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Tropomyosin receptor kinase antagonism in cylindromatosis

Submission date	Recruitment status
22/10/2014	No longer recruiting
Registration date	**Overall study status**
22/10/2014	Completed
Last Edited	**Condition category**
02/07/2018	Skin and Connective Tissue Diseases

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
This study aims to evaluate a new ointment to treat an inherited skin tumour condition called cylindromatosis. Patients from families with this condition carry an error in their DNA (CYLD mutation) that results in the development of multiple skin tumours on the face, scalp and trunk. These tumours are disfiguring, can be painful, and may ulcerate and bleed. Surgery is the only available treatment, and up to 1 in 4 patients with this condition undergo removal of their entire scalp to manage this condition. We have recently discovered an abnormal signal in the tumour cells called TRK. This signal is recognised to give tumour cells the ability to survive, and in laboratory tests blocking it with drugs called TRK inhibitors results in the tumour cells dying. We propose a study of an ointment form of TRK inhibitor as a means to reduce tumour growth in these patients. We have partnered with a drug company (Creabilis) who have already produced this ointment (called CT327) for trials in skin conditions. Should this be effective, it potentially could be used by patients in the future to treat early tumours and reduce the number of operations they would otherwise undergo.

Who can participate?
Patients aged 18 and over from families with known CYLD mutations, who are scheduled to have a tumour removed.

What does the study involve?
This is a two-part study. In part 1 participants are provided with active CT327 ointment and a spatula to help them to apply the correct amount of ointment. The dose is one application (two spatulas) in the evening to the selected tumour (scheduled for removal) as directed. The aim of part 1 is to determine the safety of CT327 in CYLD mutation carriers. The number of patients who experience severe treated skin site reactions is measured over a 4-week period. In part 2 participants are randomly allocated to one of two groups and provided with active CT327 and placebo (dummy) ointment. One group applies the active ointment to tumours on the right side of their body and placebo ointment to the left side. The other group applies the placebo ointment to tumours on the right side of their body and active ointment to the left side. The dose is one application (one spatula) in the evening to each selected tumour (4-5 on each side) as directed. The number of tumours responding to treatment is measured after 12 weeks.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
Royal Victoria Infirmary (UK)

When is the study starting and how long is it expected to run for?
October 2014 to November 2016

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
Amy Cranston
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Protocol serial number
17398

Study information

Scientific Title
Topical tropomysin kinase (TRK) inhibitor as a treatment for inherited CYLD-defective skin tumours (TRAC)

Acronym
TRAC

Study objectives

Repurposing study, using CT327 ointment, previously used in patients with psoriasis and eczema, in patients with CYLD defective skin tumours in a 2 part clinical trial to determine safety and investigate if the tumours reposed to CT327.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee North East - Tyne and Wear South, 04/09/2014, ref: 14/NE/1080

Primary study design
Interventional

Study design
Both; Interventional; Design type: Treatment

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Topic: Cancer, Genetics, Dermatology; Subtopic: Head and Neck Cancer, Genetics Research and Congenital Disorders (all subtopics), Skin (all Subtopics); Disease: Head and Neck, Genetics Research and Congenital Disorders, Dermatology

Interventions
Cohort 1: active trial medication containing CT327 at 0.5%w/w will be provided as ointment in 20 g glass jars. Patients will be provided with a spatula to help them to apply the correct amount of ointment. The dose will be one application (2 standardised spatulas) in the evening to the selected tumour (scheduled for excision) as directed.

Cohort 2: patients will be randomised to either right side active and left side placebo (RALP) or right side placebo, left side active (RPLA) and allocated a kit of treatment. Active and placebo trial medication will be provided at baseline and visit 4 to supply enough ointment for the 12 week period. The dose will be one application (1 standardised spatula) in the evening to each selected tumour (4-5 on each side) as directed.

Intervention Type
Other

Phase
Not Applicable

Primary outcome(s)
Cohort 1: Number of patients with severe treated skin site reactions as determined by Modified Draize score.
Cohort 2: The proportion of tumours responding to treatment by 12 weeks.

