Zilurgisertib in Patients With Fibrodysplasia Ossificans Progressiva: Interim Results From the PROGRESS Study

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Summary

- Patients who received zilurgisertib developed fewer new areas of abnormal bone growth than those who received placebo
- Patients treated with zilurgisertib also had less abnormal bone growth and experienced fewer flare-ups than those who received a placebo
- Zilurgisertib was generally well tolerated, with no side effects that caused patients to lower their treatment dose or stop treatment altogether
- Results from the PROGRESS study suggest that zilurgisertib may be a promising treatment option for adolescents and adults with FOP

What is fibrodysplasia ossificans progressiva (FOP)?

FOP is a disease where bone forms in places it should not, such as muscles and soft tissues, making movement difficult. This happens because of changes in a protein called ALK2[1]

What is zilurgisertib and how does it work?

Zilurgisertib is an experimental treatment for FOP that works by selectively blocking the ALK 2 protein

PROGRESS: a clinical study of zilurgisertib in patients with FOP

Patients

- Female and male patients 12 years or older
- Patients diagnosed with FOP who had disease activity in the past year
- Disease severity score (CAJIS) of less than 24

Treatment

- Patients were randomly placed into 1 of 2 groups:

Zilurgisertib	Placebo
100 mg once daily	(sugar pill)

- Neither patients nor doctors knew who was getting which treatment for the first 24 weeks
- After 24 weeks, everyone knowingly received zilurgisertib during the open-label extension period

Outcomes

- The main outcome was the percentage of patients who developed new areas of abnormal bone growth at 24 weeks
- The study also looked at the number of new areas of abnormal bone growth, the total amount of new bone formed, and how many FOP flare-ups occurred

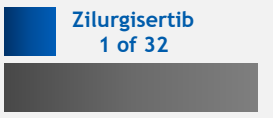
Patient characteristics:

Zilurgisertib group:
- **47.9% female**
- **Average age of 20.5**

Placebo group:
- **54.8% female**
- **Average age of 22.0**

CAJIS, Cumulative Analogue Joint Involvement Scale.

Efficacy



The number of patients with **new areas of abnormal bone growth** at 24 weeks was **lower with zilurgisertib** than **placebo**

Amount of new abnormal bone and **total abnormal bone** was **lower with zilurgisertib** than **placebo** at Week 24

New: 0.003 cm³
Total: 330.1 cm³

New: 6.6 cm³
Total: 405.1 cm³

2.3 Number of **yearly new FOP flares was lower with zilurgisertib** than **placebo** (number estimated based on number of flares at Week 24) **4.5**

At **48 weeks**, no patients had new areas of abnormal bone growth, and total amount of abnormal bone decreased for those who stayed on **zilurgisertib** or switched from **placebo** to **zilurgisertib**

Safety

Most side effects experienced by patients treated with **zilurgisertib** were mild or moderate

0% No side effects led patients treated with **zilurgisertib** or **placebo** to leave the study or stop taking treatment

Safety was similar between adults and adolescents

The most common side effects for more than 10% of patients in the zilurgisertib group were:

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1. Rivera LM, et al. *Biomedicines*. 2024;12(4):779.

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Zilurgisertib in Patients With Fibrodysplasia Ossificans Progressiva: Interim Results From the PROGRESS Study

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*Potential conflict of interest may exist.

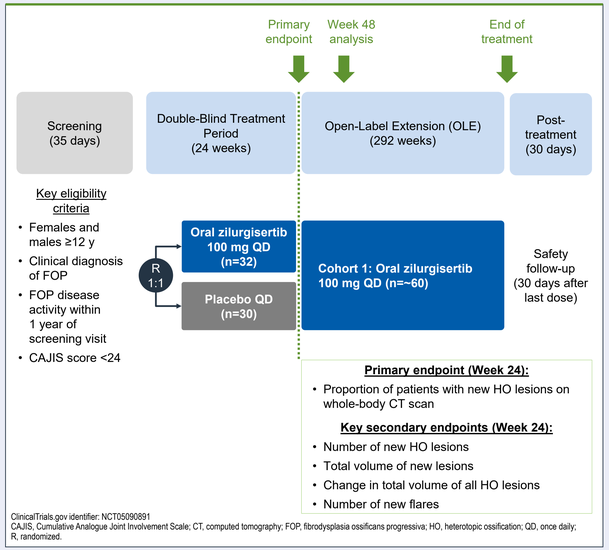
Introduction

- Fibrodysplasia ossificans progressiva (FOP) is a rare, autosomal dominant genetic disorder characterized by disabling heterotopic ossification (HO) in skeletal muscles, tendons, and ligaments[1]
- Pathogenic variants in activin receptor–like kinase 2 (ALK2) have been implicated in the pathophysiology of FOP[1]
- Zilurgisertib is an oral, highly selective investigational ALK2 inhibitor in clinical development for FOP
- Phase 1 studies established the safety of zilurgisertib in healthy controls[2]
- Here, we present interim analysis of the phase 2 PROGRESS trial evaluating zilurgisertib in patients ≥12 years of age with FOP through 48 weeks of treatment (24 weeks of placebo-controlled treatment, then 24 weeks open-label zilurgisertib)

Methods

- PROGRESS is a phase 2, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of zilurgisertib for FOP (**Figure 1**)

Figure 1. PROGRESS Phase 2 Study Design Cohort 1



ClinicalTrials.gov identifier: NCT05090891
CAJIS, Cumulative Analogue Joint Involvement Scale; CT, computed tomography; FOP, fibrodysplasia ossificans progressiva; HO, heterotopic ossification; QD, once daily; R, randomized.

