

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

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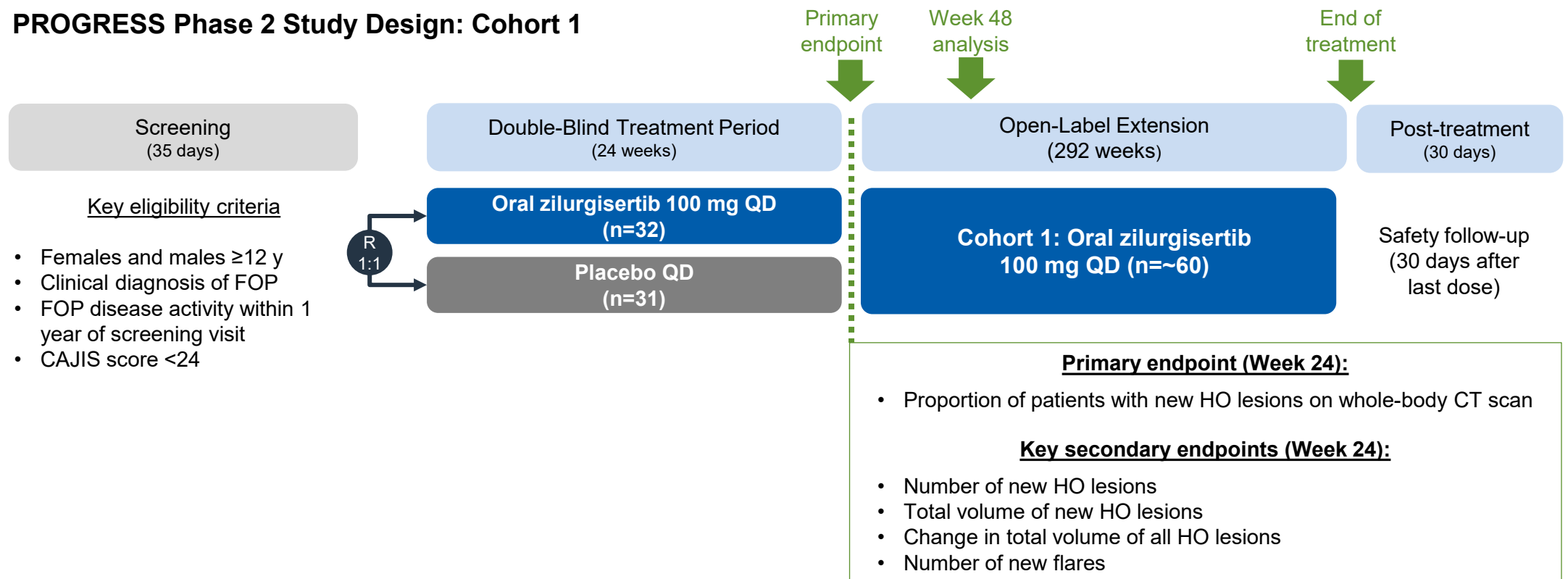
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The views expressed in this educational program are those of the faculty and do not necessarily represent the views of the Endocrine Society.

Zilurgisertib for Fibrodysplasia Ossificans Progressiva (FOP)

- FOP is characterized by disabling heterotopic ossification (HO) due to pathogenic variants in activin receptor–like kinase 2 (ALK2)¹
- Zilurgisertib is an oral, small molecule selective inhibitor of ALK2

PROGRESS Phase 2 Study Design: Cohort 1



ClinicalTrials.gov identifier: NCT05090891.

CAJIS, Cumulative Analogue Joint Involvement Scale; CT, computed tomography; QD, once daily; R, randomized.

