GLPG1837 IN SUBJECTS WITH CYSTIC FIBROSIS AND THE S1251N MUTATION: RESULTS FROM A PHASE IIA STUDY (SAPHIRA2)

NACFC 2016

Poster #253

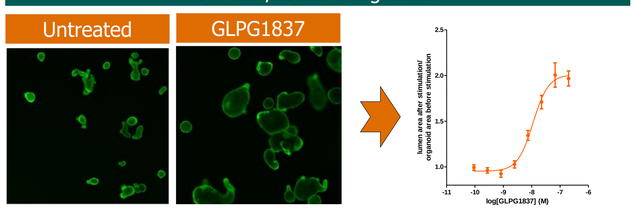
De Boeck, K.[1]; Van Braeckel, E.[2]; van der Ent, C.K.[3]; Verhulst, S.[4]; Weersink, E.J.[5]; Conrath, K.[6]; Kanters, D.[6]; Namour, F.[7]; de Kock, H.[6]; Van de Steen, O.[6]

1. Department of Pediatrics, University of Leuven, Leuven, Belgium; 2. Department of Respiratory Medicine, Ghent University and Hospital, Ghent, Belgium; 3. Cystic Fibrosis Center and Department of Pediatric Respiratory Medicine, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, Netherlands; 4. Cystic Fibrosis Center, University Hospital Antwerp, Antwerpen, Belgium; 5. Department of Respiratory Medicine, Academic Medical Center, Amsterdam, The Netherlands; 6. Galapagos NV, Mechelen, Belgium; 7. Galapagos SASU, Romainville, France

Background

GLPG1837 is a novel cystic fibrosis transmembrane conductance regulator (CFTR) potentiator[1]. GLPG1837 was generally safe and well tolerated in healthy subjects up to the highest dose of 800 mg twice daily for 2 weeks. The SAPHIRA1 and 2 studies evaluate GLPG1837 mono-therapy for G551D or S1251N CFTR mutations, respectively.
In vitro assays on S1251N CFTR showed GLPG1837 to open this dysfunctional channel with a high potency, supporting its clinical evaluation.

S1251N/F508del organoids

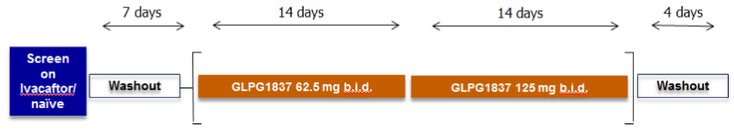


In the forskolin-induced swelling of organoids derived from patients heterozygous for S1251N/F508del, GLPG1837 has an EC_{50} of 7.8 nM (determines target plasma C_{trough} of 12 ng/ml)

[1]Conrath K., *et al.*,(2013) Novel potentiators for treating Cystic Fibrosis NACFC

Design and objectives

- SAPHIRA2 is a phase IIa, open-label, multicentre study to evaluate two doses of GLPG1837 sequentially administered for two weeks each
- Evaluations of safety and tolerability, sweat chloride concentration and pulmonary function (FEV_1), and GLPG1837 plasma levels



Baseline demographics & disease characteristics

Subject	Age	Gender	Prior Ivacaftor	SwCl (mmol/L)	$ppFEV_1$	CFTR Genotype
1*	42	M	Yes	19	65	S1251N / R117H - 7T/7T
2	51	M	No	83	35	S1251N / F508del
3	38	M	Yes	90	79	S1251N / F508del
4	19	M	Yes	92	93	S1251N / F508del
5	18	M	Yes	65	80	S1251N / F508del
6	30	M	No	87	96	S1251N / F508del
7	22	F	No	52	58	S1251N / 3272-26A>G

* Excluded from PD analysis – EC50 for R117H is outside current plasma exposure window

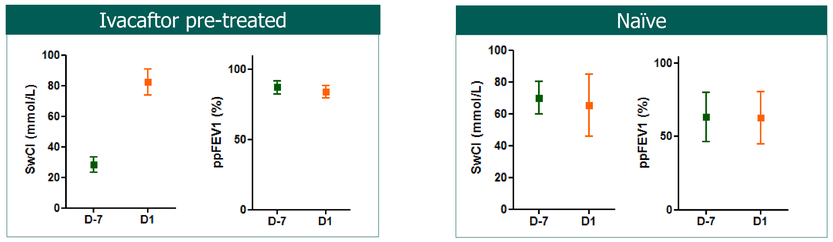
Safety and tolerability

- 5 subjects reported at least 1 treatment emergent adverse event (TEAE). The most frequent TEAE was headache (2 subjects at the low dose and 2 at the high dose)
- All TEAEs were mild or moderate, except for one case of severe abdominal pain. None of the TEAEs led to study drug discontinuation
- No serious adverse events (SAEs) occurred during the study
- No clinically significant changes in safety laboratory parameters were observed

