



ARTICLE

Exposure–response analysis of efficacy and safety for pexidartinib in patients with tenosynovial giant cell tumor

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Abstract

This analysis was conducted to assess exposure–response relationships for efficacy and safety of pexidartinib in patients with tenosynovial giant cell tumor. Efficacy was assessed categorically by overall response rate (ORR) with Response Evaluation Criteria in Solid Tumors version 1.1 and longitudinally (changes in tumor size and volume). Safety included hepatic parameters (i.e., alanine aminotransferase [ALT], aspartate aminotransferase [AST], and total bilirubin). Average pexidartinib concentration (C_{avg}) was identified as the primary exposure parameter correlated with response. In categorical and longitudinal analyses, higher C_{avg} coincided with greater ORR and tumor size reduction, respectively, with smaller joint size having a greater impact. For safety, a significant relationship was observed between C_{avg} and incidence of ALT-related and AST-related adverse events (AEs). With increased exposure, an increase in efficacy was predicted with near maximum effect at 800 mg/day. Higher initial dose (1000 mg/day) during the first 2 weeks did not improve efficacy. Higher doses were associated with an increased risk of ALT-related and AST-related AEs. These results support the US Food and Drug Administration–approved dose (400 mg two times/day without initial loading dose).

STUDY HIGHLIGHTS

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Dosing for pexidartinib in phase III trials was based on a phase I trial. Exposure–response analyses for pexidartinib have not been previously published.

WHAT QUESTION DID THIS STUDY ADDRESS?

It assesses the effect of pexidartinib exposure on efficacy and safety parameters to support the currently approved dose regimen and identify covariates impacting this exposure–response relationship.

[†]At time of study.

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WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Increasing the dose from 400 mg/day to 800 mg/day was associated with improved efficacy; a higher initial dose (1000 mg/day) did not improve efficacy. There was an increased risk of adverse events with higher doses.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This study supports the US Food and Drug Administration–approved dose of 400 mg twice daily and provides clinicians with insights into understanding of the exposure–response relationship for efficacy and safety.

INTRODUCTION

Tenosynovial giant cell tumor (TGCT) is a rare and aggressive neoplasm that affects joints, tendon sheaths, and bursae.¹ Pexidartinib is a novel, small-molecule tyrosine kinase inhibitor that targets colony-stimulating factor 1 receptor (*CSF1R*).^{2,3} In the ENLIVEN study, pexidartinib was associated with a robust tumor response and improvement in symptoms and functionality in adult patients with severe symptomatic TGCT.⁴ Thereafter, pexidartinib was approved in the United States for the treatment of adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery.²

In the ENLIVEN study, patients randomly assigned to pexidartinib received 1000 mg/day for 2 weeks and 800 mg/day thereafter. Following the randomization phase (Part 1), patients receiving the placebo could cross over to pexidartinib 800 mg/day (Part 2) (Figure 1). Patients in the crossover group who started pexidartinib at 800 mg/day had lower mixed or cholestatic hepatotoxicity compared with those randomly assigned to pexidartinib at 1000 mg/day.⁴

The objectives of the present analysis were to evaluate the exposure–response relationships for efficacy and safety to support the pexidartinib dose recommendation in patients with TGCT. Assessments included the pexidartinib exposure–response relationship for tumor response

using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and tumor volume score (TVS), longitudinally measured tumor size (RECIST and TVS), and adverse events (AEs) related to elevations in hepatic laboratory values.

METHODS

Data sources and study populations

Pharmacokinetic (PK) data, clinical efficacy, and safety measures from studies PLX108-01 and ENLIVEN were assessed (Table 1). ENLIVEN was a two-part, randomized, double-blind, placebo-controlled phase III study in 120 patients with TGCT (Figure 1). Patients received pexidartinib 1000 mg/day for 2 weeks and then 800 mg/day for 22 weeks with crossover allowed for placebo-treated patients at the initiation of the long-term treatment phase; 30 patients crossed over.

PLX108-01 was a two-part phase I study evaluating the safety, PKs, and pharmacodynamics of pexidartinib in patients with advanced, incurable, solid tumors, including TGCT. In Part 1, patients underwent sequential dose escalation from 200 mg/day up to 1200 mg/day followed by an extension phase (Part 2) in which 39 patients with TGCT received pexidartinib 1000 mg/day.

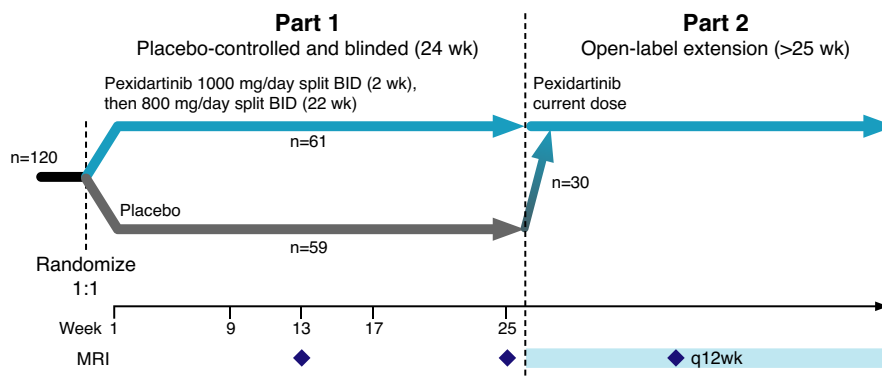


FIGURE 1 ENLIVEN study design. BID, twice daily; MRI, magnetic resonance imaging; q12wk, every 12 weeks

TABLE 1 Summary of studies, end points, and covariates included in the exposure–response analysis

