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Original Article

GLPG1837, a CFTR potentiator, in p.Gly551Asp (G551D)-CF patients: An open-label, single-arm, phase 2a study (SAPHIRA1)☆

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ABSTRACT

Background: Investigation of novel cystic fibrosis transmembrane conductance regulator (CFTR) potentiators, such as GLPG1837, for CF patients with gating mutations is challenging as trials require patients to withhold ivacaftor, the current standard of care. This study explored the feasibility of such a study and the impact of one-week ivacaftor withdrawal.

Methods: This open-label, single-arm study aimed to enrol 32 adults ≥18 years of age with CF and at least one p.Gly551Asp (G551D) mutation. Patients received three increasing GLPG1837 dosages twice-daily for two 7-day and one 14-day period following a one-week ivacaftor washout. The primary outcome was safety; secondary outcomes were changes in sweat chloride concentration, spirometry outcomes, and pharmacokinetics.

Results: Twenty-six patients enrolled; 24 completed the study. Adverse events were reported by 53.8–76.9% of patients (dosage-dependent), with respiratory adverse events most common. Mean sweat chloride concentrations decreased from 97.7 mmol/L (baseline) to 68.7 mmol/L (end of GLPG1837 treatment). In ivacaftor-pre-treated patients, mean sweat chloride concentrations rose from 42.5 mmol/L at screening to 98.5 mmol/L after ivacaftor washout. Levels were decreased following GLPG1837 treatment (to 68.8 mmol/L at treatment end). Percent predicted forced expiratory volume in 1 s declined from 73.3% at screening to 68.5% after ivacaftor washout but returned to screening level at treatment end (73.1%).

Conclusions: Patient willingness to participate in the study suggests that the need for a short period of ivacaftor withdrawal may not be a barrier to development of novel potentiators, such as GLPG1837. A one-week ivacaftor washout was generally well tolerated, but resulted in a decline in lung function, which was reversed with GLPG1837 treatment to pre-washout levels. Combined with the concentration-dependent decrease in sweat chloride concentration, results show that GLPG1837 increases CFTR activity in G551D-CF patients.

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Clinical trial registration numbers: NCT02707562; EudraCT 2015-003291-77.

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Abbreviations: AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CI, confidence interval; CK, creatine phosphokinase; C_{trough}, lowest plasma drug concentration reached before next dose administered; FEV_1, forced expiratory volume in 1 s; GGT, gamma glutamyl transferase; ITT, intent-to-treat population; LOCF, last observation carried forward; $ppFEV_1$, percent predicted forced expiratory volume in 1 s; SAE, serious adverse event; SEM, standard error of the mean; SD, standard deviation; ULN, upper limit of normal.

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1. Introduction

Cystic fibrosis (CF) is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene. More than 2000 mutations have been identified and are grouped into six classes (Class I–VI) [1,2]. p.Gly551Asp (G551D) is the most common CFTR gating (class III) mutation, present in about 4% of patients with CF (1.4% in Europe) [3,4].

Ivacaftor (Vertex Pharmaceuticals Inc., Boston, MA, USA) is a CFTR potentiator licensed to treat patients harbouring at least one G551D mutation [5]. Phase 3 and post-approval clinical studies demonstrate that ivacaftor improves pulmonary function and symptoms, reduces pulmonary exacerbations and the risk of death, and significantly improves patient quality of life [6–10]. However, ivacaftor is not available in every country, due at least in part to cost.

The novel potentiator molecule GLPG1837 (Galapagos NV, Mechelen, Belgium) [11] was well tolerated in healthy adults [12]. A potent effect on G551D was demonstrated using in vitro cellular assays [11]. Data from such assays, together with plasma profiles in healthy adults, suggest that a dose of 500 mg GLPG1837 every 12 h would be needed to maintain predicted efficacious concentrations of 80 ng/mL, and should lead to efficacy equivalent to that of ivacaftor in patients with the G551D mutation. In this study we investigated the safety, tolerability, pharmacokinetics, and efficacy of GLPG1837 in patients with CF with the potentiator-responsive G551D mutation. We describe the impact of one-week ivacaftor withdrawal on biomarkers for CFTR activity and safety parameters. Investigation of novel potentiators — such as GLPG1837 — in this patient group is challenging, as patients are required to withhold their standard of care treatment prior to inclusion. We therefore explored the extent to which a washout period would hamper the willingness of patients on ivacaftor to participate in this study.

