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Safety, Pharmacokinetics, and Pharmacodynamics of the Autotaxin Inhibitor GLPG1690 in Healthy Subjects: Phase 1 Randomized Trials

Ellen van der Aar, PhD[1], Julie Desrivot, PhD[2]*, Sonia Dupont, PhD[2], Bertrand Heckmann, PhD[2], Ann Fieuw, MD[1], Simone Stutvoet, PhD[1], Liesbeth Fagard, MSc[1], Karen Van de Wal, MSc[1], and Eric Helmer, PharmD, CHP[3]

Abstract

GLPG1690 is a novel autotaxin inhibitor in development for the treatment of idiopathic pulmonary fibrosis (IPF). We report phase 1 studies investigating the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of GLPG1690 in healthy subjects. We performed a first-in-human randomized, double-blind, placebo-controlled trial of single (20, 60, 150, 300, 600, 1000, 1500 mg) and multiple (14 days: 150 mg twice daily; 600 and 1000 mg once daily) ascending oral doses of GLPG1690 (NCT02179502), and a randomized, open-label, crossover relative bioavailability study to compare the PK of tablet and capsule formulations of GLPG1690 600 mg and to assess the effect of food on PK of the tablet formulation (NCT03143712). Forty and 13 subjects were randomized in the first-in-human and relative bioavailability studies, respectively. GLPG1690 was well tolerated, with no dose-limiting toxicity at all single and multiple doses. GLPG1690 was rapidly absorbed and eliminated, with a median t_{max} and mean $t_{1/2}$ of approximately 2 and 5 hours, respectively. GLPG1690 exposure increased with increasing dose (mean C_{max}, 0.09-19.01 μg/mL; mean $AUC_{0\text{-}inf}$, 0.501-168 μg·h/mL, following single doses of GLPG1690 20-1500 mg). PD response, evidenced by rapid reduction in plasma lysophosphatidic acid (LPA) C18:2 levels, increased with increasing GLPG1690 plasma levels, plateauing at approximately 80% reduction in LPA C18:2 at around 0.6 μg/mL GLPG1690. Tablet and capsule formulations had similar PK profiles, and no clinically significant food effect was observed when comparing tablets taken in fed and fasted states. The safety, tolerability, and PK/PD profiles of GLPG1690 support continued clinical development for IPF.

Keywords

drug-food interactions, clinical pharmacology, clinical trials, pharmacokinetics and drug metabolism, pharmacodynamics, pulmonary

Autotaxin is a key enzyme responsible for the production of lysophosphatidic acid (LPA), a bioactive lipid that regulates a range of cellular processes.[1] Autotaxin is widely expressed, with the highest mRNA levels found in adipose tissue, brain, testis, and ovary.[2] In the lungs, autotaxin is expressed in bronchial epithelial cells and alveolar macrophages and is upregulated in lung tissue from patients with idiopathic pulmonary fibrosis (IPF).[3] Correspondingly, LPA levels are elevated in the bronchoalveolar fluid and exhaled breath condensate of patients with IPF.[4] LPA has been implicated in pulmonary fibrosis through its effects on fibroblasts, promoting migration, proliferation, and survival.[5–7] Furthermore, deletion of autotaxin from bronchial epithelial cells or macrophages in a mouse bleomycin-induced pulmonary fibrosis model diminishes disease severity.[3]

IPF is a progressive, debilitating, fibrotic lung disease of unknown cause that is associated with significant morbidity and mortality; the median survival time is just 2-5 years postdiagnosis.[8–10] The only treatment options currently available for IPF are pirfenidone and nintedanib, which have been shown to slow deterioration of lung function.[11–13] However, neither agent halts disease progression or improves lung function, and both are associated with tolerability issues.[12–17] Thus, there is an unmet need for novel therapeutic approaches for the treatment of IPF that are more effective and better tolerated than current treatments.

Because autotaxin is involved in the pathogenesis of lung fibrosis, autotaxin inhibition may confer clinical benefits in patients with IPF. GLPG1690

[1]Galapagos NV, Mechelen, Belgium
[2]Galapagos SASU, Romainville, France
[3]Galapagos Biotech Limited, Cambridge, United Kingdom

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Corresponding Author:
Eric Helmer, PharmD, CHP, Galapagos Biotech Limited, Salisbury House, Station Road, Cambridge, CB1 2LA, United Kingdom
Email: eric.helmer@glpg.com

*Current affiliation: Pierre Fabre Médicament, Toulouse, France

(2-[[2-ethyl-6-[4-[2-(3-hydroxyazetidin-1-yl)-2-oxoethyl] piperazin-1-yl]-8-methylimidazo[1,2-α]pyridin-3-yl]-(methyl)amino]-4-(4-fluorophenyl)thiazole-5-carbonitrile; compound code G451990; Supplemental Figure S1) is a first-in-class inhibitor of autotaxin being investigated as a novel therapy for IPF.[18] GLPG1690 selectively inhibits autotaxin, with ex vivo human plasma LPA release assays indicating a half maximal inhibitory concentration (IC_{50}) of approximately 100 nM.[19] In preclinical studies, GLPG1690 has demonstrated efficacy in a mouse bleomycin-induced pulmonary fibrosis model (therapeutic setting): GLPG1690 was superior to pirfenidone and similar to nintedanib in reducing the Ashcroft fibrotic score and collagen content.[19,20] Furthermore, a recent phase 2a study (FLORA study) in 23 patients with IPF demonstrated that GLPG1690 was well tolerated, reduced plasma LPA C18:2 levels, and stabilized forced vital capacity (FVC) after 12 weeks of treatment.[21]

This article presents data from the first-in-human study of GLPG1690, which aimed to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and multiple ascending oral doses of GLPG1690 in healthy subjects. The study also aimed to compare the PK of oral suspension and capsule formulations of GLPG1690. In addition, we present data from a relative bioavailability study in healthy subjects that aimed to further compare different formulations of GLPG1690 (comparing capsules, as used in the first-in-human and phase 2a [FLORA][21] studies, with tablets, as used in phase 3 studies) and the effect of food (for the tablet formulation) on the PK of GLPG1690.

Methods

Both the first-in-human and relative bioavailability studies were approved by the Ziekenhuisnetwerk Antwerpen Institutional Review Board at SGS Life Science Services (LSS) Clinical Pharmacology Unit in Antwerpen, Belgium. Both studies were conducted at this site in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All subjects provided written informed consent prior to enrollment.

Study Designs

Two phase 1 studies were conducted in healthy male subjects. The first-in-human study was a randomized, double-blind, placebo-controlled study of single and multiple ascending oral doses of GLPG1690 (ClinicalTrials.gov number NCT02179502). The primary objective of the study was to evaluate the safety and tolerability of single ascending doses (SADs) and multiple ascending doses (MADs) of GLPG1690 in healthy subjects; secondary objectives included evaluation of the PK and PD of GLPG1690 and comparison of the PK of oral suspension and capsule formulations of the drug.

The relative bioavailability study was a randomized, open-label crossover study to compare the relative bioavailability of tablet and capsule formulations of GLPG1690 (ClinicalTrials.gov number NCT03143712). The primary objectives of the study were to compare the PK of tablet and capsule formulations of GLPG1690 under fed conditions, and to evaluate the effect of food on the PK of GLPG1690 administered as a tablet; the secondary objective was to evaluate the safety and tolerability of GLPG1690.

