# Population pharmacokinetic-pharmacodynamic analysis of elafibranor and metabolite GFT1007 to support exposure-response characterization and dose selection in patients with primary biliary cholangitis

I-004

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## Background

- Elafibranor is a dual peroxisome proliferator-activated receptor α/δ agonist.
- It is an orally administered, liver-targeted drug candidate developed for the treatment of primary biliary cholangitis (PBC), which is a rare, chronic cholestatic liver disease.

## Objective

**To provide dose justification and inform on the elafibranor efficacy in patients with PBC, by describing the relationship between elafibranor and GFT1007 exposure, and ALP and TBIL response.**

## Methods

- Patients with PBC received oral doses of elafibranor (80 mg/day or 120 mg/day) or placebo for up to 12 weeks (GFT505B-216-1) or 52 weeks (GFT505B-319-1).
- Equipotency between elafibranor and the main metabolite (GFT1007) was assumed from in-vitro data.
- $AUC_{\tau,ss\ sum}$ was predicted using individual PK parameter estimates from a previous PK analysis (PAGE poster IV-050[1]) and was used as driver for drug effects.
- The influence of covariates was evaluated using the stepwise covariate model building procedure and visualized using Forest plots. Clinical relevance was defined as an effect outside of the 0.8 to 1.25-fold interval.

## Results

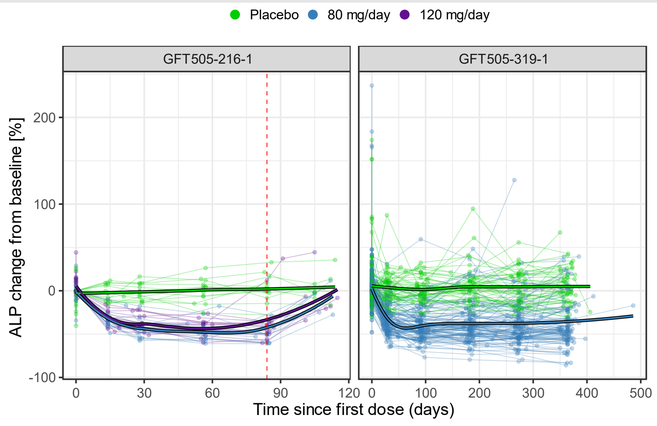
- Data from 206 adult patients with PBC were included and a total of 1892 and 1693 plasma concentrations of ALP (Figure 1) and TBIL (Figure 2) were evaluated, respectively.
- An indirect response PD model with $AUC_{\tau,ss\ sum}$ as PK driver inhibiting the $k_{in}$ was used to describe the delay in the placebo and drug effects on ALP (Figure 3) and TBIL (Figure 4).
- An $E_{max}$ model and a linear model were used to describe the drug effects on ALP and TBIL, respectively.
- The final joint ALP-TBIL model consisted of the structure of the final ALP model, the structure of the final TBIL model, and an IIV correlation between the baselines of ALP and TBIL.
- Based on the Forest plot (Figure 5), patients with mild to moderate hepatic impairment by NCI-ODWG classification had approximately 30% higher baseline ALP concentrations compared to patients with no hepatic impairment. No clinically relevant effect was identified for the other covariates.
- Saturation in ALP response was observed for $AUC_{\tau,ss\ sum}$ of approximately >30 µmol·h/L (Figure 6), showing that the 80 mg/day dose is efficacious.
- The 80 mg/day regimen showed a clear effect compared to placebo (Figure 6):
  - 53% simulated patients achieved ALP <1.67 times the ULN, 91% achieved a relative ALP decrease from baseline of at least 15%, and 97% had TBIL ≤ULN at week 52.

## CONCLUSIONS

- The proposed dose of 80 mg/day was considered to be the lowest efficacious dose in the treatment of PBC in adult patients.

## ALP

**Figure 1.** Individual observed ALP change from baseline versus time since first dose




The thick lines represent the LOESS fit. The red vertical dashed line marks the end of the treatment period in study GFT505B-216-1.

