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Title	CFTR activity is enhanced by the novel corrector GLPG2222, given with and without ivacaftor in two randomized trials
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Publication date	2019-05-03
Original Citation	Bell, S.C., Barry, P.J., De Boeck, K., Drevinek, P., Elborn, J.S., Plant, B.J., Minić, P., Van Braeckel, E., Verhulst, S., Muller, K. and Kanters, D. (2019) 'CFTR activity is enhanced by the novel corrector GLPG2222, given with and without ivacaftor in two randomized trials'. Journal of Cystic Fibrosis, 18(5), pp.700-707. doi:10.1016/j.jcf.2019.04.014
Type of publication	Article (peer-reviewed)
Link to publisher's version	https://www.sciencedirect.com/science/article/pii/S1569199319300736 - 10.1016/j.jcf.2019.04.014
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Download date	2026-11-06 17:45:46
Item downloaded from	https://hdl.handle.net/10468/9100



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Journal of Cystic Fibrosis xxx (2019) xxx

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Original Article

CFTR activity is enhanced by the novel corrector GLPG2222, given with and without ivacaftor in two randomized trials☆

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ARTICLE INFO

Article history:
Received 8 February 2019
Revised 12 April 2019
Accepted 15 April 2019
Available online xxxx

Keywords:
Cystic fibrosis
F508del
Gating mutation
GLPG2222
Ivacaftor
CFTR modulator

ABSTRACT

Background: Several treatment approaches in cystic fibrosis (CF) aim to correct CF transmembrane conductance regulator (CFTR) function; the efficacy of each approach is dependent on the mutation(s) present. A need remains for more effective treatments to correct functional deficits caused by the F508del mutation.

Methods: Two placebo-controlled, phase 2a studies evaluated GLPG2222, given orally once daily for 29 days, in subjects homozygous for F508del (FLAMINGO) or heterozygous for F508del and a gating mutation, receiving ivacaftor (ALBATROSS). The primary objective of both studies was to assess safety and tolerability. Secondary objectives included assessment of pharmacokinetics, and of the effect of GLPG2222 on sweat chloride concentrations, pulmonary function and respiratory symptoms.

Results: Fifty-nine and 37 subjects were enrolled into FLAMINGO and ALBATROSS, respectively. Treatment-related treatment-emergent adverse events (TEAEs) were reported by 29.2% (14/48) of subjects in FLAMINGO and 40.0% (12/30) in ALBATROSS; most were mild to moderate in severity and comprised primarily respiratory, gastrointestinal, and infection events. There were no deaths or discontinuations due to TEAEs. Dose-dependent decreases in sweat chloride concentrations were seen in GLPG2222-treated subjects (maximum decrease in FLAMINGO: −17.6 mmol/L [GLPG2222 200 mg], $p < 0.0001$; ALBATROSS: −7.4 mmol/L [GLPG2222 300 mg], $p < 0.05$). No significant effects on pulmonary function or respiratory symptoms were reported. Plasma GLPG2222

Abbreviations: ANCOVA, Analysis of covariance; b.d., bis die (twice daily); BMI, Body mass index; CF, Cystic fibrosis; CFTR, Cystic fibrosis transmembrane conductance regulator; CFQ-R, Cystic Fibrosis Questionnaire-Revised; CI, Confidence interval; ECG, Electrocardiogram; GI, Gastrointestinal; LOCF, Last observation carried forward; LS, Least-squares; (m)ITT, (Modified) intent-to-treat; N/A, Not applicable; OC, Observed cases; PE, Point estimate; PK, Pharmacokinetics; (pp)FEV_1, (Percent predicted) forced expiratory volume in one second; SE, Standard error; q.d., quaque die (once daily); TEAE, Treatment-emergent adverse event; T_{max}, Time to maximum observed plasma concentration.

☆ Previous presentations: Data from the FLAMINGO and ALBATROSS trials have been presented as a poster and oral presentation, respectively, at the 41st European Cystic Fibrosis Conference, 6–9 June 2018 in Belgrade, Serbia [1,2] and at the 32nd North American Cystic Fibrosis Conference, 18–20 October 2018 in Denver, Colorado, USA [3,4].

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https://doi.org/10.1016/j.jcf.2019.04.014
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concentrations in CF subjects were consistent with previous studies in healthy volunteers and CF subjects.

Conclusions: GLPG2222 was well tolerated. Sweat chloride reductions support on-target enhancement of CFTR activity in subjects with F508del mutation(s). Significant improvements in clinical endpoints were not demonstrated. Observed safety results support further evaluation of GLPG2222, including in combination with other CFTR modulators.

Funding: Galapagos NV.