Analysis	Study	No. of patients	End points	Covariates
Exposure pharmacodynamics	PLX108-01; ENLIVEN	141	Longitudinally measured tumor size by RECIST or TVS	<ul style="list-style-type: none"> • Age (years) • Body weight (kg) • Sex • Race (White vs. non-White) • Baseline tumor size (mm) • Location of investigational site (United States vs. non-United States) • Joint size (small vs. large) • Primary tumor location (upper vs. lower extremity) • Study period (1 vs. 2)
Exposure efficacy	ENLIVEN	113	Tumor response at Week 25 reported by RECIST or TVS	<ul style="list-style-type: none"> • Age (years) • Body weight (kg) • Sex • Race (White vs. non-White) • Baseline tumor size (mm) • Location of investigational site (United States vs. non-United States) • Joint size (small vs. large) • Primary tumor location (upper vs. lower extremity) • Study period (1 vs. 2)
Exposure safety	PLX108-01; ENLIVEN	241	<ul style="list-style-type: none"> • ALT >3× ULN • AST >3× ULN • TBIL >2× ULN • TBIL >2× baseline 	<ul style="list-style-type: none"> • Age (years) • Body weight (kg) • Sex • Race (White vs. non-White) • Tumor type (TGCT vs. non-TGCT) • Identifier for ENLIVEN placebo crossover patients • Baseline laboratory value for corresponding end point

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; RECIST, Response Evaluation Criteria in Solid Tumors; TBIL, total bilirubin; TGCT, tenosynovial giant cell tumor; TVS, tumor volume score; ULN, upper limit of normal.

Assessments

PK data were analyzed using population PK (PopPK) modeling previously described to obtain exposure metrics in individual patients.⁵ The primary exposure metric in the exposure–response analysis was the PopPK model, which predicted the average drug concentration (C_{avg}) during 25 weeks of dosing. Efficacy end points were longitudinal tumor size and tumor response assessed using RECIST (version 1.1) and TVS by blinded independent central review. AEs of interest were liver enzyme (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and total bilirubin [TBIL]) elevations and cholestatic laboratory results based on laboratory values.

Exposure–response modeling of longitudinal tumor size

The longitudinal tumor-size modeling population included all patients in the intent-to-treat analyses of ENLIVEN and

PLX108-01 who had two or more observations (baseline plus one or more after baseline) and were included in the PK analysis. Nonlinear mixed effects models were used to describe longitudinal tumor growth. Models and analyses were developed and conducted using R version 3.3 (R Foundation for Statistical Computing) and NONMEM version 7.4 (ICON Development Solutions). The first-order conditional estimation with η - ϵ interaction method was used for all model runs. Initial model development for natural tumor growth (placebo model) was guided by the change in tumor size in the absence of treatment (i.e., patients receiving placebo, Part 1 of ENLIVEN). Selection of the structural form of the placebo model was based on exploratory analysis and common methods of modeling tumor data.⁶

Covariates included age and body weight at baseline, sex, race (White vs. non-White), joint size (small vs. large), and primary tumor location (upper vs. lower extremity). Once natural tumor growth was described (i.e., placebo model), the drug exposure effect on tumor size reduction was assessed. Overall, the model incorporated tumor growth magnitude and onset of drug effect:

$$Y_{ij} = Y_{0,i} \left(1 - E_{\max} \times \left(1 - e^{-k_{\text{drug}} \times \text{Cavg}_{ij}} \right) \left(1 - e^{-k_{\text{onset}} \times \text{TAFD}_{ij}} \right) \right) + \theta_i \times \text{time}_{ij}$$

$Y_{0,i}$ is the baseline tumor size, E_{\max} is the maximal achievable effect, θ_i is tumor natural growth, Cavg_{ij} is average concentration up to tumor measurement time j , and TAFD is time after first dose. k_{drug} and k_{onset} are rate constants of exposure effect and onset effect, respectively.

Assessment of model adequacy and adjustments to the model were driven by data and goodness-of-fit criteria. These included visual inspection of diagnostic plots, successful convergence of the minimization routine, plausibility of parameter estimates, precision of parameter estimates for structural parameters correlation between model parameter estimation errors <0.95 , the Akaike information criterion, and preference for NONMEM's covariance step completion.

The final model adequacy and parameter estimates were investigated with a visual predictive check, assuming that parameter uncertainty is negligible relative to inter-individual and residual variance.⁷ A total of 1000 Monte Carlo simulations were generated using the final models compared with the observed data in a visual predictive check.

Exposure–response modeling of overall response

Overall response rate (ORR; RECIST and TVS) was measured in the intent-to-treat population in ENLIVEN; patients received pexidartinib in either the randomization or the long-term extension phases of the study or received placebo (not crossed over). Responses at Week 25 by RECIST and TVS were classified as complete response (CR), partial response (PR), or nonresponse (neither CR/PR). Nonevaluable patients for response were classified as nonresponders. The exposure metric was C_{avg} in specific time intervals. Proportional odds logistic regression models with potentially nonlinear effects of exposure (e.g., sigmoidal E_{\max} relationships) were developed in Stan (Stan Development Team; <https://mc-stan.org/>). Response variables were ordered as nonresponse ($Y = 0$), PR ($Y = 1$), and CR ($Y = 2$):

$$\text{logit}[P(Y_i \leq j)] = \alpha_j + (E_{\max} \times \text{Cavg}_i^Y) / (EC_{50}^Y + \text{Cavg}_i^Y), \quad (1)$$

for $j = 0, 1,$

α_j is the intercept for response j , and Cavg_i is the average concentration for patient i .