Dose Selection Rationale. Dosing was determined on the basis of preclinical toxicology studies in rats and dogs (Galapagos data on file), which demonstrated a clear window between therapeutic efficacy and toxicity signals. The maximum recommended starting dose was determined to be around 400 mg (based on conversion of the no-observed-adverse-effect level from preclinical studies to a human equivalent dose, using a standard conversion paradigm and applying a 10-fold safety factor). However, to establish a starting dose that was not expected to exceed the minimum anticipated biological effect level, the starting dose for the first-in-human study was set at 20 mg, which was lower than the anticipated pharmacologically active dose based on available in vitro and in vivo pharmacology data.[20] Safety margins for the highest planned dose (1500 mg) were 6 (rat) and 11.5 (dog) based on predicted exposures corrected for plasma protein binding (>99% across all species[18]).

Although it is known that rodent models are not necessarily predictive of humans for food effect, preclinical studies showed no effect of food on the bioavailability of GLPG1690 in rodents (Galapagos data on file). Therefore, the potential impact of food on PK was expected to be negligible or minor; GLPG1690 was administered in a fed state during the first-in-human study to minimize inconvenience to volunteers. Therefore, the fed state also provided the reference state for evaluation of food effect in the relative bioavailability study.

First-in-Human Study. During the first-in-human study, GLPG1690 was administered as an oral suspension, which allowed for incremental dose increases (not restricted to multiples of the dose contained per capsule) or as oral hard-gelatin capsules (300-mg dose level only, for comparison between formulations, as the capsule formulation was used for the phase 2a study). Placebo was provided as a matching suspension or capsule. For both the SAD and MAD parts of the study, the screening visit took place within 21 to 2 days before administration of the first study drug, and

subjects returned for a follow-up visit 7-10 days after the last dose.

The SAD part of the study comprised 2 cohorts (A and B, n = 8 each). Subjects received sequentially increasing single oral doses of GLPG1690 after a standard breakfast in an alternating panel manner: cohort A received 20, 150, 600, and 1500 mg GLPG1690 as oral suspension (or matching placebo); and cohort B received 60, 300, and 1000 mg GLPG1690 as oral suspension and 300 mg GLPG1690 as capsules (or matching placebo). At each dose level, subjects were randomized to receive GLPG1690 or placebo in a 3:1 ratio, such that 6 subjects received GLPG1690 and 2 subjects received placebo; every subject who received placebo also received GLPG1690 at another dose level. Subjects were housed from the evening of day -1 to approximately 26 hours postdosing. An interval of at least 3 days was enforced between administrations of 2 dose levels, during which time a blinded interim analysis of safety and tolerability (and PK when available) was conducted before proceeding to the next dose level. Because of the alternating panel design (ascending doses alternating between cohorts A and B), there was an interval of at least 6 days between dose administrations for each subject.

The MAD part of the study comprised 3 cohorts (C, D, and E; n = 8 each). Subjects received escalating doses of a GLPG1690 oral suspension after a standard breakfast (and supper for twice-daily dosing): cohort C received GLPG1690 150 mg twice daily or placebo, cohort D received GLPG1690 600 mg once daily or placebo, and cohort E received GLPG1690 1000 mg once daily or placebo. Within a cohort, subjects were randomized to receive GLPG1690 or placebo in a 3:1 ratio. A dosing period of 14 days was used to provide adequate assessment of potential cumulative toxicity. Subjects were housed from the evening of day -1 to approximately 26 hours after the first dose and from the evening of day 13 to the morning of day 15. Administration of the study drug was performed daily (once or twice a day) at the clinical pharmacology unit by nurses/investigators/experts. Initiation of dosing was staggered between cohorts, with an interval of at least 6 days during which a blinded interim analysis of safety and tolerability was conducted; a higher dose was only initiated in the next cohort once the preceding dose level was judged to be safe and well tolerated.

Relative Bioavailability Study. In the relative bioavailability study, GLPG1690 was administered as oral hard-gelatin capsules or film-coated tablets. Two subjects each were randomized to 1 of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, CBA): treatment A was a single dose of GLPG1690 600 mg (3 × 200-mg capsules) administered in a fed state (30 minutes after the start of a high-fat, high-calorie breakfast); treatment B was a single dose of GLPG1690 600 mg (2 × 300-mg tablets) administered in a fed state; and treatment C was a single dose of GLPG1690 600 mg (2 × 300-mg tablets) administered in a fasted state.

The screening visit took place within 21 to 2 days before the first administration of the study drug, and subjects were housed from day -1 to approximately 24 hours postdosing. Administration of all treatments was separated by a washout period of at least 6 days.

Study Participants

Both the first-in-human and relative bioavailability studies enrolled healthy men aged 18-50 years with a body mass index of 18-30 kg/m^2. Subjects were nonsmokers who did not receive any medications at least 2 weeks prior to the first administration of the study drug. Exclusion criteria for both studies are detailed in Supplemental Table S1.

Randomization and Blinding

In both studies, subjects were assigned randomization numbers after they were confirmed to be eligible for participation. Allocation to a given treatment was described in a randomization list prepared by the Secure Data Office department of SGS LSS using SAS software (SAS Inc., Cary, North Carolina). In the first-in-human study, the subjects, clinical study staff, and sponsor were blinded to treatment. In the relative bioavailability study, treatment was open label.

Safety and Tolerability Assessments

Safety and tolerability were assessed by monitoring adverse events (AEs) throughout the studies. Additional safety assessments included clinical laboratory tests, vital signs, physical examination, and electrocardiogram (ECG); in the SAD part of the first-in-human study and the relative bioavailability study these were assessed at the screening visit, on the day of and day after administration of each study drug, and at the follow-up visit, whereas in the MAD part of the first-in-human study, they were assessed at the screening visit, on days 1, 2, 8, 14, and 15, and at the follow-up visit.

PK Assessments

In the SAD part of the first-in-human study and in the relative bioavailability study, blood samples for PK assessments were obtained predose and at multiple times on the day of administration of study drug, and 24 and 48 hours postdose. In the MAD part of the first-in-human study, blood samples for PK assessments were obtained on days 1-6, 8, and 14-16; on days 1 and 14, blood samples were obtained predose and at multiple time intervals throughout the day. Urine samples were obtained on days 1, 2, 14, and 15; on

days 1 and 14 subjects were required to collect all urine passed during the intervals 0-6, 6-12, and 12-24 hours postdose.

Concentrations of GLPG1690 in plasma and urine were measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. Prior to injection into the analytical system, extraction of GLPG1690 and its deuterated internal standard (GLPG1690-d8) from either 20 µL of urine or human Li-heparin plasma was performed by off-line solid-phase extraction with CUBCX1 100-mg cartridges (Screening Devices, Amersfoort, The Netherlands). The extract was then evaporated under a stream of nitrogen at 50°C. After reconstitution with 300 µL of a acetonitrile/purified water (25/75 v/v with 0.01% of NH_4OH) mixture, 10 µL of the reconstituted sample was injected into the chromatographic system. Chromatographic separation was performed on an XBridge C18 column (Waters, Zellik, Belgium) set at 40°C using a Prominence high-performance liquid chromatography system (Shimadzu, Kyoto, Japan) in isocratic elution mode. The aqueous mobile phase consisted of 46.75% acetonitrile in purified water containing 0.02% NH_4OH. An API 4000 tandem mass spectrometer (AB Sciex, Nieuwerkerk aan den Ijssel, The Netherlands) equipped with a TurboIonSpray probe operated in the multiple reaction monitoring in positive mode was used for quantification. The precursor-to-product ion pairs at the mass-to-charge ratio (m/z) were 589 to 256 and 597 to 264 for GLPG1690 and GLPG1690-d8, respectively. The calibration curves were linear over the range of 1-1000 ng/mL for both urine and plasma samples with $1/x^2$ as the weighting factor. The limit of quantification of the assays for the plasma and urine samples was set at 1 ng/mL. Precision and accuracy for the determination of GLPG1690 in human plasma and urine complied with acceptable criteria (Supplemental Table S2).