1. Rivera LM, et al. *Biomedicines*. 2024;12(4):779. doi:10.3390/biomedicines12040779.

Demographics and Baseline Characteristics

Cohort 1 (≥12 years of age)

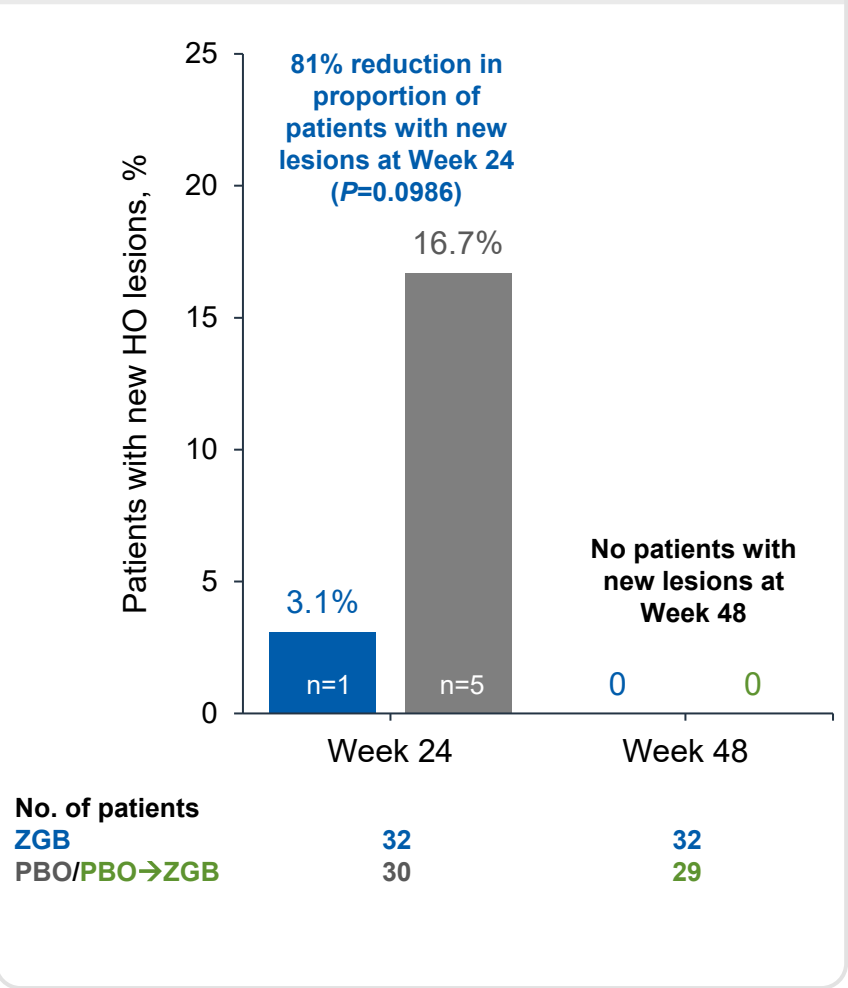
n (%)	Zilurgisertib 100 mg (n=32)	Placebo (n=31)
Age, mean (SD), y	20.5 (11.7)	22.0 (11.0)
Male, n (%)	17 (53.1)	14 (45.2)
Race,^a n (%)		
White	17 (53.1)	18 (58.1)
Asian	8 (25.0)	10 (32.3)
Black	2 (6.3)	1 (3.2)
Multiracial	1 (3.1)	0
Time since initial diagnosis, mean (SD), y	12.6 (9.9)	13.2 (9.1)
Baseline 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)

^aData 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 placebo group.
CAJIS, Cumulative Analogue Joint Involvement Scale; HO, heterotopic ossification.