Results

- A total of 63 patients were randomly assigned to zilurgisertib (n=32) or placebo (n=31)
  - All patients in the zilurgisertib group completed treatment
  - 1 patient in the placebo group discontinued treatment due to patient withdrawal
- Baseline characteristics and demographics were generally similar between groups (**Table 1**)

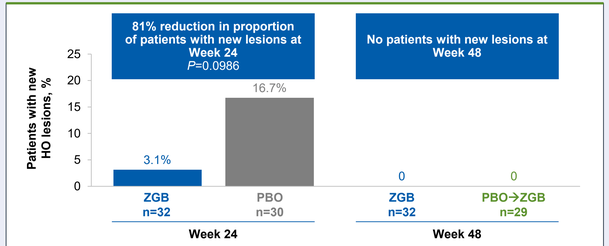
Table 1. Demographics and Baseline Characteristics (Cohort 1, ≥12 years of age)

n (%)	Zilurgisertib 100 mg (n=32)	Placebo (n=31)
Age, mean (SD), y	20.5 (11.7)	22.0 (11.0)
Male, n (%)	17 (53.1)	14 (45.2)
Race,[a] n (%)		
White	17 (53.1)	18 (58.1)
Asian	8 (25.0)	10 (32.3)
Black	2 (6.3)	1 (3.2)
Multiracial	1 (3.1)	0
Time since initial diagnosis, mean (SD), y	12.6 (9.9)	13.2 (9.1)
Baseline CAJIS score		
<18	27 (84.4)	26 (83.9)
18-23	5 (15.6)	5 (16.1)
Time since last flare-up, mean (SD), y	0.7 (0.6)	0.4 (0.2)
Location of last flare-up occurring in ≥10% of patients in either group, n (%)		
Upper back	4 (12.5)	5 (16.1)
Lower back	4 (12.5)	5 (16.1)
Right hip	4 (12.5)	4 (12.9)
Right leg	2 (6.3)	4 (12.9)
Total volume of HO lesions at baseline, median (range), cm³	270.0 (21.3–1140.1)	265.6 (5.7–1672.0)

[a]Data were missing in 2 patients in the zilurgisertib group and 1 patient in the placebo group; data were not reported in 2 patients in the zilurgisertib group and 1 patient in the placebo group.
CAJIS, Cumulative Analogue Joint Involvement Scale; HO, heterotopic ossification.

- At Week 24, 1 of 32 patients in the zilurgisertib group had new lesions versus 5 of 30 patients in the placebo group (primary endpoint, *P*=0.0986; **Figure 2**)
- No patients had new lesions during the OLE period from Week 24 to 48

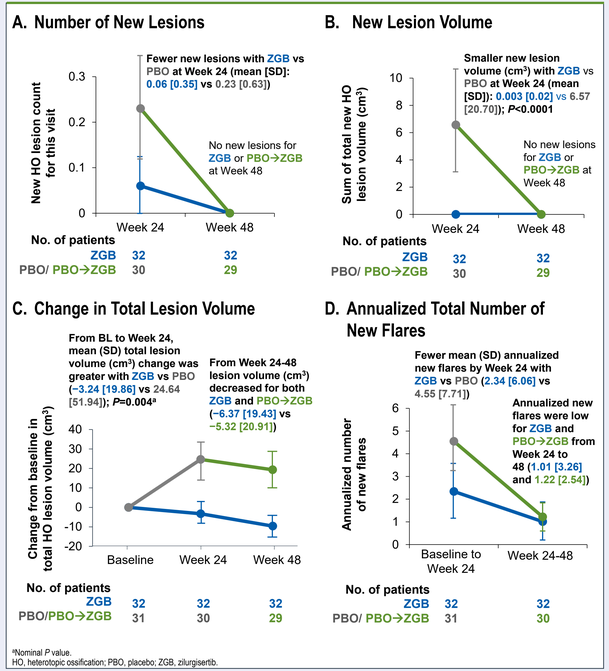
Figure 2. Primary Endpoint (Week 24) and Interim Analysis (Week 48) in Cohort 1



HO, heterotopic ossification; PBO, placebo; ZGB, zilurgisertib.

