

Safety, tolerability and pharmacokinetics of a novel CFTR potentiator GLPG2451 with and without a novel CFTR corrector GLPG2222 in healthy volunteers

Brearley, C.J.¹; Gesson, C.²; Kanters, D.¹; Cock, P.³; Conrath, K.¹; Corveleyn, S.¹; Van de Steen, O.¹; de Kock, H.¹; van 't Klooster, G.¹

¹ Galapagos NV, Generaal De Wittelaan L11A3, 2800 Mechelen, Belgium

² Galapagos SASU, Romainville, France

³ SGS Life Sciences Services, CPU, Antwerp, Belgium

Introduction

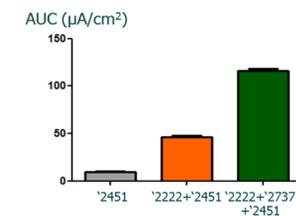
GLPG2451 is a novel cystic fibrosis transmembrane conductance regulator (CFTR) potentiator in clinical development for the treatment of cystic fibrosis (CF).

In cellular assays, GLPG2451 exhibits potent *in vitro* activity in primary patient cells harboring the CFTR F508del/F508del mutation. M31 is an active metabolite of GLPG2451 observed in humans which has similar potency and efficacy as the parent compound.

GLPG2222 is a novel CFTR corrector in clinical development for the treatment of CF. In cellular assays, GLPG2222 exhibits potent *in vitro* activity, partially restoring F508del CFTR cell surface expression.

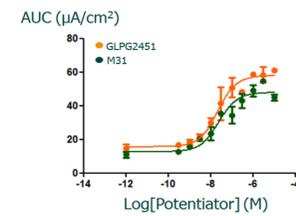
GLPG2451 and GLPG2222 represent two components of a potential future potentiator/corrector(s) combination therapy targeting CF patients harbouring at least one F508del mutation.

Activity of GLPG2451 in HBE cells (F508del/F508del)



TECC data in primary HBE cells from F508del/F508del CF patients, comparing single compound with dual- and triple combinations.

Similar potency and efficacy of GLPG2451 and metabolite M31



TECC data in primary HBE cells from F508del/F508del CF patients. Dose response curves of GLPG2451 and M31 on GLPG2222 corrected cells.

Objectives

- To assess the safety, tolerability of SAD and MAD of GLPG2451 in healthy volunteers
- To assess the pharmacokinetic properties of GLPG2451 after single and multiple oral administrations
- To evaluate safety, tolerability and pharmacokinetics of the combination of GLPG2451 and GLPG2222 given for 14 days

Methods

- Randomized, double-blind, placebo-controlled (3:1 randomization)
- SAD:** 4 cohorts of 8 subjects received single oral doses ranging from 5 mg to 80 mg of GLPG2451
- MAD:** 3 consecutive cohorts of 8 subjects received GLPG2451 administered orally with loading doses from 35 mg up to 80 mg with maintenance doses from 1.5 mg up to 5 mg q.d.
- Combination: 2 consecutive cohorts of 8 subjects received GLPG2451 as in the MAD, combined with two dose levels of GLPG2222 q.d.
- GLPG2451 and GLPG2222 were administered once-daily as an oral suspension after standard breakfast

