Health-related quality of life from a phase 4 global clinical study to evaluate discontinuation and rechallenge of pexidartinib in patients with tenosynovial giant cell tumor (TGCT) previously treated with pexidartinib

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PURPOSE

- This phase 4, multicenter, global clinical study of pexidartinib (ClinicalTrials.gov Identifier: NCT04526704) was designed to evaluate outcomes in patients with tenosynovial giant cell tumor (TGCT) following pexidartinib discontinuation and rechallenge
- The objective of this analysis was to evaluate health-related quality of life (HRQOL) during treatment and discontinuation/rechallenge with pexidartinib

CONCLUSIONS

- Many patients with TGCT experience a deterioration in HRQOL due to repeated surgeries or disease recurrence.[1] In this small phase 4 study, HRQOL was generally sustained for pexidartinib users during the 2-year follow-up
- For patients who have previously benefited from pexidartinib and are in the midst of disease or symptomatic progression without pexidartinib, reinitiating treatment may be associated with symptomatic improvement
- Further HRQOL investigations for patients on long-term continuous and intermittent pexidartinib treatment are warranted

INTRODUCTION

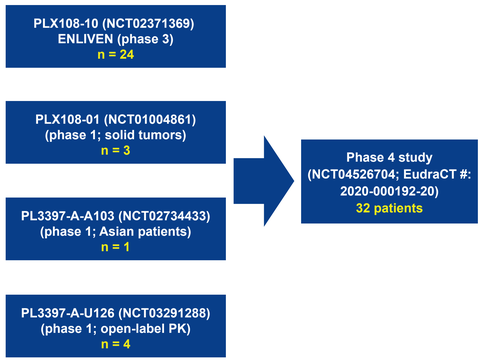
- Pexidartinib is an orally administered, small-molecule tyrosine kinase inhibitor with selective activity against the colony-stimulating factor 1 receptor[2-4]
- Pexidartinib was approved by the US Food and Drug Administration in 2019[4] and by the Korean and Taiwanese authorities in 2021 and 2022,[5,6] respectively, for the treatment of adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery (or other treatment [eg, local radiotherapy] in Taiwan)
  - This approval was based on results from the phase 3 ENLIVEN study (ClinicalTrials.gov Identifier: NCT02371369)[3]
- Patients with TGCT experience worse HRQOL compared with the general population[7-9]
  - Specifically, patients experience pain or discomfort, decreased mobility, and reduced performance of usual activities, which can be measured using the EuroQol 5-dimension 5-level visual analog scale (EQ-5D-5L VAS) and the Patient-Reported Outcomes Measurement Information System–Physical Function (PROMIS-PF) questionnaire[8,9]
  - Repeated surgical intervention is associated with diminishing HRQOL[1]
- This phase 4 study evaluated the effects of drug discontinuation and retreatment with pexidartinib in patients with TGCT who previously benefited from the drug; the proportion of patients who were treatment free at Months 12 and 24 (primary endpoint) was 73% (95% confidence interval [CI], 37, 90)
  - For patients who continued pexidartinib, no progressive disease was observed per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; 55% of patients who discontinued pexidartinib had progressive disease within 2 years, and 100% of patients who then rechallenged with pexidartinib had new disease stabilization per RECIST v1.1
  - No new safety signals were observed, and the safety profile was consistent with previous findings[3]
- The present analysis evaluated HRQOL over the 24-month study period in patients who remained on pexidartinib, those who discontinued pexidartinib, and those who restarted treatment

METHODS

Study Design

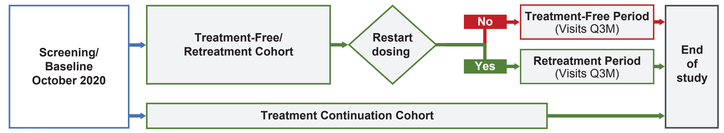
- Patients with TGCT from 1 of 4 previous studies (ClinicalTrials.gov Identifiers: NCT02371369, NCT01004861, NCT02734433, and NCT03291288) enrolled after the previous studies' end-of-treatment visit (**Figure 1**)
- At the investigator's and patient's discretion, patients chose to continue pexidartinib (Treatment Continuation Cohort) or discontinue pexidartinib with the option to reinitiate (Treatment-Free/Retreatment Cohort; **Figure 2**)
  - Patients in the Treatment Continuation Cohort remained at the same pexidartinib dose they were receiving in the prior study and underwent assessments every 3 months for the duration of the study
  - Patients who discontinued treatment enrolled in the Treatment-Free/Retreatment Cohort and had assessments 1 month after enrollment, 3 months after enrollment, and then at 3-month intervals for the duration of the study
  - The decision to retreat with pexidartinib was at the investigator's and patient's discretion based on tumor assessment, symptomatic worsening, subjective/functional measures, and safety

Figure 1. Study overview



PK, pharmacokinetics.

