ANDECAL, A Phase 2/3 study to determine the efficacy of the MMP9-inhibitor Andecaliximab to block new heterotopic ossification in fibrodysplasia ossificans progressiva (FOP): Methodology for Part 1 of the Study

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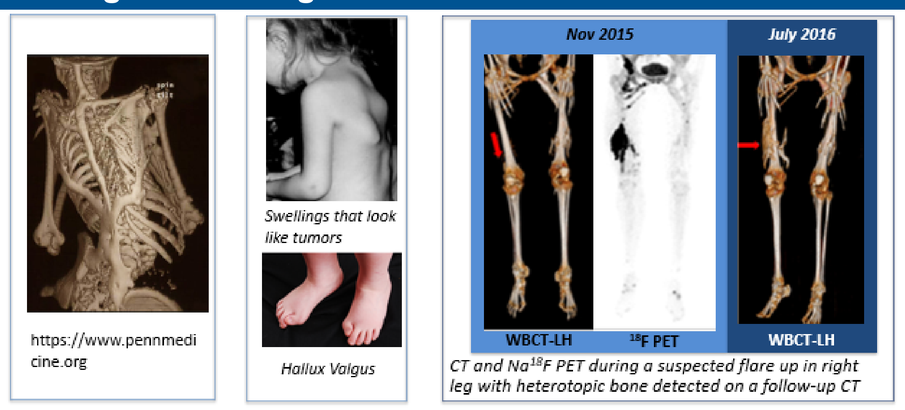
Introduction

Fibrodysplasia Ossificans Progressive (FOP):

- An ultra-rare, severely disabling, autosomal dominant disorder, resulting from an activating mutation in activin A type I (*ACVR1)* gene[1]
- Characterized by painful debilitating inflammatory flare-ups and immobilizing transformation of skeletal muscles, tendons, ligaments, fascia, and aponeuroses[2] into an immobilizing exoskeleton of heterotopic ossification (HO)
- Most patients are confined to a wheelchair by the third decade of life[3]

Figure 1. Background FOP[4] and Na18F PET/CT[5]



CT and Na[18]F PET during a suspected flare up in right leg with heterotopic bone detected on a follow-up CT

Matrix Metalloproteinase-9 (MMP9) & FOP:

- Novel target for FOP, identified through studying a "resilient patient" (Patient-R) who, at age 35 years (yrs), had minimal flare-ups or heterotopic ossification[6]
- Patient-R carries the classic *ACVR1* mutation (R206H) for FOP and 2 MMP9 gene variants that result in decreased expression and/or activity of MMP9[6].
- MMP9 knock-out abrogates injury-induced HO in a mouse model of FOP, and pharmacologic inhibition with an anti-MMP9 murine antibody inhibited the development of HO[6].

Current FOP Management &Treatment:

- Management focuses on early diagnosis & supportive care
- Palovarotene (a retinoic acid receptor gamma agonist) is approved for use in the US, Canada, Australia, and the UAE. Its primary mechanism of action is downstream of the early events leading to HO and flare-ups. It decreases BMP signaling and subsequently inhibits the SMAD1/5/8 signaling pathway.
- Palovarotene provides modest reduction in annualized new HO volume in patients with FOP with no positive effect on flare-ups and cannot be used in girls age <8 yrs nor boys age <10 yrs (a time of active flare-ups and new HO accrual)

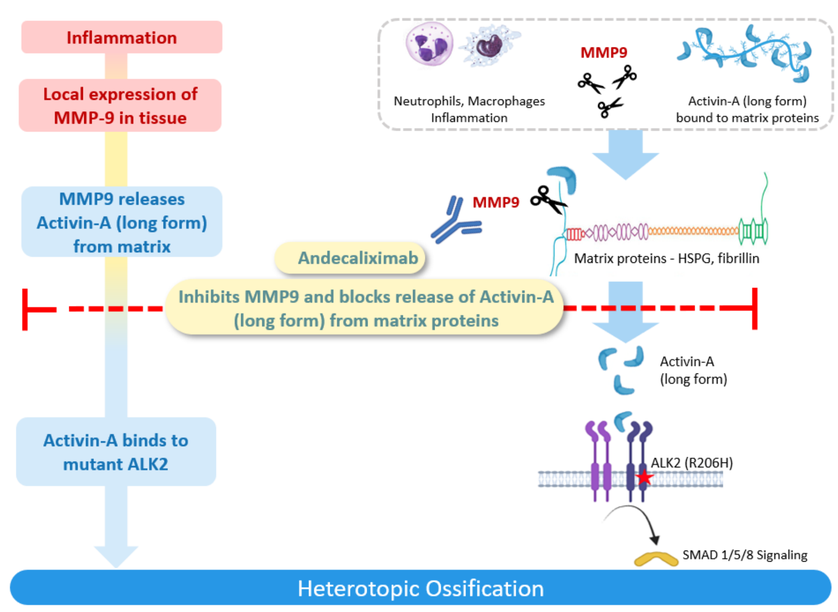
MMP9:

- MMP9 has limited expression in healthy tissues and is associated with chronic inflammation and dysfunctional tissue repair in disease.
- MMP9 releases signaling molecules tethered to the extracellular matrix, such as activin A[6], thereby modulating inflammation, neovascularization, and differentiation.

Andecaliximab:

- Humanized monoclonal antibody specific to MMP9[7-11]
- Primary mechanism of action is inhibiting activation of MMP9[7-11]
- Demonstrated a favorable safety profile in prior clinical trials[8,9,11] involving ~1000 adults
- Toxicology studies support the use in ages ≥ 12 yrs; additional toxicology results supporting younger ages should be available before the initiation of ANDECAL Part 2.

