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

IV-050

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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 characterize the PK of elafibranor and its main active metabolite GFT1007, and to evaluate the impact of covariates.

Methods

- Separate population PK models for elafibranor and GFT1007 were developed in NONMEM based on 12,205 elafibranor and 10,592 GFT1007 samples from 894 adult participants originating from 13 Phase I studies, 2 Phase II studies, and 2 Phase III studies. The observed data is partly shown in **Figure 1**.
- 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.

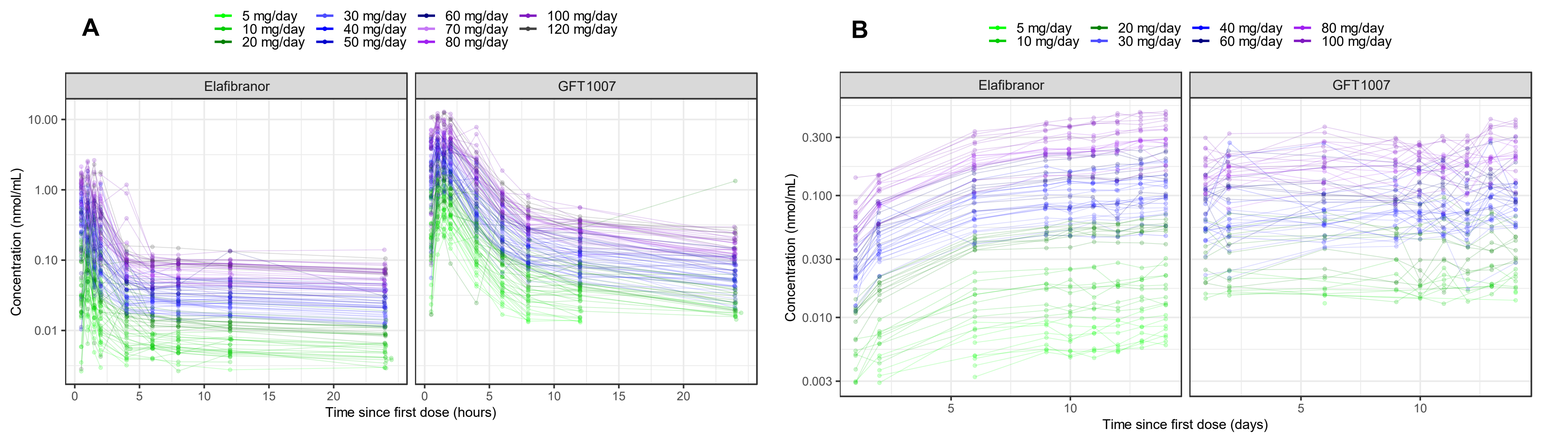
Results

- Elafibranor and GFT1007 are described by structurally similar models (**Figure 2**).
- The absorption of elafibranor and formation of GFT1007 was associated with large variability relative to the disposition process.
- A more than proportional decrease in elafibranor exposure is observed with doses below 50 mg/day.
- Limited GFT1007 formation is dependent on the systemic elimination of elafibranor:
  - GFT1007 elimination half-life (median 10.7 90% confidence interval [9.84, 11.9] hours) being much shorter than for elafibranor (59.7 [52.1, 67.3] hours).
  - GFT1007 having a much higher C_{max} (>7-fold of parent) and similar $T_{max,ss}$ compared to elafibranor, already after administration of the first dose (**Figure 1**).
  - Plateauing GFT1007 concentrations seem invariant to the continued increase in elafibranor concentrations over time (**Figure 1**).
- Following elafibranor administration at the proposed dose level of 80 mg, exposure to GFT1007 in patients with PBC is higher than the exposure to elafibranor (**Table 1**).
- The impact of identified covariates on elafibranor and GFT1007 PK is generally small (**Figure 3**).
  - The largest covariate effect is CRCL on GFT1007 $C_{min,ss}$, but its effect on $AUC_{T,ss}$ (used as driver in PKPD modeling presented on PAGE poster I-004[1]) is limited.

