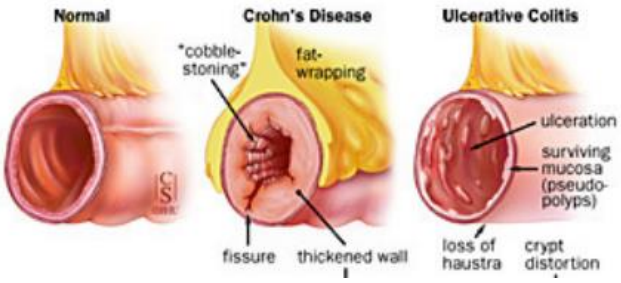
Background on Crohn's and Ulcerative Colitis

Crohn's disease and ulcerative colitis are two of the most common forms of inflammatory diseases (IBD) affecting over 1 million patients in the US. We have approximated the US incidence for Crohn's to be about ~650k patients and ~700k for UC. Typically, Crohn's affects all regions and layers of the intestine (although ~70% of cases are limited to the large and small intestine), with the affected area showing cobble stoning and wall thickening, while UC affects mostly the large intestine, with ulceration and abscesses limited to the top layer (Figure 35).

Figure 35. Crohn's is generally more severe versus UC and affects all layers of the intestine

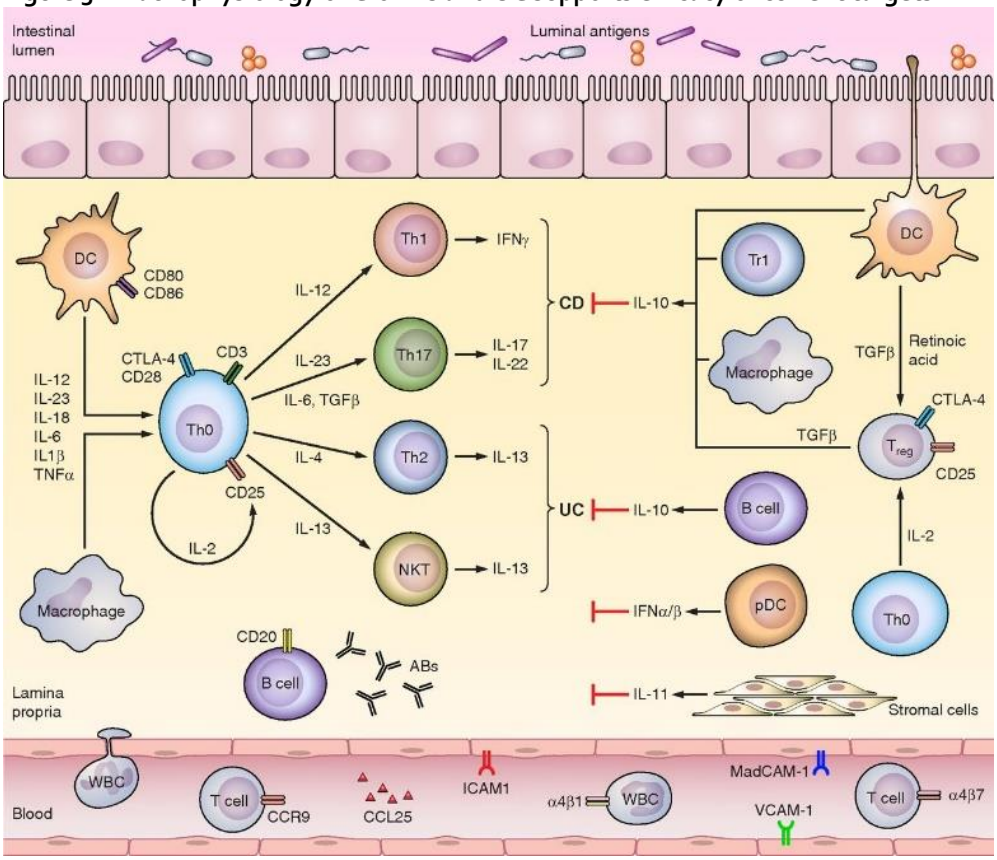


Source: John's Hopkins College of Medicine. 2017.

Development of Crohn's and UC remains highly misunderstood, but has been attributed to an imbalance of regulatory T cell and T helper cells: The immune system functions by modulating the balance between T-helper cells-1 (Th1), Th2, Th9, Th17 and Tregs, and a lack of self-tolerance in UC and Crohn's can potentially be attributed an imbalance. Crohn's disease is generally thought to be associated with an increase in Th1/Th17 cytokine profile, dendritic cells, and macrophages, while an increase in Th2 cytokines and natural killer cells are said to be associated with UC.[11,6] Th1 and Th17 cells mediate immune responses against intracellular pathogens, and are driven by the production of IL-2, IL-23, IL-18, IL-6, and TGFβ, and secrete IL-22, IL-17, INFγ and TNFα. Th2 cells mediate host defence against extracellular parasites and are driven by the production by IL-5 and secrete IL-13.[6] These T helper cells can also activate other effector cells to further promote immunity, which can be dampened by Tregs. Although the theory remains heavily debated, in both Crohn's and UC, an ultimately lower proportion of Tregs express the transcription factor Forkhead box P3, relative to healthy controls. Therefore, major therapeutic strategies have generally involved mechanisms to enhance the innate immune system or limit proinflammatory cytokines produced by Th1 cells, Th2 cells, and APCs.

[6] Valatas V. The value of experimental models of colitis in predicting efficacy of biological therapies for inflammatory bowel diseases. Am J Physiol Gastrointest Liver Physiol. 2013 Dec;305(11):G763-85.

Figure 36. Pathophysiology of Crohn's and UC supports efficacy of current targets



Source: Valatas V. Am J Physiol Gastrointest Liver Physiol. 2013 Dec;305(11):G763-85

Both diseases are highly symptomatic. Crohn's patients with severe disease have persistent weight loss, abdominal pain, nausea, vomiting, or anemia and the Crohn's disease activity index (CDAI) is commonly used to grade severity. Ulcerative colitis patients have frequent and loose bloody stools, severe cramps, tachycardia, anemia, weightless etc, and the Mayo score is typically used. CDAI scores ≥200-300 is considered moderate to severe disease, while a mayo score >6 is considered moderate to severe disease.[Error! Bookmark not defined.]

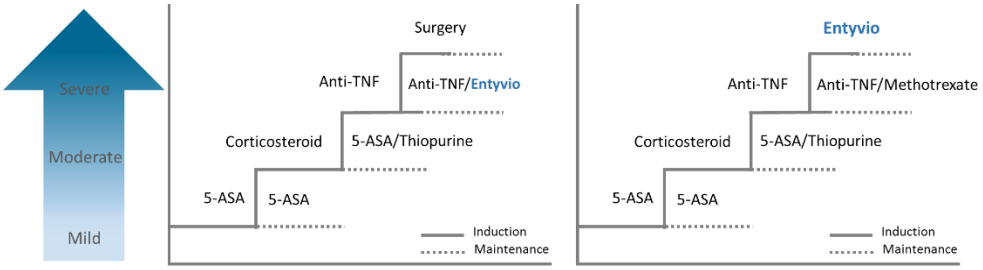
Approximately, 11 – 22% of Crohn's and UC patients will have moderate to severe disease activity, but only 50% will achieve remission with conventional therapy.[7] Crohn's and UC both have active and quiescent periods of disease activity with about one-half of patients achieving remission, however some patients will continue to have chronically active disease requiring maintenance therapy. 50% of Crohn's patients will be in remission or have mild disease over the next five years, 35% will have one or two relapses, and 11% will have chronically active disease.[8] In ulcerative colitis, 48% of patients are in remission, 30% have mild disease activity, 21-22% have moderate to severe disease activity. Therefore, in our model, we have narrowed the addressable moderate-severe patient population to 11% for Crohn's, and 22% for Ulcerative Colitis.

[7] Feldman et al. Medical Management of Crohn's Disease. Clin Colon Rectal Surg. 2007 Nov; 20(4): 269–281.
[8] 2017 Updated IBD Fact book. The Colitis Foundation.

Limitations of conventional therapies is creating an opportunity for earlier line use of alternative therapies, especially in Ulcerative Colitis. The usual course of induction therapy to treat moderate to severe UC & CD is 40–60 mg of prednisone (or another corticosteroid) daily until the resolution of symptoms, which generally occurs between 7 and 28 days after the initiation of therapy. This is typically followed by a tapering of prednisone by 5 to 10 mg every 1 to 2 weeks. Prolonged corticosteroid use is associated with an increased risk of infections, bone loss, steroid dependence (~40%), etc. and with limited potential for mucosal healing. Therefore, they are usually limited to the induction phase which is typically between 2 to 3 months. In ~20% of patients who fail to respond to corticosteroid therapy and in patients requiring maintenance therapy, immunosuppressants (e.g. Azathioprine, 6-mercaptopurine, methotrexate) perform well, but are also associated with adverse events.

Anti-TNFs (eg. infliximab, adalimumab, and centrolizumab pegol) is then recommended for the ~40% of patient not responding to immunomodulators or in patients with CDAI scores >300 on a failed corticosteroid. However, 20-25% of patients either do not respond to anti-TNFs (primary non-responders) or lose response (secondary non-responders) within 1 year.[7] Physicians are typically willing to try a 2nd anti-TNF like Humira (adalimumab) after an initial failure, but not a 3rd, with 3rd line options typically including vendolizumab. However, with anti-TNF therapy being associated with an increased risk of infections, a 4–90-fold increased risk of tuberculosis reactivation, and other immunological issues, Entyvio is no2 being increasingly used in earlier lines of therapy, especially in UC (Figure 37).

Figure 37. Prescribing trends in Crohn's and Ulcerative Colitis

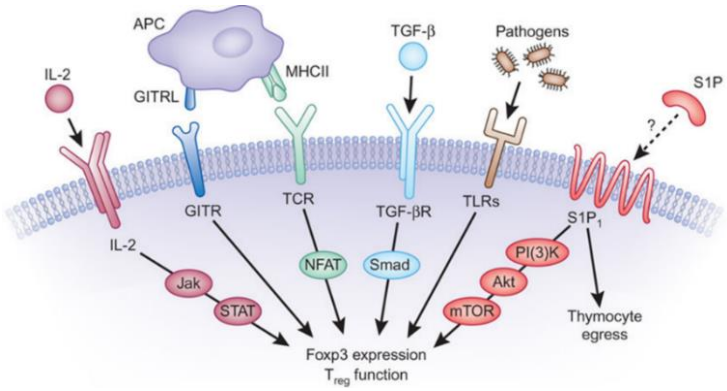


Source: Adopted from Shire 2017 Company Update Presentation, Kornbluth A. et al. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, PracticeParameters Committee. Am J Gastroenterol. 2010 Mar;105(3):501-23;

Molecular Targets of Autoimmune Intestinal Damage

Foxp3 expressing Tregs can potentially be regulated by most of the known pleiotropic targets against IBD including JAKs, TGF beta (Smad), TNFS etc. with the potential to have a broad effect on Th cells relative to the interleukin class (Figure 37). However, understanding the efficacy and safety of these compounds based on their targets and selectivity for each target is highly challenging, due to overlaps in signaling and the ability of these immune cells to change from foxp3+ to foxp3, etc.

Figure 38. Pleiotropic targets influencing Foxp3 expression on Tregs



Source Ohkura N. et al. A novel modifier of regulatory T cells. 2009.

Anti-TNFs are widely used since TNF-α can disrupt Tregs suppressive properties. TNF-α can increase the expression of 'protein phosphatase 1' (PP1) enzyme which inhibits the expression of Foxp3.[9] Therefore, following anti-TNFα infusion therapy, in patients with IBD, there is a significant increase in the frequency of circulating Treg cells, and up to a 3-fold increase in Foxp3 expression, which parallels a reduction of IBD.[10] Anti-TNF therapy also decreases the expression of the Th1 and Th17 cytokines IL-2 and IL-17 in CD patients (Δ13% in IL-2 and Δ13% in IL-17).[11] However, the increased expression of Foxp3 cells suppression of the immune system by Tregs is associated with susceptibility to increased infection rates, and potentially other malignancies. High doses of anti-TNF-α treatment is associated with statistically increased risks of severe infection.[12] With anti-TNFs like adalimumab and infliximab blocking both TNF receptors (TNF-1, TNF-2), it is possible that that the side-effects could also be a result of the non-specificity.[13]

[9] Nie H et al.Phosphorylation of FOXP3 controls regulatory T cell function and is inhibited by TNF-α in rheumatoid arthritis. Nat Med. 2013 Mar;19(3):322-8.
[10] Yamada A et al. Role of regulatory T cell in the pathogenesis of inflammatory bowel disease. World J Gastroenterol. 2016 Feb 21; 22(7): 2195–2205.
[11] Katz LH et al. Expression of IL-2, IL-17 and TNF-alpha in patients with Crohn's disease treated with anti-TNF antibodies. Clin Res Hepatol Gastroenterol. 2014 Sep;38(4):491-8
[12] Xie X. et al. Meta-analysis of infection risks of anti-TNF-α treatment in rheumatoid arthritis. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2013 Jul;38(7):722-36.
[13] Mira JP et al. Association of TNF2, a TNF-alpha promoter polymorphism, with septic shock susceptibility and mortality: a multicenter study. JAMA. 1999 Aug 11;282(6):561-8.

Jak1 inhibition could reduce autoimmune intestinal damage by selectively limiting β receptor signalling. Th1 and potentially Th2 cytokines can signal through α (CD25), β (CD122), and γ (CD-132) chain receptors. Blocking of the CD122 receptor in a preclinical model of autoimmune intestinal damage successfully reversed the damage since CD122+ T cells can be potent immunosuppressors.[14,15] Since Jak1 is associated with CD122 signalling, the benefits of Jak1 inhibition in Crohn's could be a result of blocking CD122 signalling cytokines by IL-4, IL-7, IL-9, and IL-15.[16] However, the inhibition of β signalling may only be a partial inhibition since Jak3 can also bind to the β receptor in the absence of Jak1. Therefore, drugs like tofacitinib, that bind both Jak1 and Jak3 can lead more complete blockade of these cytokines. The caveat is that although inhibition of Jak3 could be more efficacious, the risk of more severe adverse events increases. This therefore supports the use of a more selective Jak 1 inhibitor like filgotinib and upadacitinib.

Figure 39. Role of JAK-1, 2, and 3 on interleukin signalling[17]

JAK 1:	IL-6, interferon-γ, TNF-α, IL-2β, etc
JAK2:	EPOr, GHr, and PRL and IL-3 (IL-3r, I-5r, and GM-CSFr)
JAK3:	IL-2γ as well as other receptors that utilize the γ-chain including (IL-4, IL-7, IL-9, IL-15, and IL-21)

Source: Schindler C et al. J Biol Chem. 2007 Jul 13;282(28):20059-63

Filgotinib selectivity for Jak1 over other JAK family members (Jak2, Jak3 and Tyk2), could potentially block the JAK/STAT signalling without the negative side effects of 1st generation JAK inhibitors: JAK inhibition affects an array of downstream targets which can impair the body's ability to fight infection, and modify hematopoietic function. Filgotinib, although not as potent as the other molecules (Figure 39), has over 30-fold selectivity over Jak2 and 50-selectivity over Jak3, and upadacitinib has a 74-fold selectivity over Jak 2 and a 54-fold selectivity over Jak 3.[18] Tofacitinib (Jak3, Jak1, Jak2) which blocks all 3 JAKs is associated with reduced hemoglobin levels, elevations in both liver enzyme and lipid levels and has a black box warning of increased risk of infections and malignancies. Baricitinib that blocks both Jak1 and Jak2 can result in inhibition of β and γ-receptor signalling, and is associated with a greater impact on lymphocyte and platelet counts. Although intended for use in patients naïve to conventional synthetic or biologic drugs in the EU, baricitinib was limited to patients who have responded inadequately or were intolerant to one or more DMARDs, with the FDA recently requesting additional data to fully understand the drug profile following submission of an NDA. However, it is evident that the FDA is viewing

[14] Yokoyama S et al. Antibody-mediated blockade of IL-15 reverses the autoimmune intestinal damage in transgenic mice that overexpress IL-15 in enterocytes. Proc Natl Acad Sci U S A. 2009 Sep 15; 106(37): 15849–15854.
[15] Liu J. et al. CD8+CD122+ T-Cells: A Newly Emerging Regulator with Central Memory Cell Phenotype. Front Immunol. 2015 Oct 19;6:494
[16] Zhu MH. et al. Delineation of the Regions of Interleukin-2 (IL-2) Receptor β Chain Important for Association of Jak1 and Jak3 Jak1-Independent Functional Recruitment of Jak3 to IL-2Rβ. J Biol Chem. 1998 Apr 24;273(17):10719-25. J Biol Chem. 2007 Jul 13;282(28):20059-63
[17] Schindler C. et al. JAK-STAT Signaling: From Interferons to Cytokines
[18] Genovese MC et al. Efficacy and Safety of ABT-494, a Selective JAK-1 Inhibitor, in a Phase IIb Study in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate. Arthritis Rheumatol. 2016 Dec.

the profile of each JAK inhibitor uniquely since Jakafi (ruxolitinib) another Jak1,2 inhibitor does not have a black box warning. The same can be said for natalizumab and vendolizumab, which have similar MOAs but with only natalizumab having a black box warning. Therefore, we think filgotinib and upadacitinib could be rewarded for their selectivity relative to tofacitinib and baricitinib, supporting greater market adoption.

Figure 40. Filgotinib has a 30-fold selectivity for Jak1 over Jak2

Compound	JAK1 IC_{50} nM	JAK2 IC_{50} nM	JAK3 IC_{50} nM
filgotinib [Jak 1]	10	28	810
upadacitinib [Jak 1]	8	600	40
baricitinib [Jak 1| Jak 2)	5.9	5.7	>400
toficitinib [Jak 3| Jak 1]	1.3	1.9	.2

Source: Galapagos, Form F-1, April 15, 2015, Genovese MC et al. Arthritis Rheumatol. 2016

Competition is Good for Cystic Fibrosis Patients

The introductions of Kalydeco and Orkambi provided patients with Cystic Fibrosis (CF) significant advancements in the management of the most common Caucasian autosomal recessive disease. While the advancement of small molecule drugs that can help restore function of the CFTR protein have been important steps in alleviating the effects of CF, the absolute improvements in clinical outcomes such as lung exacerbations and lung function are still far below normal, especially for patients with minimal CFTR function versions (mutations) of the disease.

Our current projections anticipate that the AbbVie/ Galapagos team is able to complete pivotal studies with a triple-combination therapy for patients harboring F508del mutations (homozygous and heterozygous) and then receive regulatory approval during 2022. This would put the timeline roughly 6 – 12 months post a triplet therapy approval for Vertex, which we estimate occurs during 2021.

Timeline assumptions for Galapagos are based upon a successful Phase 1 study of GLPG2222 + '2737 + '2451 leading into a Phase 2 start during 1H2018, which would support Phase 3 initiation by YE2018. Vertex will have Phase 2 triplet data for Teza + Iva + VX-440 and Teza + Iva + VX-152 during 2H2017, and will presumably begin Phase 3 studies during 1H2018. We use the pivotal TRAFFIC and TRANSPORT study timelines as a guide for both companies, which suggests ~2.5 years from Phase 3 start to approval.

Critical to the success of AbbVie/ Galapgos will be development of a once-daily triplet, which would incorporate the GLPG2451 once daily potentiators versus the twice daily potentiator GLPG1837. Currently, Vertex is using ivacaftor as the backbone potentiator of triplet combination therapies, which requires twice daily dosing of 150mg.

We model Galapagos attaining 25 – 35% market share across the major Cystic Fibrosis phenotypes by 2026, and reaching ~$2.7bn in sales, although Galapagos will only realize a 15 – 20% royalty on those sales from AbbVie (Figure 41). Our estimates for Galapagos could prove conservative if the company produces comparable results with a once daily triplet-therapy versus a twice daily with Vertex, even considering a later market entry. **The biggest risk to Galapagos from a timeline perspective is if they are unable to start pivotal studies for a triplet therapy before Vertex gains approval, as that could trigger a request from regulators to run head-to-head studies.**

We think that the current race between Galapagos and Vertex to create the next generation of disease modifying drugs for Cystic Fibrosis will greatly advance the effectiveness of current therapies. Vertex is the incumbent, and has the advantage of a much longer and more methodical runway to developing a next generation triple-combination therapy for the more severe phenotypes, but we do think that certain aspects of the development process level the playing field with Galapagos, and also think Galapagos will likely carve out market share across the various subsets of Cystic Fibrosis mutations.

Figure 41. Cystic Fibrosis Market Model

Cystic Fibrosis Market Model	2012	2013	2014	2015	2016	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E
Total Revenues Vertex (BTIG)	171.6	371.3	463.8	982.3	1683.0	2056.6	2707.7	3280.6	3864.8	4386.3	5395.8	6084.2	6785.9	7500.9	8229.6
Consensus VRTX						*2055.0*	*2626.0*	*3337.0*	*3883.0*	*4408.0*	*4819.0*	*5281.0*	*5557.0*	*5726.0*	
Total Revenues Galapagos (BTIG)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	73.9	566.9	965.1	1446.7	2013.9	2669.2
Consensus GLPG									*11.7*	*40.1*	*57.1*	*58.4*	*63.2*	*64.6*	
Royalty adjusted						0	0	0	0	13	99	169	253	352	467
>Age 6 with G551D mutation	**3689**	**3765**	**3842**	**3920**	**4000**	**4040**	**4080**	**4121**	**4162**	**4204**	**4246**	**4289**	**4331**	**4375**	**4418**
Patients Treated	875	1893	2364	3220	3586	3622	3658	3695	3732	3769	3807	3845	3883	3922	3961
Total Corrector Penetration %	24%	50%	62%	82%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%
Kalydeco (Vertex) market share	100%	100%	100%	100%	100%	100%	100%	100%	100%	90%	85%	80%	75%	70%	65%
Price of Kalydeco	$196,151	$196,151	$196,151	$196,151	$196,151	$196,151	$196,151	$196,151	$196,151	$196,151	$196,151	$196,151	$196,151	$196,151	$196,151
Kalydeco sales	**171.645**	**371.285**	**463.75**	**631.674**	**703.432**	**710.466**	**717.571**	**724.747**	**731.994**	**665.383**	**634.701**	**603.339**	**571.287**	**538.533**	**505.067**
Galapagos market share						0%	0%	0%	0%	10%	15%	20%	25%	30%	35%
Price of Galapagos drug						$00	$00	$00	$00	$196,151	$196,151	$196,151	$196,151	$196,151	$196,151
Galapagos sales						**0.000**	**0.000**	**0.000**	**0.000**	**73.931**	**112.006**	**150.835**	**190.429**	**230.800**	**271.959**
>Age 12 F508del homozygous	**23059**	**23530**	**24010**	**24500**	**25000**	**25250**	**25503**	**25758**	**26015**	**26275**	**26538**	**26803**	**27071**	**27342**	**27616**
Patients Treated				1986	5547	7117	9739	12412	15137	17916	19422	20957	22520	24112	25734
Total Corrector/ Potentiator Penetration %				8%	22%	28%	38%	48%	58%	68%	73%	78%	83%	88%	93%
Orkambi (Vertex) market share				100%	100%	100%	100%	100%	100%	100%	90%	85%	80%	75%	70%
Price of Orkambi				176604	176604	176604	176604	176604	176604	176604	176604	176604	176604	176604	176604
Orkambi sales	**0**	**0**	**0**	**350.663**	**979.59**	**1256.941**	**1719.894**	**2191.981**	**2673.338**	**3164.102**	**3430.079**	**3701.059**	**3977.115**	**4258.323**	**4544.756**
Galapagos market share						**0**	**0**	**0**	**0**	**0**	10%	15%	20%	25%	30%
Price of Galapagos drug						**0**	**0**	**0**	**0**	**0**	$196,151	$196,151	$196,151	$196,151	$196,151
Galapagos sales						**0**	**0**	**0**	**0**	**0**	**380.973**	**616.605**	**883.463**	**1182.412**	**1514.335**
<Age 12 F508del/F508del					**10,000**	**10,100**	**10,201**	**10,303**	**10,406**	**10,510**	**10,615**	**10,721**	**10,829**	**10,937**	**11,046**
Patients Treated						505	1,530	2,061	2,602	3,153	3,715	4,289	4,873	5,468	6,075
Total Corrector/ Potentiator Penetration %						5%	15%	20%	25%	30%	35%	40%	45%	50%	55%
Orkambi (Vertex) market share						100%	100%	100%	100%	100%	95%	90%	85%	80%	75%
Price of Vertex drug						$176,604	$176,604	$176,604	$176,604	$176,604	$176,604	$176,604	$176,604	$176,604	$176,604
Vertex sales						**89.185**	**270.230**	**363.910**	**459.437**	**556.837**	**656.140**	**757.373**	**860.565**	**965.745**	**1072.943**
Galapagos market share						0%	0%	0%	0%	0%	5%	10%	15%	20%	25%
Price of Galapagos drug						$00	$00	$00	$00	$00	$196,151	$196,151	$196,151	$196,151	$196,151
Galapagos sales						**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**36.438**	**84.120**	**143.372**	**214.527**	**297.925**
Primarily Residual Function Mutations					**5000**	**5050**	**5101**	**5152**	**5203**	**5255**	**5308**	**5361**	**5414**	**5468**	**5523**
Patients Treated						0	0	0	0	0	531	804	1,083	1,367	1,657
Total Corrector/ Potentiator Penetration %						0	0	0	0	0%	10%	15%	20%	25%	30%
Vertex market share						0%	100%	100%	100%	100%	95%	90%	85%	80%	75%
Price of Vertex drug						$00	$00	$00	$00	$176,604	$176,604	$176,604	$176,604	$176,604	$176,604
Vertex sales						**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**93.734**	**142.007**	**191.237**	**241.436**	**292.621**
Galapagos market share						0%	0%	0%	0%	0%	5%	10%	15%	20%	25%
Price of Galapagos drug						$00	$00	$00	$00	$00	$196,151	$196,151	$196,151	$196,151	$196,151
Galapagos sales						**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**5.205**	**15.773**	**31.861**	**53.632**	**81.252**
F508del/Minimal CFTR Function					**24000**	**24240**	**24482**	**24727**	**24974**	**25224**	**25476**	**25731**	**25989**	**26248**	**26511**
Patients Treated						0	0	0	0	0	2,548	3,860	5,198	6,562	7,953
Total Corrector/ Potentiator Penetration %						0	0	0	0	0%	10%	15%	20%	25%	30%
Vertex market share						0%	100%	100%	100%	100%	95%	90%	85%	80%	75%
Price of Vertex drug						$00	$00	$00	$00	$176,604	$176,604	$176,604	$176,604	$176,604	$176,604
Vertex sales						**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**449.925**	**681.636**	**917.936**	**1158.894**	**1404.580**
Galapagos market share						0%	0%	0%	0%	0%	5%	10%	15%	20%	25%
Price of Galapagos drug						$00	$00	$00	$00	$00	$196,151	$196,151	$196,151	$196,151	$196,151
Galapagos sales						**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**24.986**	**75.708**	**152.930**	**257.433**	**390.011**
Other mutations (VRTX assumes ~75k Cystic Fibrosis patients globally)					**7,000**	**7,070**	**7,141**	**7,212**	**7,284**	**7,357**	**7,431**	**7,505**	**7,580**	**7,656**	**7,732**
Patients Treated						0	0	0	0	0	743	1,126	1,516	1,914	2,320
Total Corrector/ Potentiator Penetration %						0	0	0	0	0%	10%	15%	20%	25%	30%
Vertex market share						0%	100%	100%	100%	100%	95%	90%	85%	80%	75%
Price of Vertex drug						$00	$00	$00	$00	$176,604	$176,604	$176,604	$176,604	$176,604	$176,604
Vertex sales						**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**131.228**	**198.810**	**267.731**	**338.011**	**409.669**
Galapagos market share						0%	0%	0%	0%	0%	5%	10%	15%	20%	25%
Price of Galapagos drug						$00	$00	$00	$00	$00	$196,151	$196,151	$196,151	$196,151	$196,151
Galapagos sales						**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**7.288**	**22.082**	**44.605**	**75.085**	**113.753**

Source: Company Reports, Bloomberg, FactSet, BTIG Estimates, June 2017

Triplet-therapy is expected to greatly expand use of CFTR modulators

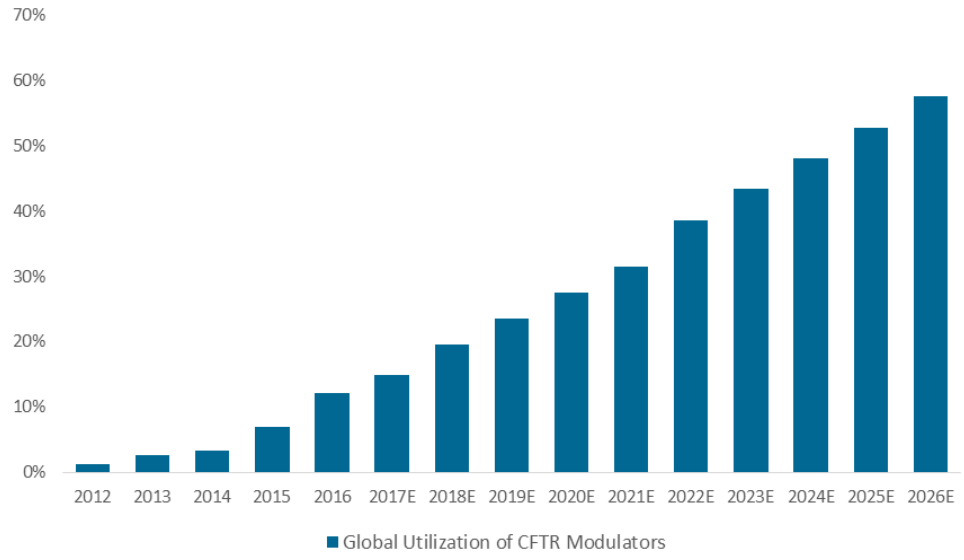
The first disease modifying drugs approved for the treatment of Cystic Fibrosis, Kalydeco and Orkambi, are currently only used within a subset of the ~75,000 global Cystic Fibrosis patients, the rarer G551D mutations, certain residual function mutations (age 2+) and with patients +12 years of age that are F508del homozygous.

During March 2017, Vertex announced positive outcomes from two Phase 3 studies evaluating the combination of tezacaftor and ivacaftor (TEZ/IVA) in the treatment of CF patients with either the homozygous F508del phenotype (EVOLVE study) or residual plus F508del mutations (EXPAND study). Based upon the outcomes data, we would expect that the TEZ/IVA combo cannibalizes share from Orkambi and expands the market within the homozygous F508del phenotype population, while opening up a new market for residual plus F508del mutations.

The largest singular subset of CF patients is the F508del with a minimal function CFTR allele, and remains a sizeable opportunity for drug development, approximately ~1/3 of the total CF population. The combination of Ivacaftor plus Vertex's next generation correct tezecaftor (VX-661) was stopped early based on a futility analysis announced during August 2016. Triple combination therapy, with a potentiator plus two correctors, is what has been viewed as the most likely course needed to produce a disease modifying effect.

We expect the introduction of triple-therapy for CF to increase the overall penetration of CFTR modulators to +50% by 2026 versus ~15% forecast for 2017 (Figure 42). Effectiveness of the triplet-therapies is still unknown, although preclinical testing suggests a substantial benefit from the addition of a secondary corrector for the F508del CFTR protein. Our penetration assumption will also prove variable due to the noted heterogeneity of CFTR modulator response within the F508del homomzygous population.

Figure 42. We forecast +50% of CF patients treated with a CFTR modulator by 2026E



Source: Company Reports, Bloomberg, FactSet, BTIG Estimates, June 2017

Cystic Fibrosis is a Disease of Many Phenotypes

Clinical manifestations of Cystic Fibrosis are driven by impaired activity of the cystic fibrosis transmembrane conductance regulatory (CFTR) protein. Since the gene encoding the CFTR protein was discovered during 1989, over +2000 mutations of the CFTR gene have been identified, with ~242 mutations being directly associated with Cystic Fibrosis. Despite the diversity of genetic disturbances identified with the CFTR gene, the F508del mutation (deletion) has been associated with 85 – 90% of Cystic Fibrosis clinical cases within the Caucasian population. The F508del mutation is a 3 base pair deletion leading to the loss of a key amino acid and causes misfolding of the CFTR protein, resulting in premature degradation by the proteasome[19].

The CFTR protein is a transmembrane transporter of anions (chloride) for epithelial cells, which facilitates fluid secretion. Absence or dysfunction of the CFTR protein leads to thickened secretions and obstructions in key epithelial structures such as the lungs, pancreas and biliary tract. End organ damage occurs overtime and is exacerbated by acute infections from common bacteria, such as Pseudomonas aeruginosa, which are cleared in the general population through properly functioning mucus secretions.

Phenotypes of Cystic Fibrosis range from mild to severe, depending on the underlying mutations, with a generally distinction being used between mutations such as F508del that prevent the CFTR protein from reaching the cell membrane versus the G551D mutation that leads to gating issues of the ion channel. Different approaches have been used for the classification of the various CF phenotypes (Figure 43), with more severe disease being found within the Traditional Class I – III mutations, or 'Minimal Function' for homozygotes, and Class IV+ classifications being viewed as 'Residual Function' mutations[20] [21].

Figure 43. Cystic Fibrosis is classified by CFTR mutation with Class I-III considered more severe

Traditional Classification	Class I		Class II	Class III	Class IV	Class V	Class VI
Proposed Classification (Marson, Bertuzzo, Ribeiro)	Class IA	Class 1B	Class II	Class III	Class IV	Class V	Class VI
De Boeck and Amaral's classification	Class VII	Class I	Class II	Class III	Class IV	Class V	Class VI
CFTR defect	No mRNA	No protein	No traffic	Impaired gating	Decreased conductance	Less protein	Less stable
Mutation examples	Dele2, 3 (21kb), 1717 - 1G->A	Gly542X, Trp1282X	Phe508del, Asn1303Lys, Ala561Glu	Gly551Asp, Ser549Arg, Gly1349Asp	Arg117His, Arg334Trp, Ala455Glu	3272-26A->G, 3849+10 kg C->T	c. 120del123, rPhe580del
Corrective therapy	Unrescuable	Rescue Synthesis	Rescue traffic	Restore channel activity	Restore channel activity	Correct splicing	Promote stability
Drugs (approved)	Bypass therapies (no)	Read-through compounds (no)	Correctors (yes)	Potentiators (yes)	Potentiators (no)	Antisense oligonucleotides, correctors, potentiators? (No)	Stabilizerss (no)
Clinical features (global aspect)	More-severe disease				Less-severe disease		
Functional Class	'Minimal Function' Presence of Class only				'Residual Function' Presence of at least one mutation		

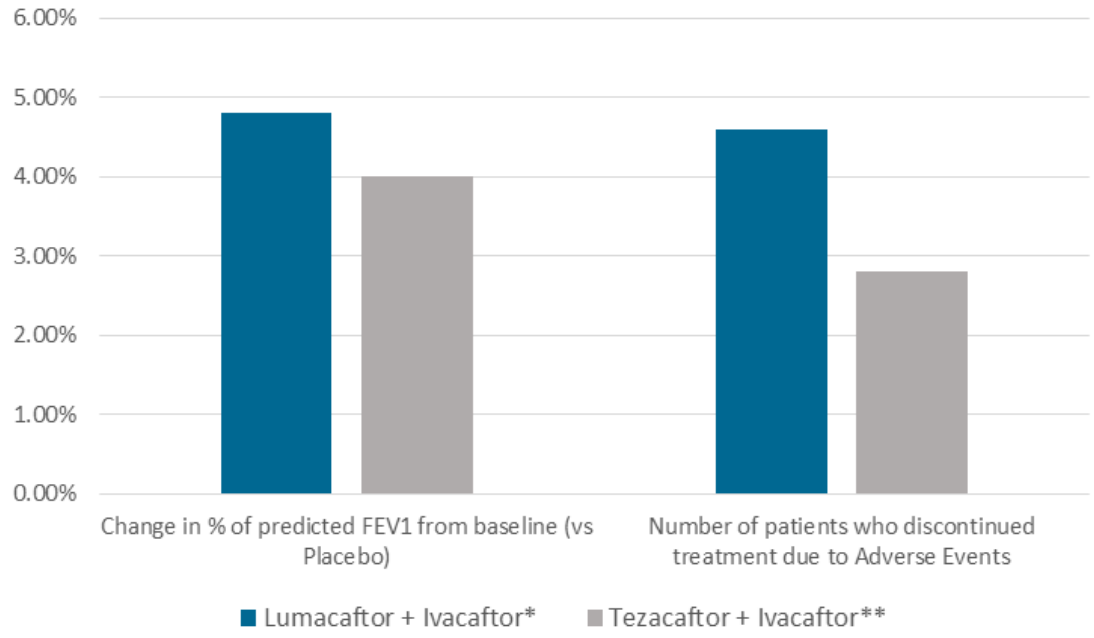
Source: Progress in therapies for cystic fibrosis; De Boeck and Amaral et al.; *Lancet Respir Med;* Aug 2016; 4(8): 662 - 74, *Classification of CFTR mutation classes*; Marson and Ribeiro et al.; *Lancet Respir Med;* Aug 2016; Vol 4

[19] *New and Emerging Targeted Therapies for Cystic Fibrosis;* Quon and Rowe et al.; *BMJ;* 2016l 352: i859
[20] *Progress in therapies for cystic fibrosis;* De Boeck and Amaral et al.; *Lancet Respir Med;* Aug 2016; 4(8): 662 - 74
[21] *Classification of CFTR mutation classes*; Marson and Ribeiro et al.; *Lancet Respir Med;* Aug 2016; Vol 4

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