2. Methods

2.1. Study design and participants

SAPHIRA1 (ClinicalTrials.gov identifier: NCT02707562) was a multicentre, non-randomised, open-label, single-arm, ascending-dose phase 2a study conducted at 15 CF centres in the United Kingdom, Ireland, Australia, Germany, and Czech Republic. Patients were aged 18 years or older with a confirmed diagnosis of CF, with the G551D mutation on at least one CFTR allele, and a forced expiratory volume in 1 s (FEV_1) at screening of at least 40% of the predicted value for age, sex, and height. Patients naïve to ivacaftor or on a stable ivacaftor-containing dosage regimen for at least 2 weeks were eligible; the latter were required to undergo a one-week washout period before the start of the first treatment period. Patients remained on other stable pulmonary medications (e.g., antibiotics, corticosteroids, inhaled bronchodilators, hypertonic saline, mannitol, dornase alfa) throughout the study.

The study consisted of three consecutive ascending-dose treatment periods: two 7 day periods followed by a 14 day period, with a total treatment duration of 28 days. Eligible patients received twice daily (every 12 h) oral GLPG1837 at three dosages: 125 mg for 7 days, 250 mg for 7 days, and 500 mg for 14 days, with the 500 mg dose expected to have an effect similar to ivacaftor (see Supplementary Methods).

An independent ethics committee for each site/region approved the protocol, and each patient provided written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local and national regulations. An independent medical safety review was conducted during the study.

2.2. Procedures

Safety and tolerability were assessed at weekly visits, including a follow-up visit seven to ten days after final study drug administration. At each visit, sweat samples were collected in a standardised manner using a Macroduct collection device. Spirometry was performed according to standard operating procedures [13]. Blood samples were collected to determine GLPG1837 plasma levels using a validated liquid chromatography-tandem mass spectrometry method. More details are available in the Supplementary Methods.

2.3. Outcomes

The primary outcome measure was safety and tolerability, using assessments of adverse events (monitored throughout the study from screening), clinical laboratory tests, electrocardiograms, vital signs, physical examination, and oxygen saturation by pulse oximetry. Secondary outcome measures included changes from baseline (Day 1 pre-dose) in sweat chloride concentration and in pulmonary function (percent predicted forced expiratory volume in 1 s [$ppFEV_1$]). In ivacaftor pre-treated patients, changes from screening, i.e., from before ivacaftor washout, were evaluated. Other secondary outcome measures included GLPG1837 pharmacokinetics. This report focuses on pre-dose GLPG1837 concentrations, which are anticipated to be relevant to assess correlations with efficacy outcomes.

2.4. Statistical analysis

Sample size calculation assumed a standard deviation (SD) of change in sweat chloride concentration of 20 mmol/L, after one week of treatment [14]. We estimated that with 32 planned patients, the study would be able to detect a difference between treatment dosages of 16.52 mmol/L at a 1.67% two-sided type-I error, with an 80% power. All patients who received GLPG1837 were included in the analyses. The intent-to-treat (ITT) population comprised those patients for whom at least one post-line efficacy assessment was available.

Adverse events were coded by system organ class and preferred terms using the Medical Dictionary for Regulatory Activities, version 18.1, and were summarised descriptively. For ivacaftor pre-treated patients, a pre-specified exploratory comparison of changes in sweat chloride and $ppFEV_1$ versus screening (i.e., versus when taking ivacaftor) was done. A post-hoc exploratory subgroup analysis of change versus baseline in sweat chloride concentration was done for patients reaching pre-dose GLPG1837 plasma levels of ≥80 ng/mL.

Sweat chloride concentration and pulmonary function results presented in this report are based on analysis using the last observation carried forward (LOCF) imputation for missing visits, as well as early dropouts (see Supplementary Methods for further details). Observed cases are also presented for absolute data. SAS version 9.2 was used for the analyses.

3. Results

3.1. Patient disposition and baseline characteristics

Between February 23 and August 30, 2016, 26 eligible patients were enrolled, and all received at least one dose of study treatment (safety population) and completed the first two treatment periods. Two patients discontinued from the study during the third treatment period (one due to a serious adverse event [SAE]; one withdrawal by patient, not adverse event-related). The trial design is shown in Fig. 1, and the participant flow diagram in Supplementary Fig. 1.

All patients had the G551D mutation on at least one CFTR allele, 18 (69.2%) patients had the Phe508del (ΔF508) CFTR mutation on the second allele. Twenty-five patients were receiving stable ivacaftor treatment at screening and agreed to a one-week ivacaftor washout prior to the start of GLPG1837 dosing (baseline); one patient was ivacaftor-naïve (Table 1).