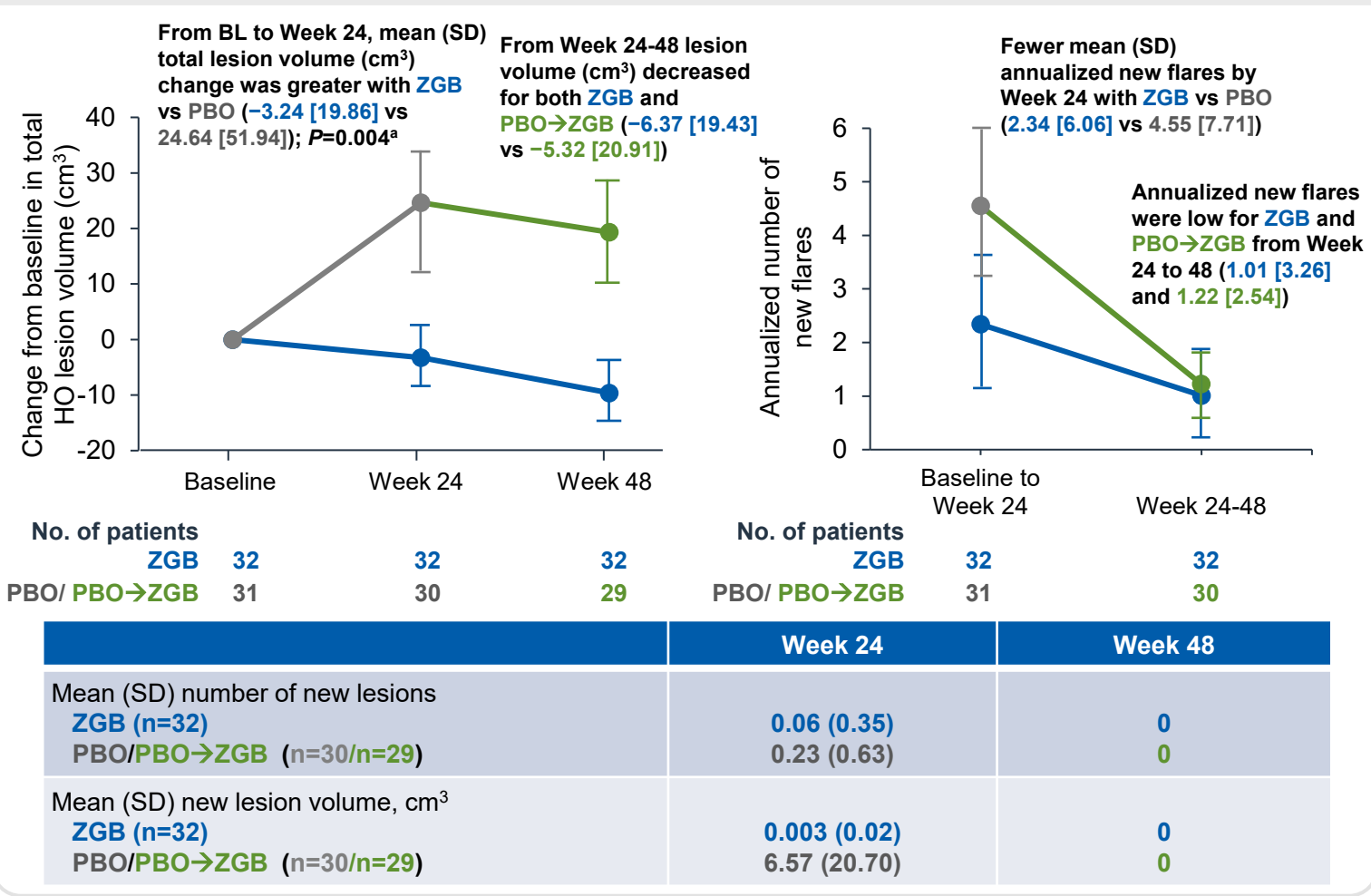
Efficacy Outcomes for Zilurgisertib Versus Placebo

Cohort 1 (≥12 years of age)

Primary endpoint



Key secondary endpoints



^aNominal P value.
BL, baseline; HO, heterotopic ossification; OLE, open-label extension; PBO, placebo; ZGB, zilurgisertib.

Safety

Cohort 1 (≥ 12 years of age)

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

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	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)

No Grade ≥ 3 TEAEs occurred in more than one patient through Wk 24. ZGB (n=2 patients; [dehydration, dyspnea, gastroesophageal reflux disease, hypotension, nausea, oxygen saturation decreased, pneumonia, urinary tract infection] and skull fracture base); PBO (n=4 patients; [arthralgia, shoulder fracture, back pain, traumatic pain], lipase increased, FOP flare-up, and femoral neck fracture).

AE, adverse event; FOP, fibrodysplasia ossificans progressiva; OLE, open-label extension; TEAE, treatment-emergent adverse event.

Conclusions

Cohort 1 (≥ 12 years of age)

- 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

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