Weakly informative prior distributions were provided for exposure–response parameters (E_{\max} , half maximal

effective concentration [EC_{50}], and Hill coefficient [γ]) and intercept (α_0, α_1). The base model was:

$$P(Y = j | E_{\max}, EC_{50}, \gamma) = P(Y \leq j) - P(Y < j)$$

$E_{\max} \sim N(0,5)$, $EC_{50} \sim \text{scale} \times N^+(0,5)$, $\gamma \sim N^+(0,3)$, $P(Y \leq j)$ is given in Equation (1), $N(\mu, \sigma)$ denotes a normal distribution with mean μ and standard deviation σ , and $N^+(\mu, \sigma)$ denotes a corresponding half-normal distribution. The scale factor in the prior distribution for EC_{50} was approximately equal to the median exposure among the patients treated with pexidartinib.

The covariates evaluated were the same as the longitudinal analysis plus baseline tumor size (mm), location of investigational site (United States vs. non-United States), and study period (active phase vs. crossover phase).

To assess covariate effects, modeling proceeded in three steps. First, the full model with all covariates was estimated using a Bayesian regularization method regularized horseshoe priors⁸; covariates with effects for which the 50% central credible interval (CrI) excluded the null value were selected. Second, a reduced full model was fitted with these selected covariates using noninformative $N(0,5)$ prior distributions. A final model was selected including all covariates for which, in the reduced full model, the 90% central CrI excluded the null value. Model qualification was performed using posterior predictive checks with distributions summarized by both the proportion of responders and complete responders by covariate strata (e.g., exposure tertile) and by the smoothed expected probability of ORR and CR as a function of exposure. Also, models were fitted using nonregularizing prior distributions (e.g., $N[0,5]$) for covariate effects to assess sensitivity of the inference to the choice of prior distribution.

Exposure–response modeling of adverse events

The AE modeling population included all patients from study PLX108-01 and those from ENLIVEN who were in the intent-to-treat analysis if they received pexidartinib in either the randomization or the long-term extension phases of the study or who received placebo (either crossed over or not). Patients who met the criterion for an AE at baseline were excluded from the analysis set for that AE end point.

The AEs of interest were related to hepatic function and described as time-to-event distributions for the following:

- Time to first ALT $>3 \times$ upper limit of normal (ULN)
- Time to first AST $>3 \times$ ULN
- Time to first TBIL $>$ ULN
- Time to first TBIL $>2 \times$ baseline

For each AE, an exposure–response analysis for the time to the first event using C_{avg} as the exposure metric was performed to describe the rate of onset and overall AE incidence.

In piecewise-exponential time-to-event models with hazards assumed to be constant over time intervals (0–4 weeks, 4–8 weeks, 8–12 weeks, 12–80 weeks), 80 weeks is the longest time at-risk in ENLIVEN. For subjects with an event, time averaging continued through the time of event. For subjects without an event, time averaging continued through time of censoring. If time of censoring was not directly observed, it was assumed to be 2 weeks after the last recorded dose. Linear, log-linear, and sigmoidal E_{max} structural exposure–response models were evaluated:

$$\log h(t) = a_k + \text{slope} \times \text{Cavg}_{ik}, t \in I_k, k = 1, 2, 3, 4, 5$$

$$\log h(t) = a_k + \text{slope} \times \log(\text{Cavg}_{ik} + 0.01), t \in I_k, k = 1, 2, 3, 4, 5$$

$$\log h(t) = a_k + E_{max} \times \text{Cavg}_{ik}^Y / (EC_{50}^Y + \text{Cavg}_{ik}^Y), t \in I_k, k = 1, 2, 3, 4, 5$$

Cavg_{ik} is the average concentration for patient i in interval I_k . To account for the planned dose reduction following Week 2 of the randomization phase of study PLX108-10, average concentrations were calculated over the following five time intervals: 0–2 weeks, 2–4 weeks, 4–8 weeks, 8–12 weeks, and 12–80 weeks, that is, $I_1 = [0,2)$, $I_2 = [2,4)$, $I_3 = [4,8)$, $I_4 = [8,12)$, and $I_5 = [12,80)$ weeks. At the same time, to ensure model consistency with the assumption that the AE hazard is constant over the 0–4 weeks time interval, the intercept during the first 4 weeks was kept constant by setting $\alpha_1 = \alpha_2$.

Models were fit in a Bayesian paradigm using Stan. Prior distributions were chosen as weakly informative. Specifically, baseline hazard parameters were $\alpha_k \sim N(-3,5)$ for $k = 2, \dots, 5$. For linear and log-linear models, we used $\text{slope} \sim N(0,2)$. For the sigmoidal E_{max} model, $E_{max} \sim N(0,5)$, $EC_{50} \sim N^+(0,5)$, and $\gamma \sim N^+(0,3)$. Covariates evaluated included age and body weight at baseline, sex, race (White vs. non-White), tumor type (TGCT vs. non-TGCT), identifier for placebo crossover patients, and baseline laboratory value for the analysis end point.

Model qualification was performed using posterior predictive checks, including a summary of proportion of patients experiencing the AE stratified by covariate group and posterior predictive distribution for the Kaplan–Meier estimated time to AE distribution stratified by covariate groups.

Population simulations

Population simulations were performed for efficacy and safety end points with dosing scenarios (25 weeks of dosing):

- 400 mg/day AM
- 600 mg/day (200 mg AM, 400 mg PM)
- 800 mg/day (400 mg AM and PM)
- 1000 mg/day (400 mg AM + 600 mg PM) \times 2 weeks, then 800 mg/day for 23 weeks

Complete covariate cases were generated for 1000 individuals by resampling the ENLIVEN population. Individual PK parameters of these 1000 patients were simulated based on their covariates and interindividual random effect distributions from the PopPK model. The respective exposure metric for each efficacy/safety end point was calculated for all 1000 patients. The exposure–response models were used to simulate efficacy and safety given these exposure metrics. To include parameter uncertainty, the parameter set was resampled either from the asymptotic distribution (NONMEM output) or the joint posterior distribution (Stan). A total of 1000 simulations were conducted for efficacy or safety end points.

