attenuated decline in FVC % predicted at week 48 (2.85% vs. 7.17% for placebo, p=0.0001), with the drug's reduction in fibrotic build up in the lungs being confirmed by quantitative lung fibrosis (QLF) measurements as captured by HRCT (Exhibit 14) and changes in QLF correlating with the attenuation of decline in FVC % predicted.

With respect to the Saint George's Respiratory Questionnaire (abstract) the mean baseline SGRQ scores were 48.3 and 50.4 units for pamrevlumab and placebo, respectively. The pamrevlumab mean total score and the 3 subscales (symptoms, activity, and impacts) showed improvement from baseline at week 48, while mean placebo scores showed worsening in all subscales and in total score. The difference at week 48 between the two arms was -5.28 symptoms, -6.14 activity, -4.79 impacts subscales, and -5.37 units in total score. While these results did not reach statistical significance, the trend was consistent across all subscales. As a reference, (i) treatments for COPD with an improvement of 4 units or more in clinical trials have subsequently found wide acceptance in clinical practice and (ii) delta in the pooled INPULSIS Ofev trials was -1.43 units.

We cautioned earlier on cross trial comparisons but a ~180mL FVC benefit is comparable to both Esbriet and Ofev and given the entirely different mechanism, combination use with either approved therapy may be realistic. We are yet to see sub-population data from the study of outcomes for patients in combination. The product is clearly interesting but surprisingly, physicians seemed less receptive to the data (not convinced by the progression of lung fibrosis measurement) and where we still scratch out heads is (i) why did the p2b take so long to complete (was it a struggle to get drug naïve patients given the approvals of Esbriet/Ofev during trial) and (ii) why hasn't the p3 trials begun considering the p2b read-out was over 12 months ago and will they still attempt to target drug naïve patients, (iii) will the older population be receptive to every 3 week drives to their respiratory clinic to receive IV when existing treatment is oral. Fibrogen are adamant they will so we shall wait and see.

Promedior's PRM-151 was the product that seemed to garner the most interest from our physician discussions following an interesting phase 2 data set (link). The product is a recombinant human pentraxin 2, which is a naturally circulating protein known to regulate the innate immune system and activate tissue damage repair processes in fibrotic and inflammatory diseases. Ultimately the product binds to damaged tissue and monocytes and directs monocyte differentiation towards resolution of fibrosis.

In the initial p1 safety study (1 mg/kg, 5 mg/kg, or 10 mg/kg administered IV days 1,3,5,8 and 15) we saw very encouraging trends at 57 days with an improvement in FCV (+2.4% vs. -1.5%) and an increase in 6-MWT (+8m vs. -10.5m). What was very interesting was that in 3 of the 15 drug patients we saw a +10% change in FVC prediction (another 3 at +5%). Clearly good enough to progress to p2.

In p2 study (117 patients), the drug was dosed at 10mg/kg IV every 4-weeks to 28 weeks. Treatment reduced the decrease in FVC % predicted (-2.5% vs -4.8% for placebo, p=0.001), but the minimal clinically relevant difference was suggested to be 2% to 6%, and the reported difference was just 2.3% (Exhibit 58). There was no significant treatment differences in total lung volume (93.5mL) or quantitative parenchymal features on HRCT (normal lung volume difference, —1.2%; interstitial lung abnormalities difference. The change in 6-MWT was -0.5m for vs. -31.8 m for placebo (minimal clinically important difference was 24-45m).

What was interesting about the study is that 78% of patients were on the background therapy of Esbriet or Ofev and the effect was independent of concurrent IPF therapy status (p=0.65, Exhibits 59-60) when assessing the sub-population data (please ask for paper). This combined with a patient population were the duration since IPF diagnosis prior to enrollment was much longer (3.8 years), gives us insight in to why KOLs were positive on the product.