Figure 2. Andecaliximab Mechanism of Action



Methods

ANDECAL is a Phase 2/3, two-part study of andecaliximab in FOP:

- Part 1 (Part 1a & Part 1b) is the Lead-in Study to assess safety, pharmacokinetics/ pharmacodynamics, and preliminary efficacy
- **Part 1a and Part 1b** are 13-week, double-blind studies (see Figure 3).
- Part 2 (Main Study) is a Phase 2/3 randomized, double-blind, placebo-controlled trial

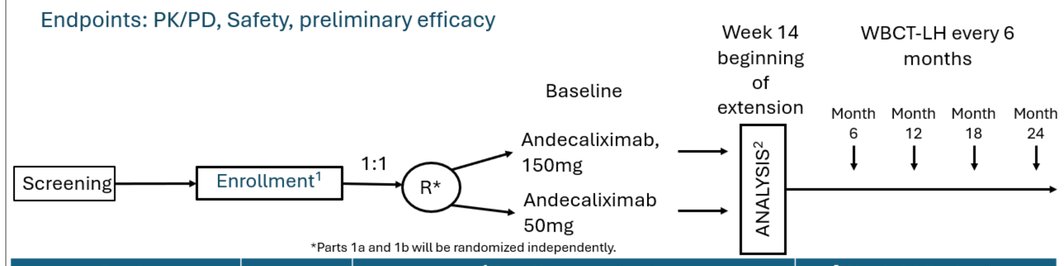
Enrollment Criteria: All participants must have clinical FOP from any activin A receptor type I (ACVR1), pathogenic or likely pathogenic variant, without other potentially confounding chronic disease or active treatment (allowances have been made for use of steroids, etc. per the International Clinical Council [ICC] on FOP guidelines). They must also have evidence of active disease within the past year documented by:

- History of symptoms confirmed by physician as being consistent with flare-up, or
- Physician-confirmed clinical progression (e.g., new HO, or worsening of joint function including new ankylosis).

Figure 3. Study Design

Part 1 (a & b)—will run simultaneously but will randomize participants independently.
They differ in enrollment criteria & preliminary efficacy endpoint.

Endpoints: PK/PD, Safety, preliminary efficacy



*Parts 1a and 1b will be randomized independently.

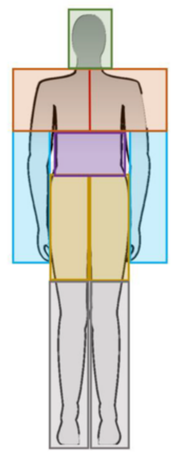
Study	n	[1]Enrollment criteria	[2]Week 14 Endpoints
Part 1a The Na[18]F PET/CT	Up to 6	Active lesion at baseline by Na[18]F PET determined by site (age: 15+)	Change in SUVmax (PET)
Part 1b The Flare-up	Up to 6	21 days of flare-up over past 6 months (age: 12+)	Flare-up #, duration and characteristics

In Part 1a and 1b, site visits are required at Screening, Day 1 of dosing, Week 14, every 26 weeks while on study treatment, and the Safety Follow-up Visit.
Flare-ups are to be captured by a weekly diary as depicted in Figure 4.

Figure 4. Weekly Flare-up Questionnaire

Data collection

a. The date it **started** (best guess)
b. The date it **ended** (best guess)
c. The **area**(s) of the body involved: front/back, left/right & region at onset (see figure)
d. The overall **severity** of each flare-up (1=mild, 2=moderate, 3=severe)
e. The **symptoms** associated with each flare-up (Pain, Swelling, Joint stiffness, or Decreased range of motion of any severity and Redness or Warmth that is detectable by others)



- Head
- Neck, shoulder, upper arm, and/or upper torso or chest
- Midriff [Abdomen (front) or lower back]
- Lower arm from above elbow to fingertips
- Below waist, buttocks, hips to mid-thighs
- Lower leg from lower thigh (above knees) to end of toes

Results

MMP9 is a novel target for FOP, identified through studying a patient with minimal flare-ups or HO and 2 MMP9 gene variants with decreased expression and/or activity of MMP9. Homozygous and heterozygous knock-out of MMP9 protects against HO in a mouse model of FOP, as does pharmacologic inhibition with a murine anti-MMP9 antibody[6]. ANDECAL, is a Phase 2/3 study designed to test the effect of inhibiting MMP9 in participants with FOP.

Conclusions

Enrollment in Part 1 of ANDECAL study is expected to initiate in the second half of 2024.
Part 1 of ANDECAL study will evaluate the safety, PK/PD and preliminary efficacy (exploratory) of andecaliximab in participants with FOP and will serve as a lead-in for Part 2 of the study.

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Disclosures

Receiving salary and stock options (DW, VS, PB) or consulting fees (ES) from āshibio; Co-inventor on the patent for Methods of Treating HO, including MMP-9 as a target (FSK, RJP); Member ICC on FOP and IFOPA Registry Advisory Board (voluntary) [FSK (also founder and past president of ICC), RJP, MMAM, ECH] and Fibrous Dysplasia Foundation (ECH); Research Investigator: for āshibio (MMAM, ECH), Clementia/Ipsen (FSK, MMAM, ECH), Incyte (FSK, MMAM), Ascendis (ECH).

Acknowledgements

We thank Maggie Ward for help in creating this poster.