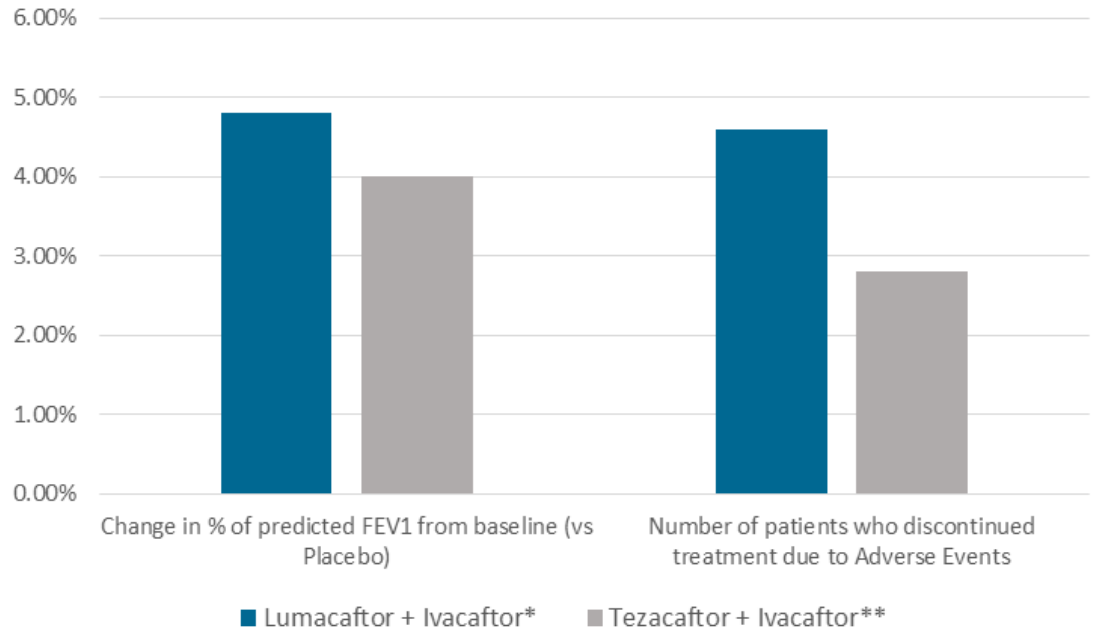
Achieving Clinically Meaningful Outcomes for Patients with CF

There are currently no cures for Cystic Fibrosis, which makes tolerability of disease modifying drugs as critical as effectiveness. During 2012, Kalydeco (ivacaftor) was the first drug ever approved that directly improved the function of the CFTR protein, but the drug was approved for a very limited number of patients that have a G155D gating factor mutation. The subsequent approval of Orkambi, a combination of ivacaftor plus lumacaftor, provided a disease modifying solution for an additional ~25% of the CF patient population, but tolerability issues have limited adoption and ~20 – 30% of patients starting Orkambi discontinue therapy.[22] Phase 3 results from the first studies of Tazacaftor in combination Ivacaftor demonstrated similar lung improvement as Orkambi, but with a side effect profile more similar to placebo, suggesting patients will not have the same tolerability issues as Orkambi (Figure 44).

Figure 44. Tazacaftor+Ivacaftor combo shows similar efficacy to Orkambi but with improved tolerability



*Pooled analysis from the TRAFFIC / TRANSPORT Studies for Lumacaftor + Ivacaftor: Lumacaftor - Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTRl

**Analysis from the EVOLVE study of Tezacaftor + Ivacaftor: Tezacaftor (VX-661) /Ivacaftor Phase 3 Study Results Call

Source: Wainwright and Boyle et al.; N Engl J Med; July 16, 2015; 373:220-31

[22] March 2017 Conference Teza/ Iva Phase 3 Study Results Call

The potential improvement of tolerability issues with next generation correctors such as Tezacaftor, allows focus to shift towards the improvement of CFTR function. Clinical response has been defined across study endpoints measuring improved lung function, Forced Expiratory Volume in 1 Second (FEV1), reduction in pulmonary infective exacerbations (relative number of infections), change in Body Mass Index (relative BMI from start to finish), and quality of life patient questionnaires (standardized change in CFQ-R start to finish). In the most common F508del population, modest improvements have been experienced with FEV1, Pulmonary Exacerbations and CFQ-R, but there have been more limited changes in BMI (Figure 45).