EXHIBIT 57: **Pamrevlumab reduced the decline in QLF (as measured by HRCT) and FVC**

	PRAISE	
	Pamrevlumab (n=50)	Placebo (n=53)
QLF change from baseline (mL):		
24 weeks	24.8 (p=0.0090)	86.4
48 weeks	75.4 (p=0.038)	151.5
FVC % predicted change from baseline 48 weeks	2.85%	7.17%
FVC change from baseline 48 weeks (mL)	129	308

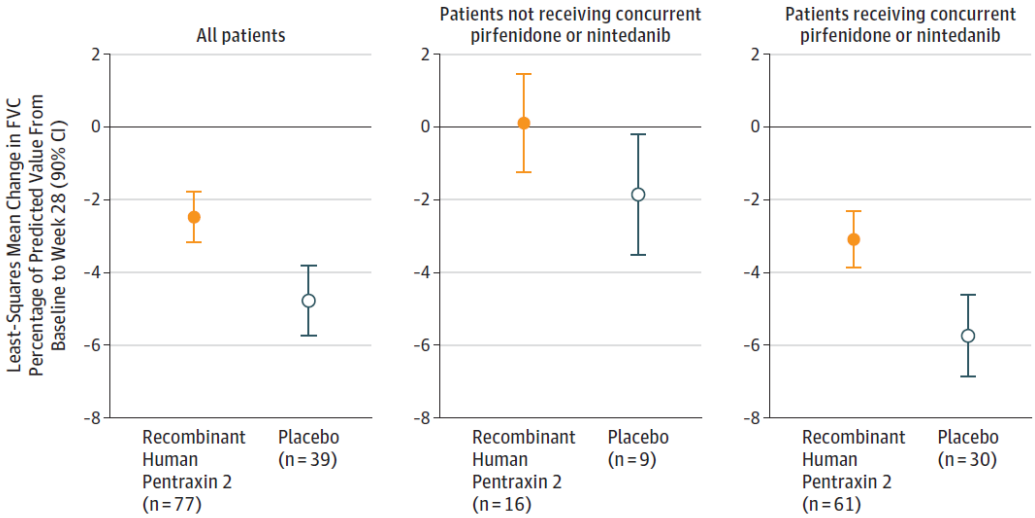
Source: Source: Raghu et al (2016) Eur Respir J (link); PRAISE results announcement at ATS (link and link); press reports (link), Bernstein analysis

EXHIBIT 58: **PRM-151 met FVC primary endpoint**

	PRM-151 Phase 2	
	PRM-151 (n=77)	Placebo (n=39)
FVC % predicted change from baseline 28 weeks	-2.50%	-4.80%

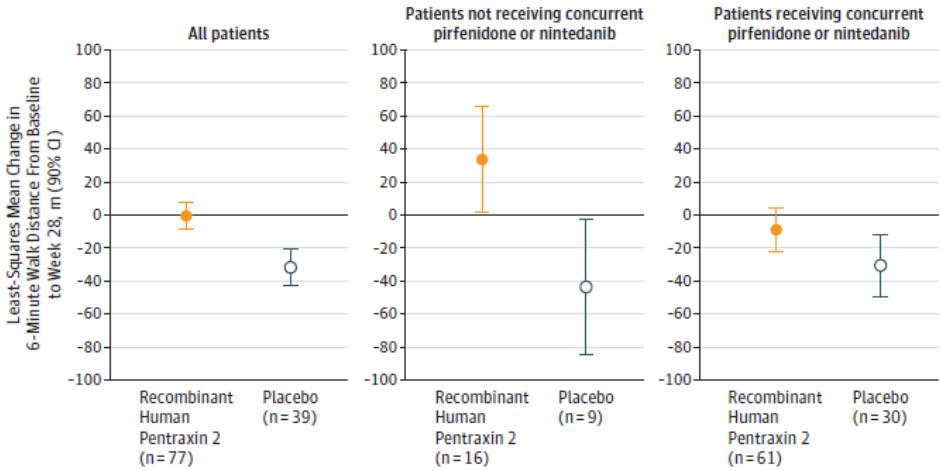
Source: Raghu et al (2018) JAMA (link), Bernstein analysis

EXHIBIT 59: **PRM-151 - Change in Forced Vital Capacity Percentage of Predicted Value From Baseline to Week 28**



Source: Raghu et al (2018) JAMA (link)

EXHIBIT 60: **PRM-151 - Change in 6-Minute Walk Distance From Baseline to Week 28**



Source: Raghu et al (2018) JAMA (link)