CONCLUSIONS

- For the proposed dose of 80 mg/day, the absorption and disposition of elafibranor and GFT1007 is expected to be linear.
- The parent-metabolite dynamics showed that only limited GFT1007 formation is dependent on the systemic elimination of elafibranor.
- The PD effect is likely to be driven more by GFT1007 than by elafibranor under the assumption of equipotency.
- No clinically relevant covariate effects on $AUC_{T,SS}$ were found.

Figure 1. Observed (**A**) concentrations and (**B**) trough concentrations versus time since first dose



Observed concentrations up to 25 hours since first dose are shown for the healthy participants in the elafibranor and GFT1007 analysis data set receiving formulation 1 in a fasted state.

Observed trough concentrations are shown for the healthy participants in the elafibranor and GFT1007 analysis data set receiving repeated doses of formulation 1 in a fasted state and with concentrations analyzed without separation of the interfering peak (elafibranor only) and without addition of formic acid (elafibranor only).

Figure 2. Model schematic of the elafibranor and GFT1007 PK models without covariate effects

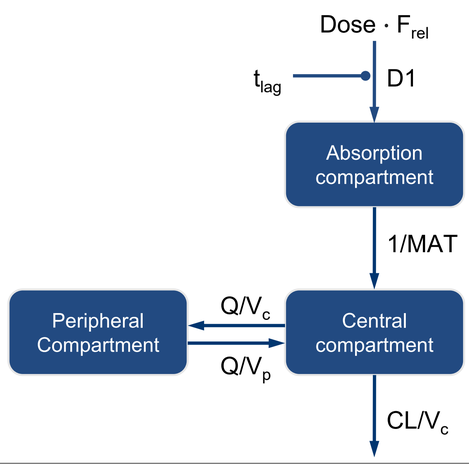
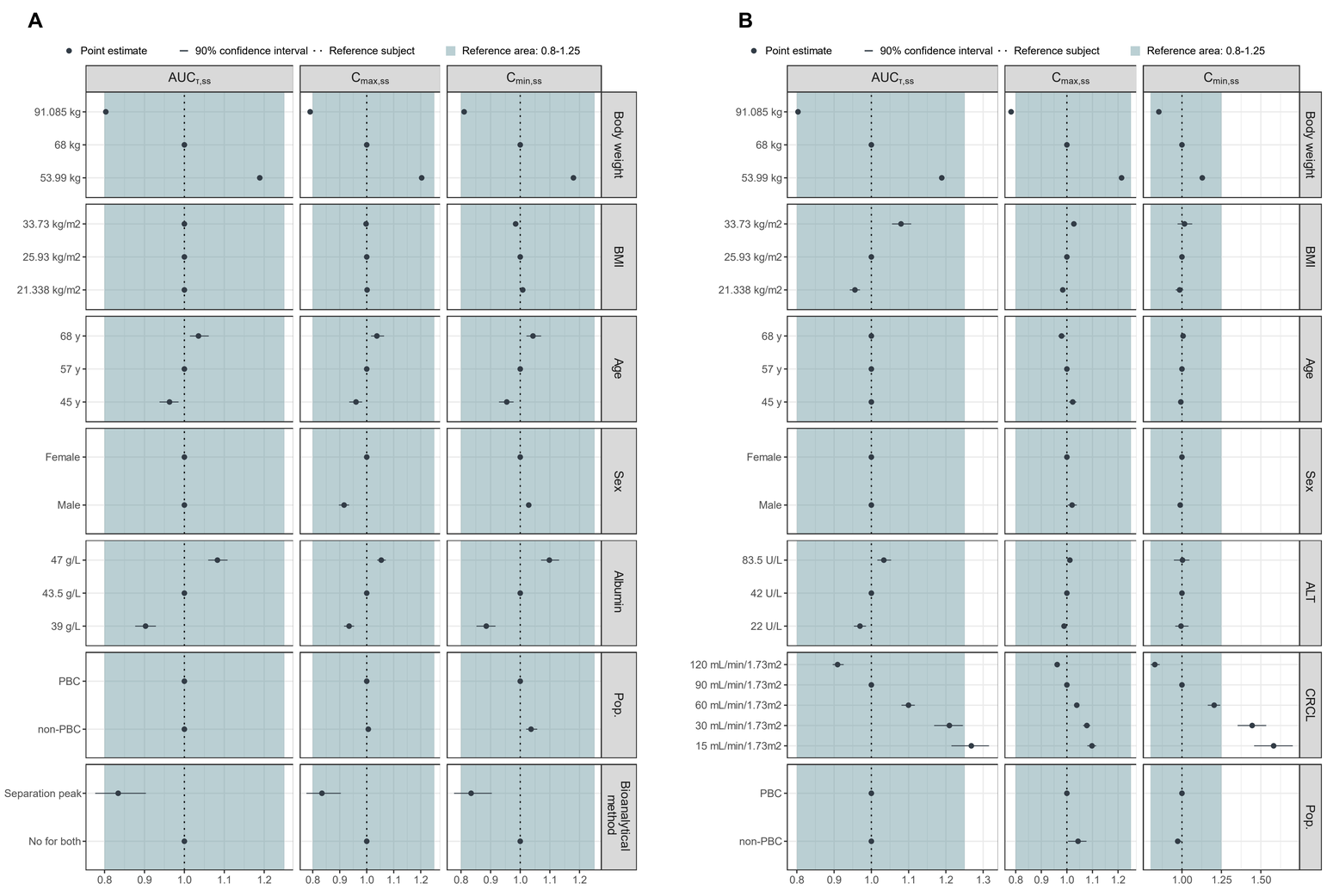


