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Pharmacokinetics and safety of a novel CFTR corrector molecule GLPG2222 in Healthy Subjects and in Subjects with Cystic Fibrosis (CF): results from two Phase I Studies

O. Van de Steen[1], F. Namour[2] , K. Conrath[1], D. Kanters[1], K. De Boeck[3], S. Corveleyn[1], D.E. Geller[4], H. de Kock[1]

[1] Galapagos NV, Generaal de Wittelaan L11 A3, 2800 Mechelen, Belgium
[2] Galapagos SASU, 102 Avenue Gaston Roussel, 93230 Romainville, France
[3] Pediatric Pulmonology, Department of Pediatrics, University of Leuven, Leuven, Belgium
[4] AbbVie Inc, North Chicago, IL., USA

Introduction

GLPG2222 (GLPG2222/ABBV-2222) is a novel cystic fibrosis transmembrane conductance regulator (CFTR) corrector in clinical development for the treatment of cystic fibrosis (CF). In cellular assays, GLPG2222 was shown to be a potent corrector partially restoring F508del CFTR cell surface expression when using a CFBe41o- cell line harbouring HRP-tagged F508del CFTR. In primary bronchial epithelial cells derived from patients homozygous for F508del, the combination of GLPG2222 and a CFTR potentiator restores the function of F508del CFTR and exhibits potent activity. GLPG2222 represents one component of a future potentiator/corrector(s) combination regimen targeting a broad CF patient population. Following successful completion of preclinical safety evaluations, GLPG2222 was progressed to Phase 1 clinical evaluations in healthy subjects and in subjects with CF.

Methods – Phase 1

Randomized, double-blind, placebo-controlled study in healthy subjects:

- SAD: 2 alternating cohorts of 8 subjects received single oral doses ranging from 50 to 800 mg of GLPG2222 (or placebo)
- MAD: three sequential cohorts of 8 subjects received GLPG2222 orally administered at doses of 150, 300, or 600 mg q.d. (or placebo) for 14 days

For every cohort, subjects were randomized in a 3:1 ratio (active versus placebo).

Study drug was administered as oral nanosuspension after standard breakfast.

Methods – Phase 1b

Figure 1: Study Design

Single Arm, Open-Label 2-Treatment Period

- Male subjects ≥ 18 years of age with confirmed clinical diagnosis of CF and ppFEV1≥40%
- F508del mutation on one allele; class I or class II or class III mutation on the 2nd allele
- Exocrine Pancreatic insufficiency

Safety results – Phase 1

- No deaths or serious adverse events occurred during the study. All TEAEs were rated mild in intensity
- No clinically significant findings in physical examinations, vital signs, safety laboratory tests and ECGs were observed
- No clinically significant changes in forced expiratory volume in one second (FEV1) were observed following single doses

Safety results – Phase 1b

- Overall, single doses of GLPG2222 were generally well tolerated when administered to adult subjects with CF
- Three transient adverse events were reported, two were mild (cough and productive cough) and one was moderate (headache)
- No clinically significant changes in safety laboratory parameters, ECGs, physical examinations, vital signs and spirometry outcomes were reported

Pharmacokinetic results

Figure 2: Mean (±SE) GLPG2222 plasma levels after multiple oral doses as nanosuspension in fed state in healthy subjects

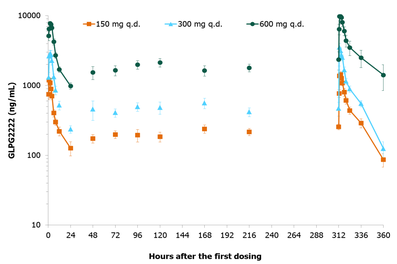


Figure 3: Mean (±SE) GLPG2222 plasma levels after single oral dosing as nanosuspension in fed state in CF patients

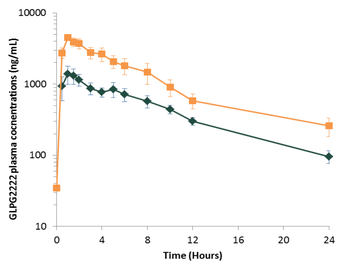
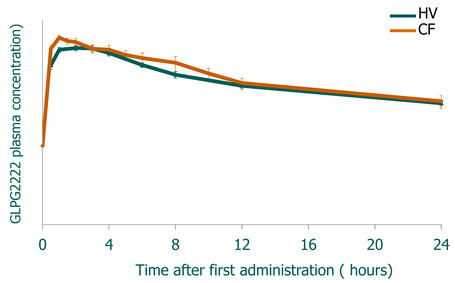
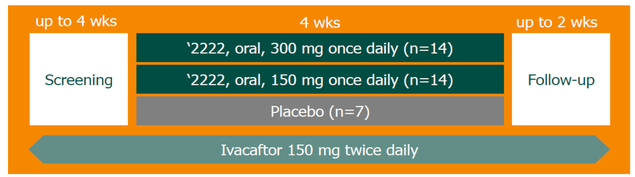


Figure 4: Mean (±SE) plasma levels of GLPG2222 in CF patients and healthy volunteers (HV)

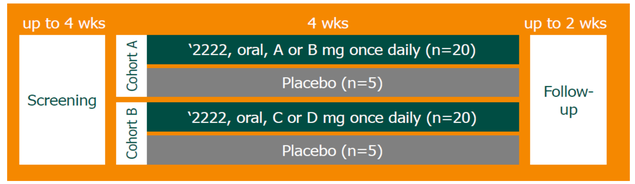


Ongoing Clinical Studies with GLPG2222 in CF subjects

- ALBATROSS: randomized, double-blind, placebo-controlled, parallel group study in adult subjects with CF harbouring a gating (class III) mutation and on stable treatment with ivacaftor (NCT03045523)



- FLAMINGO: randomized, double-blind, placebo-controlled, parallel group study in adult subjects with CF homozygous for the F508del CFTR mutation (NCT03119649)



Conclusions

- GLPG2222 is generally well tolerated in adult healthy subjects and in subjects with CF
- Overall, PK of GLPG2222 after single dosing is similar between healthy subjects and subjects with CF
- Several clinical studies with GLPG2222 are ongoing

Poster available online at: www.glpg.com

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