NACFC 2016

Poster #252

Safety, Tolerability and Pharmacokinetics of a novel CFTR corrector molecule GLPG2222 in healthy volunteers

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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 (see Poster #192), 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 with an EC50<10nM. 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. We present results from this first clinical study.

Objectives

- To evaluate the safety and tolerability of single ascending oral doses (SAD) and multiple ascending oral doses (MAD) of GLPG2222 administered to healthy subjects
- To characterize the pharmacokinetics (PK) of GLPG2222 after single and multiple oral administrations
- To evaluate the potential of cytochrome 450 3A4 (CYP3A4) induction using urinary 6β-OH cortisol over cortisol ratio as marker

Methods

Randomized, double-blind, placebo-controlled study:

- 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 administered orally 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 suspension after standard breakfast

Safety results

- No deaths or serious adverse events occurred during the study. None of the treatment emergent AEs (TEAEs) led to study drug discontinuation. 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 (FEV_1) were observed following single doses

Table 1: Incidence of TEAE (MAD part)

Preferred Term, N	Pooled Placebo N=6	GLPG2222 150 mg q.d. N=6	GLPG2222 300 mg q.d. N=6	GLPG2222 600 mg q.d. N=6	Total GLPG2222 N=18
Headache	4	0	1	0	1
Asthenia	0	0	0	1	1
Catheter site pain	1	0	0	0	0
Diarrhea	1	1	0	0	1
Abdominal discomfort	0	1	0	0	1
Abdominal upper pain	0	1	0	0	1
Vomiting	1	0	0	0	0
Gastroenteritis	0	1	0	0	1
Conjunctivitis	0	1	0	0	1
Nasopharyngitis	0	0	0	1	1
Oropharyngeal pain	1	0	0	0	0
Pruritus	0	1	0	0	1
Rash	1	0	0	0	0
Palpitations	0	1	0	0	0
Back pain	1	0	0	0	0

Pharmacokinetics

SAD

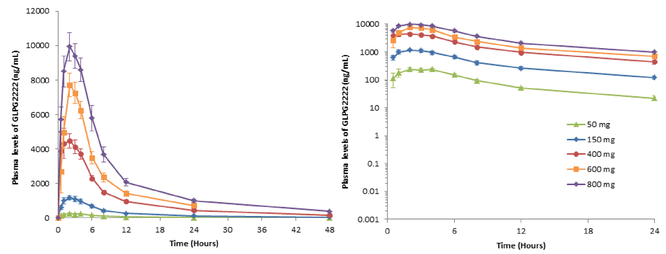

Figure 1: Mean (±SE) GLPG2222 plasma levels after single oral dose as oral nanosuspension in fed state; linear (left) and semi-logarithmic (right) plots

MAD

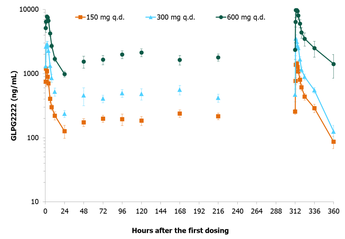

Figure 2: Mean (±SE) GLPG2222 plasma levels after multiple oral dose as oral nanosuspension in fed state

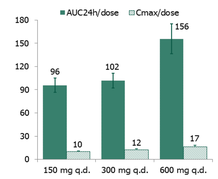

Figure 3: Dose proportionality – dose normalized C_{max} and AUC

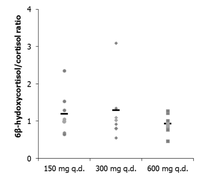

Figure 4: CYP3A4 induction 6β-OH cortisol/cortisol ratio

Conclusions

- GLPG2222 was generally safe and well tolerated when dosed up to 600 mg q.d. for 14 days in healthy subjects
- GLPG2222 is rapidly absorbed. Its mean apparent elimination half-life is 12 hours. After q.d. dosing, steady state was attained within 2 days of dosing, with minimal accumulation
- Urinary 6β-OH-cortisol/cortisol ratio was not impacted by once-daily repeated dosing indicating that GLPG2222 is not a CYP3A4 inducer
- Overall, these results support the progression of GLPG2222 into Phase II clinical studies in CF patients

Poster available online at: www.glpg.com

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