RESULTS

Exposure–response of longitudinal tumor size

There were 159 patients with 781 longitudinal RECIST and TVS observations in the exposure–response analysis of longitudinal tumor size; 18 patients were excluded (for no tumor observations [$n = 10$], for exclusion from PK modeling [$n = 7$], and for only having a single observation [$n = 1$]). Demographics and baseline characteristics of the RECIST population are summarized in Table S1. All continuous and categorical covariates were well balanced across treatment cohorts.

Raw RECIST scores (cm) are illustrated in Figure 2a. Tumor size in placebo-treated patients in ENLIVEN remained unchanged over 24 weeks, whereas the patients receiving pexidartinib in ENLIVEN (either randomly assigned to pexidartinib or crossed over to pexidartinib) or who received pexidartinib in study PLX108-01 showed varying decreases in RECIST scores, ranging from no improvement to complete reduction of the tumor. The rate of tumor response was dependent on whether patients were randomly assigned to pexidartinib or crossed over to pexidartinib.

For the placebo model, following examination of covariate relationships, only joint size had a statistically significant effect on baseline tumor size with small joints associated with a lower baseline tumor size versus large joints. Accounting for joint extremity, joint size, and age, the tumor growth rate was estimated to be 0.227 (95% confidence interval [CI], $-0.13, 0.583$) cm/year. Since the 95% CI included zero, the growth rate was fixed to zero for subsequent drug effect model development.

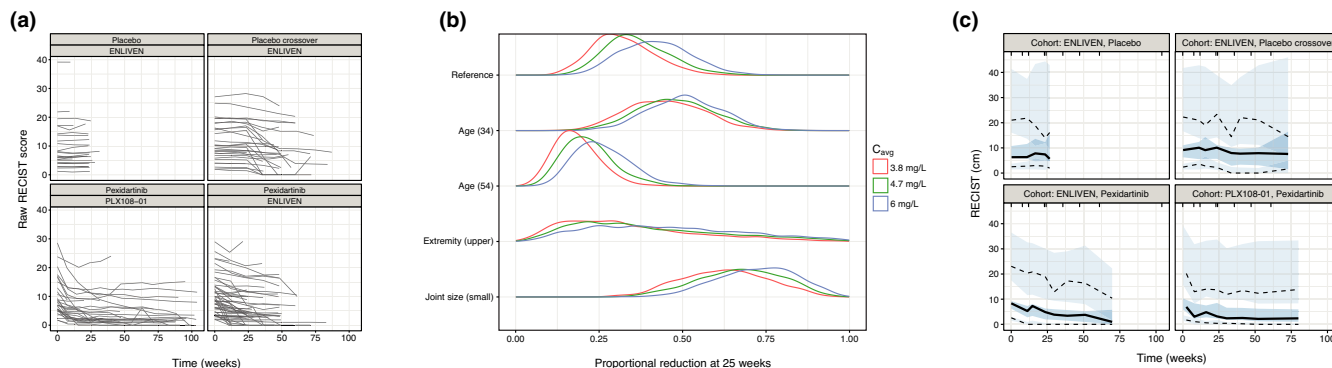


FIGURE 2 Longitudinal RECIST-based tumor size pharmacokinetic/pharmacodynamic modeling. Reference is the 44-year-old patient presenting with a tumor in the lower extremity in a large joint. (a) Observed data: each line represents the observed tumor size measured over time in individual subject. (b) Forest plot for covariate effects: for each of the covariates in the final model (age, joint extremity, and joint size), the density represents the conditional mean drug effect at 25 weeks of onset of the drug. (c) Visual predictive check: observed median RECIST score (cm) is shown as the solid black line, and the 5th and 95th percentiles are shown as dashed lines. Shaded regions show the 95% confidence intervals around each quartile of interest (the median and the 90% prediction interval). Binning intervals are shown with the rug across the top of the image. No parameter uncertainty was included in simulations. C_{avg} , average drug concentration; RECIST, Response Evaluation Criteria in Solid Tumors

For the drug effect model, based on the visual evidence of residual trend in the random effects distributions for the drug effect and onset effect relative to joint extremity, joint size, and age, these covariates were added to the model parameters k_{drug} and k_{onset} , resulting in the final longitudinal tumor model (Table S2). The covariate effect is further illustrated in Figure 2b, where the top graph shows the effect of different C_{avg} values for pexidartinib on tumor size in a reference patient (i.e., 44-year-old with a tumor located in the lower extremity in a large joint). At C_{avg} values of 3.8 (median 25th percentile), 4.7 (median 50th percentile), and 6 mg/L (median 75th percentile), there was a directional exposure–response trend with mean reductions in tumor size of 32%, 36%, and 42%, respectively, at these concentrations. Similar trends were seen for each of the covariates with the largest effect seen with joint size. However, differences in response were not statistically significant as concentration extremes (i.e., 3.8 and 6 mg/L) had overlapping 95% CIs within age, extremity, and joint size.

The visual predictive check replicated observed RECIST measurements well across all cohorts (Figure 2c), indicating that the model structure was sufficient to capture the observed trends in the data. Similar results were observed for the longitudinal assessment of TVS. This is not surprising because the RECIST and TVS scores were positively correlated (Pearson correlation $\rho = 0.65$ on the raw scale).