Figure 45. Tezacaftor+Ivacaftor combo shows modest improvement in FEV1 and limited changes in BMI

EVOLVE : a Phase 3 randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of the tezacaftor/ ivacaftor combination in people with CF aged 12 and older who have two copies of the F508del mutation

Mean absolute change in ppFEV1 from baseline through week 24	**Placebo**	**TEZ/ IVA**
Treatment Difference	N/A	+4.0 (p<0.0001)
Within Group	-0.6 (p=0.0601)	+3.4 (p<0.0001)
Number of Patients	256	248
Relative ppFEV1 through week 24	**Placebo**	**TEZ/ IVA**
Treatment Difference	N/A	+6.8 (p<0.0001)
Within Group	-0.5 (p=0.3823)	+6.3 (p<0.0001)
Number of Patients	256	248
# of Pulmonary Exacerbations	**Placebo**	**TEZ/ IVA**
Rate Ratio	N/A	0.65 (p=0.0054)
# of Events (rate per 48 wks)	122 (0.99)	78 (0.64)
Number of Patients	256	248
Change in BMI (kg/m^2) at week 24	**Placebo**	**TEZ/ IVA**
Treatment Difference	N/A	+0.06 (p=0.4127)
Within Group	+0.12 (p=0.0134)	+0.18 (p=0.0004)
Number of Patients	256	248
Change in CFQ-R through week 24	**Placebo**	**TEZ/ IVA**
Treatment Difference	N/A	+5.1 (p<0.0001)
Within Group	-0.1 (p=0.8889)	+5.0 (p<0.0001)
Number of Patients	256	248

Source: Company Reports, Two Phase 3 Studies of the Tezacaftor/Ivacaftor Combination Treatment Met Primary Endpoints with Statistically Significant Improvements in Lung Function (FEV1) in People with Cystic Fibrosis. Mar 2017.

Unfortunately, the modest improvements, even with the next generation corrector Tezacaftor, have been unable to produce clinical effects in the most severe CF population that harbor F508del and a minimal function mutation. As a result, many hope that the combination of two next generation CFTR correctors (tezacaftor) and a potentiator (ivacator), or triplet combo, will help to increase clinical effect. Patient baseline characteristics for the F508del studies have centered on a mean FEV1 of +60% with a range in function of +30 - +90%. Baseline mean FEV1 of 60% may explain why the combo studies have been successful within the F508del population, but have not achieved meaningful clinical improvement within the more severe minimal function mutation, as below 60% FEV1 is where the risk curve of disease progression begins to rise dramatically regardless of bacterial status[23] (Figure 46, Panel a)

Figure 46. Disease progression rises dramatically below a baseline mean FEV1 of 60%