Clinical trial registration numbers

FLAMINGO, NCT03119649; ALBATROSS, NCT03045523

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1. Introduction

Approximately 90% of people with cystic fibrosis (CF) have at least one copy of the F508del mutation and around half of these individuals are F508del homozygous [5]. Current treatment approaches aimed at CF transmembrane conductance regulator (CFTR) modulation in F508del homozygous subjects have their limitations. Lumacaftor, a CFTR corrector, demonstrated no clinical benefit on pulmonary function and sweat chloride levels (a measure of CFTR activity) as a monotherapy in this population [6,7], while the combination of lumacaftor and the CFTR potentiator ivacaftor reduced pulmonary exacerbations but offered modest effects on lung function and quality of life [7–9]. Drug intolerances necessitated frequent discontinuation particularly in individuals with a forced expiratory volume in one second (FEV_1) below or equal to 40% treated with this combination [10,11]. In addition, lumacaftor is a strong cytochrome P4503A inducer and drug–drug interactions can complicate its use [12,13]. Tezacaftor is a CFTR corrector with similar clinical efficacy to lumacaftor but is associated with fewer adverse effects and drug–drug interactions. In combination with ivacaftor, tezacaftor has demonstrated CFTR channel activity with an acceptable safety profile in F508del homozygous subjects [12,14]. However, a need remains for more effective treatments for CF subjects with F508del mutation, and novel doublet and triplet potentiator and corrector combinations are under clinical evaluation (NCT03525444, NCT03525574, NCT03447249, NCT03447262, NCT03500263). Class III gating mutations (e.g., G551D), which result in the failure of CFTR channels to function on the cell surface [5,15], are less common than the F508del mutation [16] and functioning can be partially restored with CFTR potentiators. However, as the majority of people with a gating mutation also have the F508del mutation on their second allele (83% in the USA [17] and 87% in Europe [18]), these patients may benefit from being treated with a corrector in addition to a potentiator.

GLPG2222 is a novel, potent CFTR corrector in development for the treatment of CF [15,19,20]. In primary bronchial epithelial cells from F508del homozygous subjects, GLPG2222 in combination with a potentiator partially restored CFTR function and was over 25-fold more potent than lumacaftor [15]. In phase 1 studies, GLPG2222 was well tolerated in healthy and CF subjects, and single-dose pharmacokinetics (PK) were similar in both populations [19,20]. The results from two phase 2a studies evaluating GLPG2222 are reported here; the FLAMINGO study (NCT03119649) in F508del homozygous subjects and the ALBATROSS study (NCT03045523) in subjects heterozygous for F508del and a class III gating mutation, who were receiving ivacaftor. The primary objective of both studies was to assess the safety and tolerability of GLPG2222. Secondary objectives included assessment of markers of CFTR activity, pulmonary function, respiratory symptoms, and PK.

2. Methods

2.1. Study participants

Adult subjects aged ≥18 years with a confirmed clinical diagnosis of CF were eligible for inclusion in these studies. Subjects enrolled in the FLAMINGO study were homozygous for the F508del CFTR mutation. In the ALBATROSS study, the main inclusion criteria were an F508del mutation on one allele of the CFTR gene and a gating mutation (one of the following: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R) on the other, and a stable concomitant medication regimen (including ivacaftor [150 mg *b.d.*]) for ≥4 weeks prior to first study drug administration. In both studies, subjects were required to have $FEV_1 \geq 40\%$ of predicted at their first baseline visit.

For both studies, exclusion criteria included: a history of clinically important concomitant disease which, in the opinion of the investigator, made the subject unsuitable for the study; unstable pulmonary status or respiratory tract infection (including rhinosinusitis) that necessitated a change in therapy within 4 weeks prior to first study drug administration; and use of supplemental oxygen during the day or at a rate of >2 L/min while sleeping. An additional exclusion criterion for the FLAMINGO study was the use of CFTR modulator therapy (e.g. lumacaftor and ivacaftor) within 4 weeks prior to first study drug administration.

The studies conformed to Good Clinical Practice guidelines and Declaration of Helsinki principles, and all subjects provided written, informed consent. The protocol and consent forms were approved by an independent ethics committee/institutional review board at each center.

2.2. Study designs and procedures

Two phase 2a, multicenter, randomized, double-blind, placebo-controlled, parallel-group trials were performed (Fig. S1). Treatments were administered orally once daily for 29 days. GLPG2222 was administered as a tablet in the FLAMINGO study and as an oral suspension in the ALBATROSS study (as the tablet formulation was not available at the time of study conduct).

In the FLAMINGO study, eligible subjects were enrolled sequentially. The first 25 subjects were randomized 2:2:1 to receive either GLPG2222 50 mg, GLPG2222 100 mg, or matching placebo, and the last 34 subjects were randomized 2:2:1 to receive either GLPG2222 200 mg, GLPG2222 400 mg, or matching placebo. In the ALBATROSS study, eligible subjects were randomized 2:2:1 to receive either GLPG2222 150 mg, GLPG2222 300 mg, or matching placebo in addition to their current ivacaftor treatment (150 mg *b.d.*). In both studies, randomization was performed via a computerized interactive web response system. Subjects, investigators, study coordinators, sponsor, and study team remained blinded to treatment assignment until study completion. Doses of GLPG2222 were selected based upon in vitro data and the exposures seen in phase 1 studies in healthy volunteers and CF subjects [15,19,20].

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2.3. Study endpoints and assessments

The primary endpoint in both studies was safety and tolerability as assessed by treatment-emergent adverse events (TEAEs), clinical laboratory evaluations, 12-lead electrocardiogram (ECG), vital signs, spirometry, oxygen saturation (pulse oximetry), and physical examinations.