## TBIL

**Figure 2.** Individual observed TBIL change from baseline versus time since first dose

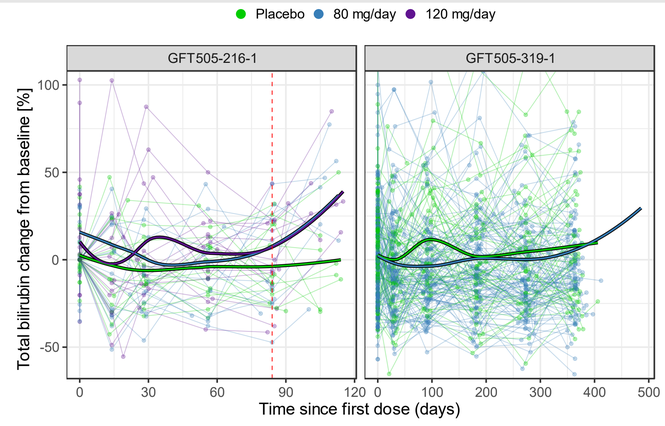



**Figure 3.** Schematic of the ALP model without covariate effects

$$Effect_{Elafibranor} = 1 + \frac{Emax \cdot AUC_{\tau,ss,sum}}{AUC_{\tau,ss,sum,50} + AUC_{\tau,ss,sum}}$$

$$Effect_{Placebo} = \begin{cases} 1 & if\ time \le 0 \\ Placebo\ effect & if\ time > 0 \end{cases}$$

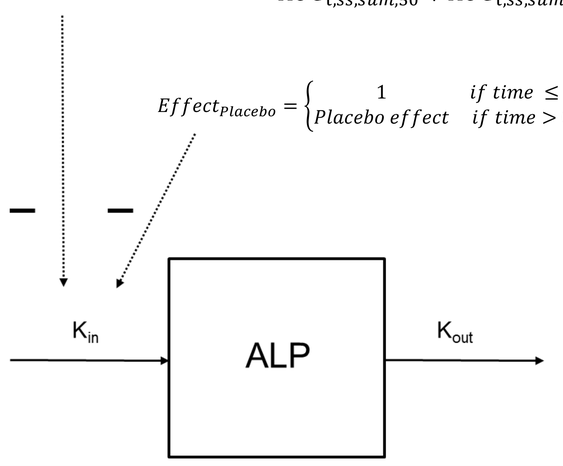



**Figure 4.** Schematic of the TBIL model without covariate effects

$$Effect_{Elafibranor} = 1 + Slope \cdot (AUC_{\tau,ss,sum})$$

$$Effect_{Placebo} = \begin{cases} 1 & if\ time \le 0 \\ Placebo\ effect & if\ time > 0 \end{cases}$$