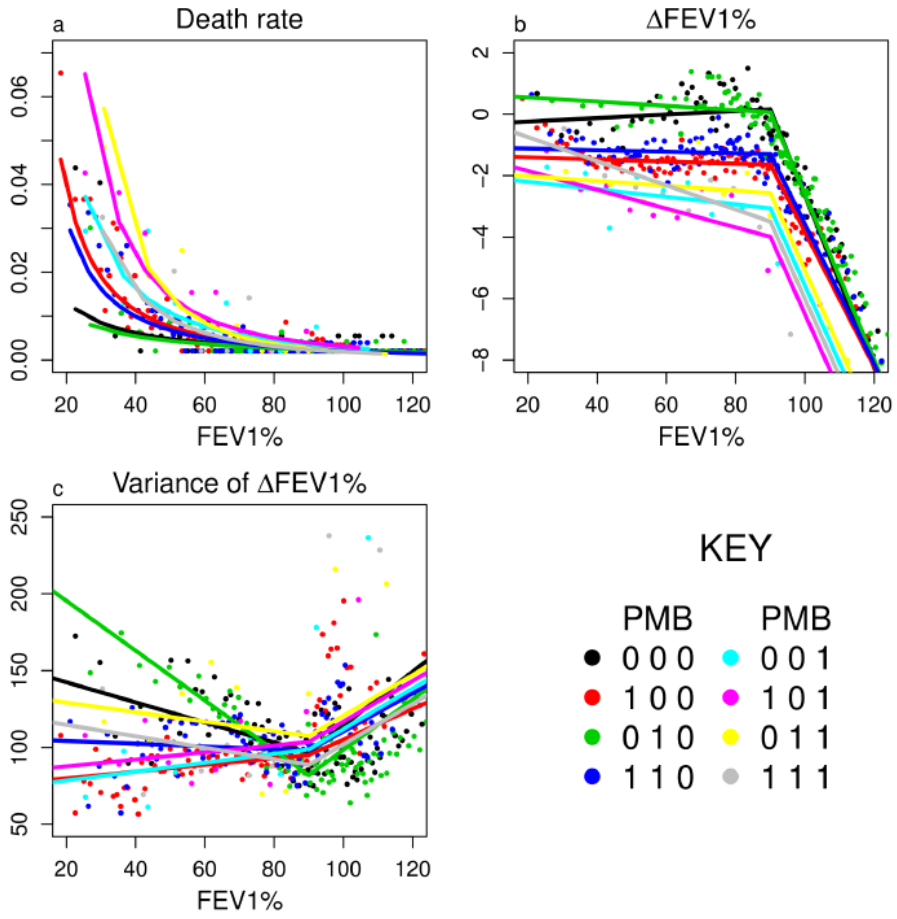


Fig 2. Annual death rate, annual change in FEV1% (ΔFEV1%), and variance of ΔFEV1% as a function of current FEV1% and bacterial infection state. Colors indicate the current bacterial status of patients based on testing for *P. aeruginosa*, MSSA and *Burkholderia* (given as PMB in the legend, with 1 and 0 indicating a positive or negative test respectively). Each dot shows the average value for patients broken into FEV1% bins by quantile for each bacterial status group, and the curves show the untransformed results of linear regression of log transformed mortality against log FEV1% (a), and piecewise linear fits with a breakpoint at FEV1% = 90% (b-c).