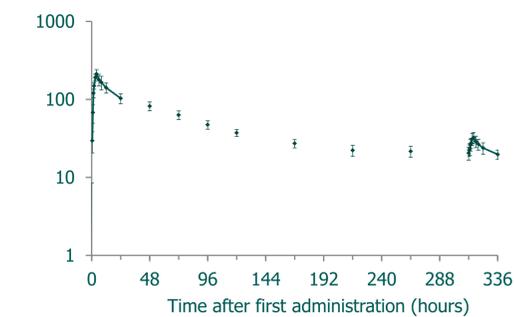
Safety results

- GLPG2451 administered alone and in combination with GLPG2222 for 14 days was well tolerated.
- All treatment emergent AEs (TEAEs) were mild or moderate in intensity and did not lead to discontinuation of study drug. No deaths or serious adverse events occurred during the study.
- In Part 1 (MAD, GLPG2451 alone) adverse events reported by 2 or more subjects who received GLPG2451 were nasopharyngitis (5 subjects), headache (3 subjects), dry skin (3 subjects), diarrhoea (3 subjects), oropharyngeal pain (3 subjects), musculoskeletal stiffness (3 subjects), migraine (2 subjects), and back pain (2 subjects).
- In Part 2 (MAD, combination of GLPG2451 and GLPG2222) TEAEs reported by 2 or more subjects were diarrhoea (4 subjects) and headache (3 subjects).
- In Parts 1 and 2 of the study between approximately 62% and 77% of study participants reported TEAEs, respectively, started within 14 days of treatment. There was a low incidence of TEAEs which developed during the extended follow up period (Days 61-168) when circulating levels of both GLPG2451 and its active metabolite M31 were low.

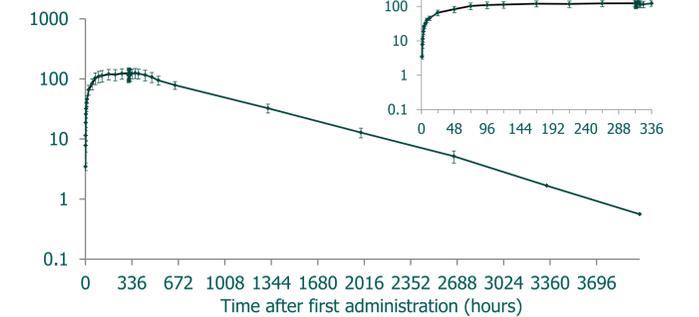
Pharmacokinetics

MAD – Exposure of GLPG2451 & active metabolite M31

GLPG2451 plasma concentration (ng/mL)



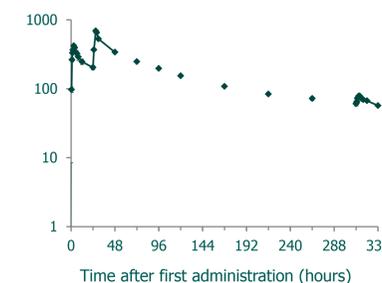
M31 plasma concentration (ng/mL)



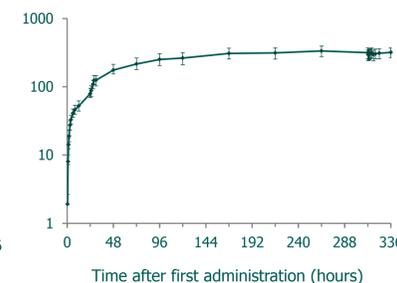
Mean (±SE) GLPG2451 (left) and M31 (right) plasma levels after multiple oral doses of GLPG2451 (35 mg loading dose on Day 1, followed by 1.5 mg q.d.) as oral suspension in fed state.

Combination GLPG2451 & GLPG2222

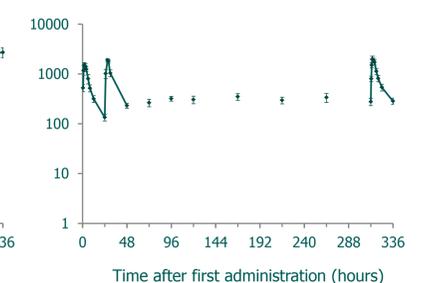
GLPG2451 plasma concentration (ng/mL)



M31 plasma concentration (ng/mL)



GLPG2222 plasma concentration (ng/mL)



Mean (±SE) plasma levels after multiple oral doses of GLPG2451 (left) and GLPG2222 (right) under fed state. GLPG2222 (150 mg q.d.) was combined with a loading/maintenance dose regimen of GLPG2451 previously explored in the MAD.

Conclusions

- CFTR potentiator activity is supported by both GLPG2451 and its major metabolite
- GLPG2451 was generally well tolerated at all doses, on treatment for 14 days and in 6 months follow up
- The pharmacokinetic profile is dose-proportional, and allows for low dose once-daily maintenance treatment
- The exposures of GLPG2451 and of GLPG2222 are similar when combined or when dosed separately
- Overall, these results support the progression of GLPG2451 into Phase II clinical studies in CF patients