ISRCTN10422213 https://doi.org/10.1186/ISRCTN10422213

A trial to test the use of HIV drugs to treat neurofibromatosis type 2 (NF2) related tumours

Submission date
23/11/2023

Recruitment status
Suspended

Registration date
22/02/2024

Overall study status
Completed

Last Edited
28/10/2026

Condition category
Nervous System Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
This study aims to provide important information about the way two drugs called ritonavir and lopinavir are taken up into skin schwannoma tissue. Skin schwannomas are non-cancerous (benign) tumours which may develop on the skin of patients who have the condition NF2-related schwannomatosis (formerly Neurofibromatosis Type 2). NF2 is caused by changes to the genetic material inside the body's cells. Surgery and radiotherapy are used to treat these tumours, but they are often not possible and can have unpleasant side effects. Therefore, new drugs that target specific molecules in the cell could offer a better treatment for patients with this condition.
Ritonavir and lopinavir are used to treat human immunodeficiency virus (HIV). The drugs have been shown to reduce tumour growth and survival in the lab. The safe and effective long-term use of these drugs is well documented in healthy volunteers and those with HIV, making them good candidates to study further.

Who can participate?
Patients over 18 years of age with skin schwannomas caused by NF2

What does the study involve?
Participants will have a biopsy of a skin schwannoma and a blood sample taken prior to 30 days of treatment with Lopinavir/Ritonavir plus additional ritonavir. On Day 30 of treatment, a second (post-dose) biopsy will be taken along with a blood sample. The aim of the study is to investigate the uptake and activity of the drugs in the cutaneous tumours (whether they inhibit the molecular pathways they should) and how they affect the blood. Participants will attend a further "end of study" visit around Day 60 as a final safety check. The information obtained will be used to decide whether Ritonavir and Lopinavir should be investigated further as a treatment for the tumours caused by NF2.

What are the possible benefits and risks of participating?
The possible risks include:
1. Pain, discomfort and infection resulting from tumour biopsies. Procedures will only be performed by trained staff and the wounds will be checked at subsequent trial visits.
2. Pain, discomfort, bleeding, bruising and infection resulting from venipuncture. Venipuncture

will only be performed by trained staff. The number of blood draws has been minimised.
3. Risk of side effects from the use of trial IMP in a new indication. The IMPs are both licensed HIV medications that are well tolerated with a known safety profile. However, participants will be closely monitored (in-person visits, telephone visit and safety blood test at the end of dosing).
4. This phase 0 is not designed to investigate therapeutic benefit in the participants. The trial design allows efficient assessment of candidate drugs in a small number of participants (rather than conducting larger phase II/III trials). This will be clearly communicated to potential participants both in the patient information sheet and in the recruitment/consent discussions.
5. Risk of pregnancy (in women of childbearing potential) as the trial medication is known to reduce the effectiveness of hormonal contraception. All participants are required to take adequate contraceptive measures. For women of childbearing potential this means using two barrier methods. This will be clearly stated in the patient information sheet and emphasised by the investigator during screening

Where is the study run from?
Peninsula Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
November 2023 to July 2026

Who is funding the study?
Children’s Tumor Foundation (USA)

Who is the main contact?
1. Dr Katherine Beaney, katherine.beaney@plymouth.ac.uk
2. Dr Sarah Kingon, sarah.kingdon@nhs.net

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Integrated Research Application System (IRAS)
1008579

Central Portfolio Management System (CPMS)
58653

Study information

Scientific Title
Repurposing anti-retroviral drugs to treat NF2 related tumours

Acronym
RETREAT

Study objectives
Primary objective:
To determine the biological effect of ritonavir and lopinavir (Kaletra plus Norvir) at steady state concentration by investigation of molecular target inhibition in peripheral subcutaneous schwannoma (CS) tissues after oral drug administration for 30 days in comparison to baseline (first biopsy).

Secondary objectives:
1. To determine steady-state plasma and Intra-tumoural (CS) concentration of ritonavir and lopinavir (Kaletra plus Norvir) after 30 days of oral dosing.
2. Assessment of biomarkers for treatment response in patients by testing target inhibition in PBMC after 30 days of dosing.
3. Determine minimal biological effective dose.
4. To assess toxicity of ritonavir and lopinavir (Kaletra plus Norvir) in patients treated at this dose schedule for 30 days for meningioma or schwannoma.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 21/02/2024, West of Scotland REC 1 (West of Scotland Research Ethics Service, Ward 11, Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE, United Kingdom; +44 141 314 0212; WosRec1@ggc.scot.nhs.uk), ref: 23/WS/0178

Primary study design
Interventional

Study design
Single-arm non-randomized study

Study type(s)
Safety

Health condition(s) or problem(s) studied
NF2-related schwannomatosis (formerly Neurofibromatosis Type II) (NF2)

Interventions
All participants recruited will commence both drugs, orally, Kaletra (AbbVie) at a strength of 100 mg Lopinavir + 25 mg Ritonavir and Norvir (AbbVie) Ritonavir dose at 200 mg, twice daily from Day 1, following completion of the baseline procedures for 30 days (in total 100 mg Lopinavir and 225 mg Ritonavir twice daily).

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Lopinavir, ritonavir

Primary outcome(s)
Target inhibition will be analysed in the tumour before and after drug treatment via Wes™, an automated capillary-based immunoassay quantitative system to determine the levels of:
1. Phosphorylated (active) and total (phosphorylated and non-phosphorylated) ERK1/2 (proliferation marker)
2. Cyclin D1 (cell cycle progression marker)
3. Cleaved (active) Caspase 3 (apoptosis marker)
4. Cleaved PARP1 (apoptosis) as main targets

This will be complemented by an extended biomarker investigation looking for the effect of ritonavir and lopinavir on:
1. Phospho FAK/FAK, p53
2. Phospho S6 Ribosomal Protein/s6
3. cJun, phospho AKT/AKT
4. P-Glycoprotein (MDR-1)

Measured at Day 0 and Day 30

Key secondary outcome(s)
1. Steady-state plasma and Intra-tumoural (CS) concentration of ritonavir and lopinavir (Kaletra plus Norvir) after 30 days of oral dosing - drug concentration (µg/kg) from pharmacokinetic blood and tissue samples.
2. Assessment of biomarkers for treatment response in patients by testing target inhibition in PBMC after 30 days of dosing - Western blotting will be performed for detection of:
2.1. Phosphorylated (active) and total (phosphorylated and non-phosphorylated) ERK1/2 (proliferation marker),
2.2. Cyclin D1 (cell cycle progression marker),

2.3. Cleaved (active) caspase 3 (apoptosis marker).
3. Minimal biological effective dose - the dose level is declared effective if at least two of the initial five or second stage 8 (5+3) patients demonstrate a PD response which is significant at the 0.05 level. Measured at Day 0 and Day 30.
4. Toxicity of ritonavir and lopinavir (Kaletra plus Norvir) in patients treated at this dose schedule for 30 days for meningioma or schwannoma - assessment of adverse events (AEs), serious adverse events (SAEs), ARrs, serious adverse reactions (SARs) and suspected unexpected serious adverse reactions (SUSARs). Measured at Day 0 and Day 60.

Completion date
31/07/2026

Eligibility

Key inclusion criteria
1. Written informed consent
2. Diagnosis of NF2-related schwannomatosis as defined using the 2022 criteria
3. Meningioma as identified by imaging
4. Over 18 years of age
5. Peripheral schwannomas under the skin (CS) biopsies amenable to biopsy
6. Karnofsky performance status >60%
7. Adequate bone marrow function within 28 days prior to the baseline visit: WBC >3.4 x 10e9/l, platelets >99 x 10e9/l
8. Adequate renal function within 28 days prior to the baseline visit: creatinine <2.5 x upper limit of normal
9. Adequate hepatic function within 28 days prior to the baseline visit: LFT <1.5 x upper limit of normal, serum amylase <1.5 x upper limit of normal
10. Prothrombin (PT) or INR (International Normalised Ratio) and Prothrombin Time (PTT) < 1.5 x upper limit of normal
11. Able to swallow tablets
12. Patients with the potential for pregnancy or impregnating their partner must agree to use acceptable methods of birth control to avoid conception. Female patients must agree to employ two barrier methods of contraception (e.g. condom, diaphragm with spermicidal jelly) during the trial and for 3 months following the end of their trial participation. Post-menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential.
13. Women of childbearing potential with a negative serum pregnancy test at screening and a negative urine pregnancy test at the baseline visit.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit

99 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Hypersensitivity to ritonavir or lopinavir or any of its excipients
2. Current or expected use of any medications or substances that are highly dependent on Cytochrome P450 3A4 (CYP3A4) for clearance or are strong inducers of CYP3A4. See current SmPC for details of medications. Participants who have not had their contraindicated medication either discontinued or switched to a different medication at least 2 weeks prior to starting the trial drug.
3. Cardiac arrhythmias requiring anti-arrhythmics (beta-blockers and digoxin are allowed)
4. Symptomatic coronary artery disease or ischemia
5. Myocardial infarction (MI) within the last 6 months; congestive cardiac failure >NYHA Class II
6. Active clinically serious bacterial or fungal infections
7. Known diagnosis of human immunodeficiency virus (HIV) infection or chronic hepatitis B or C
8. Prior treatment with Norvir/Kaletra
9. Pregnant or breastfeeding
10. Patients with uncontrolled hypertension
11. Serious uncontrolled concomitant medical or psychiatric illness
12. Grade 3 or higher impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the trial drug (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhoea, malabsorption syndrome)
13. History of acute pancreatitis within one year of trial entry or medical history of chronic pancreatitis
14. History of another primary malignancy that is currently clinically significant or currently requires active intervention
15. Any other clinically significant medical or surgical condition which, according to the CI/PI's discretion, should preclude participation
16. History of significant congenital or acquired bleeding disorder
17. Patients taking warfarin or cytotoxic drugs

Date of first enrolment
01/04/2024

Date of final enrolment
31/03/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Derriford Hospital
Derriford Road
Plymouth
England
PL6 8DH

Study participating centre
Manchester Centre for Clinical Neurosciences
Northern Care Alliance NHS Foundation Trust
Salford
England
M6 8HD

Sponsor information

Organisation
University Hospitals Plymouth NHS Trust

ROR
https://ror.org/05x3jck08

Funder(s)

Funder type
Charity

Funder Name
Children's Tumor Foundation

Alternative Name(s)
Children's Tumor Foundation, Inc., Children's Tumor Fdn, CTF

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan

Data generated from the trial (target inhibition and pharmacokinetic analysis) will be uploaded to the funder's data-sharing platform Synapse Neurofibromatosis Open Science Initiative (NF-OSI). Data will be embargoed during the award period and for 12 months thereafter. The data will then be made available to the broader research community as per the trial's Data Sharing Plan.

IPD sharing plan summary

Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		16/06/2026	17/06/2026	Yes	No