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# Inhibition of MMP9 as a novel treatment strategy for fibrodysplasia ossificans progressiva (FOP): Safety analysis of the anti-MMP9 antibody andecaliximab in development for FOP

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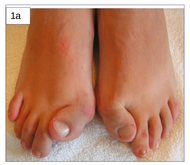
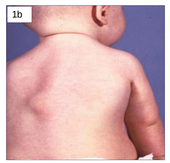
## INTRODUCTION

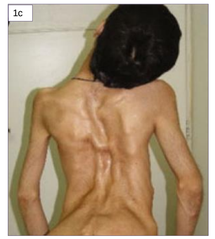
**Fibrodysplasia Ossificans Progressive (FOP):**

Characterized by:

- Congenital malformations [e.g., Short great toes with hallux valgus (1a)]
- Flare-ups [Inflammatory lesions (1b)]
- Progressive transformation of connective tissues and muscle into bone (1c: Ribbons of HO on a young man) (Kitterman 2012)



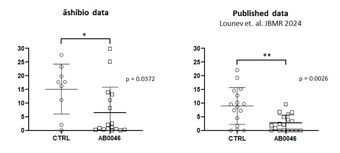

**MMP9:**

- Associated with chronic inflammation and dysfunctional tissue repair in disease and has limited expression in healthy tissues
- Releases the long-form of Activin A tethered to the extracellular matrix that plays a critical role in HO formation in FOP

**Matrix metalloproteinase-9 (MMP9) and FOP:**

- Identified as a novel target for FOP through the study of a "resilient patient" (Patient-R), age 35 years (yrs) with congenital manifestations of FOP (hallux valgus) but minimal postnatal manifestations (of heterotopic ossification (HO) or flare-ups).
- Patient-R carries both the classic *ACVR1* FOP mutation (R206H) and 2 MMP9 gene variants with decreased expression and/or activity of MMP9.
- In mouse studies Mmp9 knock-out abrogates injury-induced HO in FOP mice bearing Acvr1 R206H mutation, and pharmacologic inhibition with a murine Mmp9 antibody inhibited the development of HO in multiple mouse models (Lounev 2024 and āshibio data, see Figure 2).

**Figure 2. Surrogate Murine Antibody AB0046 is Active in ALK2 R206H FOP Mouse Models**

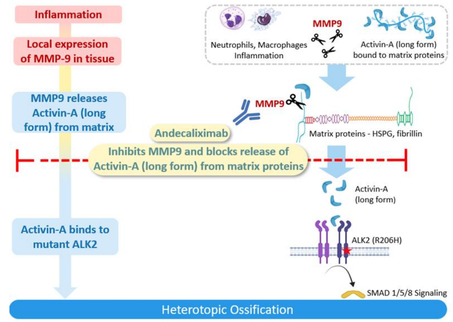



AB0046 is a murine surrogate of andecaliximab that partially recapitulates its MMP9 inhibitory activity.
CTRL, control; HO, heterotopic ossification.

**Heterotopic ossification formation typically starts in an area of inflammation (Figure 3)**

- The long form of Activin A, which is expressed by inflammatory cells, is bound to heparan sulfate proteoglycans (HSPG) in the extracellular matrix.
- MMP9, also expressed by inflammatory cells, releases the stored long form of Activin A from HSPG.
- MMP9 has no effect on short circulating form of Activin A nor on the function of Activin A.

**Figure 3**




Role of MMP9 in HO formation and its inhibition by anti-MMP9 antibody, andecaliximab

**Andecaliximab:**

- Humanized monoclonal antibody specific to MMP9
- Demonstrated a favorable safety profile in prior clinical trials involving ~ 1000 adults (see Table 1)
- Toxicology studies support the use of in ≥ 12 yrs