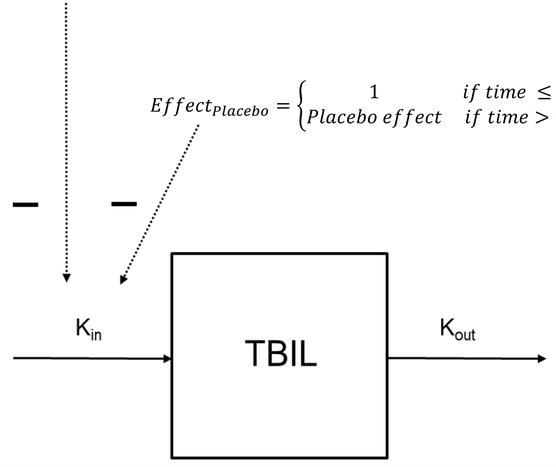
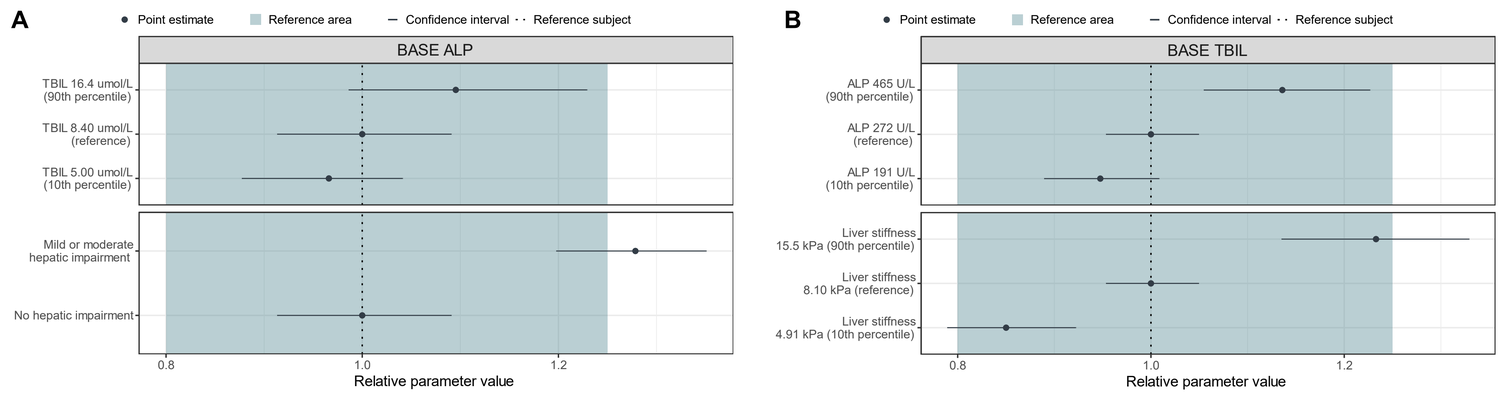
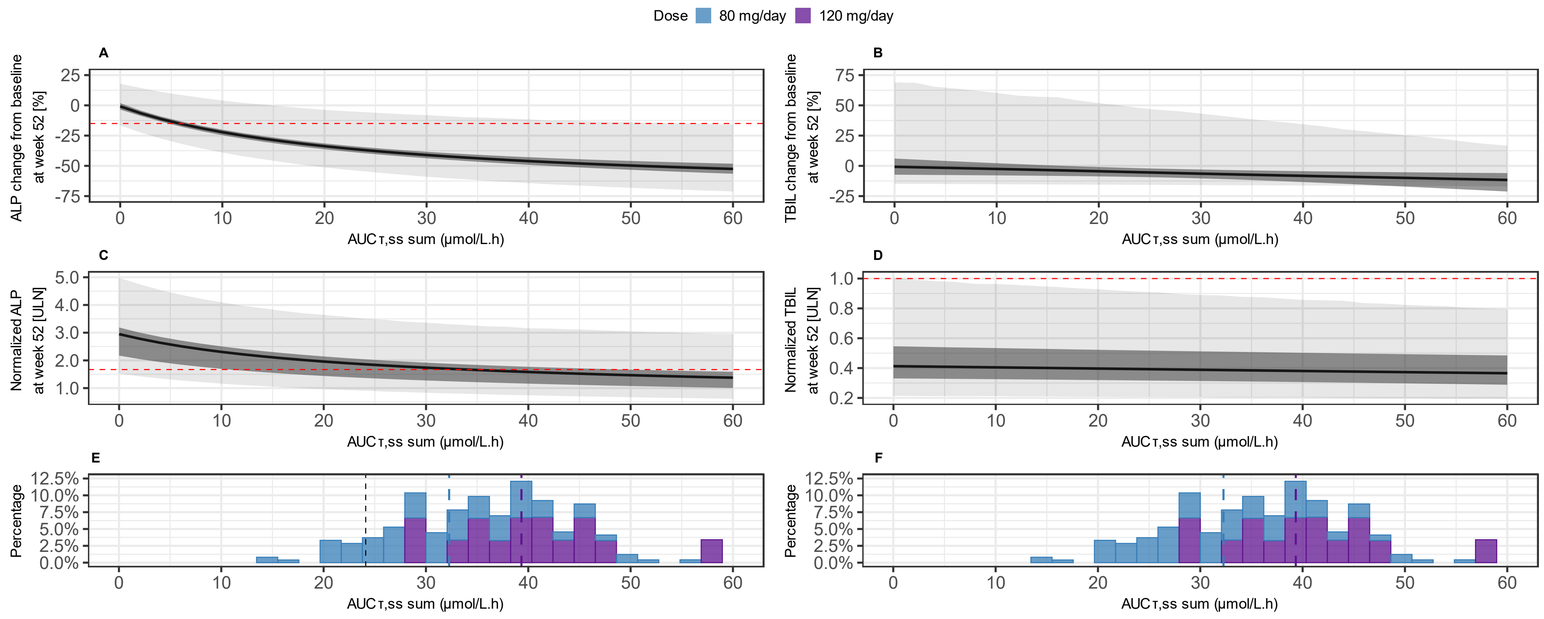



