A Phase 2 study to assess the efficacy and safety of 2 dosage regimens of oral fidrisertib (IPN60130) for the treatment of fibrodysplasia ossificans progressiva in male and female paediatric and adult participants

Published: 08-09-2021
Last updated: 19-09-2024

This study has been transitioned to CTIS with ID 2024-511469-13-00 check the CTIS register for the current data. Main objective:• Evaluate the efficacy of IPN60130 monotherapy compared with placebo recipients in inhibiting new HO volume in adult and...

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

Summary

ID

NL-OMON54489

Source
ToetsingOnline

Brief title
D-CA-60130-452 (0299-0074)

Condition

- Musculoskeletal and connective tissue disorders congenital

Synonym
fibrodysplasia ossificans progressiva (FOP); fibrous tissue that is being progressively converted into bone tissue

Research involving
Human

Sponsors and support

Primary sponsor: Ipsen Pharmaceuticals
Source(s) of monetary or material Support: the study sponsor as listed in B7

Intervention

Keyword: fibrodysplasia ossificans progressiva (FOP), fidrisertib (IPN60130), Phase 2, placebo controlled

Outcome measures

Primary outcome

Primary End Point

• The annualized change from baseline in HO volume as assessed by low-dose WBCT (excluding the head) in treated participants receiving IPN60130 through M12 compared with placebo

• Adverse events / serious adverse events (AEs/SAE), cardiac outcomes (electrocardiogram (ECG), echocardiograms, cardiac biomarkers), vital signs, physical examinations, body weight and height, eye exams, laboratory parameters, serum or urine pregnancy tests for females of childbearing potential (FOCBP), concomitant medications

Secondary outcome

Secondary End Point

• Change from baseline in HO volume of new HO lesions as detected by WBCT in participants receiving IPN60130 compared with placebo recipient at M12.

• Change from baseline in number of HO lesions by WBCT in participants receiving IPN60130 compared with placebo recipients at M12.

• Rate of flare-up (as confirmed by Investigator evaluation) and number of flare-up days in participants receiving INP60130 compared with placebo at M12

• The number of body regions with new HO in participants treated with IPN60130 compared with placebo recipients at M12

• Change from baseline in pain intensity over time assessed using the NRS in participants >=13 years of age and the Wong Baker FPS in participants <13 years of age for participants receiving IPN60130
compared with placebo recipients through M12

• The proportion of participants with any new HO in participants receiving IPN60130 compared with placebo recipients through M24.

• Change from baseline in HO volume as detected by WBCT in participants receiving IPN60130 compared with placebo recipients and with participants receiving the standard of care in the National History Study (NHS) in al available timepoints

• Change from baseline in CAJIS by treatment arm compared with placebo recipients and participants receiving the standard of care in the
NHS across all available timepoints.

• Change from baseline in the FOP-PFQ by treatment arm compared with placebo recipients and participants receiving the standard of care in the
NHS across all available timepoints

Pharmacokinetic

• Pharmacokinetic parameters by population PK modelling using all sparse samples collected through Month 1

• Pharmacokinetic parameters by population PK modelling using all sparse samples collected during the study

Exposure-Response

• Exposure-response analysis by modelling using relevant efficacy and safety parameters

Study description

Background summary

FOP is characterized by episodic soft tissue oedema (flare-ups) and the progressive replacement of skeletal muscle and connective tissue by heterotopic bone. The International FOP Association, a US-based patient group organization, reports approximately 800 confirmed cases of FOP globally. The prevalence is estimated at 1.36 per million individuals in the Americas and 1.58 per million in West Europe, with no geographic, ethnic, racial, or gender preference. FOP is misdiagnosed in approximately 80% of patients often resulting in harm to the patient.
FOP is a genetic condition caused by single gain-of-function mutation in the ALK2 (also known as activin A receptor type I, or ACVR1) gene, which encodes ALK2, a bone morphogenetic protein (BMP) type-1 receptor. This ALK2 gain-of-function mutation aberrantly activates the BMP Smad1/5/8 signalling pathway, diverting normal connective tissue (muscle, tendons and ligaments) injury repair mechanisms away from tissue regeneration by promoting chondrogenesis and heterotopic bone formation. In FOP, HO (or myositis ossificans) proceeds in 2 phases: a catabolic phase of inflammation and tissue destruction followed by an anabolic phase of tissue formation ultimately leading to HO. Most patients with FOP (approximately 97%) have the same point mutation, R206H, although other FOP variants are associated with progressive HO.
Progressive HO is severely disabling and ultimately becomes life-threatening due to thoracic insufficiency syndrome. Lesions begin in early childhood and lead to progressive ankyloses of major joints with resultant loss of movement. Individuals with FOP appear normal at birth except for the pathognomonic malformation of the great toes, which are typically short (lack a phalange) and deviated in hallux valgus. The majority of patients with FOP are confined to a wheelchair in their twenties and require caregiver assistance to perform daily living activities. Thoracic insufficiency syndrome leads to a markedly