Figure 2. Study design



Q3M, every 3 months.
At Screening/Baseline, patients were given the choice of cohort to enroll in.
Patients who reinitiated pexidartinib underwent weekly liver monitoring tests for the first 8 weeks, then every 2 weeks for 1 month, then Q3M or as directed by the investigator.

Patients

- Key eligibility criteria are shown in **Table 1**

Table 1. Key Eligibility Criteria

Inclusion criteria	Exclusion criteria
• ≥18 years of age • Pathologic diagnosis of TGCT • Currently enrolled and on pexidartinib treatment in one of the following studies: – PLX108-10 (ENLIVEN) – PLX108-01 – PL3397-A-A103 – PL3397-A-U126 • Willing and able to complete the PROMIS-PF questionnaire and EQ-5D-5L VAS throughout the study	• Clinically significant abnormality that would preclude the patient's safe completion of the study • Exposure to other investigational drugs or procedures, besides pexidartinib studies, within 1 month prior to the start of study treatment

EQ-5D-5L VAS, EuroQol 5-dimension 5-level visual analog scale; PROMIS-PF, Patient-Reported Outcomes Measurement Information System–Physical Function; TGCT, tenosynovial giant cell tumor.

Endpoints and Assessments

- The primary endpoint was the proportion of patients in the Treatment-Free/Retreatment Cohort who remained treatment free at Months 12 and 24
- Mean change from Baseline in patient-reported outcomes (measured using the PROMIS-PF questionnaire and EQ-5D-5L VAS) was a secondary endpoint
- Safety was assessed throughout the study using laboratory assessments, vital signs, and physical examination
- This was a hypothesis-generating study, and all analyses are descriptive in nature

RESULTS

Baseline Characteristics

- From October 2020 to April 2021, 32 patients were enrolled: 21 in the Treatment Continuation Cohort and 11 in the Treatment-Free/Retreatment Cohort
- Patients had a median age of 47.5 (range: 21-81) years, a median of 7.8 (range: 4.6-32.6) years from diagnosis to informed consent, and a median of 55.7 (range: 26.7-91.0) months of prior pexidartinib treatment
- Demographic and Baseline characteristics for the 32 patients included in the study are shown in **Table 2**

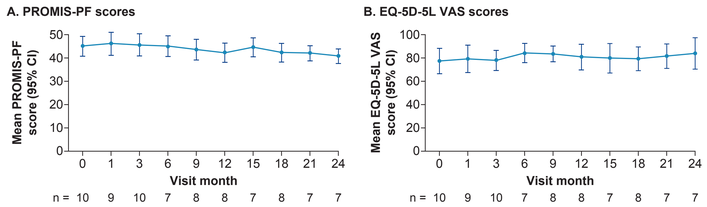
Table 2. Demographic and Baseline Characteristics

Characteristic	Treatment Continuation Cohort (n = 21)	Treatment-Free/Retreatment Cohort (n = 11)	Total (N = 32)
Age, median (range), years	47.0 (21-78)	51.0 (27-81)	47.5 (21-81)
Sex, n (%)			
Male	9 (42.9)	7 (63.6)	16 (50.0)
Female	12 (57.1)	4 (36.4)	16 (50.0)
Race, n (%)			
Asian	1 (4.8)	1 (9.1)	2 (6.3)
White	19 (90.5)	8 (72.7)	27 (84.4)
Not collected per local regulations	1 (4.8)	2 (18.2)	3 (9.4)
Duration of pexidartinib treatment in prior study, median (range), months	55.3 (26.7-91.0)	56.7 (52.3-74.1)	55.7 (26.7-91.0)
Best response before entering the study, n (%)			
Complete response	6 (28.6)	5 (45.5)	11 (34.4)
Partial response	14 (66.7)	3 (27.3)	17 (53.1)
Stable disease	1 (4.8)	3 (27.3)	4 (12.5)
Progressive disease	0	0	0
Total daily pexidartinib dose prescribed during the prior study, n (%)			
800 mg	10 (47.6)	5 (45.5)	15 (46.9)
600 mg	6 (28.6)	2 (18.2)	8 (25.0)
400 mg	5 (23.8)	4 (36.4)	9 (28.1)
Time from diagnosis to informed consent, median (range), years	10.8 (4.61-32.6)	6.0 (4.8-15.9)	7.8 (4.6-32.6)
Tumor subtype, n (%)			
Diffused	10 (47.6)	8 (72.7)	18 (56.3)
Localized	11 (52.4)	3 (27.3)	14 (43.8)
Tumor joint location, n (%)			
Lower	18 (85.7)	9 (81.8)	27 (84.4)
Knee	10 (47.6)	6 (54.5)	16 (50.0)
Ankle	4 (19.0)	2 (18.2)	6 (18.8)
Hip	3 (14.3)	0	3 (9.4)
Foot	1 (4.8)	1 (9.1)	2 (6.3)
Upper	3 (14.3)	2 (18.2)	5 (15.6)
Shoulder	1 (4.8)	1 (9.1)	2 (6.3)
Hand	1 (4.8)	0	1 (3.1)
Spine	1 (4.8)	0	1 (3.1)
Wrist	0	1 (9.1)	1 (3.1)