PK calculations were performed using Phoenix WinNonlin 6.2 or higher (Pharsight Corporation, Palo Alto, California). The PK parameters determined for GLPG1690 included the maximum observed plasma concentration (C_{max}), the time of occurrence of C_{max} (t_{max}), the plasma concentration observed 24 hours postdose ($C_{24\,h}$), the trough plasma concentration observed at the end of the dosing interval (ie, 12 or 24 hours for twice-daily and once-daily dosing, respectively; C_τ), area under the plasma drug concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$), area under the plasma drug concentration-time curve over the dosing interval (ie, 12 or 24 hours for twice-daily and once-daily dosing, respectively; AUC_τ), area under the plasma drug concentration-time curve over 24 hours ($AUC_{0\text{-}24}$), the first-order terminal half-life ($t_{1/2,\lambda z}$), average plasma concentration (C_{avg}), accumulation ratio (R_{ac}), renal clearance (CL_R), and amount excreted unchanged in urine (Ae_τ).

PD Assessments

PD assessment was based on the effects of GLPG1690 on levels of LPA C18:2, one of the major species of LPA found in human blood.[22] In the SAD part of the first-in-human study, blood samples for PD assessments were obtained predose, at multiple points on the day of study drug administration, and 24 and 48 hours postdose. In the MAD part of the study, blood samples for PD assessments were obtained on days 1-3 and 14-16; on days 1 and 14, blood samples were obtained predose and at multiple points throughout the day.

LPA for target engagement was assessed in plasma (LPA C18:2) using a LC-MS/MS method, based on analyte over internal standard (LPA C17:0) peak area ratio using QTRAP 5500 (AB Sciex, Nieuwerkerk aan den Ijssel, The Netherlands; TurboIonSpray coupled with a Nexera ultra-high-performance liquid chromatograph [Shimadzu, Kyoto, Japan], electrospray ionization), analytical standard LPA C20:4 (Echelon Biosciences, Inc., Salt Lake City, Utah), and LPA C17:0 (Avanti Polar Lipids, Inc., Alabaster, Alabama), whereas LPA C18:2 was analyzed using a theoretical Q1 and common Q3 fragments. Plasma samples were thawed at 4°C. Then 50 µL samples were deproteinized by the addition of 600 µL cold (+4°C) protein precipitation solution containing internal standard (10 ng/mL LPA C17:0 in methanol) and vortex mixed for 15 seconds. Samples were then centrifuged at 19 060*g* for 15 minutes at 4°C; clear supernatants were transferred into 96-well plates, sealed, and submitted for LC-MS/MS analysis. Then 10 µL was injected into an Atlantis HILIC Silica 3 µm, 2.1 × 100 mm column (Waters, Zellik, Belgium) at 50°C and analyzed. The mobile phases, 50 mM ammonium formate in 0.2% formic acid (aqueous) and acetonitrile with 0.2% formic acid (organic, B), were used. The following gradient was applied with a constant flow rate of 0.4 mL/min: 90% B to 1.2 minutes, then gradient from 90% to 40% B in 2.49 minutes; from 2.51 to 4 minutes 100% B; and from 4.01 to 5 minutes 90% B. Total run time was 5 minutes. Specific multiple reaction monitoring transitions were monitored in electrospray ionization negative mode: 457 to 153, 433 to 153, and 423 to 153 for LPA C20:4, LPA C18:2, and LPA C17:0, respectively. Retention time for all LPA species was 2.96 minutes. LPA C20:4-based quality control samples at 3 concentrations (low, mid, high) were included in every analysis for validation of the run. Precision for the determination of LPA in human plasma was within ±15%.

Peak area and peak area ratios were calculated using Analyst 1.6 software (AB Sciex, Nieuwerkerk aan den Ijssel, The Netherlands). The effect of GLPG1690 on

LPA C18:2 was expressed as the percentage reduction versus baseline (percentage LPA C18:2 peak area ratio reduction from baseline). The maximum percentage reduction from baseline observed (E_{max}) was determined from individual effect time profiles on days 1 (SAD and MAD) and 14 (MAD only).

Statistical Analyses

In both studies, all subjects who were exposed to GLPG1690 and had evaluable data were included in the PK analysis, all subjects who received at least 1 dose of study drug excluding all major protocol violations were included in the PD analysis, and all subjects who received at least 1 dose of study drug were included in the safety analysis. Strict statistical criteria were not used to determine the sample size for each study; the number of subjects included gave a reasonable precision around the estimates derived for PK and PD evaluations.

In the first-in-human study, dose proportionality was assessed based on ln-transformed, dose-normalized PK parameters. In the SAD part, a mixed-effects analysis of variance (ANOVA) model (with cohort and dose as fixed effects and subject as random effect) was applied to C_{max}/dose, $C_{24\,h}$/dose, $AUC_{0\text{-}24}$/dose, and $t_{1/2,\lambda z}$, with pairwise comparisons between doses by Tukey's test. In the MAD part, a mixed-effects model, with subject as the random effect and day, dose, and dose × day interaction as fixed effects, was applied to C_{max}/dose, C_T/dose, AUC_T/dose, Ae%, CL_R, $t_{1/2,\lambda z}$, and C_{avg}/dose.

In the relative bioavailability study, comparisons between treatment groups were assessed on ln-transformed parameters by means of a mixed-effects model with subject (nested to sequence) as a random effect and treatment, period, and sequence as fixed effects. Point estimate was calculated as the geometric mean of the individual ratios of each parameter for the test/reference treatments and expressed as a percentage. The 90% confidence interval (CI) of the point estimate was calculated using the mean square error of the analysis of variance. As t_{max} is a discrete variable dependent on selected blood sampling times, comparisons were assessed using Friedman as the overall test and Hodges-Lehmann for the pairwise comparisons. Statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Subject Disposition and Demographics

The first-in-human study was conducted from June 3, 2014, to November 13, 2014. A total of 16 and 24 healthy subjects were randomized in the SAD and MAD parts of the study, respectively, and all randomized subjects completed the study (Supplemental Figure S2). Subjects enrolled in the SAD part of the study were all white men with a median age of 44 and 37 years for cohorts A and B, respectively (Table 1A). The median age of subjects enrolled in the MAD part of the study ranged from 33 to 43 years for the different dose groups, and the majority of subjects were white men (Table 1B).