Exposure–response of overall response rate

There were 120 patients with odds ratio (OR) data (91 pexidartinib, 29 placebo) from ENLIVEN included in the ORR analysis. Of the 91 patients treated with pexidartinib, 7 were excluded

from the PK modeling due to incorrect dosing history. Patients included in this analysis are largely the same as those in the ENLIVEN group in longitudinal tumor size analysis.

The base model estimated a shallow exposure–response relationship for ORR and CR across a range of C_{avg} values, reflecting observed ORRs of 21%, 50%, and 29% in the first, second, and third tertiles of C_{avg} values, respectively (compared with 0% for those receiving placebo). In the full model, age, weight, and joint size were identified as having effects on the variability in ORR, and these variables were carried forward to the reduced model for refitting with noninformative prior distributions. The resulting final model parameters are presented in Table S3. Results showed an effect of joint size, with disease in patients in small joints having a higher probability of response compared with those patients with disease in large joints (posterior median of the log OR of large vs. small was 0.85; 90% CrI, 0.04, 1.65). Note that as a log OR, the lower bound of the CrI can exceed zero and the upper bound can exceed one. Furthermore, increased C_{avg} was associated with an increased probability of a PR or CR with the exposure–response effect tending to be more pronounced in patients with small joint involvement (Figure 3a). Posterior predictive checks for the probability of ORR (Figure 3b) or CR (Figure 3c) indicate that the model fits the data well over C_{avg} exposure values. Similar results were observed for the TVS analysis with a shallow exposure–response relationship across the range of exposures explored.

Exposure–response of safety

The AE analysis set included patients from PLX108-01 and ENLIVEN. A total of 11 patients were excluded due to exclusion from PK modeling ($n = 7$) or having no

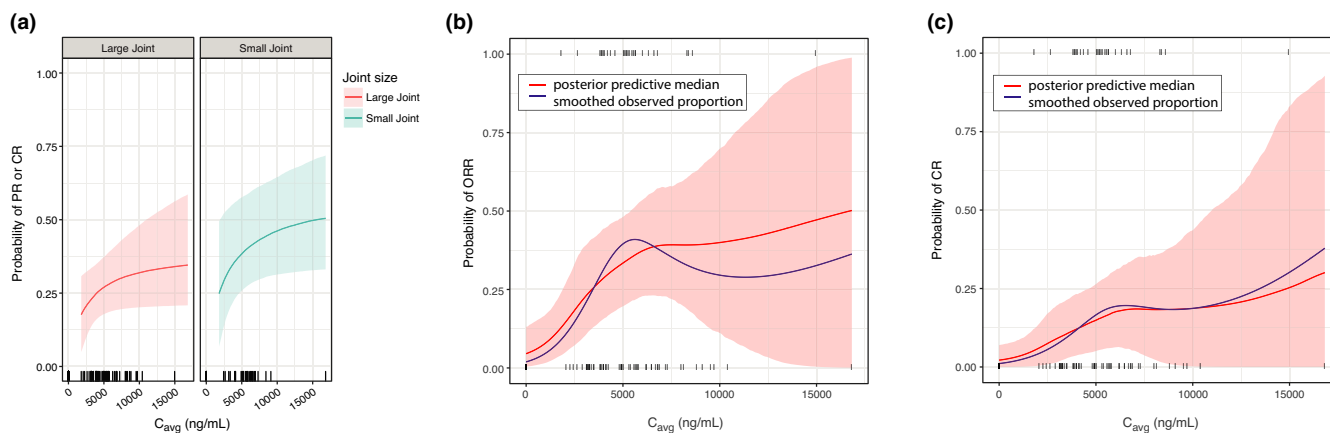


FIGURE 3 Logistic regression of Response Evaluation Criteria in Solid Tumors—based response: (a) probability of a PR or CR from final model stratified by joint size, (b) posterior predictive check for probability of PR or CR, and (c) posterior predictive check for probability of CR. C_{avg} , average drug concentration; CR, complete response; ORR, overall response rate; PR, partial response

postbaseline laboratory values ($n = 4$), resulting in a population of 241 patients. Of these, one patient was excluded from the analysis because of $ALT > 3 \times ULN$, one patient was excluded from the analysis because of $AST > 3 \times ULN$ and $> 5 \times ULN$, and five patients were excluded from the analysis because of $TBIL > ULN$ due to meeting the AE criteria at baseline. Demographics and baseline variables of the AE population are summarized in Table S4.

Although there was a large variability in observed ALT and AST values, ALT/AST showed similar trends over time with an initial increase after treatment initiation followed by a gradual decline. Clinical observations from ENLIVEN suggested a lower rate of aminotransferase elevations (30.0% vs. 41.0%) in the crossover subjects who received pexidartinib 800 mg/day versus those who received 1000 mg/day for 14 days followed by 800 mg/day.

In Kaplan–Meier estimates of the time-to-event distributions, there was a probable relationship between pexidartinib exposure in weeks 0–2 and the incidence of $ALT > 3 \times ULN$ (Figure 4a). Higher exposure tended to be associated with a higher incidence and rate of AE onset, and most $ALT > 3 \times ULN$ events occurred within the first 16 weeks of treatment.

Among the three base models (E_{max} , log-linear, and linear), the log-linear model had the lowest leave-one-out information criterion and therefore was selected for further covariate modeling. Parameter estimates of the final full model for $ALT > 3 \times ULN$ are presented in Table S5. Adjusting for covariates, the estimated exposure–response slope was 0.34 (90% CrI, 0.14, 0.67). Across a range of average pexidartinib concentrations from 2000 ng/mL (5th percentile) to 8000 ng/mL (95th percentile), the hazard ratio (HR) ranges from approximately 0.75 to 1.15.