shortened survival (Kaplan-Meier median survival estimate, 56 years) with cardiorespiratory failure and pneumonia the most common causes of death. Presently there are no approved medical treatment options to prevent the formation of heterotopic bone in FOP, although several are under clinical investigation. Available treatments are aimed at the symptomatic management of the disease. Removal of heterotopic bone and other trauma are avoided, as surgical trauma to tissues is likely to induce additional bone formation. Several other triggers may lead to flare ups and ensuing HO such as intramuscular immunizations, blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises, or falls, or influenza-like viral illnesses. Falls in particular are a severe form of trauma. In one survey of FOP patients, flare-ups were induced in two-thirds of falls and resulted in permanent loss of movement in 93% of patients.
Glucocorticoids are used to manage symptoms of flare-ups affecting major joints of the appendicular skeleton and jaw, especially when used immediately after the onset of a flare-up. Nonsteroidal anti-inflammatory agents, cyclooxygenase-2 inhibitors, mast cell stabilizers, and leukotriene inhibitors manage chronic pain and ongoing disease progression. Although some patients experience clinical benefit from one of these treatments, treatment for the condition itself is ineffective, FOP usually progresses, or intolerance to these therapies hinders effective treatment. Managing symptoms is the only course of treatment for patients with FOP. Therefore, there is a great unmet medical need for new therapeutic treatments that can help improve clinical outcomes for patients with FOP.

Study objective

This study has been transitioned to CTIS with ID 2024-511469-13-00 check the CTIS register for the current data.

Main objective:
• Evaluate the efficacy of IPN60130 monotherapy compared with placebo recipients in inhibiting new HO volume in adult and paediatric participants with FOP as assessed by low-dose WBCT (excluding the head)
• Evaluate the safety of IPN60130 in adult and paediatric participants with FOP

Secondary objectives:
• Change in HO volume of new HO lesions over time by WBCT at M12.
• Number of new HO lesions by WBCT at M12.
• Rate and number of flare-up days at M12
• The number of body regions with new HO at M12.
• To evaluate the effect of IPN60130 on pain intensity over time through M12.
• Proportion of participants with new HO by WBCT
• Change in HO volume over time as detected by WBCT.
• To evaluate the effect of IPN60130 on ROM as evaluated by CAJIS over time.
• To evaluate the effect of IPN60130 on physical function as evaluated by FOP-PFQ overt time.

Pharmacokinetic
• From the PK interim analysis, to evaluate the plasma pharmacokinetics of low and high doses of IPN60130.
• From the overall study, to evaluate the plasma PK of low and high doses of IPN60130.

Exposure-Response
• To evaluate the exposure-response relationship, if feasible.

Study design

Study 60130-452 is a Phase 2 study to evaluate the efficacy, safety, and tolerability of IPN60130 as a monotherapy in adult and paediatric participants with FOP comprising 2 parts.

• Part A will be a 12-month, randomised, placebo-controlled, parallel-group, 3-arm, double-blind treatment period. Participants will be randomised with a ratio 1:1:1 to weight-based IPN60130 high dosage arm , low dosage arm, or placeboarm (summarized in protocol section 6.1). Participants aged >=15 years will be enrolled first with the first 12 participants included in a sentinel cohort. Younger paediatric participants (5 to <15 years of age) will start to be enrolled if the DMC deems favourable the 6-month safety and cardiac safety profiles of the sentinel cohort of 12 participants aged >=15 years (protocol section 8.2).

• Part B will be a 12-month, double-blind treatment period during which participants will receive high or low weight-based dosages of IPN60130. On entering Part B, placebo recipients from Part A will be randomized to one of the IPN60130 dosage arms with a 1:1 ratio, whereas participants receiving IPN60130 in Part A will remain in their initially assigned dosage arms.