Prometic's PBI-4050 is also promising, although it is yet to report placebo-controlled study results. It is an orally active drug candidate that activates GPR40 (shown in mouse models of kidney fibrosis to be protective) and suppresses GPR84 (shown to be damaging in fibrotic disease). These two receptors are involved in the regulation of cells involved in fibrosis, including macrophages, epithelial cells and fibroblasts, and modulate disease progression. There has not been a placebo controlled study, but an open label phase 2 study of daily oral doses of 800mg PBI-4050 alone, or with nintedanib or pirfenidone, demonstrated that PBI-4050 might slow the progressive decline in respiratory function usually seen in IPF patients. After 12 weeks of treatment, the change in FVC for patients receiving PBI-4050 either alone or in combination with nintedanib were not significantly different, while patients receiving PBI-4050 in combination with pirfenidone had significant decreases in FVC vs. patients receiving it in combination with nintedanib (Exhibit 61).

Kadmon Therapy's KD025 has also demonstrated some proof of concept in phase 2 trials. This candidate is an inhibitor of ROCK2 (Rho-associated coiled coil kinase) which decreases STAT3-dependent production of IL-21 (a stimulator of B cells) and IL-17 (a stimulator of Th17 cells), both of which have been implicated in fibrosis. In phase 2 trials KD025 400mg per day monotherapy was associated with a decrease in FCV decline at 24 weeks (median -48mL vs. -175m for the best supportive care, BSC, control group, Exhibit 62) but this was in a small cohort (20 completed treatment, 9 completed BSC). The trial is still recruiting, and patients have the option to extend treatment beyond the primary endpoint to 96 weeks, so we wait to see more data on efficacy. Given ROCK2 is involved in several other pathways (many of which are required for normal repair and epithelium generation), tolerability will be a major consideration for the product.

EXHIBIT 61: **FVC change: PBI-4050 with and without nintedanib or pirfenidone**

	PBI-4050 Phase 2 Open Label		
	PBI-4050 alone (n=9)	PBI-4050 with nintedanib (n=16)	PBI-4050 with pirfenidone (n=15)
FVC baseline (L)	2.88	2.76	2.85
FVC change from baseline (mL)	-13	+7	-105
vs. PBI-4050 + pirfenidone	*p=0.1319*	*p=0.0272*	

Source: Parker et al (2017) Am J Respir Crit Care Med (link), Bernstein analysis

EXHIBIT 62: **Phase 2 study of KD025 is ongoing**

	KD025 Phase 2	
	KD025 (n=20)	BSC control (n=9)
FVC decline from baseline 24 weeks (mL)	48	175

Source: Press release (link); BSC = best supportive care, Bernstein analysis

In short, the competitor pipeline is real and we must factor this in to our modelling of the opportunity for Galapagos. Promedior and Fibrogen are the products most debated but with such an array of targets and such early stage data, it is too hard to call who offers the biggest threat. Regardless, there is enough unmet need (even on top of existing treatment) that success for one may not limit success for others.

IPF has big potential - we forecast revenues of €1.3B by 2030 at 30% probability

Our US IPF market model is summarised in Exhibit 63 but we make a few comments.

+ *Treatment rates seem low.* Despite the lack of alternatives, our estimates suggest less than 20% of the addressable population is currently treated with either Esbriet or Ofev (we used prescriptions volumes as our guide here). What is interesting is Galapagos suggest that 1/3 of patients are on Ofev, another 1/3 on Esbriet, with the remainder on no drug. Physicians suggest if their patients are diagnosed with the disease, typically they would use one of the 2 products, suggesting identification remains a major challenge. We expect treatment of these baseline products to continue on an upward trajectory towards 30%.
+ *Majority of volumes will come from combination use.* KOLs suggest use on top of existing products is the most likely outcome for pipeline assets and that is how we model GLPG1690. Galapagos have designed their p3 study with flexibility ensuring that outcomes for monotherapy and in combination can be determined.
+ *Pricing in-line with existing treatment.* The annual costs for Ofev and Esbriet are $120k. We see no reason why Galapagos would not charge a similar level, although based on the gross to net for Esbriet, we assume a 25% rebate to the list. In Europe we assume a significant (65%) discount to the US price.
+ *Generics will help if the product is used on-top.* Esbriet will go generic in 2026 and Ofev most likely in 2024. Assuming GLPG1690 is used in combination with these products, generics can be considered a positive driver of use.
+ *Competition will limit penetration.* There is enough in the competitor pipeline for us to be cautious on market share, although it remains unclear if competitors will seek a similar strategy to be used in combination with existing treatment. Our base assumption is that 30% of Esbriet/Ofev patients will also receive GLPG1690, equivalent to 13.5k patients in 2030 in the US, below the number of patients being treated today for the disease.