Figure 4b illustrates the effect of covariates on the incidence of $ALT > 3 \times ULN$. The HR for $ALT > 3 \times ULN$ was significantly lower in men versus women (HR, 0.48;

90% CrI, 0.24, 0.97), non-TGCT versus TGCT (HR, 0.20; 90% CrI, 0.08, 0.47), and placebo crossover patients versus those who received pexidartinib at randomization (HR, 0.40; 90% CrI, 0.14, 0.97). The visual predictive check showed that the full covariate model reliably captured the time-to-event distribution for $ALT > 3 \times ULN$ events when stratified by quartile of pexidartinib exposure (Figure 4c).

The Kaplan–Meier estimates of the time-to-event distribution also showed a relationship between pexidartinib exposure in the weeks 0–2 time interval and the incidence of $AST > 3 \times ULN$ (Figure 5a). Men (HR, 0.45; 90% CrI, 0.2, 0.93), non-TGCT (HR, 0.24; 90% CrI, 0.1, 0.56), and placebo crossover patients (HR, 0.28; 90% CrI, 0.08, 0.75) had significantly lower HRs for $AST > 3 \times ULN$ (Figure 5b).

The Kaplan–Meier estimate found a very shallow exposure–response relationship for $TBIL (> 1 \times ULN$ or $> 2 \times$ baseline). No statistically significant relationship was identified, possibly because of the low frequency of these events.

Population simulations

Model-predicted outcomes based on dose are summarized in Table 2. Predicted ORR at Week 25 increased as the daily dose increased from 400 mg/day to 800 mg/day but with no discernable difference between the 800 mg/day and 1000/800 mg/day regimens. Similar results were observed for TVS-based ORR with the probability of OR increasing from 0.47 (90% CrI, 0.33, 0.59) at 400 mg/day to 0.57 (90% CrI, 0.47, 0.66) at 1000 mg/day. In the population simulations, the predicted incidence rates of ALT and AST elevations were lower for the 600 mg/day and 400 mg/day regimens versus the higher dose groups. For example, the predicted median probability of $ALT > 3 \times ULN$ within 16 weeks of the start of dosing ranged from

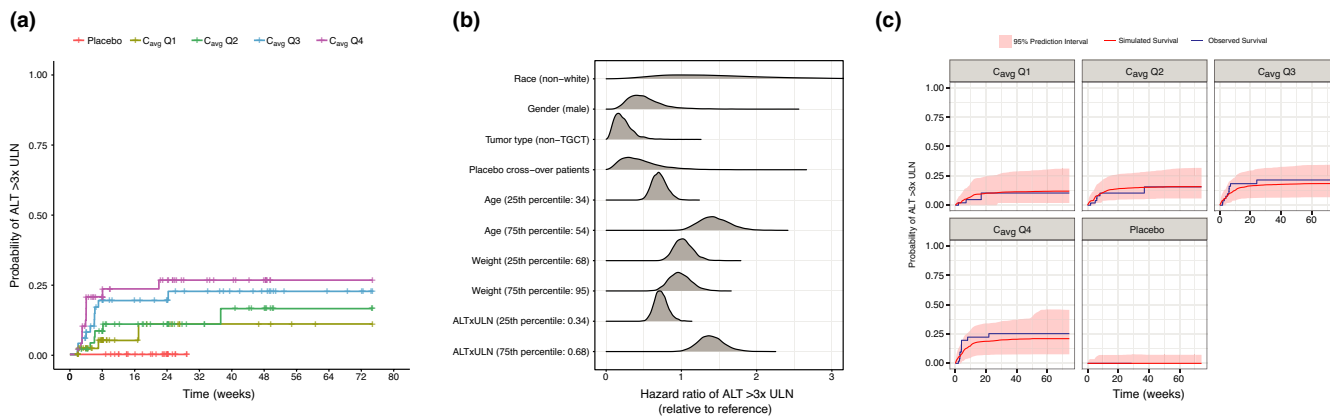


FIGURE 4 Time-to-event modeling of ALT >3x ULN. Reference individual is a 44-year-old, 80 kg, White female with a baseline ALT/ULN of 0.48 in the ENLIVEN who did not cross over from placebo: (a) Kaplan–Meier plot of probability of event-free survival by C_{avg} quartile, (b) forest plot of covariate effects, and (c) visual predictive check. Q1, Q2, Q3, and Q4 refer to Quartiles 1, 2, 3, and 4, respectively, of C_{avg} , where Q1 has the lowest C_{avg} and Q4 has the highest C_{avg} . ALT, alanine aminotransferase; C_{avg} , average drug concentration; TGCT, tenosynovial giant cell tumor; ULN, upper limit of normal