- Number of new lesions, overall volume of new lesions, total lesion volume, and annualized total number of new flares decreased with zilurgisertib (**Figure 3**)
  - Zilurgisertib had fewer new lesions and smaller new lesion volume compared to placebo at Week 24; at Week 48, both groups (zilurgisertib and placebo crossover to zilurgisertib) exhibited no new lesions
  - From baseline to Week 24, total lesion volume decreased in the zilurgisertib group but increased in the placebo group, while from Week 24 to 48, total lesion volume decreased from baseline in both groups
  - FOP flares were less prevalent in the zilurgisertib versus placebo group by Week 24; from Week 24 to 48, both groups reported a low annualized number of flares
- In the open-label period, no new lesions were reported regardless of double-blind treatment assignment

Figure 3. Key Secondary Endpoints (Cohort 1)



[a]Nominal *P* value.
HO, heterotopic ossification; PBO, placebo; ZGB, zilurgisertib.

- Most adverse events (AEs) were mild or moderate through Week 24, and no AEs led to dose reduction or discontinuation of zilurgisertib (**Table 2**)
- Safety was similar between adults and adolescents; this was also observed during the OLE

Table 2. TEAEs During the 24-Week Placebo-Controlled Treatment Period (Cohort 1)

n (%)	Zilurgisertib 100 mg (n=32)	Placebo (n=31)
TEAE	29 (90.6)	30 (96.8)
Patients with treatment-related TEAE	15 (46.9)	11 (35.5)
Patients with serious TEAE	2 (6.3)	3 (9.7)
Patients with grade ≥3 TEAE[a]	2 (6.3)	4 (12.9)
Patients with fatal AE	0	0
Patients with treatment-related serious TEAE	1 (3.1)	0
Patients with TEAE leading to study drug dose interruption	2 (6.3)	1 (3.2)
Patients with TEAE leading to study drug dose reduction/withdrawal	0	0
Most common TEAEs occurring in >10% of patients receiving zilurgisertib, n (%)		
FOP flare-up or aching/pain due to FOP	8 (25.0)	17 (54.8)
Headache	7 (21.9)	5 (16.1)
Upper respiratory tract infection	7 (21.9)	3 (9.7)
Arthralgia	6 (18.8)	1 (3.2)
Epistaxis	4 (12.5)	0
Nausea	4 (12.5)	1 (3.2)

[a]No Grade ≥3 TEAEs occurred in more than one patient through Week 24. Zilurgisertib (n=2 patients; [dehydration, dyspnea, gastroesophageal reflux disease, hypotension, nausea, oxygen saturation decreased, pneumonia, urinary tract infection] and skull fracture base); placebo (n=4 patients; [arthralgia, shoulder fracture, back pain, traumatic pain], lipase increased, FOP flareup, and femoral neck fracture).
AE, adverse event; FOP, fibrodysplasia ossificans progressiva; TEAE, treatment-emergent adverse event.

Conclusions

- Fewer patients taking zilurgisertib (1 of 32) had new HO lesions versus placebo (5 of 30)
- In addition, zilurgisertib demonstrated reduced volume of total HO lesions and fewer flares versus placebo
  - Improvements were maintained or further improved in the OLE
- Treatment with zilurgisertib was generally well tolerated, with no AEs leading to dose reduction or discontinuation
- These results support orally-administered zilurgisertib as a promising treatment option for adolescents (≥12 years old) and adults with FOP
- The open-label period of PROGRESS for adolescents and adults is ongoing, and enrollment of younger age groups has begun

Disclosures
R.J.P. is a clinical trial investigator for Ashibio, Incyte, Ipsen, and Regeneron; a member of the Medical Registry Advisory Board of the IFOPA; a consultant for Incyte, Ipsen, and Regeneron; and is a co-inventor for the use of andecaliximab in conditions of heterotopic ossification. **F.S.K.** is a clinical trial investigator for Ashibio, Incyte, Ipsen, and Regeneron and serves in an unpaid capacity on the Medical Registry Advisory Board of the International Fibrodysplasia Ossificans Progressiva Association, the International Clinical Council on FOP, and Tin Soldiers. **M.A.M.** is a clinical trial investigator for Ashibio, Incyte, Ipsen, and Regeneron and serves in an unpaid capacity on the Medical Registry Advisory Board of the International Fibrodysplasia Ossificans Progressiva Association, the International Clinical Council on FOP, and Tin Soldiers. **J.B.C.** is a principal investigator on clinical trials sponsored by Regeneron Pharmaceuticals, Inc; Clementia/Ipsen; and Incyte. **C.L.** has no competing interests to declare. **A.M., S.M.,** and **Q.L.** are employees and stockholders of Incyte.

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Abbreviations
AE, adverse event; ALK2, activin receptor–like kinase 2; CAJIS, Cumulative Analogue Joint Involvement Scale; CT, computed tomography; FOP, fibrodysplasia ossificans progressiva; HO, heterotopic ossification; OLE, open-label extension; PBO, placebo; QD, once daily; R, randomized; TEAE, treatment-emergent adverse event; ZGB, zilurgisertib.

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1. Rivera LM, et al. *Biomedicines*. 2024;12(4):779.
2. Yang YO, et al. *Eur J Drug Metab Pharmacokinet*. 2025;50(1):65-80.

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