Key secondary outcome(s)
Cohort 1:
1. Patient reported quality of life using patient reported QoL tools (EQ5D, DLQI)
2. Acceptability of treatment according to patient treatment questionnaire

3. Adverse events within a planned 4-week treatment period
4. Compliance including reasons for non-compliance

Cohort 2:
1. Change in tumour volume from baseline (pre-randomisation) to 12 weeks
2. Adverse events within a planned 12-week treatment period
3. Compliance including reasons for non-compliance
4. Confirmation of the definition of response (currently according to WHO RECIST criteria where response is defined as >30% reduction in tumour volume, this will be used as a benchmark)
5. Expression of targets of TRK signalling in tumour biopsies as determined by QPCR and immunohistochemistry
6. Patient reported quality of life using patient reported QoL tools (EQ5D, DLQI)
7. Assessment of acceptability of trial treatment according to patient treatment questionnaire

Completion date
30/11/2016

Eligibility

Key inclusion criteria
Cohort 1:
1. Males and females age 18 years and older
2. Patients from genotyped pedigrees with known CYLD mutations; or if they have a clinical phenotype compatible with this diagnosis
3. Patients that are suitable for the trial will have at least one eligible tumour
4. The eligible tumour will be scheduled for removal >4 weeks from consent
5. The eligible tumour must be no more than 3cm in size
6. For women of childbearing age: a negative pregnancy test is required prior to study entry, and on completion of trial treatment. The patient must be using an adequate contraception method and agree to continue using this throughout the trial and for at least 2 weeks after stopping trial medication
7. Sexually active men must agree to use barrier forms of contraception
8. The recruiting clinician must be confident that the patient understands the consent process and has the capacity and willingness to provide fully informed consent for participation in the trial

Cohort 2:
1. Males and females age 18 years and older
2. For women of child bearing age: a negative pregnancy test is required prior to study entry, and on completion of trial treatment. The patient must be using an adequate contraception method and agree to continue using this throughout the trial and for at least 2 weeks after stopping trial medication
3. Patients from genotyped pedigrees with known CYLD mutations, or if they have a clinical phenotype compatible with this diagnosis
4. Patients will optimally have 8-10 eligible tumours
5. Eligible tumours will be less than 1 cm in diameter and no more than 2 cm in diameter at the base
6. Eligible tumours must be spaced at least 1 cm apart from other eligible tumours to avoid crosscontamination
7. The recruiting clinician must be confident that the patient understands the consent process and has the capacity and willingness to provide fully informed consent for participation in the

trial
8. Patients who have completed Phase 1b without adverse reaction and after completing a minimum 2 week treatment free washout period

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
Cohort 1:
1. Patients aged <18 years
2. Patients without CYLD defective tumours
3. CYLD defective tumours which are ulcerated (these tumours will be managed according to standard practice of care)
4. The eligible tumour is due to be removed <4 weeks from consent
5. Pregnancy or lactation
6. Women of childbearing age and sexually active men whom do not wish to use contraception whilst on the study
7. Severe incapacity of higher function such that fully informed consent cannot be achieved, to be determined by clinical judgement
8. Use of any other topically administered treatments at the treatment site

Cohort 2:
1. Patients aged <18 years
2. Patients without multiple CYLD defective tumours
3. Pregnancy or lactation
4. Women of childbearing age and sexually active men whom do not wish to use contraception whilst on the study
5. CYLD defective tumours which are ulcerated, have recently changed or are painful (these tumours will be managed according to standard practice of care)
6. Severe incapacity of higher function such that fully informed consent cannot be achieved, to be determined by clinical judgement
7. Significant concurrent illness
8. Patients who developed an adverse reaction to CT327 in cohort 1(score of 4 or above on the modified Draize score)
9. Patients who have taken part in cohort 1and not completed a minimum 2 week treatment free washout period
10. Large tumours >2cm base diameter will not be eligible
11. Any tumour within 10cm of an excision scar of a cohort 1 treated site will not be eligible
12. Use of any other topically administered treatments at the treatment site

Date of first enrolment
01/10/2014

Date of final enrolment
30/11/2016

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Royal Victoria Infirmary
Newcastle Upon Tyne
United Kingdom
NE1 4LP

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust (UK); Grant Codes: 100935

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype

International organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/08/2018		Yes	No
Protocol article	protocol	07/03/2017		Yes	No
HRA research summary			28/06/2023	No	No