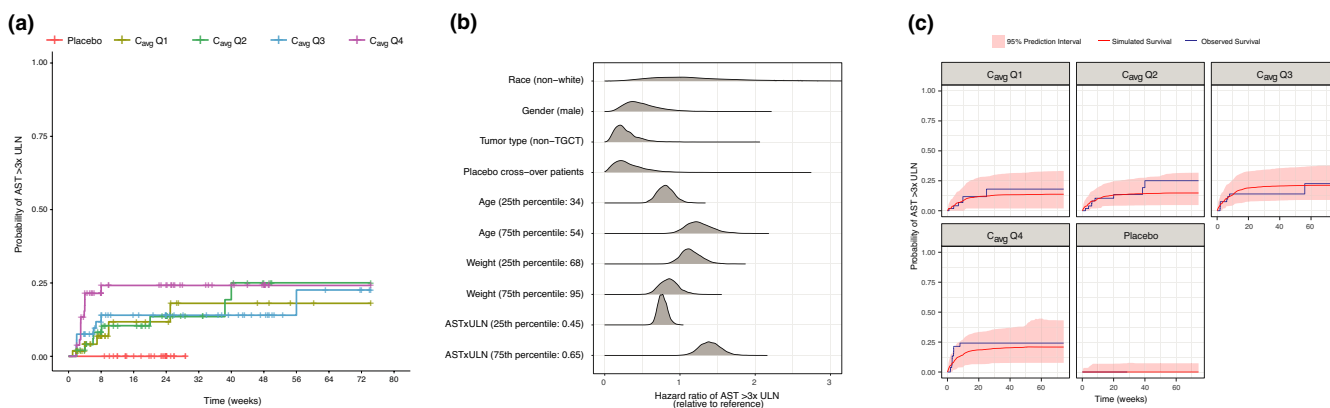


FIGURE 5 Time-to-event modeling of AST >3x ULN. Reference individual is a 44-year-old, 80 kg, White female with a baseline AST/ULN of 0.53 in the ENLIVEN study population who did not cross over from placebo. (a) Kaplan–Meier plot of probability of event-free survival by C_{avg} quartile: time to AST >3x ULN by pexidartinib exposure quartile in the weeks 0–2 time interval. (b) Forest plot of covariate effects: hazard ratio for AST >3x ULN. (c) Visual predictive check: time to AST >3x ULN stratified by quartile of average concentration in weeks 0–2. Q1, Q2, Q3, and Q4 refer to Quartiles 1, 2, 3, and 4, respectively, of C_{avg} , where Q1 has the lowest C_{avg} and Q4 has the highest C_{avg} . AST, aspartate aminotransferase; C_{avg} , average drug concentration; TGCT, tenosynovial giant cell tumor; ULN, upper limit of normal

22% for the 800-mg and 1000-mg daily regimens to 18% for the 400-mg daily regimen.

DISCUSSION

This is the first report to describe a comprehensive exposure–response analysis evaluating the exposure effects on the efficacy and safety of pexidartinib in adult patients with TGCT with locally advanced disease. Overall, results of the longitudinal and ORR analyses both suggested that increased exposure is generally associated with increased efficacy, although the exposure–response relationship was generally shallow. In the safety exposure–response

analysis, a probable relationship between increased pexidartinib exposure and the risk of hepatic toxicity was detected, especially in the first 2 weeks of treatment.

Dose selection of anticancer agents is conventionally based on dose-escalation trials in which only a limited number of patients receive a prespecified dose. Exposure–response analyses can overcome several of these limitations and are now commonly used to support dose selection and recommendations during drug development.^{9,10} For the efficacy analysis, both continuous (via longitudinal tumor size dynamics) and categorical (via ORR analysis) parameters were assessed. The use of both types of analysis provides complementary information. Evaluation of continuous variables when assessing tumor dynamics is

Dose	RECIST-based		
	ORR	ALT >3× ULN	AST >3× ULN
400 mg/day	0.25 (0.15, 0.36)	0.18 (0.12, 0.24)	0.18 (0.13, 0.25)
600 mg/day	0.29 (0.20, 0.38)	0.20 (0.14, 0.27)	0.20 (0.14, 0.27)
800 mg/day	0.32 (0.23, 0.42)	0.22 (0.15, 0.29)	0.22 (0.16, 0.30)
1000/800 mg/day	0.32 (0.23, 0.42)	0.22 (0.15, 0.30)	0.23 (0.16, 0.30)

Note: Data are provided as median (90% credible interval).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrI, credible interval; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal.

TABLE 2 Model-predicted event rate at different doses

particularly useful because efficacy data are not lost, and the analysis allows for the assessment of other doses and schedules.¹¹ Average exposure metrics C_{avg} and average daily area under the curve (AUC_{davg}) were selected as the primary exposure metrics in exposure–efficacy and exposure–safety analysis over others because they reflect average drug exposure over pexidartinib treatment course and take into account dose reduction or interruption during the treatment. Pairwise correlation of four summary exposure measures (AUC_{davg} , minimum concentration in the dosing interval following the Week 25 morning dose [C_{min}], maximum concentration in the dosing interval [C_{max}], and area under the concentration–time curve steady state [AUC_{ss}]) showed high correlations of 0.882, 0.891, and 0.91 between AUC_{davg} and C_{min} , C_{max} and AUC_{ss} , respectively. For the ORR exposure–response analyses, sensitivity analysis was conducted by using C_{min} as the exposure metric. Qualitatively, the results using C_{min} were the same as the results of models using AUC_{davg} , with an estimated shallow exposure–response relationship. A positive exposure–response relationship was shown for efficacy in patients with TGCT treated with pexidartinib. There were several differences between models regarding covariates included in the final model, with joint size, joint extremity, and age included in the longitudinal analysis and joint size, age, and weight included in the ORR analysis. Both analyses also indicated that joint size was the most important covariate, with small joint involvement associated with a greater probability of response compared with large joint involvement. This result is consistent with clinical observations that patients with small joint involvement tend to have a greater response compared with those with large joint involvement. However, the reasons for this finding are unclear, and it is possible that this result may be confounded by other factors.