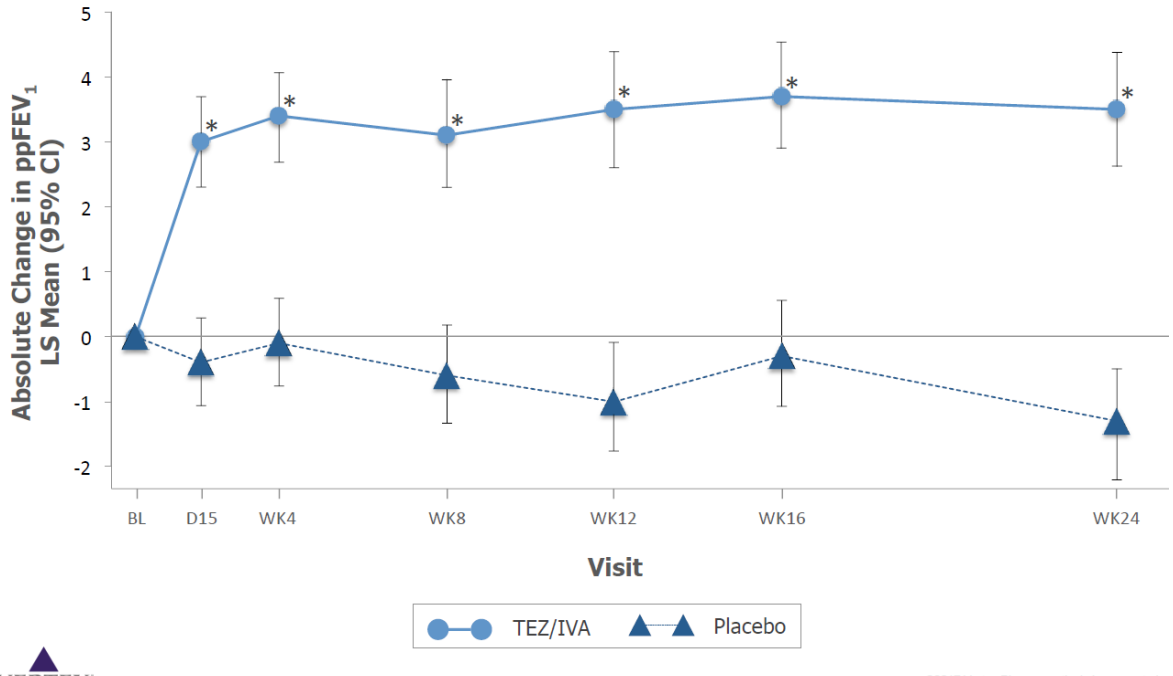
doi:10.1371/journal.pone.0156752.g002

Source: The Dynamics of Disease Progression in Cystic Fibrosis; Alder and Liou; *PLoS ONE;* June 1, 2016

[23] *The Dynamics of Disease Progression in Cystic Fibrosis*; Alder and Liou; *PLoS ONE*; June 1, 2016

The EXPAND study results have set a new bar for combination therapy for the F508del homozygous patient population, with the Tezacaftor and Ivacaftor combination generating a +4ppt increase relative to the placebo arm in mean absolute change in ppFEV1 from baseline through week 24 (Figure 47). Superiority of EXPAND dataset to the Orkambi results from the TRAFFIC and TRANSPORT study are limited, as the pooled analysis from TRAFFIC and TRANSPORT recorded a +3.3ppt increase relative to placebo in ppFEV1 from baseline (lumacaftor 600mg/day group + ivacaftor). The limitations of a next generation corrector (tezacaftor) to substantially differentiate clinical response (versus lumacaftor) continues to support the thesis that to significantly push the clinical response higher, a second complementary corrector (C2) will be needed in the drug regimen.

Figure 47. Tezacaftor+Ivacaftor increased mean ppFEV1 by +4ppt – raising the bar for combo therapies



VERTEX * p <0.0001 v. placebo and within group

Source: Company Reports, Two Phase 3 Studies of the Tezacaftor/Ivacaftor Combination Treatment Met Primary Endpoints with Statistically Significant Improvements in Lung Function (FEV1) in People with Cystic Fibrosis. Mar 2017.

The major advancement of the EXPAND and EVOLVE studies for the Tez/Iva combo was that the majority of adverse event rates were inline with the placebo arm (Figure 48). The results help confirm that tezacaftor may not have the same effects on chest tightness as lumacaftor, which has been a limiting factor of adoption for Orkambi.