Table 1. Subject Demographics in the First-in-Human Study for the (A) SAD and (B) MAD Study Populations

A

	Cohort A (n = 8)	Cohort B (n = 8)
Age, years		
Median (range)	44 (31-49)	37 (21-49)
BMI, kg/m^2		
Median (range)	26 (21-30)	24 (20-26)
Race, n (%)		
White	8 (100)	8 (100)
Sex		
Male, n (%)	8 (100)	8 (100)

B

	Pooled Placebo (n = 6)	GLPG1690 150 mg Twice Daily (n = 6)	GLPG1690 600 mg Once Daily (n = 6)	GLPG1690 1000 mg Once Daily (n = 6)
Age, years				
Median (range)	34 (28-45)	43 (37-49)	42 (28-49)	33 (24-46)
BMI, kg/m^2				
Median (range)	25 (24-27)	28 (22-30)	25 (23-28)	24 (22-28)
Race, n (%)				
White	6 (100)	6 (100)	5 (83)	6 (100)
Black	0	0	1 (17)	0
Sex, n (%)				
Male	6 (100)	6 (100)	6 (100)	6 (100)

BMI, body mass index; MAD, multiple ascending doses; SAD, single ascending doses.

The relative bioavailability study was conducted from April 18, 2017, to June 14, 2017. Initially, 12 healthy subjects were randomized, and 1 subject subsequently withdrew from the study after the first dosing period because of personal reasons; to replace this subject, 4 additional subjects were screened, of whom 1 was randomized. Thus, a total of 13 healthy subjects were randomized and received at least 1 dose of study drug, and 12 completed the study (Supplemental Figure S3). All randomized subjects were white men with a median age of 36 years (Supplemental Table S3).

Safety and Tolerability

First-in-Human Study. In the SAD part, a maximum of 2 subjects per dose group reported treatment-emergent adverse events (TEAEs); Table 2A. The most frequently reported TEAE following administration of

Table 2. Adverse Events in the First-in-Human Study for the (A) SAD and (B) MAD Study Populations

A

	Oral Suspension								Capsule	
Preferred Term, n (%)	Pooled Placebo (n = 14)	GLPG1690 20 mg (n = 6)	GLPG1690 60 mg (n = 6)	GLPG1690 150 mg (n = 6)	GLPG1690 300 mg (n = 6)	GLPG1690 600 mg (n = 6)	GLPG1690 1000 mg (n = 6)	GLPG1690 1500 mg (n = 6)	Placebo (n = 2)	GLPG1690 300 mg (n = 6)
Any TEAE	2 (14.3)	1 (16.7)	2 (33.3)	1 (16.7)	1 (16.7)	2 (33.3)	0	1 (16.7)	1 (50.0)	0
Headache	1 (7.1)	0	2 (33.3)	0	1 (16.7)	0	0	1 (16.7)	0	0
Oropharyngeal pain	0	0	0	0	0	2 (33.3)	0	0	0	0
Diarrhea	1 (7.1)	0	0	0	0	0	0	0	1 (50.0)	0
Nausea	0	1 (16.7)	0	0	0	0	0	0	0	0
Hematoma	0	0	0	1 (16.7)	0	0	0	0	0	0

B

Preferred Term, n (%)	Pooled Placebo (n = 6)	GLPG1690 150 mg Twice Daily (n = 6)	GLPG1690 600 mg Once Daily (n = 6)	GLPG1690 1000 mg Once Daily (n = 6)
Any TEAE	4 (66.7)	4 (66.7)	1 (16.7)	6 (100)
Headache	3 (50.0)	2 (33.3)	0	3 (50.0)
Diarrhea	1 (16.7)	3 (50.0)	1 (16.7)	0
Nasopharyngitis	0	1 (16.7)	0	3 (50.0)
Dry mouth	2 (33.3)	2 (33.3)	0	0
Abdominal pain	0	2 (33.3)	0	0
Pain	0	2 (33.3)	0	0
Nasal congestion	0	2 (33.3)	0	0
Conjunctival hyperemia	0	0	1 (16.7)	1 (16.7)
Nausea	1 (16.7)	1 (16.7)	0	0
Asthenia	1 (16.7)	1 (16.7)	0	0
Abdominal distension	0	1 (16.7)	0	0
Dyspepsia	0	1 (16.7)	0	0
Gastroesophageal reflux disease	0	1 (16.7)	0	0
Pharyngitis	0	1 (16.7)	0	0
Cough	0	1 (16.7)	0	0
Epistaxis	0	1 (16.7)	0	0
Decreased appetite	0	1 (16.7)	0	0
Gastroenteritis viral	0	0	0	1 (16.7)
Influenza-like illness	0	0	0	1 (16.7)
Hepatic enzyme increased	0	0	0	1 (16.7)
Back pain	0	0	0	1 (16.7)
Flatulence	1 (16.7)	0	0	0
Mouth ulcerations	1 (16.7)	0	0	0

MAD, multiple ascending doses; SAD, single ascending doses; TEAE, treatment-emergent adverse event.

GLPG1690 was headache (observed in 4 subjects), which were all considered at least possibly related to GLPG1690. No other TEAEs were considered to be treatment related.

In the MAD part of the study, a maximum of 6 subjects per group reported TEAEs (Table 2B). The most frequently reported TEAEs following administration of GLPG1690 were headache (observed in 5 subjects) and diarrhea and nasopharyngitis (both observed in 4 subjects); all cases of headache and diarrhea were considered at least possibly related to the study drug, whereas all cases of nasopharyngitis were considered unlikely to be related to the study drug.

Overall, the incidence of TEAEs did not increase with ascending GLPG1690 dose (Table 2A,B), all TEAEs were at most moderate in severity, and none of the TEAEs led to study drug discontinuation. There were no deaths or serious AEs during the study. ECGs, vital signs, and physical examinations did not reveal any clinically relevant abnormalities. One subject in the GLPG1690 1000-mg once-daily group had abnormally high aspartate aminotransferase (AST) levels (133 U/L [normal range, 9-59 U/L; baseline AST was 31 U/L]) on day 15, which was reported as an AE and considered possibly related to the study drug; a week later the AST level had returned to a normal level (51 U/L).