In short, with Galapagos owning full rights for the IPF portfolio, our peak sales estimates of €1.3B in 2030 can be a big contributor to value. It is worth noting that this must be offset against increases in S&M costs, bringing down the total contribution. However, this is the perfect opportunity for a biotech to go alone as is a highly centralised care indication meaning less sales reps on the ground.

EXHIBIT 63: **GLPG1690 IPF US market model**

	2015	2016	2017	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
US market																
TRx																
Esbriet	51,045	69,438	72,041	79,813	87,795	95,696	107,180	118,970	133,246	145,238	156,857	167,837	177,907	186,803	194,275	202,046
Ofev	32,805	58,829	71,767	79,813	87,795	95,696	107,180	118,970	133,246	145,238	156,857	167,837	177,907	186,803	194,275	202,046
Total baseline	83,850	128,267	143,808	159,627	175,590	191,393	214,360	237,939	266,492	290,476	313,714	335,674	355,815	373,606	388,550	404,092
% growth		53%	12%	11.0%	10.0%	9.0%	12.0%	11.0%	12.0%	9.0%	8.0%	7.0%	6.0%	5.0%	4.0%	4.0%
GLPG1690	0	0	0	0	0	0	21,436	38,070	50,633	69,714	78,429	87,275	96,070	104,610	112,679	121,228
Others	0	0	0	0	0	0	25,723	52,347	71,953	92,952	109,800	127,556	145,884	164,386	182,618	202,046
Total add-on	0	0	0	0	0	0	47,159	90,417	122,586	162,667	188,229	214,832	241,954	268,996	295,298	323,273
% share of baseline TRx																
Esbriet	61%	54%	50%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%
Ofev	39.1%	45.9%	49.9%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%
Add-on % share of baseline TRx																
GLPG1690	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	10.0%	16.0%	19.0%	24.0%	25.0%	26.0%	27.0%	28.0%	29.0%	30.0%
Others	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	12.0%	22.0%	27.0%	32.0%	35.0%	38.0%	41.0%	44.0%	47.0%	50.0%
Total add-on	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	22.0%	38.0%	46.0%	56.0%	60.0%	64.0%	68.0%	72.0%	76.0%	80.0%
Sales ($m)																
Esbriet	395	562	630	712	798	888	994	1,104	1,236	1,347	1,455	1,090	1,040	1,092	1,135	1,181
Ofev	293	512	663	752	844	938	1,051	1,166	1,306	1,424	1,538	1,152	1,099	1,154	1,200	1,248
Total baseline	*687*	*1,075*	*1,293*	*1,464*	*1,642*	*1,826*	*2,045*	*2,270*	*2,542*	*2,771*	*2,993*	*2,242*	*2,139*	*2,245*	*2,335*	*2,429*
GLPG1690	0	0	0	0	0	0	205	363	483	665	748	833	917	998	1,075	1,157
Other	0	0	0	0	0	0	245	499	686	887	1,048	1,217	1,392	1,568	1,742	1,928
Total add-on	*0*	*0*	*0*	*0*	*0*	*0*	*450*	*863*	*1,169*	*1,552*	*1,796*	*2,050*	*2,308*	*2,566*	*2,817*	*3,084*