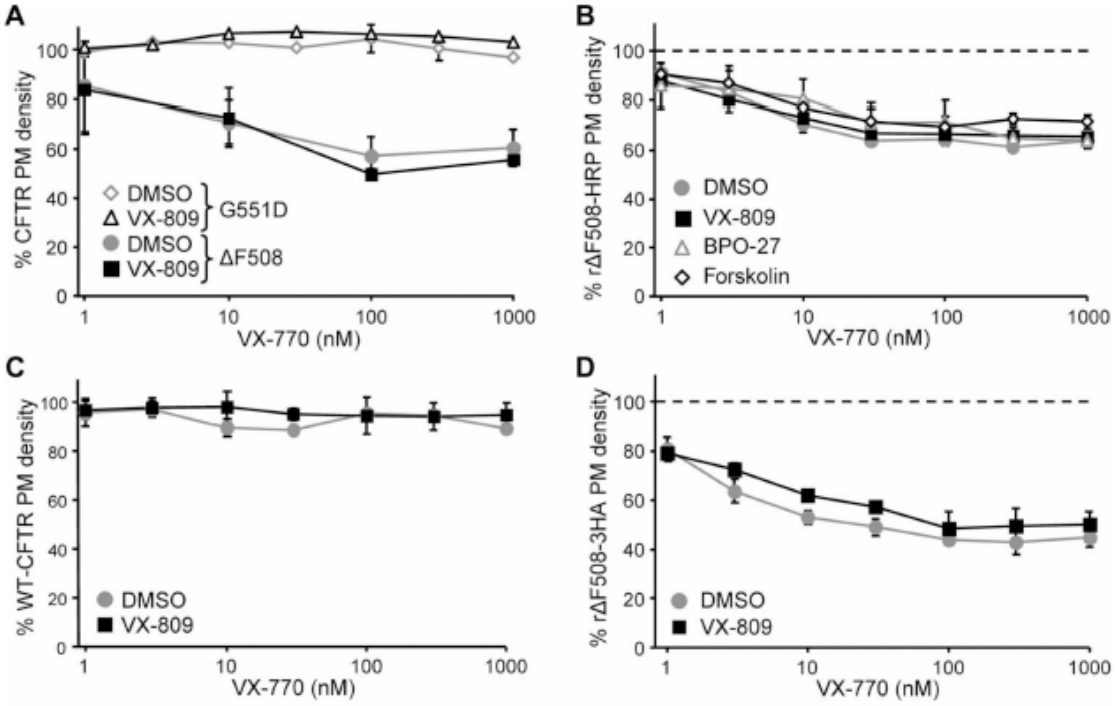
Figure 48. Adverse events from the Tezacaftor+Ivacaftor combo inline with the placebo arm

EVOLVE Study: Adverse Events	Placebo	TEZ/ IVA
Number of patients with any Adverse Event	95%	90.40%
Number of patients with a Serious Adverse Event	18.20%	12.40%
Number of patients who discontinued treatment due to Adverse Events	3.10%	2.80%
Most common Adverse Events:		
-Infective Pulmonary Exacerbation	37.20%	29.90%
-Cough	32.60%	26.30%
-Headache	14.30%	17.50%
-Nasopharyngitis	15.10%	16.70%
-Sputum Increased	16.30%	14.30%
Number of patients who experienced any respiratory adverse event:	15.90%	13.10%
Number of patients who experienced selected respiratory adverse events:		
-Dyspnea	7%	6.40%
-Respiration Abnormal	4.30%	4.40%
-Brochospasm	0.80%	0.40%

Source: Company Reports, Two Phase 3 Studies of the Tezacaftor/Ivacaftor Combination Treatment Met Primary Endpoints with Statistically Significant Improvements in Lung Function (FEV1) in People with Cystic Fibrosis. Mar 2017.

Tezacaftor also does not appear to be a strong inducer of Cyp3A4, versus lumacaftor, which upregulates clearance of ivacaftor as the molecule is a substrate for CYP3A4 (reducing tissue saturation). Furthermore, in vitro studies have suggested that a negative interaction effect exists between ivacaftor and lumacaftor, whereby sustained exposure of ivacaftor reduces the CFTR channel cell surface density by 15 – 40%, so gains in clinical efficacy could also come as a result of next generation potentiators. Specifically, *Lukacs et al. (2014)* found that ivacaftor *"diminished the folding efficiency and the metabolic stability of F508del-CFTR at the endoplasmic reticulum (ER) and the post-ER compartments, respectively, causing reduced cell surface F508del-CFTR density and function"* (Figure 49). Clearly the development of Orkambi was an important step forward for F508del CF patients, but the path forward may entail a next generation potentiator combined with two next generation correctors.