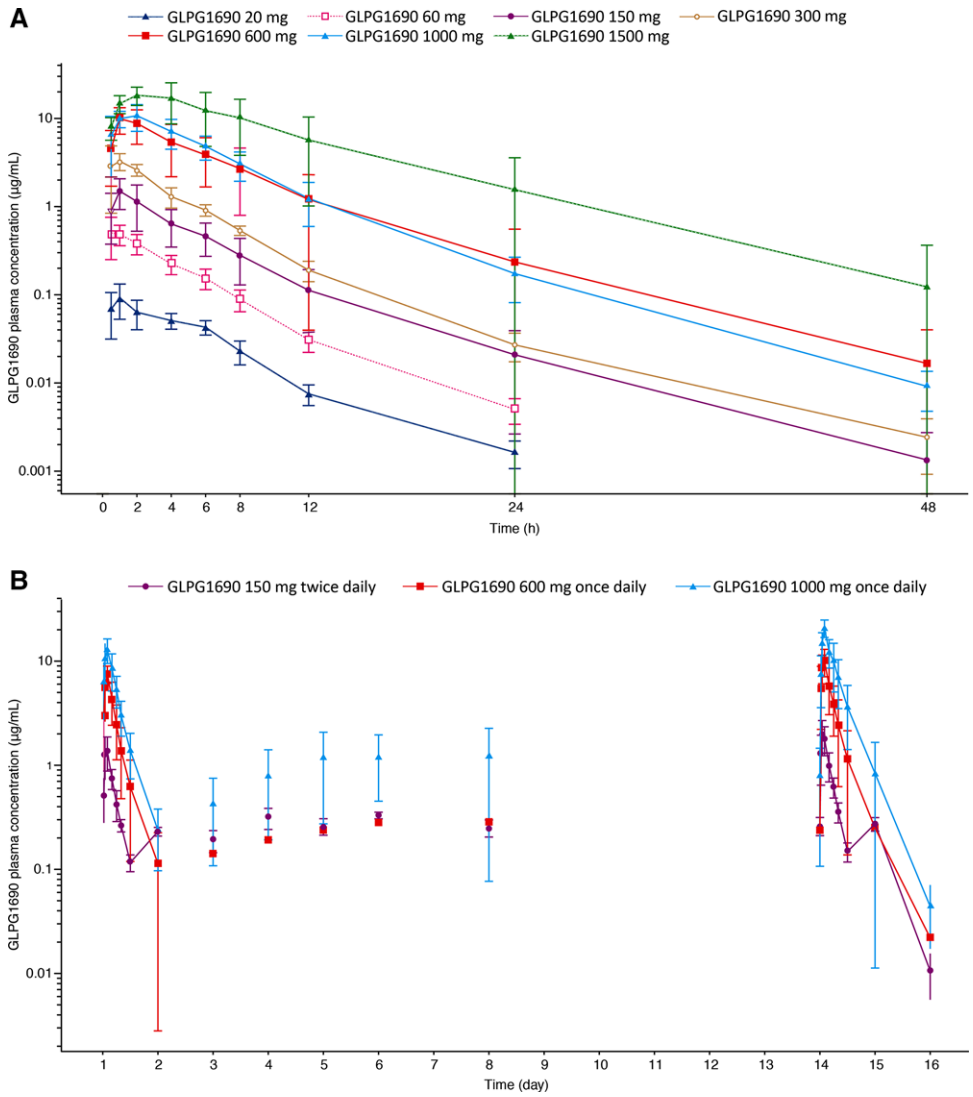

Figure 1. GLPG1690 plasma concentration-time profiles for the (A) SAD and (B) MAD study populations following administration of GLPG1690 (oral suspension). For the MAD part of the study, the last dosing day was day 14 (1 dose for GLPG1690 600 mg and 1000 mg once daily; 2 doses 12 hours apart for GLPG1690 150 mg twice daily). Data are mean ± SD. h, hour; MAD, multiple ascending doses; SAD, single ascending doses; SD, standard deviation.

Relative Bioavailability Study. In this study, a total of 3 TEAEs were reported (in 3 subjects): headache (mild), arthralgia (moderate), and rhinorrhea (mild); see Supplemental Table S4. None of the TEAEs were considered treatment related. There were no clinically relevant abnormalities in ECGs, vital signs, laboratory parameters, or physical examinations.

PK Profile

SAD (Oral Suspension). Mean ± SD GLPG1690 plasma concentration-time profiles (Figure 1A) and plasma exposure (C_{max} and $AUC_{0\text{-}inf}$; Table 3A) increased with increasing single doses. ANOVA indicated a significant dose effect on dose-normalized PK parameters; however, pairwise comparisons showed no clear dose ranking. This discrepancy could be because of the small number of subjects in the evaluation. GLPG1690 was rapidly absorbed, with a median t_{max} range of 0.5 to 2.0 hours, and rapidly eliminated, with an apparent mean terminal half-life of approximately 4-5 hours (Table 3A).

MAD (Oral Suspension). After 14 days of dosing, plasma exposure to GLPG1690 increased with increasing dose (Figure 1B; Table 3B), with no significant dose effect on dose-normalized C_{avg}, indicating minimal deviation from dose proportionality. The t_{max} was reached within 2.0 hours on day 1 and within 1.0-2.0 hours on day 14 (Table 3B). GLPG1690 was rapidly eliminated, with an apparent mean terminal half-life of approximately 5 hours (Table 3B).

Table 3. Summary of PK Parameters in the First-in-Human Study for the (A) SAD and (B) MAD Study Populations With GLPG1690 Administered as an Oral Suspension

A

PK Parameter	GLPG1690 20 mg (n = 6)	GLPG1690 60 mg (n = 6)	GLPG1690 150 mg (n = 6)	GLPG1690 300 mg (n = 6)	GLPG1690 600 mg (n = 6)	GLPG1690 1000 mg (n = 6)	GLPG1690 1500 mg (n = 6)
C_{max} (μg/mL)	0.09 (49.5)	0.58 (23.4)	1.43 (33.8)	3.79 (29.7)	9.80 (30.5)	11.79 (19.7)	19.01 (30.9)
t_{max} (h)	1.0 (0.5-1.0)	0.5 (0.5-2.0)	1.0 (1.0-1.0)	1.0 (0.5-2.0)	1.0 (1.0-2.0)	2.0 (0.5-2.0)	2.0 (1.0-4.0)
$AUC_{0\text{-}inf}$ (μg·h/mL)	0.501 (26.6)	2.38 (21.6)	6.71 (40.9)	14.9 (15.5)	53.5 (52.2)	66.0 (32.5)	168 (60.4)
$t_{1/2\lambda z}$ (h)	4.0 (6.6)	3.6 (6.9)	5.3 (27.1)	5.5 (26.9)	5.4 (9.4)	5.2 (10.6)	5.2 (21.5)

B

	GLPG1690 150 mg Twice Daily (n = 6)		GLPG1690 600 mg Once Daily (n = 6)		GLPG1690 1000 mg Once Daily (n = 6)	
PK Parameter	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
C_{max} (μg/mL)	1.42 (34.1)	2.05 (34.7)	8.15 (21.0)	10.59 (26.2)	13.24 (31.1)	20.69 (20.8)
C_{avg} (μg/mL)	0.53 (21.5)	0.75 (27.0)	1.53 (37.7)	2.28 (44.4)	2.98 (44.2)	5.48 (39.7)
t_{max} (h)	2.0 (1.0-2.0)	1.0 (0.5-2.0)	2.0 (1.0-2.0)	1.5 (0.5-2.0)	2.0 (1.0-2.0)	2.0 (1.0-2.0)
AUC_{τ}[a] (μg·h/mL)	6.37 (21.5)	9.04 (27.0)	36.7 (37.7)	54.6 (44.4)	71.4 (44.2)	132 (39.7)
$t_{1/2\lambda z}$ (h)	—	—	4.2 (15.2)	5.9 (13.9)	4.3 (12.2)	5.7 (5.8)
R_{ac}	—	1.42 (17.1)	—	1.49 (14.7)	—	1.84 (18.5)
Ae_{τ}[a] (% administered dose)	0.69 (28.6)	0.88 (16.5)	0.65 (27.8)	0.98 (29.3)	0.95 (39.2)[b]	1.69 (33.6)

Ae_{τ}, amount excreted unchanged in urine; $AUC_{0\text{-}inf}$, area under the plasma drug concentration-time curve from zero to infinity; AUC_{τ}, area under the plasma drug concentration-time curve over the dosing interval (ie, 12 or 24 hours for twice-daily and once-daily dosing, respectively); C_{avg}, average plasma concentration; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; MAD, multiple ascending doses; PK, pharmacokinetics; R_{ac}, accumulation ratio; SAD, single ascending doses; t_{max}, time of occurrence of C_{max}; $t_{1/2\lambda z}$, first-order terminal half-life.