The primary objective will be to compare the efficacy of IPN60130 monotherapy with placebo (protocol section 2.2.1) in inhibiting new HO as assessed by low-dose WBCT (excluding the head) in adult and paediatric participants with FOP. The proposed primary endpoint is the annualized change from baseline in HO volume as assessed by low-dose WBCT (excluding the head) in participants receiving IPN60130 through Month 12 compared with placebo. In addition, an imaging substudy will explore the utility of [18F]NaF PET-CT for assessing HO lesion activity. Participation in the substudy will be open to adults and older paediatric participants >=15 years of age.

During Part A, a PK interim analysis of IPN60130 will be performed by an independent clinical pharmacometrics team when PK data are available from at least 12 IPN60130-treated participants (approximately 6 in each of the low and high dose arms) at Month 1 (approximately 18 participants randomized). The interim analysis is performed to confirm PK exposure in FOP participants to achieve targeted exposures for safety and efficacy based on PK data at Day 1

and Month 1 of treatment.

All participants will undergo the procedures and assessments summarized in the SoA (protocol table 1 and table 2). Imaging with WBCT and [18F]NaF PET-CT for the exploratory substudy will occur at screening and at clinic visits every 6 months. To ensure consistent interpretation of the acquired images, a central imaging laboratory will perform blinded reads of all images obtained in this study as well as blinded re-reads of those obtained from the NHS (untreated control group for secondary endpoints) using standardized procedures that will be documented in Image Acquisition Guidelines and an Independent Review Charter.

Individuals with FOP will learn about this Phase 2 study through their participation in the NHS and through the FOP community (physicians, patient support groups, and other contacts). The total duration of study participation (from informed consent) will be approximately 26 months if participants complete all study parts.

Intervention

Study intervention for Part A will include 3 double-blind arms comprising weight-based 120 or 60 mg IPN60130 once daily or placebo. The total duration of Part A will be up to 13 months, consisting of screening that may occur up to 35 days prior and a 12-month treatment period. Part B will include 2 double-blind dosage arms of weight-based 120 or 60 mg IPN60130 once daily over 12 months followed by 1 month of follow-up and an end of study visit for a total duration of 13 months.

Should a participant experience a flare-up during the study, they will remain on the same dosage and receive the standard of care treatment for a flare-up, which may include systemic corticosteroid. There will be no dosage escalation during a flare-up. The daily dosage may be reduced during the study should tolerability become an issue until adverse events (AEs) are stabilized or resolved. Dose modifications should be captured in the e-CRF and dosing diary.

Study burden and risks

Please refer to section 6. *What side effects could you experience?* and section 7. *What are the pros and cons if you take part in the study?* in the Subject Information For Participation In Medical Research Form for an overview of the risks and side effects.

Contacts

Public

Ipsen Pharmaceuticals

1155 rue Metcalfe, Suite 1500 ----
Montreal, Quebec H3B 2V6
CA
Scientific
Ipsen Pharmaceuticals

1155 rue Metcalfe, Suite 1500 ----
Montreal, Quebec H3B 2V6
CA

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply: Age - Main Study 1. Participants must be at least 5 years of age, to be confirmed (entry for younger paediatric participants <15 years of age will only be once safety in adult and older paediatric participants >=15 years of age has been established) at the time of signing the informed participant/parent consent and, for participants who are minors, age-appropriate assent. Age - [18F]NaF PET-CT Imaging Substudy 2. Participants must be at least 15 years of age at the time of signing the informed participant/parent consent for the main study and, for participants who are minors, age-appropriate assent. Type of Participant and Disease Characteristics 3. Participants must be clinically diagnosed with FOP, with the R206H ACVR1 mutation or other FOP variants associated with progressive HO. 4. Participants must have at least one flare-up in the preceding year of the screening visit. 5. Participants who have participated in a prior clinical study using another investigational product for the treatment of FOP may be enrolled after a washout of at least 5 half-lives of the other investigational product. Participants with prior treatment such as, but not limited to, imatinib, isotretinoin, or

