Assessment of the pharmacokinetic drug-drug interaction potential of elafibranor with atorvastatin in healthy adult male participants: An open-label phase I trial

Anna Pedret-Dunn,[1] Sarah Mazain,[2] Richard Allan,[1] Rémy Hanf,[3] Carol Addy[4]

[1]Ipsen, London, UK; [2]Ipsen, Boulogne-Billancourt, France; [3]GENFIT S.A., Loos, France; [4]GENFIT Corp., Cambridge, MA, USA

Background

- Elafibranor, a dual peroxisome proliferator-activated receptor-alpha/delta agonist, is under investigation as a treatment for primary biliary cholangitis (PBC).
  - In the phase III ELATIVE trial (NCT04526665), treatment with elafibranor resulted in significantly greater improvements in biochemical indicators of cholestasis than placebo and was well tolerated.[1]
- In vitro studies have demonstrated that elafibranor and its major active metabolite, GFT1007, inhibit organic anion transporter polypeptide (OATP) 1B3.
- Atorvastatin is a known clinical substrate of OATP1B3, OATP1B1 and cytochrome P450 3A (CYP3A).[2,3]

Objective

This phase I trial aimed to evaluate:

- **The effect of elafibranor as a perpetrator on the pharmacokinetic (PK) parameters of atorvastatin.**
- **The safety of elafibranor and atorvastatin co-administration.**

Methods

- In this phase I, open-label trial (EudraCT: 2015-000723-88), healthy participants received single doses of atorvastatin 40 mg (Days 1 and 17) and once-daily doses of elafibranor 180 mg (Days 4–19) under fasting conditions (Figure 1).
- Pharmacokinetic (PK) parameters derived for each treatment included observed maximum plasma concentration (C_{max}), area under the plasma concentration curve from administration up to the last quantifiable concentration at 72 hours (AUC_{72h}), area under the plasma concentration curve from administration up to infinity with extrapolation of the terminal phase (AUC_{∞}), time to reach C_{max} (t_{max}), and plasma concentration half-life ($t_{1/2}$).
- PK parameters were analyzed using an analysis of variance model.
- Adverse events (AEs) were recorded according to MedDRA (version 18.0).

Results

- 25 participants entered the study and 24 participants completed the trial.
- PK analyses were performed using data from the 24 participants that completed the trial; baseline demographics are shown in Table 1.

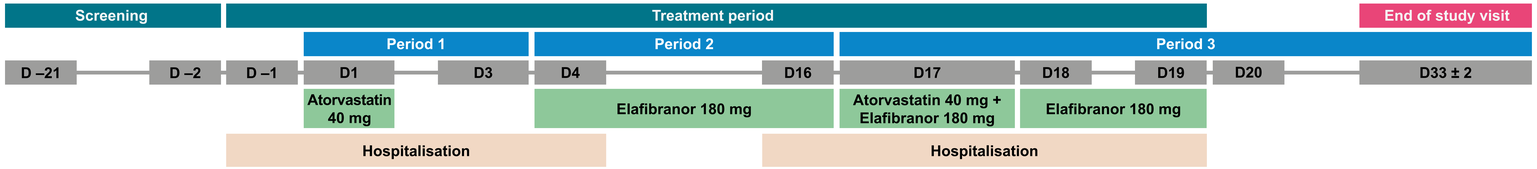
PK Parameters and Drug-Drug Interactions (DDIs)

- PK parameters for administration of atorvastatin alone or in combination with elafibranor are presented in Table 2.
  - There was no increase in the overall exposure of atorvastatin when co-administered with elafibranor.
  - Compared with atorvastatin administration alone, a 28% reduction in C_{max} was observed following co-administration of atorvastatin with elafibranor, while t_{max} increased from 0.67 to 1.00 hours.
  - There was a small decrease in AUC_{72h} following co-administration; however, confidence intervals indicated similarity between the treatment regimens.
- Overall, the observed differences between the treatment regimens were not deemed clinically significant.

Safety

- Treatment-emergent AEs (TEAEs) related to atorvastatin and elafibranor are presented in Table 3.
  - Among the 25 participants included in the safety set, a total of 16 non-serious and mild to moderate TEAEs were reported by 11 participants; all were resolved without treatment discontinuation except one unrelated event of renal colic.

Figure 1. Study design



Hospitalisation was required for 8 days from Day 1 to the morning of Day 4, as well as from the evening of Day 16 through to the morning of Day 19. Ambulatory visits occurred on Days 5–16, Day 20 and Day 33.