Values are geometric mean (geometric CV%), except median (min–max) for t_{max}.

[a] T=12 hours for twice-daily treatment and 24 hours for once-daily treatment.

[b] n = 5.

Steady state was reached after the first dose of GLPG1690 for twice-daily dosing compared with after 4 doses for once-daily dosing. After 14 days of dosing, the accumulation ratio ranged from 1.42 for GLPG1690 150 mg twice daily to 1.84 for GLPG1690 1000 mg once daily (Table 3B). The excretion of unchanged GLPG1690 in urine was low (up to 0.95% of administered dose or less on day 1 and less than 1.69% on day 14; Table 3B).

PD Profile

SAD (Oral Suspension). A reduction in plasma LPA C18:2 levels from baseline was observed following administration of single doses of GLPG1690 compared with placebo, with higher doses resulting in a stronger and more sustained effect (Figure 2A). Reductions in LPA C18:2 levels occurred rapidly following administration of GLPG1690 (Figure 2A), with the greatest E_{max} observed with the 1500-mg dose (89.3%; Table 4A). LPA C18:2 had returned to baseline levels by 48 hours postdose for all doses.

MAD (Oral Suspension). Reductions in plasma LPA C18:2 levels from baseline compared with placebo on day 1 (Figure 2B) were maintained after multiple administrations of GLPG1690 on day 14 (Figure 2C), with the greatest E_{max} observed on day 14 with GLPG1690 1000 mg once daily (92.1%; Table 4B). On day 14, reductions in LPA C18:2 levels of at least 70% were observed predose for all doses. Reduced levels of LPA C18:2 levels were sustained over time, with 66.0%, 70.9%, and 83.6% reductions from baseline 12 hours postdose on day 14 for GLPG1690 150 mg twice daily, 600 mg once daily, and 1000 mg once daily, respectively. Reductions in LPA C18:2 were still observed 24 hours postdose on day 14 (65.8% and 85.7% for GLPG1690 600 mg once daily and 1000 mg once daily, respectively). Forty-eight hours postdose, LPA C18:2 had returned toward baseline levels.

PK/PD Correlation

The percentage reduction in plasma LPA C18:2 from baseline increased with increasing GLPG1690 plasma levels, plateauing at approximately 1 μM (0.6 μg/mL) GLPG1690 and 80% reduction in LPA C18:2 (Figure 3). The IC_{50} for GLPG1690 was estimated to be 118 nM (0.07 μg/mL).

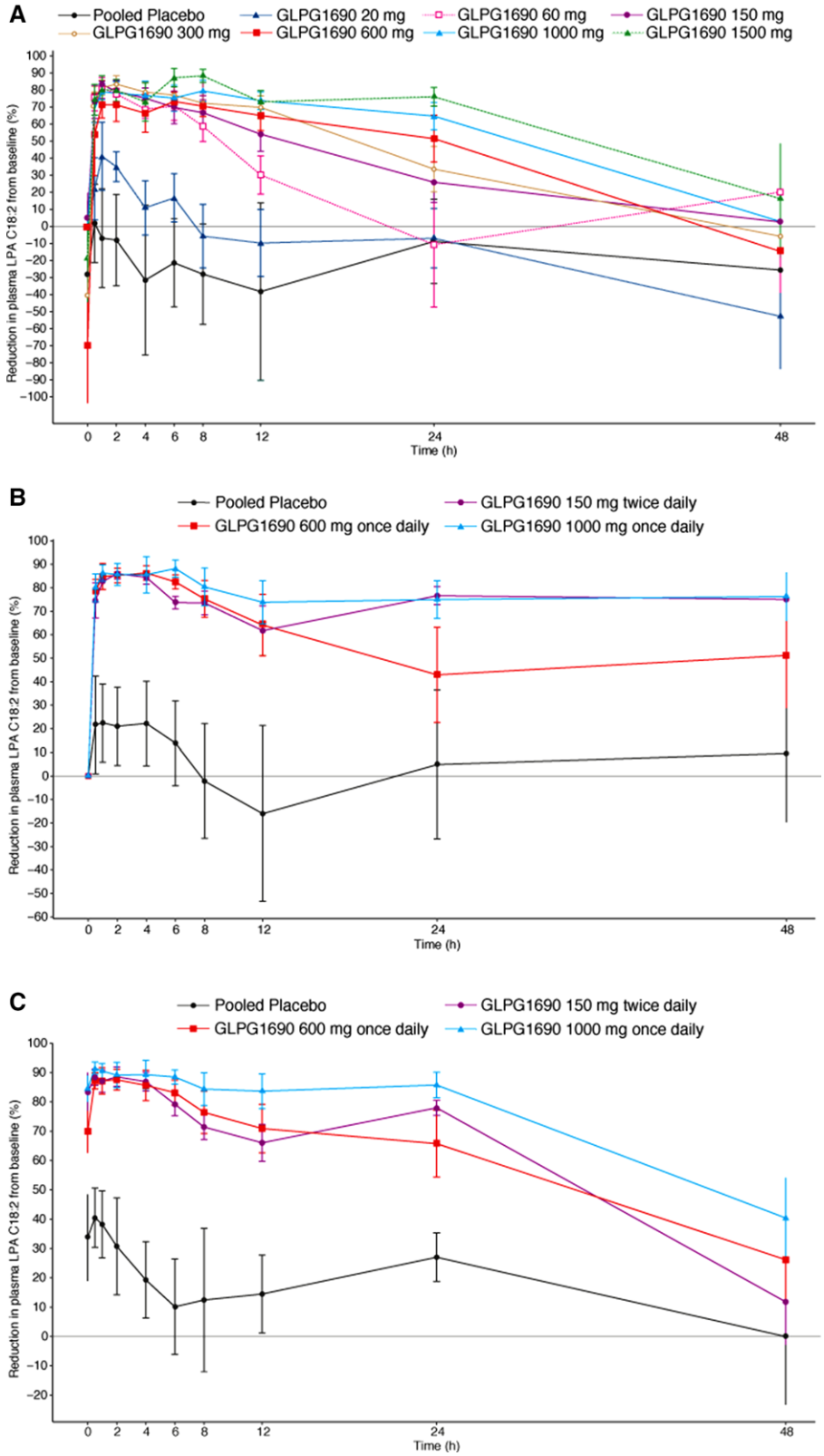

Figure 2. LPA C18:2 reduction from baseline for the (A) SAD population, (B) MAD population on day 1, and (C) MAD population on day 14 following administration of GLPG1690 (oral suspension) or placebo. Data are mean ± SD. h, hour; LPA, lysophosphatidic acid; MAD, multiple ascending doses; SAD, single ascending doses; SD, standard deviation.