Total IPF	**687**	**1,075**	**1,293**	**1,464**	**1,642**	**1,826**	**2,495**	**3,133**	**3,712**	**4,323**	**4,789**	**4,291**	**4,447**	**4,812**	**5,153**	**5,513**
Realised price per TRx																
Esbriet	7,731	8,100	8,741	8,916	9,094	9,276	9,276	9,276	9,276	9,276	9,276	6,493	5,844	5,844	5,844	5,844
Ofev	8,917	8,711	9,239	9,424	9,612	9,804	9,804	9,804	9,804	9,804	9,804	6,863	6,177	6,177	6,177	6,177
GLPG1690				9,170	9,353	9,540	9,540	9,540	9,540	9,540	9,540	9,540	9,540	9,540	9,540	9,540
Other				9,170	9,353	9,540	9,540	9,540	9,540	9,540	9,540	9,540	9,540	9,540	9,540	9,540
Growth in realised price per TRx																
Esbriet		5%	8%	2.0%	2.0%	2.0%	0.0%	0.0%	0.0%	0.0%	0.0%	-30.0%	-10.0%	0.0%	0.0%	0.0%
Ofev		-2%	6%	2.0%	2.0%	2.0%	0.0%	0.0%	0.0%	0.0%	0.0%	-30.0%	-10.0%	0.0%	0.0%	0.0%
GLPG1690				2.0%	2.0%	2.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Other				2.0%	2.0%	2.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Addressable population																
US Population ('000s)	321,040	323,406	325,719	328,123	330,540	332,965	335,387	337,799	340,189	342,552	344,877	347,154	349,378	351,545	353,651	355,695
IPF prevalence (# per 100,000)	36.5	37.0	37.5	38.0	38.5	39.0	39.5	40.0	40.5	41.0	41.0	41.0	41.0	41.0	41.0	41.0
# US patients with IPF ('000)	117,180	119,660	122,145	124,687	127,258	129,856	132,478	135,120	137,777	140,446	141,400	142,333	143,245	144,133	144,997	145,835
Implied patients treated (assumes 9 TRx per year)																
Baseline																
Esbriet	5,672	7,715	8,005	8,868	9,755	10,633	11,909	13,219	14,805	16,138	17,429	18,649	19,767	20,756	21,586	22,450
Ofev	3,645	6,537	7,974	8,868	9,755	10,633	11,909	13,219	14,805	16,138	17,429	18,649	19,767	20,756	21,586	22,450
Baseline total	9,317	14,252	15,979	17,736	19,510	21,266	23,818	26,438	29,610	32,275	34,857	37,297	39,535	41,512	43,172	44,899
% of patients treated with baseline thera	8%	12%	13%	14%	15%	16%	18%	20%	21%	23%	25%	26%	28%	29%	30%	31%
Add-on																
GLPG1690	0	0	0	0	0	0	2,382	4,230	5,626	7,746	8,714	9,697	10,674	11,623	12,520	13,470
Others	0	0	0	0	0	0	2,858	5,816	7,995	10,328	12,200	14,173	16,209	18,265	20,291	22,450
Add-on total	0	0	0	0	0	0	5,240	10,046	13,621	18,074	20,914	23,870	26,884	29,888	32,811	35,919
% of patients treated with add-on therap	0%	0%	0%	0%	0%	0%	4%	7%	10%	13%	15%	17%	19%	21%	23%	25%
GLPG revenue																
GLPG sales ($m)				0	0	0	205	363	483	665	748	833	917	998	1,075	1,157
FX (EUR/USD)				0.85	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87	0.87
GLPG US sales (€m)				**0**	**0**	**0**	**178**	**315**	**419**	**577**	**650**	**723**	**796**	**866**	**933**	**1,004**