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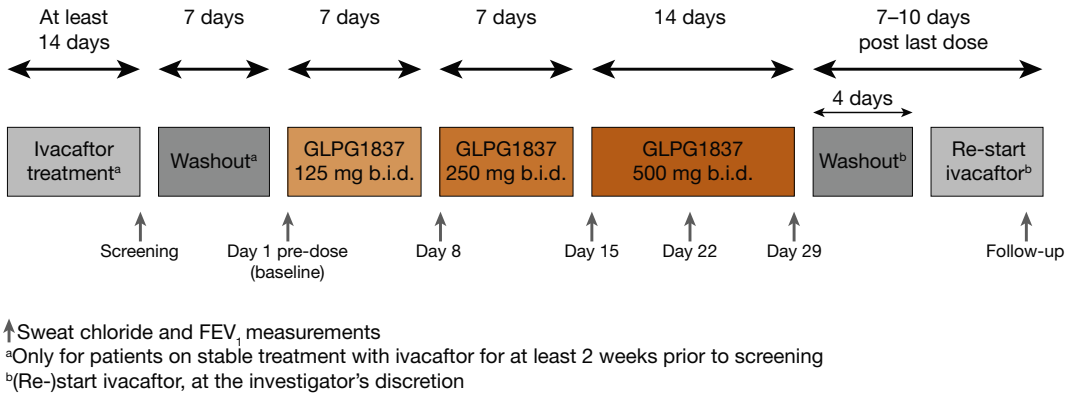


Fig. 1. Trial design. b.i.d, twice a day; FEV_1, forced expiratory volume in 1 s.

3.2. Safety

Adverse events were reported by 36.0% (9/25) of patients during ivacaftor washout. Treatment-emergent adverse events were reported by 53.8% (14/26) of patients each during the 125 mg and 250 mg GLPG1837 dosing periods, and by 76.9% (20/26) of patients during the 500 mg dosing period (Table 2). Across the dosing periods, respiratory adverse events were reported in 9/26 (34.6%), 3/26 (11.5%), and 3/26 (11.5%) patients, respectively. Two of 26 patients (7.7%) experienced at least one SAE during the study. At Day 15, one patient had an unexpected non-cardiac increase in creatine phosphokinase (CK) that led to premature discontinuation from the study (CK levels were 3434 IU/L; 15 days earlier levels had been 103 IU/L)). This patient had not done any unusual physical activity, experienced any clinical signs such as muscle pain, or taken any drugs that could explain the CK increase; the patient recovered after 8 days. The patient's GLPG1837 C_{trough} values were 11.8 ng/mL and 30.2 ng/mL at Days 8 and 15, respectively. Both were below mean and median C_{trough} for the cohort at these timepoints, suggesting CK increase was not related to outlier plasma drug concentrations. One patient had a pulmonary exacerbation leading to hospitalisation; this patient also had CF-related distal intestinal obstruction syndrome during the screening period reported as an SAE, which resolved before first GLPG1837 administration. While most adverse events were mild or moderate in intensity, four of 26 patients (15.4%) had one severe treatment-emergent adverse event while on GLPG1837 treatment: fatigue during the 125 mg period, and cough, increased blood CK, and pulmonary exacerbation during the 500 mg period.

Treatment-emergent, abnormally high gamma glutamyl transferase (GGT) levels were observed in 38.5% (10/26) of patients, predominantly during the 500 mg dose treatment. Among these, three patients had a concurrent increase in one other liver-related laboratory parameter (two with abnormally high (>1× the upper limit of normal [ULN]) alanine transferase and one with abnormally high (>1xULN) alkaline phosphatase. Of these abnormal laboratory parameters, three cases of GGT increase were reported by the investigator as adverse events (Table 2). No clinically relevant trends or changes in vital signs (including blood pressure), electrocardiogram parameters, or oxygen saturation were observed during treatment.

Table 1
Screening and baseline patient demographics and disease characteristics (safety population).

Parameter	Screening ($N = 26$)	Baseline (N = 26)
Age, years		
Mean (SD)	30.3 (8.2)	–
Range	19–51	–
Body weight, kg		
Mean (SD)	68 (14.4)	67.6 (14.0)
Range	46.5–108.0	48.9–105.0
BMI, kg/m^2		
Mean (SD)	23.72 (3.6)	23.58 (3.5)
Range	17.9–34.9	18.9–33.9
Sex, n (%)		
Female	14 (53.8)	–
Male	12 (46.2)	–
Sweat chloride concentration, mmol/L		
Mean (SEM)	43.8 (3.7)[a]	97.7 (2.5)
Range	21–80	63–116
On stable ivacaftor treatment, n (%)	25 (96.2)	–
Mean (SD) treatment duration, months	38.9 (18.2)	–
Range	3.6–77.3	–
Ivacaftor-naïve, n (%)	1 (3.8)	–
$ppFEV_1$, (%)		
Mean (SEM)	73.9 (4.0)	69.2 (4.3)[b]
Range	42–105	30–104
CFTR variant, n (%)		
G551D/ΔF508	18 (69.2)	–
G551D/other[c]	8 (30.8)	–