In the exposure–response analysis of hepatic safety (i.e., increased ALT, AST), there was a probable relationship between increased pexidartinib exposure and the risk of hepatic events, with the relationship most apparent in the first 2 weeks of treatment. There was also a lower risk of liver transaminase elevations in men versus women,

in non-TGCT disease versus TGCT, and in placebo cross-over patients versus patients originally assigned to pexidartinib. This last finding suggests that the 1000-mg dose during the first 2 weeks of therapy increases the risk of aminotransferase elevations. Due to the unpredictable risk of serious mixed or cholestatic hepatic injury seen in the clinical trials, monitoring of liver tests is required every week for the first 8 weeks and biweekly for the third month,^{3,4} which is accepted as the period of maximal risk (the first 8 weeks of treatment). Dose modifications for pexidartinib (early withholding treatment for liver test monitoring, dose reduction in 200-mg increments, and/or permanent discontinuation) have been established.²

The population simulations suggest that there is increased efficacy when the dose is increased from 400 mg/day (200 mg twice daily [b.i.d.]) to 800 mg/day (400 mg b.i.d.). However, a higher initial dose (1000 mg; 400 mg AM + 600 mg PM) during the first 2 weeks does not further improve efficacy. The analysis also suggested an increased risk of AEs with higher doses. Overall, these results suggest that the currently recommended dose of 800 mg (400 mg b.i.d.) is reasonable for the general patient population. When necessary, based on monitoring liver tests, dose modification/reduction may be required.

The primary limitation of the analysis is the limited dose range included in the analysis and the small numbers of patients in several of the covariate groups, which limit the ability to determine whether exposure–response effects are statistically significant. In addition, there could potentially be other confounding factors not assessed in the current analysis that may have a meaningful effect on pexidartinib exposure–response relationships. For example, small joint size was shown to be associated with greater response compared with large joints; however, the mechanism remains unclear and could be impacted by other confounding factors.

CONCLUSION

This exposure–response analysis along with the clinical efficacy and safety data show that pexidartinib 800 mg/

day (400 mg b.i.d.) is the appropriate dose for patients with TGCT.

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CONFLICT OF INTEREST

O.Y. reports employment with Daiichi Sankyo at the time of study. H.Z. reports employment with Daiichi Sankyo. J.F. reports consulting fees to his company from Daiichi Sankyo. D.P. reports consulting fees to his company from Daiichi Sankyo. X.W. reports consulting fees to her company from Daiichi Sankyo. M.v.d.S. reports grants to his institution from Daiichi Sankyo during the conduct of the study. W.D.T. reports a standard budget for site participation in clinical trial from Plexxikon; personal fees for serving on advisory boards and consulting from Agios Pharmaceuticals, Blueprint, C4 Therapeutics, Daiichi Sankyo, Eli Lilly, EMD Serono, GlaxoSmithKline, and Mundipharma outside the submitted work; personal fees for serving on advisory boards of NanoCarrier and Deciphera outside the submitted work; personal fees for consulting from AbMaxBio, Adcendo, Ayala Pharmaceuticals, Kowa, and Servier outside the submitted work; a patent Companion Diagnostic for CDK4 inhibitors-14/854,329 pending to Memorial Sloan Kettering Cancer Center/Sloan Kettering Institute; a patent Enigma and CDH18 as Companion Diagnostics for CKD4 inhibition-SKI2016-021-03 pending to Memorial Sloan Kettering Cancer Center/Sloan Kettering Institute; participation on the scientific advisory boards for Certis Oncology Solutions and Innova Therapeutics; stock ownership in Certis Oncology Solutions and Atropos Therapeutics; and is cofounder of Atropos Therapeutics. H.G. reports research compensation to his institution (Leiden University Medical Center) from Daiichi Sankyo. A.J.W. reports grants for research from Aadi Bioscience, Daiichi Sankyo, Deciphera, Eli Lilly, Karyopharma, and Plexxikon outside the submitted work and served on advisory boards for Daiichi Sankyo, Deciphera, Eli Lilly, and Mundipharma outside the submitted work. J.H.H. reports personal fees for consulting from Daiichi Sankyo outside the submitted work. J.G. reports employment with Daiichi Sankyo. D.S. reports employment with and stock ownership in Daiichi Sankyo during the conduct of the study and outside the submitted work and stock

ownership in Amgen, Bristol Myers Squibb, Exelixis, Merck, Pfizer, and Regeneron outside the submitted work. S.S. reports personal fees for consulting from Bayer, Bavarian Nordic, Deciphera, Eli Lilly, Epizyme Inc, Daiichi Sankyo, Karyopharm, Immune Design, Intellisphere, Maxivax, PharmaMar, and Takeda outside the submitted work; research funding to her institution from Amgen Dompé, Advenchen, Bayer, Bavarian Nordic, Blueprint, Deciphera, Eli Lilly, Epizyme Inc, Daiichi Sankyo, Karyopharm, Novartis, Pfizer, and PharmaMar outside the submitted work; travel coverage from PharmaMar outside the submitted work; and honoraria from Eli Lilly and PharmaMar outside the submitted work. No other conflicts of interest were reported. As an Associate Editor of *CPT: Pharmacometrics & Systems Pharmacology*, Jonathan French was not involved in the review or decision process for this article.

AUTHOR CONTRIBUTIONS

O.Y., H.Z., J.F., D.P., X.W., M.v.d.S., W.D.T., H.G., A.J.W., J.H.H., J.G., D.S., and S.S. wrote the manuscript. O.Y., H.Z., J.F., W.D.T., H.G., J.G., and D.S. designed the research. O.Y., D.P., M.v.d.S., W.D.T., A.J.W., and D.S. performed the research. O.Y., H.Z., J.F., D.P., X.W., W.D.T., A.J.W., J.H.H., J.G., D.S., and S.S. analyzed the data.

DATA AVAILABILITY STATEMENT

Deidentified individual participant data and applicable supporting clinical trial documents may be available upon request at <https://www.clinicalstudydatarequest.com>. In cases where clinical trial data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo, Inc., will continue to protect the privacy of our clinical trial participants. Details on data sharing criteria and the procedure for requesting access can be found at this web address: <https://www.clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-DS.aspx>.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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