Table 1. Simulated secondary PK parameters of elafibranor and GFT1007 at steady state after daily administration of elafibranor 80 mg in patients with PBC

Parameter (unit)	Parent, median (90% PI)	Metabolite, median (90% PI)
$AUC_{T,ss}$ (nmol/mL*h)	4.11 (1.96-7.89)	20.8 (11.8-36.8)
$C_{max,ss}$ (nmol/mL)	0.557 (0.227-1.40)	4.08 (1.97-7.86)
$T_{max,ss}$ (h)	0.841 (0.366-2.96)	1.42 (0.834-4.70)
$C_{min,ss}$ (nmol/mL)	0.120 (0.0525-0.261)	0.196 (0.0702-0.430)

Figure 3. Effects of covariates on (**A**) elafibranor and (**B**) GFT1007 secondary PK parameters in patients with PBC



The forest plots are conditioned on a typical PBC reference patient, based on the elafibranor and GFT1007 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 200 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 female patient with PBC with elafibranor formulation 5 administered under fasted condition with body weight of 68 kg, BMI of 25.93 kg/m^2, age of 57 years, albumin of 43.5 g/L, ALT of 42 g/L, and CRCL of 90 mL/min/1.73m^2 at baseline.

Abbreviations **ALT**: alanine aminotransferase; **$AUC_{T,ss}$**: area under the concentration-time curve during a dosing interval at steady state; **BMI**: body mass index; **CL**: clearance; **$C_{max,ss}$**: maximum concentration during a dosing interval at steady state; **$C_{min,ss}$**: minimum concentration during a dosing interval at steady state; **CRCL**: creatinine clearance; **D1**: duration of zero order input; **F_{rel}**: relative bioavailability; **MAT**: mean absorption time; **PBC**: primary biliary cholangitis; **PD**: pharmacodynamic(s); **PK**: pharmacokinetic(s); **Q**: inter-compartemental clearance; **t_{lag}**: lag time; **$T_{max,ss}$**: time at maximum concentration during a dosing interval at steady state; **V_c/V_p**: central/peripheral volume of distribution.

References 1. PAGE 32 (2024) Abstr 11090 [www.page-meeting.org/?abstract=11090]

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

Disclosures **SvB**, **QXO**: employees of Pharmetheus; **KB**, **MD**: employees of Ipsen.

Acknowledgements The authors thank all participants involved in the studies as well as the investigators and research staff in participating institutions.

Medical Writing Support The authors thank Shimaila Siddiqui of Costello Medical, Manchester, UK, for editorial support, which were sponsored by Ipsen in accordance with Good Publication Practice Guidelines.

Presented at the PAGE meeting | Rome, Italy | 26-28 June 2024

The conduct of included studies was sponsored by GENFIT; this analysis and publication development was sponsored by Ipsen.