Table 4. Summary of LPA C18:2 Percentage Reduction From Baseline in the First-in-Human Study for the (A) SAD and (B) MAD Study Populations With GLPG1690 Administered as an Oral Suspension

A

PD Parameter	Placebo (n = 14)[a]	GLPG1690 20 mg (n = 6)	GLPG1690 60 mg (n = 6)	GLPG1690 150 mg (n = 6)	GLPG1690 300 mg (n = 6)	GLPG1690 600 mg (n = 6)	GLPG1690 1000 mg (n = 6)	GLPG1690 1500 mg (n = 6)
E_{max} (%)	9.9 (21.6)	48.9 (6.3)	82.8 (4.5)	84.8 (2.3)	84.7 (5.1)	77.9 (3.3)	83.5 (2.8)	89.3 (3.7)

B

	Placebo (n = 6)[b]		GLPG1690 150 mg Twice Daily (n = 6)		GLPG1690 600 mg Once Daily (n = 6)		GLPG1690 1000 mg Once Daily (n = 6)	
PD Parameter	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
E_{max} (%)	31.9 (15.9)	42.2 (10.0)	86.8 (2.0)	89.6 (3.2)	87.4 (3.1)	88.9 (2.7)	88.8 (3.1)	92.1 (2.1)

E_{max}, maximum percentage reduction from baseline observed; MAD, multiple ascending doses; PD, pharmacodynamics; SAD, single ascending doses; SD, standard deviation.

Values are observed mean (SD).

[a]Pooled (cohorts A and B).

[b]Pooled (cohorts C, D, and E).

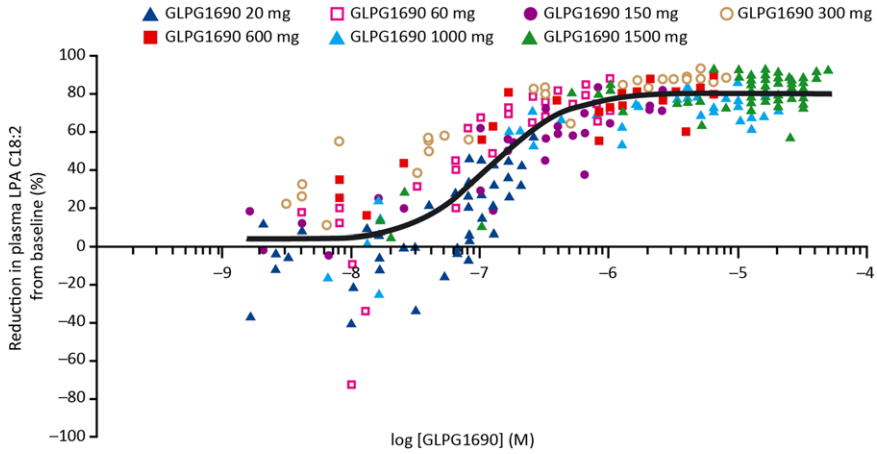

Figure 3. Correlation between LPA C18:2 percentage reduction from baseline and GLPG1690 plasma concentration for the SAD population. The IC_{50} is estimated to be 118 nM (0.07 µg/mL). 1 µM GLPG1690 = 0.6 µg/mL. IC_{50}, half maximal inhibitory concentration; SAD, single ascending doses.

Effect of Formulation and Food on GLPG1690 PK

In the first-in-human study, mean plasma concentration-time profiles were similar for a single dose of GLPG1690 300 mg given as an oral suspension or as hard-gelatin capsules in a fed state (Figure 4A). Geometric mean C_{max} and $AUC_{0\text{-inf}}$ values were similar for capsule and oral suspension formulations (3.31 µg/mL and 16.4 µg·h/mL vs 3.79 µg/mL and 14.9 µg·h/mL, respectively), although the median t_{max} was slightly later for the capsule than the oral suspension (2.0 hours and 1.0 hour, respectively). GLPG1690 was rapidly eliminated after administration of both formulations (apparent terminal half-life of approximately 5 hours).

In the relative bioavailability study, mean plasma concentration-time profiles were similar for a single dose of GLPG1690 600 mg given as capsules or tablets in a fed state or tablets in a fasted state (Figure 4B). Exposure to GLPG1690 (C_{max} and $AUC_{0\text{-inf}}$) was similar for capsule and tablet formulations administered in a fed state but approximately 20% lower (point estimates ~80%) for tablets in a fasted state (Supplemental Table S5). The mean apparent terminal half-life was similar in treatment groups (approximately 5 hours), but median t_{max} was later following administration of GLPG1690 600 mg as tablets in a fed state (3.5 hours) compared with tablets in a fasted state (1.8 hours) and capsules in a fed state (2.5 hours).

Discussion

GLPG1690 is a first-in-class autotaxin inhibitor currently being investigated as a novel therapy for IPF.[18,21] This first-in-human study demonstrated that GLPG1690 was well tolerated after administration of single doses up to 1500 mg and multiple doses up to

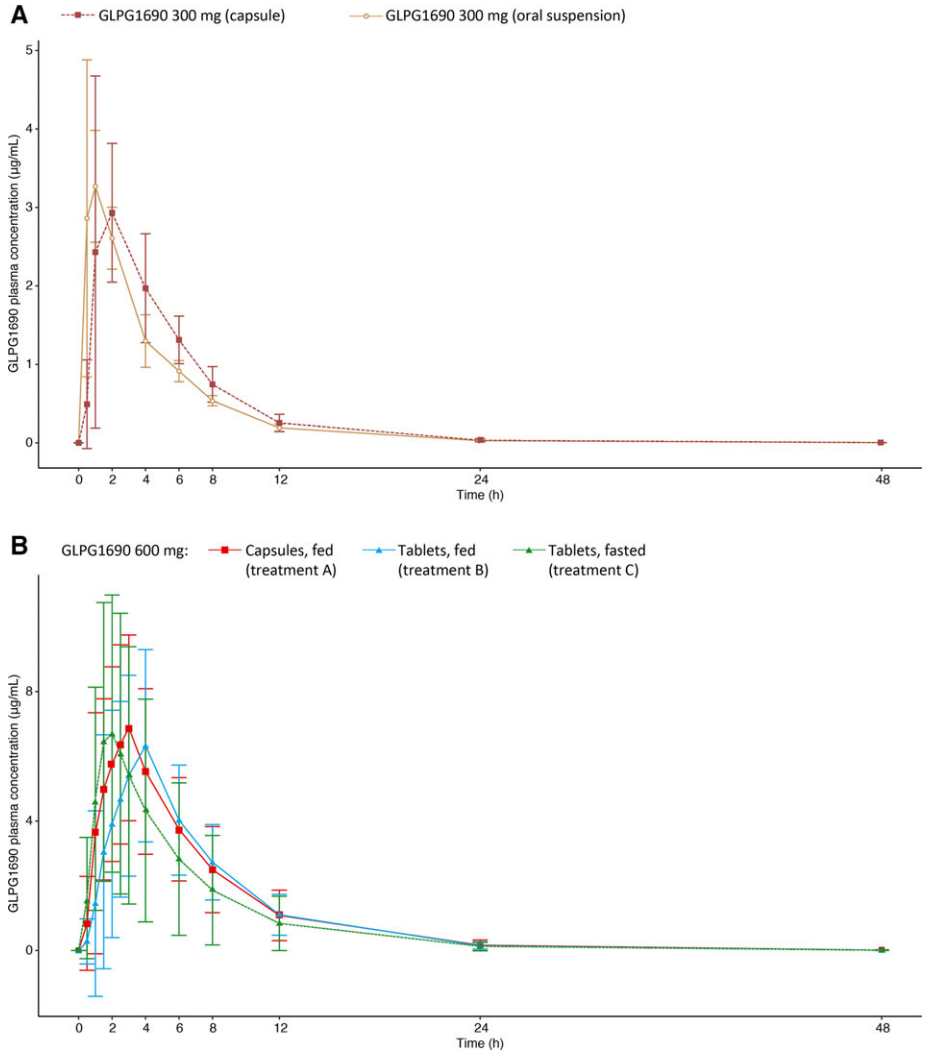

Figure 4. GLPG1690 plasma concentration-time profiles following (A) a single oral dose of GLPG1690 300 mg given as an oral suspension or capsule in a fed state (both n = 6; first-in-human study) and (B) a single oral dose of GLPG1690 600 mg given as a capsule or tablet in a fed state or a tablet in a fasted state (all n = 12; relative bioavailability study). Data are mean ± SD. h, hour; SD, standard deviation.