**Figure 5.** Effects of covariates on baseline (**A**) ALP and (**B**) TBIL in patients with PBC




The Forest plots are conditioned on a typical reference patient, based on the final separate ALP and TBIL models. Closed dots and error bars represent the median of the predicted relative change from the reference patient and its associated 90% confidence interval; these values are calculated based on 250 sampled parameter vectors from the variance-covariance matrix obtained from NONMEM. The parameter values for a reference patient are shown by the dashed vertical lines; the blue bands indicate the 80%-125% margins relative to the reference patient. The reference patient was a patient without hepatic impairment, TBIL of 8.40 µmol/L, liver stiffness of 8.10 kPa, and ALP of 272 U/L at baseline.

**Figure 6.** Relative ALP change from baseline (**A**), normalized ALP (**C**), relative TBIL change from baseline (**B**) and normalized TBIL (**D**) at week 52 versus the $AUC_{\tau,ss\ sum}$. The distribution of the $AUC_{\tau,ss\ sum}$ is also shown for the full resampled data set (**E,F**)




Based on a simulation of 100,000 typical parameter sets with uncertainty but without IIV (median and 90% confidence interval depicted by black lines and dark gray ribbons respectively) and the simulation of 100,000 virtual patients including IIV (90% prediction interval depicted by light gray ribbons). The red dashed lines represent the thresholds for the relative ALP change from baseline at -15% (A), normalized ALP at 1.67·ULN (C) and normalized TBIL at ULN (D). The black dashed line (E) represents the $AUC_{\tau,ss\ sum,50}$ , and the blue and violet dashed lines represent the median of the $AUC_{\tau,ss\ sum}$ in the 80 mg/day and 120 mg/day treatment groups, respectively (32.3 µmol·h/L for the 80 mg/day group and 39.3 µmol·h/L for the 120 mg/day group).

**Abbreviations** **ALP**: alkaline phosphatase; **$AUC_{\tau,ss\ sum}$**: sum of the areas under the concentration-time curve during a dosing interval at steady state of elafibranor and GFT1007; **$AUC_{\tau,ss\ sum,50}$**: $AUC_{\tau,ss\ sum}$ at half maximum effect; **$E_{max}$**: maximum effect; **IIV**: interindividual variability; **$k_{in}$**: zero-order production rate constant; **LOESS**: locally estimated scatterplot smoothing; **NCI-ODWG**: National Cancer Institute – Organ Dysfunction Working Group; **PBC**: primary biliary cholangitis; **PD**: pharmacodynamic(s); **PK**: pharmacokinetic(s); **TBIL**: total bilirubin; **ULN**: upper limit of normal.

**References** 1. PAGE 32 (2024) Abstr 11117 [www.page-meeting.org/?abstract=11117]

**Author Contributions** Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: **All authors**; Drafting of the publication, or reviewing it critically for important intellectual content: **All authors**; Final approval of the publication: **All authors**.

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