Table 1. Baseline demographics of the PK population

	Total (N=24)
Male sex – n (%)	24 (100.0)
Age – years, median (range)	33.5 (19–45)
BMI – kg/m^2, median (range)	24.8 (20.1–28.1)
White race – n (%)	24 (100.0)

Table 2. PK parameters for atorvastatin alone or in combination with elafibranor

	Atorvastatin[a] (Day 1; N=24)	Atorvastatin + elafibranor[b] (Day 17; N=24)	Point estimate (90% CI), %
C_{max} – ng/mL	19.7 (11.0)	14.8 (11.4)	72 (60.1, 87.2)
AUC_{72h} – ng/mL*h	81.3 (42.1)	75.0 (51.5)	88 (82.2, 93.3)
AUC_{∞} – ng/mL*h	86.3 (42.9)	80.6 (51.8)	–
t_{max} – h, median (range)	0.67 (0.50–3.00)	1.00 (0.67–4.50)	–
$t_{½}$ – h	9.64 (2.18)	10.7 (3.30)	–

Data are presented as mean (standard deviation), unless stated otherwise. [a]Administration of single dose atorvastatin 40 mg alone; [b]Administration of single dose atorvastatin 40 mg following once daily doses of elafibranor 180 mg for 14 days.

Table 3. TEAEs by System Organ Class, Preferred Term and study period

	Period 1 (n=25)[a]	Period 2 (n=25)[b]	Period 3 (n=24)[c]	All periods (N=25)
	n (%)	n (%)	n (%)	n (%)
At least one TEAE	2 (8.0)	9 (36.0)	3 (12.5)	11 (44.0)
Gastrointestinal disorders	–	7 (28.0)	–	7 (28.0)
Abdominal pain	–	2 (8.0)	–	2 (8.0)
Dyspepsia	–	1 (4.0)	–	1 (4.0)
Faeces soft	–	2 (8.0)	–	2 (8.0)
Mouth ulceration	–	1 (4.0)	–	1 (4.0)
Nausea	–	1 (4.0)	–	1 (4.0)
Infections and infestations	–	1 (4.0)	–	1 (4.0)
Pharyngitis	–	1 (4.0)	–	1 (4.0)
Investigations	–	–	2 (8.3)	2 (8.0)
ALT increased	–	–	1 (4.2)	1 (4.0)
Blood CPK increased	–	–	1 (4.2)	1 (4.0)
Musculoskeletal and connective tissue disorders	1 (4.0)	–	–	1 (4.0)
Back pain	1 (4.0)	–	–	1 (4.0)
Nervous system disorders	1 (4.0)	2 (8.0)	1 (4.2)	2 (8.0)
Headache	1 (4.0)	2 (8.0)	1 (4.2)	2 (8.0)
Renal and urinary disorders	–	1 (4.0)	–	1 (4.0)
Renal colic	–	1 (4.0)	–	1 (4.0)

n=Number of patients with at least one TEAE. [a]Participants received single dose atorvastatin on Day 1 and elafibranor on Day 4; [b]Participants received repeated elafibranor administration Day 4–17; [c]Participants received elafibranor and atorvastatin co-administered on Day 17, followed by administration of elafibranor Days 18–19; one patient withdrew from the study due to an adverse event.

CONCLUSIONS

- Co-administration of atorvastatin and elafibranor 180 mg had minimal impact on the overall exposure of atorvastatin.
- Therefore, co-administration of elafibranor 80 mg, the clinical dose for PBC, with OATP1B1, OATP1B3 and CYP3A substrates, such as other statins, is unlikely to cause clinically significant PK DDIs.
- Co-administration of atorvastatin and elafibranor was well tolerated.

Abbreviations **AUC_{∞}:** area under the plasma concentration-time curve from administration up to the last quantifiable concentration at time 72 hours; **AUC_{∞}**, area under the plasma concentration curve from administration up to infinity with extrapolation of the terminal phase; **BMI:** body mass index; **CI:** confidence interval; **C_{max}:** observed maximum plasma concentration; **CPK:** creatinine phosphokinase; **DDI:** drug-drug interaction; **OATP:** organic anion transporter polypeptide; **PBC:** primary biliary cholangitis; **PK:** pharmacokinetic; **$t_{1/2}$:** plasma concentration half-life; **TEAE:** treatment-emergent adverse event; **t_{max}:** time to reach C_{max}.

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