1000 mg once daily for 14 days. TEAEs experienced by subjects were at most moderate in severity; the most common TEAE was headache, which was considered at least possibly related to GLPG1690. Importantly, no dose-limiting toxicities were identified during the study. GLPG1690 was also well tolerated in the relative bioavailability study, with only 3 TEAEs reported that were not considered to be treatment related. One subject in the GLPG1690 1000-mg once-daily group (first-in-human MAD study) had elevated AST (~2.25 times the upper limit of normal) the day after receiving the last dose, which resolved by the follow-up visit 7 days later. No other TEAEs or laboratory abnormalities suggestive of potential hepatotoxicity were observed in these studies.

Following administration, GLPG1690 was rapidly absorbed and eliminated. Plasma exposure to GLPG1690 increased with increasing dose with minimal deviation from dose proportionality following single and multiple doses. Overall, the PK profile of GLPG1690 was similar to that reported in patients with IPF treated with GLPG1690 capsules (600 mg once daily).[21]

Steady state appeared to be reached after the first dose for twice-daily dosing. In contrast, after once-daily dosing, steady state appeared to be reached around day 3 or 4, which may be inconsistent with the observed short apparent terminal half-life. Because the accumulation ratio was similar following twice-daily and once-daily dosing, a difference in elimination between dosage regimens is unlikely and the most likely explanation is that the apparent terminal half-life had not been fully captured. Indeed, sampling time was stopped 48 hours postdose despite PK time-concentration profiles displaying plasma concentrations 48 hours postdose that were at least 20-fold greater than the lower limit of

quantification. It could therefore be speculated that the observed half-life of approximately 5 to 6 hours is a mix of distribution and elimination and probably not the terminal elimination half-life, which would be longer.

There was a reduction in plasma LPA C18:2 levels following administration of GLPG1690, reaching a maximum of approximately 90% reduction from baseline; the decrease in LPA C18:2 was rapid, with higher doses providing a more sustained effect. Reduction in LPA C18:2 was also apparent in the pooled placebo group, only in the MAD part of the study; however, this was highly variable, and there was clear separation between placebo and GLPG1690 (even at the lowest dosage) in effects on LPA C18:2. These results indicate that GLPG1690 inhibited autotaxin effectively.[18] After 14 days of GLPG1690 administration, plasma LPA C18:2 was reduced at predose by at least 70% for all doses; for GLPG1690 600 mg once daily and 1000 mg once daily, this finding indicates that GLPG1690 concentration remained at a level capable of inhibiting autotaxin for at least 24 hours postdose and that once-daily dosing is sufficient. LPA C18:2 returned toward baseline 48 hours postdose for all doses, demonstrating that the inhibition of autotaxin by GLPG1690 is reversible. The PD profile of GLPG1690 was similar to that reported in patients with IPF treated with GLPG1690 capsules (600 mg once daily).[21] PK/PD correlation analysis showed plateauing of PD effects (at around 80% reduction in LPA C18:2) when plasma concentrations of GLPG1690 reached approximately 1 μM (approximately 0.6 μg/mL), with an estimated IC_{50} of 118 nM (0.07 μg/mL; Figure 3). This is in line with results from ex vivo human plasma LPA release assays that indicated an IC_{50} of approximately 100 nM (0.06 μg/mL).[19] Reaching a plateau of maximal PD effect indicates that the dose range in this study was adequate to fully assess the PK/PD profile of GLPG1690; the maximum tolerated dose (MTD) was not defined in the evaluated dose range, although determining the MTD was not an objective of the study. Indeed, we observed plasma levels of GLPG1690 much greater than the IC_{50} over 24 hours without tolerability issues, which supports further clinical development of the drug. The degree of LPA suppression achieved, together with the favorable safety profile observed in the first-in-human study, led to the selection of GLPG1690 600 mg once daily for further clinical development.

In a recent phase 2a study in 23 patients with IPF (FLORA study), GLPG1690 600 mg once daily reduced plasma LPA C18:2 levels by at least 50% over 12 weeks; in the same treatment period, FVC showed a trend for a decline in the placebo group (mean change from baseline in week 12, -70 mL [95%CI, -208 to 68]) but remained similar to or greater than baseline values in the GLPG1690 600-mg once-daily group (mean change from baseline in week 12, +25 mL [95%CI, -75 to 124]).[21] This provides support for the concept of targeting the autotaxin-LPA axis via inhibition of autotaxin to ameliorate IPF.

Together these studies demonstrated the equivalence of 3 different formulations of GLPG1690. The first-in-human study primarily used an oral suspension for delivery of GLPG1690 over a range of doses (providing flexibility for incremental dose increases) but included a comparison between oral suspension and capsule formulations at the 300-mg dose. Relative bioavailability was similar for these 2 formulations (both administered in the fed state), and capsules were subsequently used in the phase 2a FLORA study.[21] A tablet formulation of GLPG1690 was developed to be used in phase 3 studies. We therefore compared the relative bioavailability of the capsule formulation (used in the phase 2a study) and the tablet formulation. In a fed state, the bioavailability and apparent elimination rates of the tablet and capsule formulations (600-mg dose) were similar, although the rate of absorption was slightly slower for the tablet. When comparing the PK of the tablet formulation administered in a fed or fasted state, food was found to decrease the rate of absorption of GLPG1690, as expected when gastric emptying is slowed by food intake, but there was no clinically relevant difference in exposure to GLPG1690. These results indicate that the tablet formulation is a suitable replacement for the capsule formulation for phase 3 studies with GLPG1690.

A limitation of the studies presented here was the small size of the study populations; however, they were of an appropriate size for early clinical pharmacology development studies assessing safety and tolerability, PK/PD, and formulation/food effect in healthy subjects and provide reassurance about the safety, tolerability, and PK/PD profile of GLPG1690 for continued clinical development.

Conclusions

GLPG1690 was well tolerated in the phase 1 studies. GLPG1690 had a favorable PK/PD profile, indicating that a once-daily dosing regimen is sufficient to effectively reduce plasma LPA C18:2 levels through autotaxin inhibition. The safety, tolerability, and PK/PD profiles of GLPG1690 in healthy subjects support its continued clinical development as a novel treatment for IPF.

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Declaration of Conflicting Interests

Ellen van der Aar, Sonia Dupont, Bertrand Heckmann, Ann Fieuw, Simone Stutvoet, Liesbeth Fagard, Karen Van de Wal, and Eric Helmer are employees of Galapagos. Julie Desrivot is a former employee of Galapagos. Medical writing assistance in the preparation of this manuscript was provided by Jane Murphy (CircleScience, an Ashfield Company, part of UDG Healthcare plc), and funded by Galapagos.

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Author Contributions

All authors' provided substantial contribution to the design or the acquisition, analysis, or interpretation of data. Authors critically reviewed the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

Data Accessibility Statement

Data will not be shared.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.