Source: IQVIA, World Bank, UN World Population Prospects 2017, British Lung Foundation, Nalysnyk et al (2012) Eur Respir Rev (link), Company disclosure, Bernstein analysis and estimates

Final thoughts

This is high risk, high reward. We would not call IPF a graveyard for drug development (we have better examples e.g. SLE) but given some patients may go periods of months with no worsening of disease, it will always be challenging to say with certainty, GLPG1690 will demonstrate superiority. The initial data suggests the product should do well and given the complementarity to existing treatment, we would expect to see an additive benefit for patients over 52 weeks. The way we see it, get an approval and the drug will sell. Investors will appreciate that most of our peers have a reasonable contribution from the product in their models yet spend very little time focusing on the asset. We view this as just as important as filgotinib to our investment case. Yes, we cannot say with more confidence if the product will work but we like the potential upside.

Why stop at IPF? IPF accounts for less than 1/3 of all interstitial lung disease. Several physicians we spoke to suggested use in the remaining population is a possibility as well as related indication (e.g. systemic sclerosis, neurofibromatosis, RA). With both Esbriet and Ofev current under investigation for broader use, success may not stop at IPF alone, although this is a very long-term thought.

Reimbursement is not a major challenge – think of PAH. Consistent feedback was that reimbursement was not a challenge in IPF. If patients were coming back to high co-pays, the centres would contact the companies to ensure the correct patient assistance lowered these to much lower levels. As one physician said to us, on average my patients that end up paying co-pays, normally do so at the $40-50/month level. We did consider the impact of combination therapy and the incremental cost of treatment but physicians were quick to point to PAH, where triplet therapy now sets the bar at over $250k and reimbursement continues to be strong.

CYSTRIC FIBROSIS IS UNLIKELY TO MATTER BUT IT IS NOT A ZERO

With recent data lacklustre, question marks over the partnership with AbbVie moving forwards and cautious commentary from the company, investors seem to be placing less emphasis on the CF opportunity. The key questions that remain are (i) will Galapagos pursue the opportunity alone, (ii) how far behind Vertex will they be and (iii) what is the realistic size of the opportunity.

Introduction (skip if familiar)

Cystic fibrosis (CF) is a life-limiting genetic condition. It affects ~30k people in the US and ~75k in the developed world (although we suspect higher). Improvements in diagnosis and care have significantly improved life expectancy in developed countries from a median of a few months in the 1950s to over 40 years currently. Adult patients outnumber child patients, and the adult patient population is growing.

Early diagnosis is facilitated by new-born screening programmes in most developed countries. Blood samples taken by a heel-prick are tested for immunoreactive trypsinogen (IRT) levels and checked for common genetic mutations associated with CF, with any suspected CF cases confirmed by a sweat test. Early diagnosis is important because appropriate disease management can delay or prevent the onset of symptoms and organ damage, and prolong life. That said, patients who are diagnosed as adults typically have a much less severe disease phenotype and therefore good survival.

CF is a progressive disease whereby thick, sticky mucus builds up in the lungs, pancreas and other organs. The specific manifestations tend to vary by patient age (Exhibit 64), and the signs and symptoms of CF vary in severity depending on each patient's disease phenotype (more below).

In the lungs, the mucus clogs the airways and traps bacteria, leading to recurrent infections, lung damage and respiratory failure in those patients who do not receive a lung transplant. Lung function can be seriously impaired, with as little as 20% function remaining intact in some patients. Infection risk is so high that patients with CF are urged not to meet each other face-to-face to avoid cross-contamination and CF clinics have strict isolation policies.

Pulmonary exacerbations are recurrent in patients with CF. These manifest as an increase in the symptoms of chronic lung infection, especially cough and sputum production, and are associated with increased breathlessness and fatigue. Exacerbations are diagnosed by these symptoms as well as measurement of lung function and oxygen saturation. When exacerbations occur, patients will usually require IV therapy, and some might require supplementary oxygen or even non-invasive ventilatory support.

In the pancreas, mucus blocks ducts and prevents the release of digestive enzymes, leaving patients unable to adequately digest food. This can manifest as malnutrition and poor growth despite good appetite, and can cause delayed puberty. In older patients, insulin production can be impaired resulting in CF-related diabetes (CFRD), which may manifest as thirst, hunger, weight loss and excessive need to urinate.

EXHIBIT 64: **Typical age at which potential disease symptoms manifest**

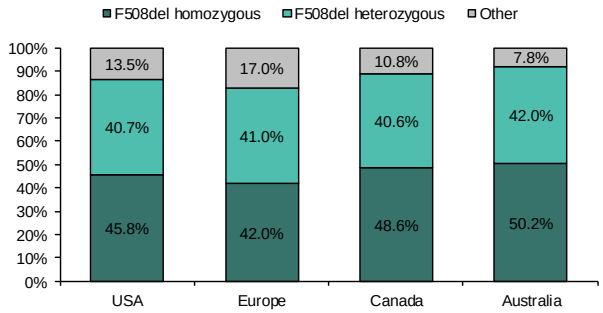
	0 to 10 years	10 to 20 years	20 to 35 years	>35 years
Lung and airways	Early mucinous plugging and bronchiectasis	Established bronchiectasis	Established bronchiectasis with haemoptysis / pneumothorax	Progressive respiratory failure / lung transplant
Common infections	*Staph aureus*	*Staph aureus / intermittent Pseudomonas aeruginosa*	*P. aeruginosa, other non-fermenting Gram -ve bacteria, allergic bronchopulmonary aspergillosis*	
Pancreas	Pangreatic exocrine insufficiency		CF-related diabetes mellitus	
Liver	Abnormal liver function test	Cirrhosis	Portal hypertension (5-10% of patients)	Liver transplant
Gut	Meconium ileus		Distal intestinal obstruction syndrome	
Reproductive system	Absence of vas deferens			
Other			Arthropathy, CF-related osteoporosis	