Patient-reported Outcomes

- Treatment-Free Period
  - Average PROMIS-PF and EQ-5D-5L VAS scores remained stable over time during the Treatment-Free Period in the Treatment-Free/Retreatment Cohort
    - During the Treatment-Free Period, the 24-month average paired change from Baseline was –1.93 (95% CI, –6.37, 2.51) and 3.4 (95% CI, –3.6, 10.4) for the PROMIS-PF questionnaire and EQ-5D-5L VAS, respectively
    - PROMIS-PF and EQ-5D-5L VAS scores over time during the Treatment-Free Period are shown in **Figure 3**

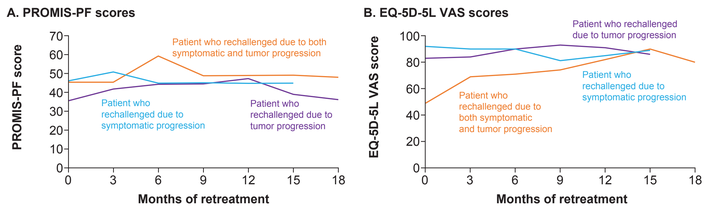
Figure 3. PROMIS-PF (A) and EQ-5D-5L VAS (B) scores over time in the Treatment-Free Period



CI, confidence interval; EQ-5D-5L VAS, EuroQol 5-dimension 5-level visual analog scale; PROMIS-PF, Patient-Reported Outcomes Measurement Information System–Physical Function.

- Retreatment Period
  - Three of the 11 patients in the Treatment-Free/Retreatment Cohort reinitiated pexidartinib treatment
  - Two of the 3 patients who reinitiated treatment had clinically significant (≥10 points) increases in PROMIS-PF and EQ-5D-5L VAS scores
  - Spaghetti plots of PROMIS-PF and EQ-5D-5L VAS scores for the 3 patients in the Retreatment Period are shown in **Figure 4**

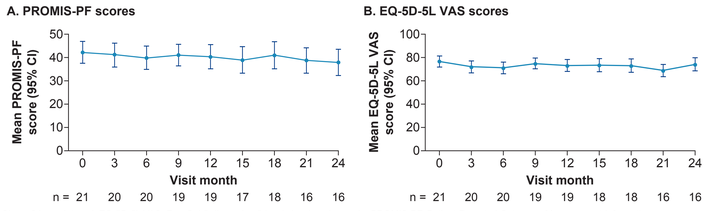
Figure 4. PROMIS-PF (A) and EQ-5D-5L VAS (B) scores during the Retreatment Period for patients who reinitiated treatment



EQ-5D-5L VAS, EuroQol 5-dimension 5-level visual analog scale; PROMIS-PF, Patient-Reported Outcomes Measurement Information System–Physical Function.

- Treatment Continuation Cohort
  - In the Treatment Continuation Cohort, mean PROMIS-PF and EQ-5D-5L VAS scores remained stable over time
    - The mean 24-month paired change from Baseline was –2.78 (95% CI, –6.20, 0.65) and –2.4 (95% CI, –9.6, 4.8) for PROMIS-PF and EQ-5D-5L VAS scores, respectively
    - PROMIS-PF and EQ-5D-5L VAS scores over time for the Treatment Continuation Cohort are shown in **Figure 5**

Figure 5. PROMIS-PF (A) and EQ-5D-5L VAS (B) scores over time in the Treatment Continuation Cohort



CI, confidence interval; EQ-5D-5L VAS, EuroQol 5-dimension 5-level visual analog scale; PROMIS-PF, Patient-Reported Outcomes Measurement Information System–Physical Function.

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PRESENTING AUTHOR DISCLOSURES

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