Figure 49. Ivacaftor (VX-770) diminishes F508del-CFTR folding and stability at the ER



Source: Some gating potentiators, including VX-770, diminish ΔF508-CFTR functional expression; Veit and Lukacs et al.; *Sci Transl Med.;* 2014 July 23; 6(246): 246ra97

To date, the only significant clinical dataset of the next generation CF therapies has come from tezacaftor, and to a lesser degree, GLPG1837. However, during the back-half of 2017 the curtain will begin to lift on the next-generation efforts of Vertex along with the new efforts of Galapagos to develop drugs for the more severe CF populations, F508del homozygotes and minimal function mutations. The goal of both Vertex and Galapagos is to bring a triplet therapy to market that has high tolerability and unprecedented efficacy. We consider Vertex to currently be in the lead for development of a triple-combo therapy, but the fast-track approach of Galapagos has them in the race, although the company can afford no missteps (Figure 50).

Figure 50. Vertex currently leads for a triplet combo but Galapagos fast-track approach has them in the race

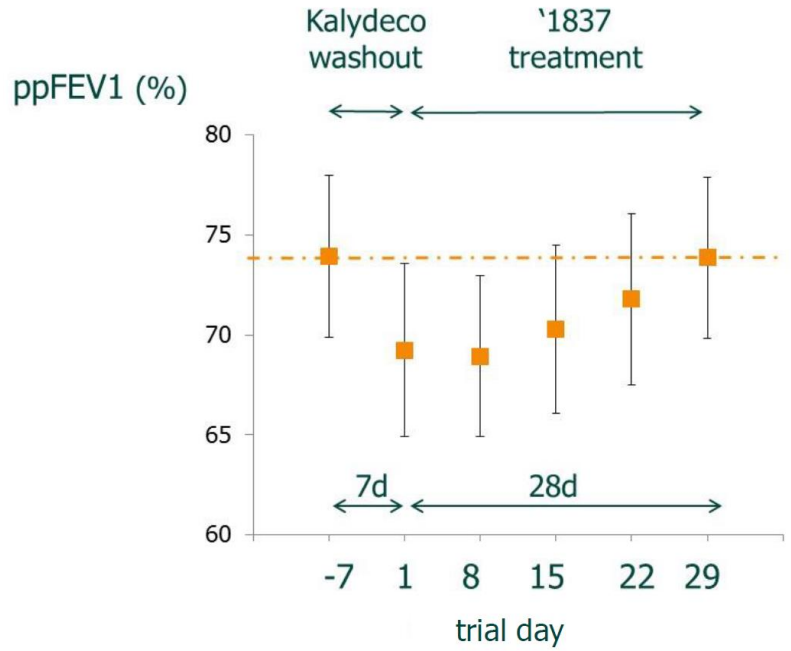
Timeline for Next-generation Cystic Fibrosis Treatment							
Class	Drug	Company	Dosing	Next Expected Datapoint	Study Details		Study Numberr
Potentiator	GLPG1837	Galapagos	Twice Daily	SAPHIRA 2 (Phase 2 results)	At least 6 cystic fibrosis patients with the S1251N mutation will be treated for 4 weeks, consisting of two consecutive treatment periods of two weeks evaluating one dose of GLPG1837 each. After the treatment period, there is a 7-10 days follow-up period. During the course of the study, subjects will be examined for any side effects that may occur (safety and tolerability). Changes in sweat chloride will be assessed as biomarker from baseline onwards, and changes in pulmonary function (efficacy) will be explored throughout the study. The amount of GLPG1837 present in the blood (pharmacokinetics) will also be determined.		NCT02690519
				SAPHIRA 1 (Phase 2 results)	32 cystic fibrosis patients with the G551D mutation will be treated for 4 weeks, consisting of three consecutive treatment periods: two 1-week periods followed by one 2-week period, evaluating one dose of GLPG1837 each. After the treatment period, there is a 7-10 days follow-up period. During the course of the study, subjects will be examined for any side effects that may occur (safety and tolerability). Changes in sweat chloride will be assessed as biomarker from baseline onwards, and changes in pulmonary function (efficacy) will be explored throughout the study. The amount of GLPG1837 present in the blood (pharmacokinetics) will also be determined.		NCT02707562
	GLPG3067	Galapagos	Not disclosed	Phase 1 start: 1H2017	Not Available		
Corrector	GLPG2222	Galapagos	Once Daily: 150mg or 300mg QD	Phase 2 ongoing (ALBATROSS)	A Study to Evaluate GLPG2222 in Ivacaftor-treated Subjects With Cystic Fibrosis (Age +18), N=35, Start Jan '17		NCT03045523
	GLPG2222	Galapagos	Once Daily: Undisclosed	Phase 2 ongoing (FLAMINGO)	A Phase IIa, Randomized, Double-blind, Placebo-controlled Study to Evaluate Multiple Doses of GLPG2222 in Subjects With Cystic Fibrosis Who Are Homozygous for the F508del Mutation, n=50, Start March 2017		NCT03119649
	GLPG2851	Galapagos	Not disclosed	Phase 1 start: 2H2017	Not Available		
	GLPG2737	Galapagos	Once Daily	Phase 1 results: 1H2017 (2Q2017) - presentation likely at NACFC	Initiated Phase 1 on 11/28/2016 - aim is to evaluate the safety, tolerability and pharmacokinetics of oral single and multiple ascending doses. Randomized, double-blind, placebo controlled, single center study is being conducted in at least 64 healthy volunteers in teh Netherlands. First part of the study single ascending doses will be evaluated, second part will evaluate multiple ascending doses administered daily for 14 days.		N/A