Baseline is pre-dose on the first day of the first treatment period (i.e., after one week of ivacaftor washout for ivacaftor pre-treated patients). Age is at signing the informed consent.
BMI, body mass index; CFTR, cystic fibrosis transmembrane conductance regulator; $ppFEV_1$, percent predicted forced expiratory volume in 1 s; SEM, standard error of the mean; SD, standard deviation.
[a] Value for 25 patients.
[b] Value for 25 patients, excluding one patient with poor quality spirometry test at baseline.
[c] Other CFTR mutations: 711 + 3A > G (2 patients), Gly1123Arg, Gly542X, Glu585X, Glu60X, Arg553X, or Val520Phe (one patient each).

3.3. Pharmacokinetics

Although between-patient variability was high (% coefficient of variation 113–375), pre-dose GLPG1837 plasma concentrations increased in proportion to dose increment. At 500 mg, the mean trough (i.e., lowest) plasma GLPG1837 concentration reached before next dose administered (C_{trough}) exceeded the target level predicted to be active in lungs (80 ng/mL), with 15/22 patients with available data reaching this threshold (Fig. 2A).

3.4. Sweat chloride concentration

In ivacaftor pre-treated patients ($N = 24$), the LOCF mean (SEM) sweat chloride concentration at screening was 42.5 (3.6) mmol/L

Table 2
Adverse events and those reported by ≥5% of patients during any treatment period (safety population).

	GLPG1837 125 mg every 12 h for 7 days (N = 26)	GLPG1837 250 mg every 12 h for 7 days (N = 26)	GLPG1837 500 mg every 12 h for 14 days (N = 26)
Any adverse event, n (%)	14 (53.8)	14 (53.8)	20 (76.9)
Adverse event occurring in ≥5% patients in any treatment period, n (%)			
Headache	4 (15.4)	6 (23.1)	6 (23.1)
Increased sputum	6 (23.1)	0	0
Cough	2 (7.7)	1 (3.8)	2 (7.7)
Haemoptysis	2 (7.7)	0	0
Chest discomfort	2 (7.7)	1 (3. 8)	2 (7.7)
Fatigue	4 (15.4)	5 (19.2)	0
Chest pain	0	0	2 (7.7)
Nausea	1 (3.8)	1 (3.8)	2 (7.7)
Upper abdominal pain	2 (7.7)	1 (3.8)	2 (7.7)
Abdominal pain	0	1 (3.8)	2 (7.7)
GGT increase	1 (3.8)[a]	0	2 (7.7)[b]

[a] One patient experienced a moderate increase in GGT during the 125 mg GLPG1837 dosing period that was considered unlikely to be related to study drug by the investigator. This AE began one day after the first dose and lasted for over 36 days. This patient had abnormally high GGT throughout the study of 95 U/L at screening, 145 U/L at baseline, 122 U/L at Day 8, 152 U/L at Day 15, 147 U/L at Day 22, 240 U/L at Day 29, and 223 U/L at follow-up on Day 36 (normal range in females 9–36 U/L). The patient also had abnormally high ALP levels throughout the study (from 306 U/L at baseline to 270 U/L on Day 36; normal range 40–150 U/L) and abnormally high AST on Day 36 (36 U/L; normal range 5–34 U/L). No abnormalities in ALT or bilirubin were identified.

[b] Two patients experienced a mild increase in GGT during the 500 mg GLPG1837 dosing period, both commencing 22 days after GLPG1837 initiation and considered possibly related to study drug by the investigator. In one of these two patients, the AE duration was 15 days, with normal GGT concentrations prior to Day 22 of 14, 20, and 24 U/L at baseline, Day 8, and Day 15, respectively This patient also had abnormally high GGT of 53 and 44 U/L at Day 22 and Day 29, respectively (normal range in females, 9–36 U/L). For the other patient, the duration of the AE was <20 days. Normal GGT levels were observed prior to Day 22 (14, 19, and 24 U/L at baseline, Day 8, and Day 15, respectively). In this patient, abnormally high GGT levels of 41 and 55 U/L were measured at Day 22 and 29, respectively. AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.

(Table 3). A one-week ivacaftor washout resulted in a statistically significant increase in sweat chloride level of 55.8 mmol (95% CI 48.5, 63.2) at baseline (Supplementary Table 1). Mean changes in sweat chloride levels from screening tended to decrease over time, but at the end of the GLPG1837 treatment period (at Day 29), mean (95% CI) sweat chloride concentrations had not returned to screening values (change from screening at Day 28: +24.4 [13.8, 34.9]; Supplementary Table 1).

In the ITT population, mean (SEM) sweat chloride concentration (with LOCF imputation) was 97.7 (2.5) mmol/L at baseline ($N = 26$; Table 1), 68.7 (5.6) mmol/L on Day 29 ($N = 25$; 500 mg GLPG1837), and 59.1 (4.1) mmol/L at follow-up ($N = 20$) (i.e., when ivacaftor pretreated patients were no longer receiving GLPG1837 but had resumed treatment with ivacaftor; Table 3). Mean (95% confidence interval [CI]) changes from baseline in sweat chloride concentration were −11.6 (−17.9, −5.2) mmol/L at Day 8 (N = 26), −15.1 (−19.6, −10.7) mmol/L at Day 15 ($N = 21$), −29.9 (−39.9, −19.9) mmol/L at Day 22 (N = 21), and − 28.8 (−39.1, −18.4) mmol/L at Day 29 (N = 25; Supplementary Table 2).

Change in sweat chloride concentration was inversely correlated with pre-dose GLPG1837 plasma concentration. Mean C_{trough} exceeded the predicted efficacious C_{trough} of 80 ng/mL at the highest dose of 500 mg GLPG1837, resulting in the largest decrease in sweat chloride concentration (Fig. 2A). A post-hoc exploratory subgroup analysis showed that in patients reaching target pre-dose GLPG1837 plasma levels of ≥80 ng/mL (15 out of 22 patients), a decrease in mean (SEM) sweat chloride levels was seen at 500 mg (from 94.0 [3.4] mmol/L at baseline to 51.5 [5.5] mmol/L at Day 29 [Fig. 2B; Supplementary Figs. 2A&2B]), while for patients with pre-dose GLPG1837 < 80 ng/mL (7 out of 22 patients), mean sweat chloride concentration remained stable

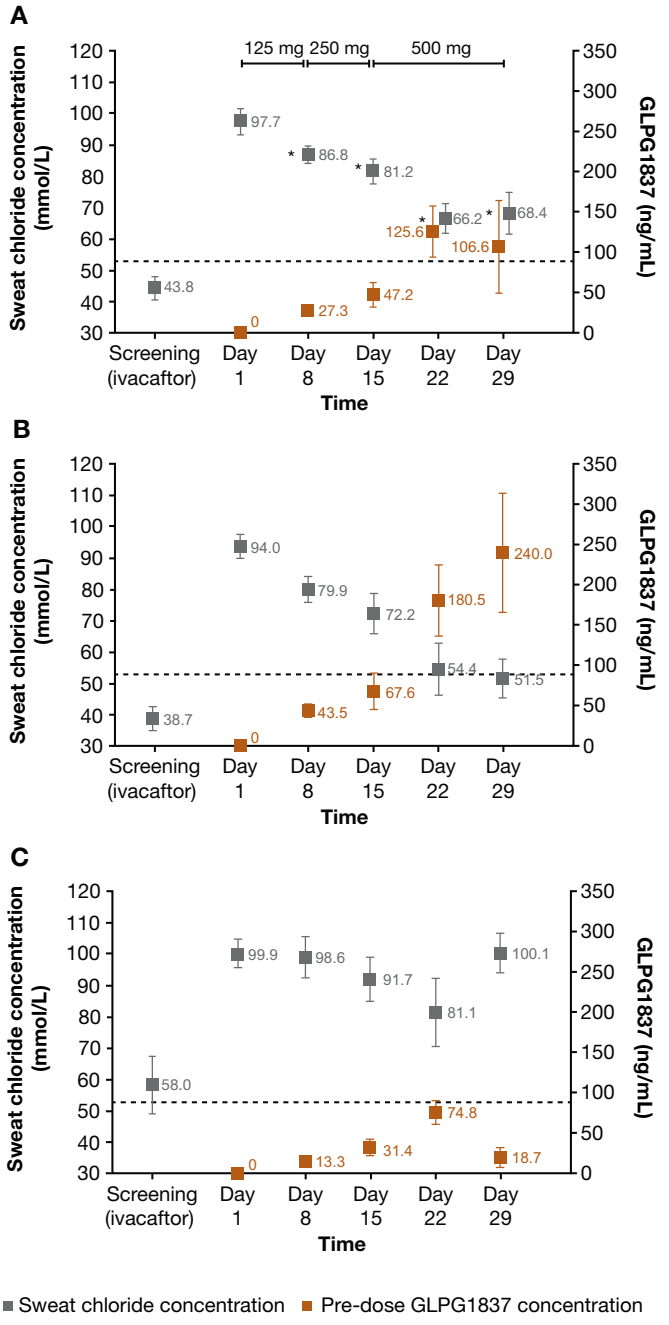


Fig. 2. Mean absolute sweat chloride concentration versus mean pre-dose GLPG1837 plasma concentration over time in the ITT population[a] (A; $N = 26$), and in the post-hoc exploratory subgroup analysis in patients reaching (B; $N = 15$)[b] or not reaching (C; $N = 7$)[c] the target pre-dose GLPG1837 plasma concentration of 80 ng/mL on Day 29 (pre-dose). Data are observed cases. Sweat chloride samples were taken at each visit before administration of study drug. Error bars show the standard error of the mean. The dashed horizontal line represents the target plasma pre-dose GLPG1837 concentration of 80 ng/mL, which is the concentration of GLPG1837 that is predicted to be efficacious. *$p < .05$ for change from baseline (Day 1 pre-dose) in sweat chloride concentration. [a]For pre-dose GLPG1837 plasma concentration, $N = 25$ at Days 8 and 15, $N = 24$ at Day 22, and $N = 22$ at Day 29. For mean absolute sweat chloride concentration, N = 26 at baseline, N = 24 at Day 8, $N = 21$ at Day 15 and Day 22, and N = 22 at Day 29. [b] For mean absolute sweat chloride concentration, N = 15 at screening and Day 1, $N = 13$ at Day 8, $N = 11$ at Day 15 and Day 22, and N = 13 at Day 29. [c] For mean absolute sweat chloride concentration, $N = 6$ at screening, N = 7 at Day 1 and Days 8, 15, 22, and 29. ITT, intent-to-treat population.

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Table 3
Sweat chloride concentration (ITT population and all ivacaftor pre-treated patients) and ppFEV$_1$ (all ivacaftor pre-treated patients) by time point.

	ITT; LOCF (N = 26)			ITT; OC (N = 26)			Ivacaftor pre-treated; LOCF (N = 25)			Ivacaftor pre-treated; OC (N = 25)		
	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM
Sweat chloride concentration, mmol/L												
Screening (receiving ivacaftor)	25	43.8	3.7	25	43.8	3.7	24	42.5	3.6	24	42.5	3.6
Day 1 baseline (after 1 week of ivacaftor washout[a])	26	97.7	2.5	26	97.7	2.5	25	98.5	2.4	25	98.5	2.4
Day 8 (receiving GLPG1837 125 mg every 12 h)	26	86.2	3.4	24	86.8	3.5	25	87.0	3.5	23	87.7	3.5
Day 15 (receiving GLPG1837 250 mg every 12 h)	21	81.2	4.2	21	81.2	4.2	20	82.3	4.2	20	82.3	4.2
Day 22 (receiving GLPG1837 500 mg every 12 h)	21	66.2	5.9	21	66.2	5.9	20	68.1	5.8	20	68.1	5.8
Day 29 (receiving GLPG1837 500 mg every 12 h)	25	68.7	5.6	22	68.4	6.2	24	68.8	6.3	21	68.5	6.3
Follow-up (receiving ivacaftor)	20	59.1	4.1	20	59.1	4.1	19	58.4	4.1	19	57.4	4.1
ppFEV$_1$, %												
Screening (receiving ivacaftor)	–	–	–	–	–	–	25	73.3	4.2	25	73.3	4.2
Day 1 baseline (after 1 week of ivacaftor washout)	–	–	–	–	–	–	24	68.5	4.4	24	68.5	4.4
Day 29 (receiving GLPG1837 500 mg every 12h[a])	–	–	–	–	–	–	21	73.1	4.2	21	73.1	4.2
Follow-up (receiving ivacaftor)	–	–	–	–	–	–	21	72.3	4.2	21	72.3	4.2

ITT, intent-to-treat population; LOCF, last observation carried forward; OC, observed cases; ppFEV1, percent predicted forced expiratory volume in 1 s; SEM, standard error of the mean.
[a] 4 hours post-dose.

over time (Fig. 2C; Supplementary Figs. 2C&2D; from baseline 99.9 (4.4) mmol/L to 100.1 (6.3) mmol/L at Day 29 [500 mg GLPG1837]). These data suggest that GLPG1837 plasma levels of at least 80 ng/mL should be reached to observe a significant decrease in sweat chloride.

3.5. Pulmonary function

Mean (SEM) ppFEV1 (with LOCF imputation) in ivacaftor pre-treated patients ($N = 25$) at screening was 73.3% (4.1). At baseline, the one-week ivacaftor washout resulted in a significant mean (95% CI) decrease from screening in ppFEV$_1$ of 5.4% (−8.1, −2.8) (Supplementary Table 3) to 68.5% (SD 21.7). During the 4-week GLPG1837 treatment, ppFEV$_1$ recovered. At the end of treatment (Day 29 post-dose, $N = 21$), ppFEV$_1$ had returned to pre-ivacaftor washout (i.e., similar to those seen at screening) levels (Supplementary Fig. 3, Supplementary Table 3).

In the ITT population, mean (SEM) ppFEV1 (with LOCF imputation) was 73.9% (4.0) at screening and 69.2% (4.3) at baseline (Table 1). At the end of GLPG1837 treatment on Day 29 post-dose, ppFEV$_1$ was 73.9% (SEM 4.0, $N = 22$) which was similar to ivacaftor pre-washout levels at screening (ppFEV$_1$: 73.9%, SEM 4.0, $N = 26$). Mean change from baseline in ppFEV$_1$ was +1.6% (95% CI, −0.9, 4.0) pre-dose and + 2.8% (0.2, 5.3) post-dose on Day 29 (Supplementary Table 4).

4. Discussion

GLPG1837 is a novel CFTR potentiator and is the first such agent — since the clinical availability of ivacaftor — to be evaluated as a treatment for patients with CF harbouring a G551D mutation. Since most patients with a G551D mutation receive ivacaftor treatment, the present study required assessment of the safety profile and changes of pharmacodynamic biomarkers of CFTR function of this investigational drug in an already treated patient population. This significantly influenced study design; we selected an open-label, single-arm, ascending-dose design, in which each patient served as their own control. While a two-arm study randomising patients to GLPG1837 or ivacaftor may have been more informative, this would lead to significant challenges, including the potentially prohibitive cost of acquiring the active comparator [15] and the need to recruit a larger number of patients from this small patient population.

Since ivacaftor confers significant clinical benefits on patients with a G551D mutation [6,9,16], it was anticipated that there may be difficulties with recruitment since a washout period was requested. However, patients were willing to participate in the study, allowing completion within 7.5 months from first patient screened to last patient out. The planned sample size for the study was 32 patients to have sufficient power to detect a difference in sweat chloride concentration between treatment doses. However, recruitment was halted when 26 patients were included, since the available population of eligible patients had been exhausted and further recruitment would therefore be difficult.

Pre-dose GLPG1837 plasma levels were similar to those previously reported in healthy individuals. In this study, the findings for secondary efficacy outcomes — sweat chloride and ppFEV$_1$ — provided preliminary evidence of efficacy, although it should be noted that evaluating efficacy was not the primary objective of the study. Even so, the activity of GLPG1837 as a potentiator was confirmed in this study, and in vivo target engagement demonstrated by a dose-dependent decrease in sweat chloride concentration that coincided with a dose-dependent increase of GLPG1837 pre-dose levels during treatment. The significant increase in sweat chloride concentration of 55.8 mmol/L after one week of ivacaftor washout confirms that sweat chloride is a rapid biomarker for the evaluation of CFTR function and that the study design was suitable to determine target activity of GLPG1837. The baseline sweat chloride concentration of 97.7 (SEM 2.5) mmol/L (ITT population) is in line with earlier observations in this patient population [16–18]. The study showed a clear relationship between threshold levels of GLPG1837 and CFTR-mediated activity. In an exploratory post-hoc subgroup analysis for GLPG1837 pre-dose levels at or above, versus below, 80 ng/mL, clear differentiation in sweat chloride response was observed. There was no effect when GLPG1837 plasma concentrations were below this threshold, relating these observations to in vitro data on G551D channel function as measured by trans-epithelial clamp circuit in primary bronchial epithelial patient cells derived from G551D/ΔF508 patients (see Supplementary Fig. 4).

Adverse events were more frequently reported in the high dose (500 mg) treatment period, although the nature of adverse events observed was typical for a CF study population, with, for example, respiratory adverse events commonly reported [19–21]. However, the single case of non-cardiac increase in CK that led to premature discontinuation, along with the observed increase in GGT levels with or without increases in other liver enzymes warrants caution for future clinical trials with this investigational compound.