Effects of ivacaftor washout vs naive

Short (7 days) washout for ivacaftor pretreated subjects (n=3):

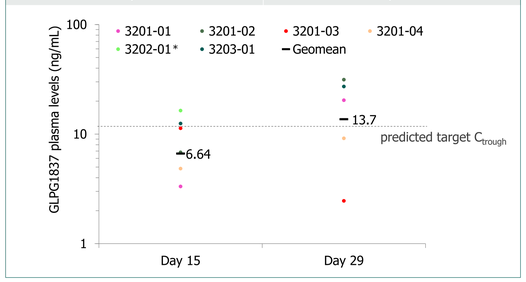
- Substantial increase of SwCl levels, confirming its value as biomarker
- Slight FEV_1 decline (-3%)



Pharmacokinetics

After 2 weeks treatment with 125 mg b.i.d., 3/5 subjects reached C_{trough} plasma levels predicted to be active in lungs

Day 15 (62.5 mg b.i.d.)	Day 29 (125 mg b.i.d.)
# Subjects above predicted target C_{trough}	
2/6	3/5



* Subject 3202-01 Pre-dose levels D29 excluded (suspected sample time error)

Pharmacodynamics

Sweat Chloride

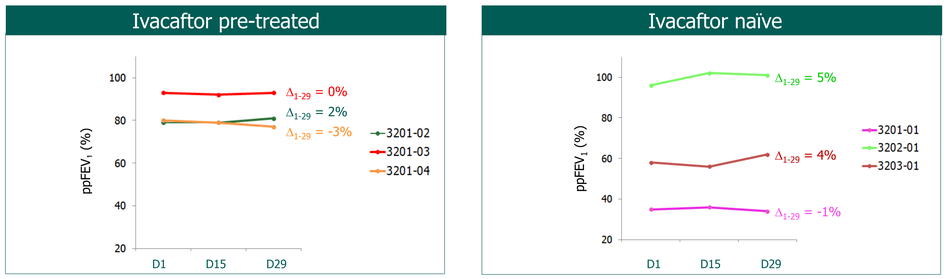
- SwCl results presented for 5 subjects
  - missing data for 6th subject
- Substantial SwCl reduction in 4/5 subjects receiving 125 mg b.i.d. for 2 weeks
- SwCl reduction when plasma concentrations of GLPG1837 exceed the organoid-predicted target C_{trough}

Day 15 (2 wks on 62.5 mg b.i.d.)		Day 29 (2 wks on 125 mg b.i.d.)	
# Subjects with ΔSwCl > 15 mmol/L	# Subjects with ΔSwCl > 50 mmol/L	# Subjects with ΔSwCl > 15 mmol/L	# Subjects with ΔSwCl > 50 mmol/L
2/5	0/5	4/5	1/5

Due to missing SwCl values, data for one subject excluded
ΔSwCl presented as reductions larger than 15 mmol/L or 50 mmol/L respectively

Pulmonary Function (FEV_1)

- Results for FEV_1 are analyzed according to pre-treatment status



- Following a washout from ivacaftor, treatment with GLPG1837 stabilizes lung function
- FEV_1 tends to increase (clinical activity) when plasma concentrations exceed the target
- Stable FEV_1 in subject with severe lung disease

Conclusions:

- GLPG1837 was generally safe and well tolerated in CF patients when dosed up to 4 weeks
- Doses/exposures exploring the lower limits of the predicted efficacious range showed dose-dependent increase in CFTR activity, with plasma levels predicted to show initial efficacy achieved at 125 mg b.i.d.
- These initial pharmacodynamic data correlate with the *in vitro* predictions of target plasma concentrations
- Small sample size (n=7) limits interpretation; ongoing SAPHIRA 1 study will provide complementary insights (NCT02707562)

Poster available online at:
www.glpg.com

Galápagos