Secondary endpoints included the change from baseline in sweat chloride concentration, pulmonary function, respiratory symptoms, and PK parameters. Assessments were performed at screening; pre-dose on days 1, 15, and 29; at early discontinuation (if applicable); and at follow-up. Additional blood samples for optional PK analysis were taken post-dose on day 15 or 29. Spirometry (assessed for safety purposes) was also performed 1–2 h after drug administration on days 1 and 29. Sweat was collected from both arms and chloride concentration determined from the arm with the greatest volume (main analysis) and the mean of both arms (sensitivity analysis). As sweat chloride derived from the mean of both arms appeared to be less subject to variability, only these data are presented. Pulmonary function was assessed by pre-bronchodilator spirometry and data for percent predicted FEV_1 ($ppFEV_1$) and change from baseline FEV_1 derived from absolute FEV_1 values. Respiratory symptoms were assessed using the change from baseline in the respiratory symptom scale score of the Cystic Fibrosis Questionnaire-Revised (CFQ-R). Drug plasma concentrations were measured using a validated liquid chromatography tandem mass spectrometry method.

2.4. Statistical analyses

As the primary endpoint of both studies was related to safety, no strict sample size calculations were done. However, with 50 and 35 subjects for the FLAMINGO and ALBATROSS studies, respectively, it was possible to detect a difference between study drug doses for sweat chloride of 14 mmol/L, at a 5% 2-sided type 1 error (assuming a standard deviation of 10 mmol/L and with a power of 80%). No adjustment for multiple testing (GLPG2222 doses versus placebo) has been carried out on this sample size calculation due to the exploratory nature of these phase 2 studies.

The safety population consisted of all subjects who received at least one dose of study drug. The PK population consisted of subjects who were exposed to GLPG2222 and who had available and evaluable PK data. The intent-to-treat (ITT) population consisted of all subjects who received at least one dose of study drug and had at least one post-baseline assessment of efficacy data. In the ALBATROSS study, one subject assigned to the placebo group inadvertently received the 150 mg dose kit; efficacy data from ALBATROSS are therefore reported for a modified ITT (mITT) population, from which this subject was excluded. Analysis of covariance (ANCOVA) of changes from baseline at each time point, with treatment as factor and baseline value as covariate, was applied to sweat chloride, FEV_1, and CFQ-R data. A sensitivity analysis was performed using non-parametric tests (Kruskal-Wallis test for overall treatment effect and Wilcoxon rank sum tests for pairwise comparisons versus the placebo group) and a mixed effects model for repeated measures – with treatment and analysis visit as fixed effects, baseline as a covariate, treatment analysis visit as an interaction term, and subject as random effect. Between-group comparisons were performed for each dose versus placebo (pooled placebo in the FLAMINGO study) without multiplicity correction. For efficacy measures, missing data were primarily imputed using the last observation carried forward method. An observed cases analysis was also performed.

3. Results

3.1. Subject disposition and baseline characteristics

The FLAMINGO study was conducted between 18 March and 19 October 2017 in the USA and Europe. The ALBATROSS study was conducted between 23 January and 24 August 2017 in Australia and Europe. Each study was conducted at 21 sites (Table S1).

Fifty-nine and 37 subjects were enrolled into the FLAMINGO and ALBATROSS studies, respectively, and all received at least one dose of study drug and were evaluated for safety. Efficacy was evaluated in 59 subjects in the ITT population in FLAMINGO and 36 subjects in the mITT population in ALBATROSS (Fig. 1). In both studies, baseline demographics and disease characteristics were generally balanced across groups, although $ppFEV_1$ was higher in the placebo groups (Tables 1 & S2). In addition, baseline sweat chloride levels were lower in ALBATROSS due to the effects of ivacaftor on the gating defect in the

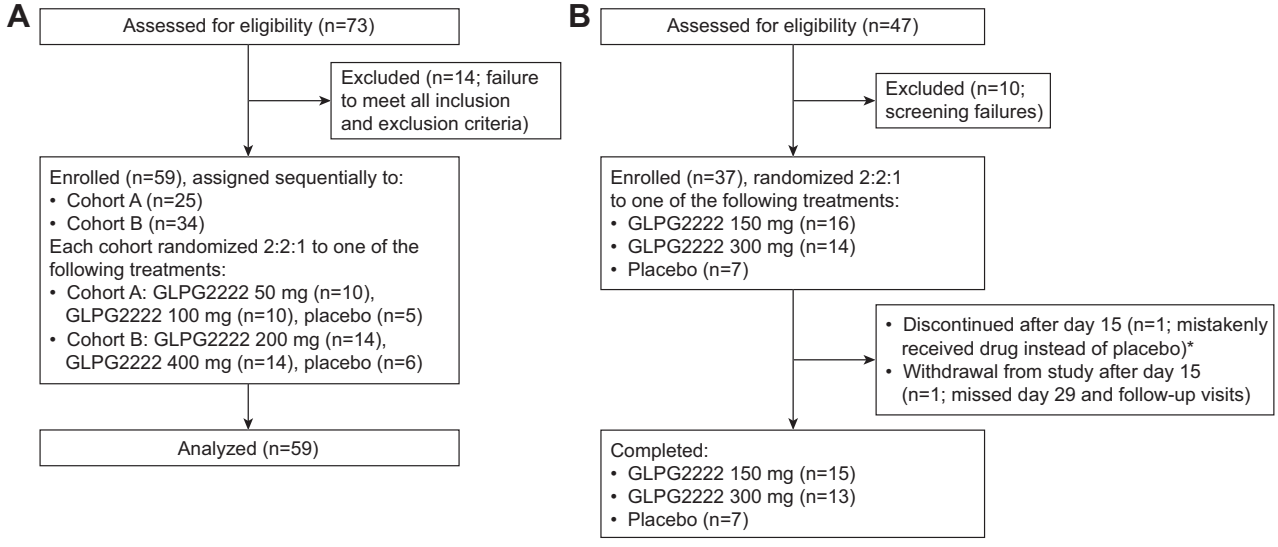


Fig. 1. Subject disposition for (A) the FLAMINGO study and (B) the ALBATROSS study. *One subject, who was randomized to the placebo treatment group, received the wrong study drug kit containing the GLPG2222 150 mg *q.d.* doses and discontinued treatment upon sponsor's decision. The subject was not included in the modified intent-to-treat population. *q.d., quaque die* (once daily).

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Table 1
Baseline demographics and disease characteristics for the FLAMINGO and ALBATROSS studies (safety populations).

Parameter	FLAMINGO (N = 59)					ALBATROSS (+ ivacaftor; N = 37)		
	Pooled placebo (n = 11)	GLPG2222 50 mg *q.d.* (n = 10)	GLPG2222 100 mg *q.d.* (n = 10)	GLPG2222 200 mg *q.d.* (n = 14)	GLPG2222 400 mg *q.d.* (n = 14)	Placebo (n = 7)	GLPG2222 150 mg *q.d.* (n = 16)	GLPG2222 300 mg *q.d.* (n = 14)
Median age, years (range)	27.0 (21–58)	26.0 (20–37)	24.0 (18–35)	32.0 (19–47)	26.0 (19–59)	46.0 (19–53)	29.0 (19–42)	29.0 (18–35)
Median BMI, kg/m^2 (range)	22.20 (16.3–25.7)	21.05 (18.7–25.1)	20.75 (14.1–23.3)	22.30 (18.5–26.8)	22.40 (18.3–23.7)	25.30 (21.2–33.6)	23.95 (19.9–31.5)	22.00 (18.4–34.3)
Male, n (%)	7 (63.6)	7 (70.0)	4 (40.0)	7 (50.0)	9 (64.3)	3 (42.9)	12 (75.0)	6 (42.9)
Median sweat chloride, mmol/L (range)[a]	108.0 (91.5–114.5)	105.5 (86.0–114.5)	110.0 (96.0–113.0)	102.8 (82.0–119.5)	105.8 (100.0–123.0)	32.5 (25–90)	38.8 (16–99)	48.8 (14–88)
Median ppFEV$_1$, % (range)	75.0 (43–92)	53.5 (35–80)	59.5 (39–113)	51.5 (40–88)	58.5 (38–92)	81.0 (37–97)	72.5 (41–113)	63.0 (37–99)
Mutation second allele, n (%)	N/A							
G178R						0	1 (6.3)	0
G551D						4 (57.1)	13 (81.3)	11 (78.6)
S1251 N						1 (14.3)	2 (12.5)	2 (14.3)
S1255P						1 (14.3)	0	1 (7.1)
S549R						1 (14.3)	0	0
Median duration of ivacaftor use, weeks (range)	N/A					213.0 (17–233)	197.5 (74–337)	117.5 (41–216)

BMI, body mass index; ppFEV$_1$, percent predicted forced expiratory volume in one second; N/A, not applicable; *q.d., quaque die* (once daily).
[a] Mean value from both arms.

sweat glands. G551D was the most prevalent gating mutation among subjects in the ALBATROSS trial (Table 1).

3.2. Safety and tolerability

In FLAMINGO, the most common TEAEs in subjects treated with GLPG2222 were headache (n = 14), cough (n = 12), pulmonary exacerbation of CF (n = 8), and sputum increase (n = 8) (Table S3). In ALBATROSS, headache (n = 10) and diarrhea (n = 8) were the most common (Table S4). There were no deaths or TEAEs leading to treatment discontinuation in either study. In GLPG2222-treated subjects, treatment-related TEAEs were reported by 29.2% (14/48) of subjects in FLAMINGO and 40.0% (12/30) in ALBATROSS. Most TEAEs were mild or moderate (Table 2).

In the FLAMINGO study, serious TEAEs were reported in two subjects in the placebo group and one in the GLPG2222 100 mg group, all of whom experienced pulmonary exacerbation of CF. None were considered study drug-related. There were no serious TEAEs reported in the ALBATROSS study (Table 2). In both studies, there were no clinically significant trends in mean and median laboratory parameters, ECG, vital signs, or pulse oximetry values observed over time.

3.3. Efficacy

3.3.1. Sweat chloride concentrations

In both studies, mean changes from baseline in sweat chloride concentration were similar whether determined from the mean of both arms or the arm with the greatest volume. Results using the sweat chloride derived from the mean of both arms are presented here. In each study, baseline concentrations were similar across groups. In subjects who received placebo, sweat chloride levels increased over time in ALBATROSS but decreased in the FLAMINGO study, likely reflecting intra-subject variability (Fig. 2A&B). Mean concentrations decreased in all GLPG2222 treatment groups at days 15 and 29 compared with baseline (Fig. 2A&B). In the FLAMINGO study, this decrease was dose-dependent up to 200 mg. On days 15 and 29, least-squares (LS)-mean differences in the GLPG2222 200 mg group versus placebo (95% confidence interval [CI]) were −11.2 (−19.1, −3.3; p = 0.0062) and −15.8 mmol/L (−23.2; −8.3; p < 0.0001), respectively. In the ALBATROSS study, the maximum decrease

Table 2
Safety summary for the FLAMINGO and ALBATROSS studies (safety populations).

Parameter	FLAMINGO (N = 59)					ALBATROSS (+ ivacaftor; N = 37)		
	Pooled placebo (n = 11)	GLPG2222 50 mg *q.d.* (n = 10)	GLPG2222 100 mg *q.d.* (n = 10)	GLPG2222 200 mg *q.d.* (n = 14)	GLPG2222 400 mg *q.d.* (n = 14)	Placebo (n = 7)	GLPG2222 150 mg *q.d.* (n = 16)	GLPG2222 300 mg *q.d.* (n = 14)
All TEAEs, n (%)	9 (81.8)	8 (80.0)	10 (100.0)	11 (78.6)	9 (64.3)	7 (100.0)	12 (75.0)	13 (92.9)
TEAEs n, (%)								
Mild	6 (54.5)	4 (40.0)	7 (70.0)	8 (57.1)	9 (64.3)	5 (71.4)	10 (62.5)	11 (78.6)
Moderate	2 (18.2)	4 (40.0)	2 (20.0)	2 (14.3)	0	2 (28.6)	1 (6.3)	2 (14.3)
Severe	1 (9.1)[a]	0	1 (10.0)[a]	1 (7.1)[b]	0	0	1 (6.3)[c]	0
Treatment-related TEAEs, n (%)	2 (18.2)	2 (20.0)	6 (60.0)	5 (35.7)	1 (7.1)	5 (71.4)	4 (25.0)	8 (57.1)
Serious TEAEs, n (%)	2 (18.2)	0	1 (10.0)	0	0	0	0	0

q.d., quaque die (once daily); TEAE, treatment-emergent adverse event.
[a] Pulmonary exacerbation of cystic fibrosis (not considered related to study drug).
[b] Bronchial secretion decrease, purulent discharge, and exercise tolerance increase.
[c] Headache.

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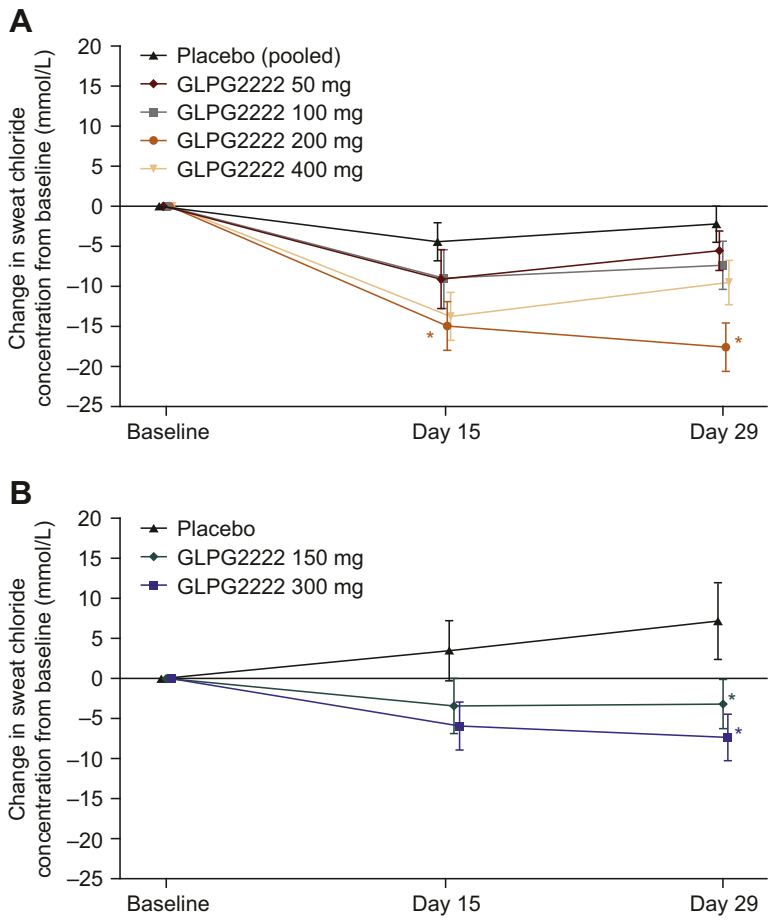


Fig. 2. Mean (±SE) change in sweat chloride concentration from baseline to days 15 and 29 using the mean value from both arms in (A) the FLAMINGO study (ITT, LOCF) and (B) the ALBATROSS study (modified ITT, LOCF). *$p < 0.05$ (treatment group versus placebo). FLAMINGO: Pooled placebo, n = 11; GLPG2222 50 mg, n = 10; GLPG2222 100 mg, n = 10; GLPG2222 200 mg, n = 14; GLPG2222 400 mg, n = 14. ALBATROSS: Placebo, n = 7; GLPG2222 150 mg, n = 15; GLPG2222 300 mg, n = 14. ITT, intent-to-treat; LOCF, last observation carried over; SE, standard error.

from baseline was in the GLPG2222 300 mg group at day 29 (LS-mean difference versus placebo was −11.7 mmol/L [95% CI −21.1, −2.2; p = 0.0170]). The results of the sensitivity analysis confirmed the primary ANCOVA analysis (Table S5). Waterfall plots of the change from baseline in sweat chloride concentration at day 29 are shown in Fig. S2A&B.

3.3.2. Pulmonary function

In the FLAMINGO study, there were no differences in the change in $ppFEV_1$ from baseline at days 15 and 29 between the pooled placebo and GLPG2222 groups (Fig. 3A and Table S6). In the ALBATROSS study, at day 29, there was a trend for higher $ppFEV_1$ with GLPG2222 300 mg versus baseline, but improvements were not significant compared with placebo (LS-mean difference [95% CI] 3.0% [−1.5%, 7.5%], p = 0.1812) (Fig. 3B and Table S6). Waterfall plots of change from baseline in $ppFEV_1$ at day 29 are shown in Fig. S3A&B. The results of the sensitivity analysis were similar to the results of the primary ANCOVA analysis (Table S6). Trends in data for change in FEV_1 from baseline were similar to those for $ppFEV_1$ in both studies (absolute FEV_1 data are shown in Figs. S4 and S5).

3.3.3. Respiratory symptoms as measured by CFQ-R

CFQ-R respiratory symptom scale scores did not change significantly in either study (Table S7).

3.4. Pharmacokinetics

Time to maximum observed plasma concentration (T_{max}) of GLPG2222 was independent of dose and occurred earlier with the oral suspension (ALBATROSS study) compared with the tablet formulation (FLAMINGO study), with a median T_{max} of 1 h versus 2–3 h, respectively. Overall, the mean concentrations of GLPG2222 increased proportional to dose in both studies.

Multiple oral doses of GLPG2222 had no effect on ivacaftor exposures (ALBATROSS study); point estimates of the geometric mean ratios for maximum observed plasma concentration of ivacaftor were close to 100%.

4. Discussion

The objective of these studies was to expand upon prior preclinical and phase 1 clinical studies of GLPG2222, providing further information about safety, tolerability, and PK in CF subjects, as well as a preliminary evaluation of efficacy. These data will help to inform subsequent studies with GLPG2222 in combination with other CFTR modulators, as part of the compound's long-term clinical development.

GLPG2222 was well tolerated when administered alone in F508del homozygous subjects (FLAMINGO) or in combination with ivacaftor in subjects heterozygous for F508del and with a gating mutation (ALBATROSS). Similar to earlier phase 1 data [19], the TEAEs reported in both these phase 2 studies were mild to moderate in severity, and typical for a CF study population (primarily respiratory, GI, and infection-related). When comparing post-dose versus pre-dose spirometry measurements in the current studies no significant differences were observed, indicating a lack of bronchoconstriction. This is reassuring as such effects (chest tightness, dyspnea) have been reported

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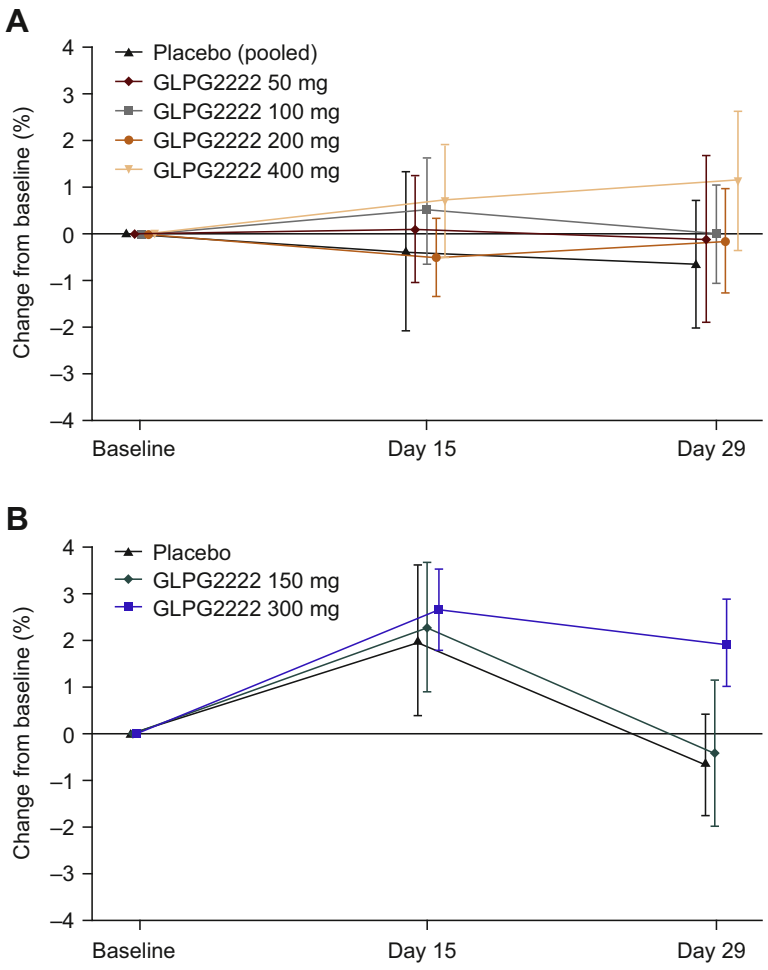


Fig. 3. Mean (±SE) change in $ppFEV_1$ from baseline to days 15 and 29 in (A) the FLAMINGO study (ITT, LOCF) and (B) the ALBATROSS study (modified ITT, LOCF). FLAMINGO: Pooled placebo, n = 11; GLPG2222 50 mg, n = 10; GLPG2222 100 mg, n = 10; GLPG2222 200 mg, n = 14; GLPG2222 400 mg, n = 14. ALBATROSS: Placebo, n = 7; GLPG2222 150 mg, n = 15; GLPG2222 300 mg, n = 14. ITT, intent-to-treat; LOCF, last observation carried over; $ppFEV_1$, percent predicted forced expiratory volume in one second; SE, standard error.

in some subjects and healthy volunteers receiving their first administration of lumacaftor/ivacaftor [7,8,21,22]. There were no permanent discontinuations of GLPG2222 due to TEAEs in either of the present studies.

The PK of GLPG2222 was consistent with previous studies. GLPG2222 did not impact the PK of ivacaftor. In both studies, there was a decrease in sweat chloride concentration, confirming on-target activity of GLPG2222 [23]. The 400 mg dose of GLPG2222 provided the highest exposure, but this did not translate to the greatest decrease in sweat chloride, which was observed at the 200 mg dose. The difference between these doses was less pronounced at day 15 compared with day 29. This leads us to postulate that a plateau may be reached at 200 mg and numerically different results between doses at or above 200 mg may be related to variability and/or limited subject numbers. Sweat chloride concentrations increased over time in the placebo group of the ALBATROSS study. The reasons for this are unclear, however baseline sweat chloride levels (i.e. on ivacaftor treatment) were low in these subjects, and when baseline sweat chloride concentrations approach normal levels it becomes more difficult to determine an effect. In all treatment arms, ivacaftor exposure levels remained stable throughout the study (data not shown), suggesting adherence to ivacaftor was also stable. A substantial effect of GLPG2222 on lung function was not expected, as only modest effects have generally been reported in studies of other drugs with a similar mechanism of action and activity on CFTR in F508del homozygous subjects [6–9,12]. Our findings are therefore consistent with data reported by others showing that Type I CFTR correctors partially restore F508del CFTR to the plasma membrane where it can reside as a low activity CFTR channel. For example, in a phase 2 study, lumacaftor did not affect lung function in doses up to 200 mg *q.d.* but did exhibit a dose–response effect on sweat chloride levels [6], while at higher doses there was a dose-related decline in FEV_1 [7]. When lumacaftor was combined with ivacaftor in a phase 3 trial, a mean 2.6–4 percentage point increase in FEV_1 was reported for those receiving the combination compared with placebo ($p < 0.001$) [8]. In a phase 2 trial of tezacaftor plus ivacaftor, a small but significant improvement in $ppFEV_1$ was reported (3.75 percentage points) in F508del homozygous subjects [14]; an observation confirmed at phase 3 [12]. In subjects who were heterozygous for F508del and a CFTR residual function mutation, tezacaftor plus ivacaftor significantly increased $ppFEV_1$ by 2.1 percentage points compared with ivacaftor alone [24]. By comparison, the greatest increase in $ppFEV_1$ in the present studies was an increase of 2.6 percentage points versus placebo in F508del heterozygous subjects in the ALBATROSS study, however this improvement was not significant.

Limitations of the current studies include the low subject numbers in each group for the efficacy outcomes. As safety was the primary endpoint and in vitro data and literature on mechanistically similar CFTR modulators indicated only small changes in $ppFEV_1$ were expected, the studies were not powered to detect differences in efficacy outcomes, including FEV_1. Also spirometry data may have been confounded by the higher baseline FEV_1 values in the placebo versus the test groups, making interpretation difficult (as subjects with lower lung function may not have responded as well to active treatment as those with higher

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function at baseline). However, FEV_1 is inherently variable and this difference between groups may have occurred by chance due to randomization of small subject numbers. It is expected that, in combination with a potentiator, GLPG2222 will demonstrate clinical efficacy on FEV_1 in F508del homozygous subjects based on in vitro data and comparisons with known dual combinations.

Development of combination therapies is challenging and evaluation of single agents, as undertaken in the FLAMINGO study, mitigates potential safety risks when combining two or more drugs. It also provides a step-wise approach to understanding safety and efficacy of compounds and allows fine-tuning of dose selection in subsequent combination therapies. Other CFTR correctors are in development for use in combination therapy for CF. For example, the next-generation correctors VX-659 (NCT03224351 and NCT03029455), VX-445 (NCT03227471), VX-440 (NCT02951182), and VX-152 (NCT02951195) have demonstrated improvements in CF outcomes when given with tezacaftor and ivacaftor in phase 1 or 2 studies in subjects homozygous for F508del or heterozygous for F508del and a minimal function CFTR mutation [25–28]. These and other investigational combinations, such as the triple combination PTI-428/PTI-801/PTI-808 (NCT03500263), may expand the treatment armamentarium available to CF patients in the future.

5. Conclusions

A range of new CFTR modulators are currently under evaluation through phase I to III clinical trials and the therapeutic landscape is changing rapidly, resulting in fewer modulator-naïve subjects available for clinical studies. This has important implications for the design and conduct of future trials, such as the evaluation of treatment combinations. Findings from FLAMINGO and ALBATROSS demonstrated that GLPG2222 is well tolerated both alone and in combination with ivacaftor, with preliminary data suggesting partial correction of CFTR function and on-target activity. These outcomes will inform the future clinical evaluation of GLPG2222 within this dynamic environment, in particular with regards to its use in combinations with additional CFTR modulators.

Contributors

SCB, PJB, KDB, PD, JSE, BJP, PM, EVB, SV, and KvdE were involved in data collection. KM, DK, HdK, DEG, KC, and OVdS were involved in study design. KM was involved in data analysis. DEG and SB were involved in data interpretation. KC and OVdS were involved in data analysis and interpretation. All authors reviewed and revised drafts of the manuscript and approved the final draft.

Declaration of interests

SCB has received grants, personal fees and travel support (to attend investigator meetings) from Galapagos NV during the conduct of the studies as global and site principal investigator, and travel support as a member of an advisory board, writing group, site PI and author of company-sponsored studies from Rempex Pharmaceuticals and Vertex Pharmaceuticals, travel support as a member of an advisory board from AbbVie Inc., and travel support from Gilead Sciences Inc. and Novartis to attend sponsored symposia and meetings outside the submitted work. PJB's institution received fees and travel support from Galapagos NV during the conduct of the studies. PJB received consultancy fees, speaker fees and an unrestricted educational grant from Vertex Pharmaceuticals outside the submitted work. KDB has received consultancy fees from Galapagos NV during the conduct of the studies, and consultancy fees from Ablynx, Boehringer Ingelheim, Novabiotics Ltd., Protalix Biotherapeutics, and Raptor, fees as a member of advisory board, steering committee and/or as principal investigator of studies for Eloxx Pharmaceuticals, PTC Therapeutics, and Vertex Pharmaceuticals, and speaker fees from Teva Pharmaceutical Industries Ltd. outside the submitted work. PD received personal fees from Galapagos NV during the conduct of the studies as principal investigator, and personal fees as principal investigator of clinical trials for Flatley Discovery Lab, Proteostasis Therapeutics Inc., and Vertex Pharmaceuticals, and conference expenses from Chiesi CZ outside the submitted work. JSE received consultancy fees and a grant to cover clinical trial costs from Galapagos NV during the conduct of the studies, and consultancy fees from Vertex Pharmaceuticals and grants to cover clinical trial costs from Corbus Pharmaceuticals, Celtaxsys and Vertex Pharmaceuticals outside the submitted work. BJP received grants and consultancy fees from Galapagos NV during the conduct of the studies and consultancy fees from Vertex Pharmaceuticals outside the submitted work. PM received consultancy fees from Galapagos NV during the conduct of the studies and from MSD and Novartis outside the submitted work. EVB's institution (Ghent University Hospital) received an institutional fee from Galapagos NV during the conduct of the studies. SV has no conflicts to declare. KM is an employee of Galapagos and was previously employed by Keyrus Biopharma as a consultant for Galapagos, during the conduct of the studies. DK and OVdS received personal fees as consultants for Galapagos during the conduct of the studies. SB is an employee of, and received warrants from, Galapagos. HdK and KC are employees of Galapagos. DG is an employee of AbbVie Inc. KvdE received grants from Galapagos NV during the conduct of the studies, and from Gilead Sciences Inc., GSK, Nutricia, ProQR, Proteostasis Therapeutics Inc., Teva Pharmaceutical Industries Ltd. and Vertex Pharmaceuticals outside the submitted work.

Source of funding

The studies were funded by Galapagos NV (Mechelen, Belgium) and conducted in collaboration with AbbVie, Inc. (Chicago, IL, USA). The sponsor supervised study design, study execution, data collection, statistical analyses, data interpretation, and the writing of the report.

Data sharing

The data that have been used are confidential.

Acknowledgements

We thank all patients and investigators involved in the studies. Medical writing support (including development of a draft outline and subsequent drafts in consultation with the authors, assembling tables and figures, collating author comments, copy-editing, fact-checking, and referencing) was provided by Kate Wicks PhD at Aspire Scientific (Bollington, UK), and funded by Galapagos NV (Mechelen, Belgium).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcf.2019.04.014.

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