The limitations of the study include the absence of a placebo arm, which makes interpretation of changes in lung function and safety results more difficult. The one-week ivacaftor washout prior to GLPG1837 treatment initiation was thought to be long enough to return sweat chloride concentrations to pre-ivacaftor treatment levels, given the maximal sweat chloride effect is already achieved by 3 days following commencement of the drug [16] and ivacaftor's half-life is 12 h [5]. This seemed to be borne out by our data. In the present study, ivacaftor washout resulted in a significant decline in ppFEV$_1$ of 5.4%, illustrating an immediate negative effect of ivacaftor withdrawal on lung function.

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This phenomenon has been reported previously [22], however, the decline observed in the present study was more limited compared to other reports. The stabilisation and gradual recovery of lung function following GLPG1837 treatment suggests target engagement whereby the high dose of GLPG1837 likely yields efficacy similar to ivacaftor with respect to lung function. It is possible that a further decline in lung function beyond one week due to ivacaftor washout was masked by activity of the lower doses of GLPG1837. Additionally, the nature of the study design leads to some uncertainty in attributing effects, including the occurrence of adverse events, to specific doses of GLPG1837. Finally, the patient population included in this study is different from the population evaluated in the early ivacaftor phase 2 studies [23]; our patients had been receiving ivacaftor for a mean of 39 months. One could speculate that patients who had experienced very large benefit in lung function when initiating ivacaftor may have been less inclined to participate in this study. Overall, the data obtained in this study might underestimate the effect of GLPG1837 on lung function improvement.

These data show the potential need to reconsider how future clinical trials could be designed and conducted in patients already receiving stable treatment with other CFTR modulators, an issue that will become more relevant as standards of care evolve. The availability of more clinical data on the effect of CFTR modulator withdrawal on patients' lung function will allow for better design of future trials. It remains unclear whether withdrawal and/or re-administration of a potentiator or potentiator/corrector(s) combinations will have a similar impact on lung function.

In summary, this study demonstrated willingness of patients to enrol in a trial with a short CFTR modulator washout period and the feasibility of such a design. It showed clear CFTR modulator activity of GLPG1837 in a G551D mutation-positive patient population, determined by changes in sweat chloride concentration and improvement in FEV_1 towards screening values. This study provides insights on how future studies could be conducted that evaluate investigational drugs in patients with CF already receiving stable treatment with licensed CFTR modulators; patients on stable therapies may be willing to stop these for defined periods to enable the testing of new agents. However, the worsening in their respiratory health should be an important ethical consideration in the design of such trials.

Contributors

HdK, KC, OVdS contributed to the study design. JCD was the principal investigator. JCD, SvK-R, PD, ND, and EMK were study investigators and enrolled patients. DK, LA, FN, KC, and OVdS were responsible for the collection, assembly, and analysis of data. JCD, KC, OVdS, FN, and HdK were involved in data interpretation. JCD, KC, and OVdS were responsible for preparing the submitted report. All authors contributed to the review and revision of the report and had final approval of the report.

Declaration of interests

JCD received advisory fees and fees for clinical trial leadership from Galapagos, paid to her institution (Imperial College London), during the conduct of the study. JCD carried out advisory activities for AbbVie Inc., Chiesi CZ, Eloxx Pharmaceuticals, Enterprise and Ionis; advisory activities and clinical trial leadership for Algipharma and Proteostatis; advisory activities, educational activities and clinical trial leadership for Vertex Pharmaceuticals; and educational activities for Teva Pharmaceutical Industries Ltd. and received fees for taking part in a grant review board for Gilead Sciences Inc. and for Roche, outside the submitted work. OVdS and DK are employed as consultants for Galapagos. SvK-R received consultancy fees from Algipharma and Proteostasis outside the submitted work. PD received fees from Galapagos during the conduct of the study as a clinical trial principal investigator, and consultancy fees and conference expenses from Chiesi CZ, consultancy fees from Proteostasis, and fees from Flatley Discovery Lab and Vertex Pharmaceuticals as a clinical trial principal investigator, outside the submitted work. ND received clinical trial compensation from Galapagos during the conduct of the study. EMK received a grant from Gilead Sciences Inc., grant and personal fees from Vertex Pharmaceuticals, and personal fees from Proteostasis and Novartis, outside the submitted work. LA was employed as a consultant for Galapagos during the conduct of the study. FN, HdK and KC are employees of Galapagos. OVdS, HdK and KC also report a patent pending (WO2018/073175).

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Data sharing

The data that have been used are confidential.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcf.2019.05.006.

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