputum, participant also experienced a sore throat and headache. Participant experienced no fever.		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Mild Catarrh	Additional description: Participant experienced long term catarrh intermittently.		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Small break in skin	Additional description: Small break in the skin on top of tumour 2. Skin healed on examination at a later visit.		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Itch			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Skin lesions	Additional description: Three skin lesions not in trial have become painful.		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infections and infestations			
Wound infection	Additional description: Surgical site wound infection		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2014	Removal of kit number, subject number and randomisation number from IMP label.
24 June 2015	Addition of a pain assessment at week 0, 4 and 12.
24 March 2016	Updates to the reference safety information (RSI) in the investigator brochure and protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported