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Safety, Tolerability and Pharmacokinetics of single and multiple doses of GLPG2737, a novel CFTR corrector molecule, in healthy volunteers

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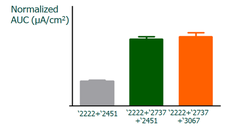
Introduction

GLPG2737 is a novel cystic fibrosis transmembrane conductance regulator (CFTR) corrector in clinical development for the treatment of cystic fibrosis (CF). GLPG2737 exhibits potent in vitro activity in primary patient cells harbouring F508del/F508del. GLPG2737 represents one component of a future potentiator/correctors combination therapy targeting a broad CF patient population. Following successful completion of preclinical safety evaluations, GLPG2737 was progressed to Phase 1 clinical evaluations in healthy subjects. We present results from this first-in-human clinical study.



TECC data in primary HBE cells from a F508del/F508del CF patient, comparing dual- versus '2737-containing triple combinations

Objectives

- To evaluate the safety and tolerability of single ascending oral doses (SAD) and multiple ascending oral doses (MAD) of GLPG2737 administered to healthy male subjects
- To characterize the pharmacokinetics (PK) of GLPG2737 after single and multiple oral administrations
- To evaluate the potential of interaction with cytochrome P450 (CYP) 3A4 after repeated dosing with GLPG2737

Methods

Randomized, double-blind, placebo-controlled study:

- SAD: sequential cohorts of 8 subjects received single oral doses from 25 mg up to 600 mg of GLPG2737 (or placebo)
- MAD: four sequential cohorts of 8 subjects received GLPG2737 administered orally at doses from 25 mg up to 250 mg q.d. (or placebo) for 14 days

Subjects were randomized in a 3:1 ratio (active versus placebo).

Administration as oral suspension after a standard breakfast.

Safety results

- No deaths or serious adverse events occurred. None of the treatment emergent AEs (TEAEs) led to study drug discontinuation. All TEAEs were rated mild or moderate in intensity. No clinically significant changes in vital signs, ECG morphology or ECG time intervals were reported.
- No clinically significant changes in laboratory safety tests were reported apart from one subject who received GLPG2737 Dose 3 (MAD) presenting asymptomatic raised ALT on Days 14, 17, 18 and at follow-up of 187, 227, 202 and 70 U/L (ALT normal range 0-68 U/L), respectively. This was associated with isolated AST elevations of 86, 79 and 70 U/L on Days 14, 17 and 18, respectively (AST normal range 0-45 U/L) and with recovery at follow-up (25 U/L); bilirubin levels remained within the normal range throughout.

Table 1: Incidence of TEAEs reported in 2 or more subjects (MAD part)

Preferred term, N	Pooled placebo N=8	GLPG2737 Dose 1 N=6	GLPG2737 Dose 2 N=6	GLPG2737 Dose 3 N=6	GLPG2737 Dose 4 N=6
Oropharyngeal pain	0	0	1	3	0
Cough	2	0	0	0	0
Dry throat	0	0	0	1	1
Productive cough	2	0	0	0	0
Dry skin	0	0	0	3	2
Acne	0	0	0	3	0
Skin irritation	2	0	0	0	0
Dry mouth	2	0	0	1	0
Catheter site reaction	0	1	1	0	0
Fatigue	0	2	0	0	0
Nasopharyngitis	1	3	0	0	0
Headache	1	0	0	1	0

Pharmacokinetics

SAD

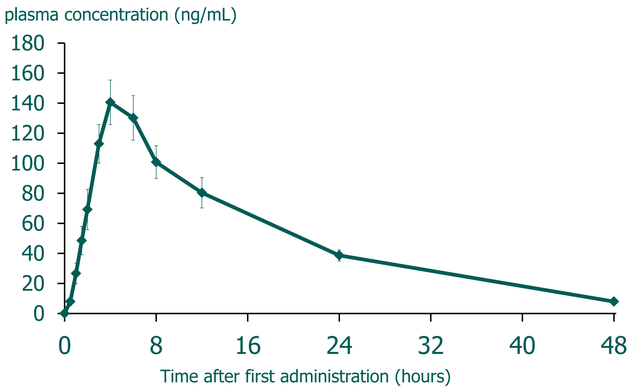


Figure 1: Mean (±SEM) GLPG2737 plasma levels after a single oral dose of 25 mg as oral suspension in fed state

MAD

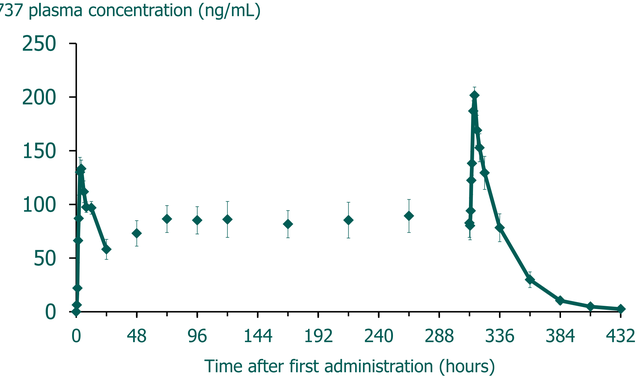


Figure 2: Mean (±SEM) GLPG2737 plasma levels after multiple once-daily oral dosing of 25 mg as oral suspension in fed state

Conclusions

- GLPG2737 was generally well tolerated when dosed up to 250 mg q.d. for 14 days in healthy subjects
- GLPG2737 is rapidly absorbed and has a mean apparent elimination half-life of 12 hours. After q.d. dosing, steady state was attained within 4 days of dosing, with minimal accumulation
- Induction of CYP4A4 is unlikely based upon lack of significant changes in the ratio 4-β-OH-cholesterol/cholesterol
- Overall, these results support the progression of GLPG2737 into Phase II clinical studies in CF patients

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