Saracatinib trial TO Prevent FOP

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This study has been transitioned to CTIS with ID 2024-515186-33-00 check the CTIS register for the current data. The three key outcome measurements and challenges of this proof of concept study are to achieve a decrease in ongoing HO bone formation...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Interventional

Summary

ID

NL-OMON56029

Source
ToetsingOnline

Brief title
STOPFOP

Condition

- Musculoskeletal and connective tissue disorders congenital
- Musculoskeletal and connective tissue disorders congenital

Synonym
Fibrodysplasia ossificans progressiva, FOP, Stone man syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Astra Zeneca,IMI EU

Intervention

Keyword: AZD0530, Fibrodyplasia ossificans progressiva, heterotopic ossification,

saracatinib

Outcome measures

Primary outcome

Primary Objectives: To assess the effectivity and safety of treatment with AZD0530 on HO formation.

The primary endpoint of the study is:

Incidence and severity of treatment-emergent adverse events

The objective change between the two arms in number of new heterotopic bone lesions measured by [18F]NaF PET/low-dose whole body computer tomography (CT) over the initial 6 month RCT;

Secondary outcome

Secondary Objectives: To assess the safety and tolerability of AZD0530 and to further assess effectivity by functional and other radiological/nuclear imaging endpoints.

The secondary endpoints are, summarised:

1. The incidence and severity of adverse events (AE)

2. Change in new heterotopic bone lesions over six and/or twelve months treatment during open label expension of AZD 0530 as measured by [18F] NaF PET/CT compared to the previous placebo arm RCT and compared to historical data as of Clemetia

3. Change in [18F] NaF PET, an imaging biomarker, that will be performed in

addition to the whole body low-dose CT between time of enrolment and after 6 and 12 months treatment to measure the clinical efficacy of the compound AZD0530 on magnitude and localization of the osteogenic activity;

4. Change in functional, clinical and patient-reported outcome measures including:

a. the cumulative analogue joint involvement scale for FOP (CAJIS),

b. the quantitative detailed multi-joint assessment,

c. the 36-item Short Form Health Survey (SF-36) and

d. FOP Independent Activity of Daily Living (FOP I-ADL) will provide the effect of the compound AZD0530 on general physical function, flare-ups (as measured by swelling, pain and other features as reported in the International Clinical Counsel (ICC) on FOP (https://www.ifopa.org/international_clinical_council_on_foparticle),

5. Change and percent change from baseline in biomarkers of bone formation levels in serum over time, including Total Procollagen Type 1 N-Terminal Propeptide (P1NP), Alkaline Phosphatase (AP) fasting cross-linked C-terminal telopeptide of type I colla-gen (βCTX) and selected miRNA*s.

A detailed description of the endpoints can be found in section 8 of the protocol.

Study description

Background summary

Fibrodysplasia ossificans progressiva (FOP) is a genetic chronic and devastating disease characterized by severe heterotopic ossifications (HO), severe contractures and early death. There are no approved medications yet. Our STOPFOP team (Paul Yu and Alex Bullock) identified AZD0530 (saracatinib) as a potent, low nanomolar inhibitor of the ALK2 kinase. The goal of this phase 2A study is to redress the activating mutations in the ALK2 kinase that cause the orphan indication of FOP, prevalence 1 in 1.5 million people, by repurposing the compound AZD0530 (saracatinib) as a low nanomolar ALK2 kinase inhibitor. AZD0530 has been shown to prevent heterotopic bone formation in an authentic genetic model of FOP. In vivo safety of AZD0530 was assessed during the efficacy experiments in the FOP mouse model.
These data strongly support the concept that AZD0530 would be effective in inhibiting ALK2 activity and HO in patients with FOP. If proven to be safe and effective in clinical trials, AZD0530 would represent a rapidly translatable therapy for FOP, having the significant advantage of extensive safety data from over 28 registered clinical trials with AZD0530 involving approximately 608 subjects (187 healthy volunteers and 421 patients with advanced cancer)

Study objective

This study has been transitioned to CTIS with ID 2024-515186-33-00 check the CTIS register for the current data.

The three key outcome measurements and challenges of this proof of concept study are to achieve a decrease in ongoing HO bone formation, decrease in numbers of disease *flare-up* episodes and to prevent the continuation of FOP induced contractures. A successful study would lead to a larger phase 2b or phase 3 study and potential licensing to an existing partner of new entity. The long term future goal of the consortium is to develop safe and effective pharmacotherapies for patients with FOP, including using such medications at the time of surgical release of disabling contractures to prevent the trauma/surgically induced HO recur-rence and exacerbation.

Study design

This is a phase 2a study, designed as an European multicentre 6-month double blind random-ized controlled trial (RCT) of AZD0530 versus placebo, followed by a 12 month trial compar-ing open-label extended AZD0530 treatment with historical control data as from the Clementia Natural History Study. In addition, the open label extension group that followed after the pla-cebo arm of the RCT will be compared to the placebo arm.

Intervention

Patients will be randomized to receive either AZD0530 100mg once daily or

matched place-bo, taken orally for the first 6 months, immediately followed by an open-label extension in which all patients will receive AZD0530 100mg (=2 tablets of 50mg) once daily oral dose for a further 12 months.

Study burden and risks

-Known and unknown side effect from medication
-Venapuncture: bruising, infection, fainting, if applied incorrectly: local disease activity (Will therefore be performed by an experienced anaesthesiologist)
-Radiation exposure PET/CT

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Male or female aged 18-65 with a clinical diagnosis of FOP at screening, including congenital malformation of the great toes and a history of spontaneous or injury-induced heterotopic ossification (HO), and have a confirmed classic-like FOP phenotype by the documentation of an ACVR1R206H/+ or variant genomic sequence.
a. Female participants who are women of child-bearing potential will be required to use a highly effective method of contraception as defined in section 5.4, in combination with a condom or diaphragm or cervical/vault caps with spermicidal foam/gel/film/suppository), from the time of enrolment until 4 weeks after final dose of study drug, unless practicing true sexual abstinence as defined in section 5.4.
b. Male participants will be required to avoid procreative sexual intercourse with women of child-bearing potential from time of enrollment until 4 weeks after final dose of study drug through use of highly effective contraceptive methods. Male participants with a pregnant female partner will be required to use a condom for the duration of the study and for 4 weeks final dose of study drug. Male study participants will not be permitted to donate sperm for from the time of enrolment and until 4 weeks after final dose of study drug.

2. Participants will have to be able to understand and complete study and willing to sign informed consent (IC). They have to be able to attend and comply with the study visits and related activities, adhere to all study-related restrictions, and able to undergo pro-cedures such as PET and CT imaging.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
1. Not willing to strictly adhere to the reproductive restrictions as defined in section 5.4
2. Women who are pregnant or breast-feeding (from the time 3 months prior to 4 weeksafter completion of participation in the study)
3. The presence of significant concomitant illness or history of significant illness such as cardiac, respiratory, renal, rheumatologic, neurologic, psychiatric, endocrine, metabolic, lymphatic disease, or infectious disease, that might confound the results of the study or pose additional risk to the patient;
4. Evidence of active bleeding (including hematuria or hematochezia,) acute or chronic gastrointestinal illness, inflammatory bowel disease, or mucositis
5. Malignant disease / cancer requiring treatment in the past 3 years (except some primary non melanoma skin cancer);

6. Severely impaired renal function defined as estimated glomerular filtration rate <30 mL/min/1.73 m2 calculated by the Modification of Diet in Renal Disease equation;
7. Showing uncontrolled diabetes mellitus with an HbA1C > 9%;
8. Significant viral illness or active infections at screening or randomisation; Subjects should not have subacute or acute fevers of >101*F at time of screening or randomisation
9. Evidence of prolonged QT interval at screening or randomization (defined as QTc of >450 ms) .or known congenital long-QT syndrome.
10. Neutropenia defined as an absolute neutrophil count of <1,500/µl,
11. Thrombocytopenia defined as platelet count <100 × 103/µl,
12. Current blood clotting or bleeding disorder, or significantly abnormal INR-prothrombin time or partial thromboplastin time at screening, or clinically significant abnormalities in other screening laboratories, including significant abnormalities in vitamin B12 or thyroid function tests would be cause for exclusion.-
13. Abnormal liver function test results defined as aspartate aminotransferase (AST) >2.0 x upper limit of normal (ULN); alanine aminotransferase (ALT) >2.0 x ULN; and / or total bilirubin >1.5 x ULN;
14. Known allergy or intolerance to AZD0530 or any excipients used in the investigational medicinal products.
15. Simultaneous participation in another interventional clinical study or a non-interventional study with imaging measures or invasive procedures (eg. collection of blood or tissue samples); Participation in the FOP Connection Registry (www.fopconnection.org) or other studies in which patients completed study questionnaires are possible.
16. Treatment with another investigational or drug that might interfere with HO formation and the interpretation of the study drug in the last 90 days
17. Current use or history of regular alcohol consumption exceeding 14 units/week (6 glasses of 13.0% wine (175ml), 6 pints of 4.0% lager or ale (568ml), 5 pints of 4.5% cider (568 ml) or 14 glasses of 10.0% spirits (25ml)) within 6 months of screening.
18. Currently active metabolic bone disease, other than FOP.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-08-2020
Enrollment:	11
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Saracatinib
Generic name:	Saracatinib

Ethics review

Approved WMO Date:	16-10-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	04-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-10-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-10-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	10-05-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-10-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-10-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-515186-33-00
EudraCT	EUCTR2019-003324-20-NL
CCMO	NL71401.029.19