palovarotene may be enrolled 30 days after discontinuation or after washout of at least 5 half-lives, whichever is longer. 6. Participants must be able to perform pulmonary function tests as defined in the protocol adequately and reliably. 7. Participants must be able to have an adequate echocardiography assessment at screening for evaluation of left ventricular structure and function as defined by the protocol. 8. Participants must be accessible for treatment and follow-up and be able to undergo all study procedures. Participants living at distant locations from the investigational site must be able and willing to travel to a site for the initial and all on-site follow-up visits. Participants must be able to undergo low-dose WBCT (excluding head) without sedation. Weight 9. Body weight >=10 kg. Sex 10.Male and/or female participants: Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. a. Male participants: Male participants of childbearing potential must agree to remain abstinent from heterosexual sex during treatment and for 90 days after treatment or, if sexually active, to use two effective methods of birth control, one of which must be highly effective during and for 90 days after treatment. The agreement to remain abstinent or use two effective methods (one of which must be highly effective) of birth control will be clearly defined in the informed consent; the participant or legally authorized representatives (e.g. parents, caregivers, or legal guardians) must sign this specific section. b. Female participants: Females of childbearing potential (defined in Appendix 10.5.1) must have a negative blood or urine pregnancy test (with sensitivity of at least 50 mIU/mL) prior to administration of study drug. FOCBP participants must agree to remain abstinent from heterosexual sex during treatment and for 1 month after treatment or, if sexually active, to use two effective methods of birth control, one of which must be highly effective during and for 1 month after treatment. Additionally, sexually active FOCBP participants in a heterosexual relationship must already be using two effective methods of birth control (one of which must be highly effective) 1 month before treatment is to start. Specific risks of study drug use during pregnancy as well as the agreement to remain abstinent or use two effective methods of birth control (one of which must be highly effective) will be clearly defined in the informed consent; the participant or legally authorized representatives (e.g. parents, caregivers, or legal guardians) must sign this specific section. Informed Consent 11. Participants must be capable of giving written, signed, and dated informed participant/parent consent; and for participants who are minors, age-appropriate assent and/ or legal guardian consent (performed according to local regulations).

Exclusion criteria

Medical Conditions 1. Participants with complete heart block and left bundle branch block on screening electrocardiogram. 2. Participants with screening echocardiograph showing septal or left ventricular free wall thickness >12 mm for adult participants or a z-score >3 compared with population norms for children and adolescent participants or LVEF <50%. 3. Participants with severe mitral or tricuspid regurgitation on echocardiograph at screening. 4. Participants with significant underlying lung disease requiring supplementary oxygen or forced vital capacity <35% of predicted at screening. 5. Participants with uncontrolled cardiovascular, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease as judged by the investigator. 6. Participants with

severe hepatic impairment. Prior/Concomitant Therapy 7. Concomitant medications that are strong inhibitors (including grapefruit juice) or inducers (including St John*s Wort) of cytochrome P450 (CYP) 3A4 activity or kinase inhibitors such as imatinib. 8. Prior use in the past year and concomitant use of bisphosphonates for participants in the PET-CT substudy. Prior/Concurrent Clinical Study Experience 9. Concurrent participation in another interventional clinical study, or a noninterventional study with radiographic measures or invasive procedures (e.g. collection of blood or tissue samples). Other Exclusions 10. Amylase or lipase >2× the upper limit of normal (ULN) or with a history of chronic pancreatitis. 11. Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5×ULN. 12. Participants with hematologic abnormalities: • Hgb<10g/dL • Platelets<75,000/mm3 • WBC<2000/mm3 • Participants with coagulation test (prothrombin time [PT]/ international normalised ratio [INR], and activated partial thromboplastin time [aPTT]) measurements outside of the normal range at screening. 13. Female participants who are breastfeeding. 14. Any reason that, in the opinion of the investigator, would lead to the inability of the participant and/or family to comply with the protocol Individuals with disqualifying laboratory abnormalities may be rescreened once within the screening window. Rescreening may be repeated more than once if the results are atypical for the participant based on prior results from preceding year (protocol section 5.4).

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:	Pending
Start date (anticipated):	25-01-2022
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	fidrisertib
Generic name:	IPN60130

Ethics review

Approved WMO Date:	08-09-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-10-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-07-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-10-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-11-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-12-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	30-01-2024
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	CTIS2024-511469-13-00
EudraCT	EUCTR2020-002858-24-NL
CCMO	NL76094.029.21