	VX-445	Vertex		Phase 1 planned for 1Q17	Not Available		
Combo Study	*VX-661 (tezacaftor)*	Vertex					
	Tezacaftor (VX-661) + Ivacaftor	Vertex	TEZ 100 mg administered once daily (qd). IVA 150 mg q12h.	**Positive Pivotal Data for EVOLVE Announced April 2017**	Phase 3: F508del/ F508del, +12 years	24 weeks (n=500)	NCT02347657
	Tezacaftor (VX-661) + Ivacaftor	Vertex	TEZ 100 mg administered once daily (qd). IVA 150 mg q12h.	**Positive Pivotal Data for EXPAND Announced April 2017**	Phase 3: Residual Function/ F508del	Two 8-week crossover treatment periods (n=300)	NCT02392234
	Tezacaftor (VX-661) + Ivacaftor	Vertex	TEZ 100 mg administered once daily (qd). IVA 150 mg q12h.	Enrollment completion in early 2017	Gating/ F508del	8 weeks (n=200)	NCT02412111
	Tezacaftor (VX-661) + Ivacaftor	Vertex		Contributes to Safety Database for VX-661	Minimal Function/ F508del	**12 weeks (n=150) - Study stopped based on futility analysis**	
	First in Human Single and Multiple Dose Study of GLPG2451 and of the Combination of GLPG2222 and GLPG2451	Galapagos	Once Daily	Phase 1 results: 1H2017	The study is a First-in-Human, Phase I, randomized, double-blind, placebo-controlled study evaluating single and multiple ascending oral doses of GLPG2451 and combined multiple doses of GLPG2451 and GLPG2222 in healthy subjects. The purpose of the study is to evaluate safety and tolerability after single ascending oral doses and of multiple doses of GLPG2451 given to healthy subjects compared to placebo as well as of multiple doses of the combination of GLPG2451/GLPG2222 compared to GLPG2451/placebo.		NCT02788721
Triplets							
	GLPG2222 (C1) + GLPG2737 (C2) + GLPG2451 (Potentiator QD) / GLPG1837 (Potentiator BID)	Galapagos	Once or Twice Daily (Targeting Once Daily)	Phase 1 start: Mid-2017	Not Available		
	Tezacaftor (VX-661) + Ivacaftor + VX-440	Vertex	TEZ 100 mg administered once daily (qd). IVA 150 mg q12h.	Phase 2 data expected during 2H2017	This is a Phase 2, randomized, double-blind, placebo- and active-controlled, parallel group, multicenter study to evaluate the safety, tolerability, and efficacy of VX-440 in dual and triple combination with tezacaftor (TEZ; VX-661) and ivacaftor (IVA; VX-770) in subjects with cystic fibrosis (CF) who are homozygous for the F508del mutation of the CF transmembrane conductance regulator (CFTR) gene (F508del/F508del), or who are heterozygous for the F508del mutation and a minimal function (MF) CFTR mutation not likely to respond to TEZ and/or IVA therapy (F508del/MF).		NCT02951182
	Tezacaftor (VX-661) + Ivacaftor + VX-152	Vertex	TEZ 100 mg administered once daily (qd). IVA 150 mg q12h.	Phase 2 data expected during 2H2017	This is a Phase 2, randomized, double blind, placebo and active-controlled, parallel group, multicenter study designed to evaluate the safety and tolerability of VX-152 in Triple Combination (TC) with tezacaftor (TEZ; VX-661) and ivacaftor (IVA; VX-770) in subjects with cystic fibrosis (CF) who are heterozygous for the F508del mutation and a minimal function (MF) CFTR mutation not likely to respond to TEZ and/or IVA therapy (F508del/MF), or who are homozygous for the F508del mutation of the CF transmembrane conductance regulator (CFTR) gene (F508del/F508del).		NCT02951195
	Tezacaftor (VX-661) + Ivacaftor + VX-659	Vertex	Dose Escalation	Phase 1 data expected during 2H2017	A Phase 1, Randomized, Double Blind, Placebo Controlled, Dose Escalation, and Bioavailability Study Evaluating the Safety and Pharmacokinetics of VX-659 in Healthy Subjects and in Subjects With Cystic Fibrosis		NCT03029455

Source: Company Reports, clinicaltrials.gov, BTIG Estimates, June 2017

Pre-clinical assay outcomes at Vertex have proven to be reliable markers for *in vivo* results, we expect the same from Galapagos: Outcomes from the EVOLVE and EXPAND studies have set a new bar for clinical data, and the burden will be on Galapagos to prove they have competitive potentiators and correctors during 2H2017. We think that sentiment on the effort at Galapagos hinges on the results of a once daily potentiator, GLPG2451, as the twice daily dose of GLPG1837 has demonstrated comparable efficacy to ivacaftor but without a dosing advantage may have trouble differentiating. Furthermore, given that the SAPHIRA 1 study only evaluated Kalydeco responders post-washout, it is hard to make an efficacy comparison between GLPG1837 as a potentiator of G551d mutation CF patients relative to Kalydeco.

***The SAPHIRA 1 study demonstrated that GLPG1837 could return patients to 'on-treatment Kalydeco baseline' FEV1% function by Day 28 post an ivacaftor washout period* (Figure 51).**

Figure 51. GLPG1837 could return patients to Kalydeco baseline FEV1% function by Day 28



Source: SAPHIRA 1 Results (December 20th 2016), Ph2a open label trial of GLPG1837

GLPG2222 is expected to be the one of the corrector backbones (C1) of a once-daily triplet combo: Two Phase 2 studies of GLPG2222 are currently enrolling for patients with F508del/ Class III mutations and homozygous F508del mutations (Figure 52).

The ALBATROSS study was started during January 2017 and will evaluate the combination of GLPG2222 + Ivacaftor in the treatment of CF patients that have the F508del allele along with an impaired gating allele. The comparator arm will be placebo, but the more demonstrative analysis will be relative to patient baseline on FEV1 and CFQ-R, as all enrolled patients will be stable on ivacaftor heading into the study. Results of the ALBATROSS study will provide some insight into the potential additive effect of '2222 to Kalydeco, but the active treatment of only 4wks with 2wks of follow-up will prevent any analysis regarding the sustainable effects of the combination.