On track to a triple combo therapy

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Galapagos at a glance

- Listed on Euronext & NASDAQ: GLPG
- Novel mode of action drugs
- Proof of platform: filgotinib in Ph 3
- Partners: GILD, ABBV, Servier, MOR
- Q2 cash ~$1B, market cap ~$3B
- 480 employees at 4 EU sites
Our strategy

- Identify novel drug targets in human cells
- Design & develop first-in-class drugs
- Deliver on our key product partnerships
- Build a commercial EU organization
- Take selected programs to market ourselves
# Diversified and maturing pipeline

<table>
<thead>
<tr>
<th>Area</th>
<th>Pre-clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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Gene mutations in cystic fibrosis
Genetic disorder

Patients with CF carry a genetic mutation that causes the key chloride channel CFTR to be not produced or trafficked properly.
CF: protein folding & function disease
Treatment strategy for improvement

CF drug discovery

Develop triple combination therapy for treatment of most CF patients

Adapted from Dr. Scott Donaldson’s Plenary Session (NACFC, 2013)
Over a decade of CF research

- **2005-2008:** target discovery with CFF
  - non-CFTR targets – 3 hits

- **2009-2010:** hit optimization and evaluation
  - finally found not to improve CFTR function
Over a decade of CF research

CFTR targeting

- 2011-2012: targeting CFTR
  - cell lines development
  - medicinal chemistry

- 2013: collaboration with AbbVie
  - Galapagos leads discovery through to clinical Phase 2
  - AbbVie leads Phase 3 and commercial

TECC data for triple, HBE cells F508del/F508del, 7 donors
Rich pipeline of CFTR modulators

Discovery
- Potentiator – GLPG1837
- Potentiator – GLPG2451
- Potentiator – GLPG3067

Preclinical
- F508del corrector C1/Early – GLPG2222
- F508del corrector C1/Early – GLPG2851

Phase 1
- F508del corrector C2/Late – GLPG2737

Phase 2
- F508del corrector(s) C2/Late – GLPGxxxx
Novel potentiators
Activity and efficacy on F508del and G551D CFTR

F508del/ F508del HBE

G551D/F508del HBE
‘1837: safe, well tolerated in Ph 1

Safe with single doses up to 2000 mg, 14-day dosing up to 800 mg b.i.d.
‘1837 in CF patients
SAPHIRA studies

- **SAPHIRA 1** in CF patients with G551D mutation
- **SAPHIRA 2** in S1251N mutation (Dutch mutation)

Primary cells - EC\textsubscript{50} = 373 nM
Efficacy = 180% of VX-770

Organoids - EC\textsubscript{50} = 15 nM
Similar potency as on F508del
Efficacy = 100% of VX-770
‘2222: C1 corrector
Expression and chloride current in F508del/F508del

Increase CFTR surface expression

Chloride current vs VX-809, 661

‘2222: potent C1 corrector
‘2222: safe, well tolerated in Ph 1

- Randomized, double blind, placebo-controlled healthy volunteer study
- SAD up to 800 mg
- 14-day MAD: 150, 300, 600 mg q.d.
- Safe and well tolerated over dose range studied
- PK profile supports once daily dosing for future development

Data presented today at NACFC
C2 corrector, series 1
Series progression to ‘2737

Cell surface expression
(combination with early corrector)

F508del/F508del HBE cells
TECC data ‘2737

% of GLPG2222 + potentiator

Triple combo with ‘2737: strong correction across multiple donors
Dual and triple combinations
F508del/F508del primary cells

% of dual combo
CFTR restoration

GLPG triple combo achieves greater CFTR vs Orkambi in vitro
Future CF clinical development


Advancing clinical development pathways for new CFTR modulators in cystic fibrosis

Nicole Mayer-Hamblett,¹,² Michael Boyle,³,⁴ Donald VanDevanter⁵

The objectives of this review are to outline the challenges and opportunities in drug development created by systemic genotype-specific CFTR modulators, highlight the advantages of sweat chloride as an established biomarker of CFTR activity to streamline early-phase development and summarise options for later phase clinical trial designs that respond to the adoption of approved genotype-specific modulators into standard of care. An optimal development framework will be needed to move the most promising therapies efficiently through the drug development pipeline and ultimately deliver efficacious and safe therapies to all individuals with CF.

- study design
- endpoints
- rare mutations
- regulatory framework
SAPHIRA studies
‘1837 Phase 2A trials – ‘translational studies’

Dose escalation with GLPG1837
Follow-up
4-wk

**SAPHIRA 1**: G551D (26 pts) enrollment completed

**SAPHIRA 2**: S1251N (7 pts) data presented

- Recruitment in 6 EU countries & Australia
- Includes Kalydeco naive & treated (after 7d washout period)
- Primary endpoints: safety & tolerability
- Secondary endpoints: sweat chloride, FEV1, plasma levels
SAPHIRA 2
Dose/exposure selection

S1251N/F508del organoids

• In S1251N/F508del organoids, GLPG1837 EC$_{50}$ is 7.8 nM, setting a clinical target plasma C$_{trough}$ of 12 ng/ml
• ‘1837 doses: 62.5 and 125 mg b.i.d.
SAPHIRA 2 PK

Day 15 (62.5 mg b.i.d.)

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GLPG1837 plasma levels (ng/mL)

- 3201-01
- 3201-02
- 3201-03
- 3201-04
- 3202-01*
- 3203-01
- Geomean

Predicted target $C_{\text{trough}}$:
- 6.64
- 13.7

Galápagos
SAPHIRA 2
Impact of ivacaftor washout, treated vs naïve

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

- substantial increase of sweat chloride levels, confirming its value as biomarker
- slight FEV₁ decline (-3%)

![Graph showing sweat chloride and ppFEV₁ levels for ivacaftor pre-treated and naïve groups.](image-url)
SAPHIRA 2
Changes in FEV$_1$ in S1251N

- 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

Confirmation of *in vitro* assays
## SAPHIRA 2
Changes in sweat chloride in S1251N

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Confirmation of *in vitro* assays
High level path for CF program

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FiH studies, Combinations in healthy volunteers, Patient evaluations
## Clinical news flow

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<tr>
<th>Disease area</th>
<th>Program</th>
<th>Partner</th>
<th>H2 ‘16</th>
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<tr>
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