- CFTR correctors improve the processing (stabilize CFTR folding) and delivery of phe508del *CFTR* to the cell surface. However, currently approved combination of potentiator and corrector provide only a modest benefit in homozygotes

Combined, these activities allow chloride ion transport yielding improved hydration of the lung surface and subsequent restoration of mucociliary clearance.

## PLAYING CATCH-UP WITH MARKET LEADER VERTEX

Playing catch up is hard, and we cannot overlook the risk to the CF program: Logically, the triple combo is only likely to move forward into Phase 3 if the data demonstrate a major improvement over Orkambi and the upcoming data from VX-661.
Following scenarios or in combination could justify moving the program forward:

- Potentiator preliminary data in CF patients suggest a clinical benefit over Kalydeco:
    - Tough hurdle considering ppFEV1 benefit will have to be in the mid-teen % for physicians to make a switch
    - The potentiators in development when used in combination do not counter act the effect of the corrector/s as has been suggested for Kalydeco
- The potentiator/corrector combination provides a numerically superior increase in ppFEV1 compared to Orkambi
    - The hurdle here is potentially lower considering the modest yet clinically significant benefit in homozygous patients with Orkambi
- Safety profile better than Orkambi
    - Real world data suggests dropout (persistence) and compliance on the Orkambi regimen is between 70% to 85%
- Clear clinical benefit in heterozygotes
    - Note, one of the ongoing VX-661 phase 3 studies was halted for futility in this harder to treat segment, hence the focus on triple combo increases

Galapagos is attempting to bridge the competitive gap by moving forward with a triple combo strategy, without the dual therapy pit stop.

## THE GALAPAGOS/ABBVIE CF PIPELINE

Galapagos has two potentiators in the clinic, which include:

- GLPG1837 and
- GLPG2451

Importantly, Galapagos has two correctors in development, which include:

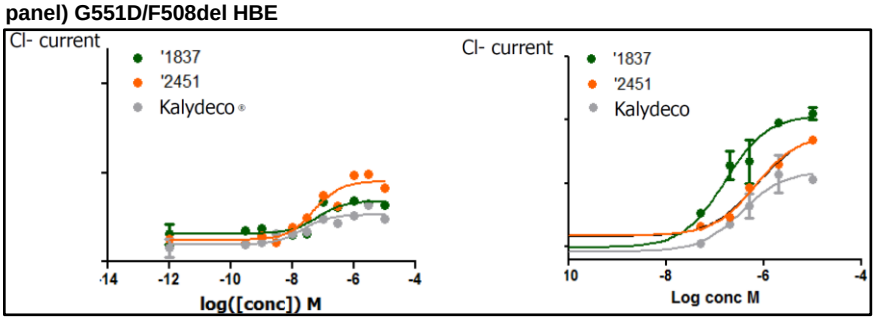
- C1- 2222, its and backup;
- And C2 – 2737

## HOW DOES THE PRELIMINARY DATA STACK UP?

GLPG1837 improved channel activity of temperature-rescued F508del-CFTR as well as G551D-CFTR:

- In Trans-epithelial Clamp Circuit (TECC) assays on primary patient cells the maximal opening of the G551D-CFTR channel exceeded that of Kalydeco (VX-770) by >200%
- Importantly, GLPG1837 did not show the adverse effects VX-770 has on rescued F508del-CFTR after chronic treatment
- Pulse chase analysis confirmed that chronic treatment of GLPG1837 did not reduce levels of drug-induced F508del-CFTR correction

**Exhibit 27: Novel potentiators: (Left panel) F508del/F508del HBE C1 corrected; and (Right panel) G551D/F508del HBE**

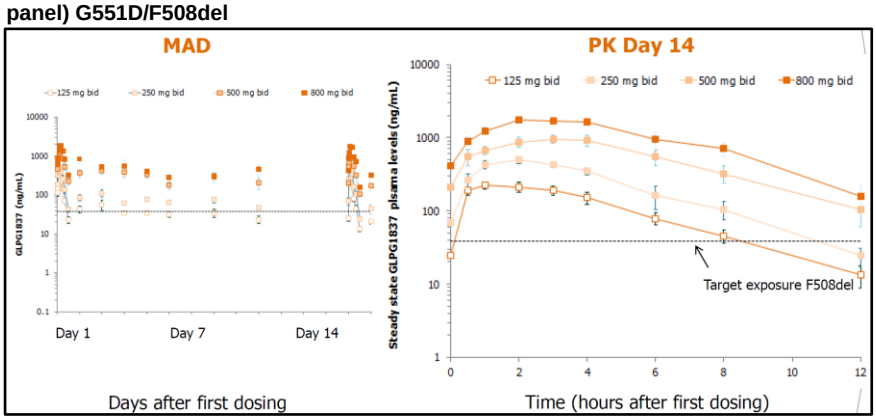



**Source:**

The randomized, double-blind, placebo-controlled study over a range of single and multiple doses of GLPG1837 in healthy, adult subjects:

- In the single ascending dose (SAD) part of the study, two alternating cohorts of subjects were exposed to single oral doses of 30 to 2,000 mg in fasted conditions and to a single dose of 500 mg after a high-fat high-calorie breakfast
- In the multiple ascending dose (MAD) part of the study, GLPG1837 was given orally at doses of 125 to 800 mg b.i.d. for a period of 14 days
- At every dose level 6 subjects were exposed to GLPG1837 and 2 to placebo

**Exhibit 28: Novel potentiators: (Left panel) F508del/F508del HBE C1 corrected; and (Right panel) G551D/F508del**




**Source: GLPG investor day June 2016**

Key take-aways on GLPG1837:

- GLPG1837 was generally safe and well tolerated in healthy volunteers, with single doses up to 2,000 mg and 14-day dosing up to 800 mg b.i.d.
- Rapid absorption, and mean terminal half-life of 6 to 15 hours after single doses
- The exposure of GLPG1837 was approximately dose proportional at steady state with improved bioavailability with food
- Steady state was attained within two days of dosing, with no accumulation
- The metabolite also had high exposure