**Table 1. Prior Andecaliximab Clinical Studies**

| Population | Route of administration | Maximum dose & duration | NCT Study ID |
|---|---|---|---|
| Healthy (N=72) | Sub Cutaneous (N=58)/ IV (N=14) | 150 mg (single dose) | NCT02209987 & GS-US-326-1885 |
| Crohn's Disease (N=159) | SC | 300 mg | NCT02405442 |
| Ulcerative Colitis (UC) (N=62) | IV and SC (up to dose levels listed) | SC: 150 mg x 4 wks; IV: 5 mg/kg (single dose) | NCT01831427 |
| UC (N=110) | SC | 150 mg x 51 wks | NCT0252084 |
| Rheumatoid Arthritis (N=25) | SC (N=10) & IV (N=15) | SC: 300 mg x 12 wks; IV: 400 mg x 4 wks | NCT02862574 & NCT02176876 |
| Cystic fibrosis (N=3) | SC | 600 mg x 8wks | NCT02759562 |
| COPD (N=8) | IV | 400 mg x 4wks | NCT02077465 |
| Solid tumors (N=232) | IV | 1800 mg x 180.9 wks | NCT01803282 |
| Gastric or GEJ adenocarcinoma (N=321) | IV (N=34) | 1200 mg x 82.4 wks | NCT02862535 |
| | IV (N=287) | 800 mg x 161.7 wks | NCT02864381 & NCT02545504 |

## AIM

To present a pooled analysis of andecaliximab safety data relevant to an upcoming Phase 2/3 trial of andecaliximab in participants with FOP.

## METHODS

A pooled safety analysis was conducted of the studies considered relevant to an upcoming trial in FOP (ANDECAL). Of the ~1000 participants in prior trials, 347 participants were enrolled in a randomized, double blind (DB), placebo-controlled clinical trial where andecaliximab was administered subcutaneously (SC), as a monotherapy, in non-oncologic conditions (N=347).

## RESULTS

- Median age: 40 (18 to 70) yrs
- Median treatment duration
  - DB = 8 wks
  - DB + open label extension (OLE)= 17 wks (max 75 wks)

During the DB treatment period, treatment-emergent adverse event (TEAE) assessed as related to study drug occurred in:

- 19/107 (17.8%) participants receiving 150 mg every 2 weeks (Q2W)
- 23/114 (20.2%) receiving 150 mg andecaliximab QW
- 13/58 (22.4%) receiving 300 mg andecaliximab QW
- None (0/3) receiving 600 mg andecaliximab QW
- 20/91 (22.0%) receiving placebo

**Table 2. Treatment-related AEs Occurring In ≥1% of Participants In Placebo-controlled Trials of SC Andecaliximab Monotherapy**

| Participants with treatment-related AE, (%) | Double-blind (doses ranging from 150 mg Q2W to 600 QW SC) | | DB + OLE |
|---|---|---|---|
| | Andecaliximab (N=282) | Pooled placebo (N=91) | Andecaliximab (N=347) |
| Injection site erythema | 6 (2.1) | 1 (1.1) | 8 (2.3) |
| Injection site bruising | 4 (1.4) | 1 (1.1) | 4 (1.2) |
| Injection site pain | 3 (1.1) | 0 | 4 (1.2) |
| Anemia | 3 (1.1) | 0 | 6 (1.7) |
| Headache | 4 (1.4) | 0 | 5 (1.4) |
| Nausea | 4 (1.4) | 1 (1.1) | 5 (1.4) |
| Worsening of Crohn's | 0 | 1 (1.1) | 5 (1.4) |
| Eczema | 1 (0.4) | 0 | 4 (1.2) |
| Lymphopenia | 1 (0.4) | 0 | 4 (1.2) |
| Oral herpes | 2 (0.7) | 0 | 4 (1.2) |

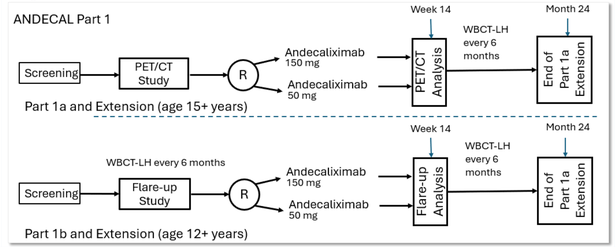
AE, adverse events; DB, double-blind; OLE, open-label extension; QW, once a week; Q2W, once every 2 weeks; SC, subcutaneous.

## CONCLUSIONS

MMP9 inhibition represents a novel strategy to block HO formation in FOP. Preclinical toxicology studies and prior safety experience (including with SC doses higher than planned in ANDECAL) support the initiation of a Phase 2/3 study of andecaliximab in patients with FOP aged 12 yrs and older.

Enrollment in Part 1 (a and b) of the ANDECAL study will initiate later this year.

**Figure 4**

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## ACKNOWLEDGEMENTS

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## CONTACT INFORMATION

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