Source: Elborn (2016) Lancet (link); Bernstein analysis. Note not all patients will have every symptom

Many genetic variants have been implicated in CF. The disease is caused by functional failure of the cystic fibrosis transmembrane conductance regulator (CFTR), which is a chloride-conducting transmembrane channel responsible for the regulation of anion transport (e.g., chloride, bicarbonate) and in turn mucociliary clearance of the lungs. The disease is autosomal recessive in that both copies of the CFTR gene must be mutated in order for the disease to manifest (individuals with a single mutated CFTR gene are carriers but will not develop symptoms).

More than 2,000 variants have been identified, of which about 85% are associated with disease. The most common mutation is F508del (also known as Phe508del, a Class II type mutation), which is common in populations of northern European ancestry: 46% of patients with CF in USA are homozygous for F508del, with similar genotype prevalence in Canada (49%) and Europe (42%) (Exhibit 65). People from other regions have a wider range of mutations with F508del being less common. Other common mutations in western countries include G542X (Class I) and G551D (Class III) (Exhibit 66).

EXHIBIT 65: **Prevalence of F508del mutation**



Source: National Cystic Fibrosis Registries, Bernstein analysis

EXHIBIT 66: **Common CFTR mutations**

	USA	Europe	Canada	Australia
F508del	86.4%	83.0%	89.2%	92.2%
G542X	4.7%	2.7%	3.5%	3.0%
G551D	4.4%	1.4%	3.0%	7.7%
R117H	3.0%	1.0%	2.1%	3.7%
N1303K	2.4%	2.1%	2.1%	1.4%
W1282X	2.3%	1.1%	2.0%	0.9%
R553X	1.8%	0.8%	n/a	0.8%
1717-1G->A	1.6%	0.9%	n/a	1.5%
3849+10kbC->T	1.5%	0.9%	n/a	n/a
621 + 1G->T	1.5%	n/a	6.1%	1.5%

Source: National Cystic Fibrosis Registries, Bernstein analysis and estimates (for Europe). Note data is proportion of patients carrying one or more copy of each mutation. As each patient carries 2 alleles, the total is not 100%.

Different types of mutations can be classified into CFTR classes (Exhibit 67). Patients with mutations falling into Classes I to III typically have no CTFR function and severe disease, while patients with mutations falling into Classes IV to VI have some residual CTFR function and more mild disease. The disease manifestation of heterozygotes is typically somewhere between Classes IV-VI and healthy.

EXHIBIT 67: **Classes of CFTR mutations and their disease phenotype**

	Class I	Class II	Class III	Class IV	Class V	Class VI	Heterozygote carrier	Healthy
Disease severity	Most severe						Least severe	
CTFR defect	No functional CTFR	CFTR is degraded rather than trafficked to membrane	Impaired channel opening	Reduced flow of ions	Very little production of functional CTFR	Membrane instability		
% of population	16.4%	80%+	3.9%	3.3%	3.0%			
Mutation examples	G542X W1282X R553X 621 +1G → T	F508del N1303K I507del R560T	G551D G178R G551S S549N S1251N	R117H R347P R117C R334W	3849 + 10kbC → T 2789 + 5G → A 3120 + 1G → A 5T	4326delTC Q1412X 4279insA		
CTFR function	0%			50%				100%
Sweat chloride	100 mmol/L			30 - 60 mmol/L			*(Signs and symptoms intermediate to those of classes IV to VI and healthy people)*	<30 mmol/L
Lung phenotype	Bronchiectasis			Airway wall thickening				Normal airways
Bacteriology	*Pseudomonas aeruginosa*			*Staphylococcus aureus*				Normal microbiome
Pancreas	No function			50% pancreatic insufficiency				Normal function
Male fertility	Infertile			Infertile				Fertile

ource: Elborn (2016) Lancet (link); De Boeck et al (2014) J Cystic Fibrosis (link); Bernstein analysis

Most treatments for CF focus on symptom control rather than addressing the underlying disease. Airway clearance is particularly important, with daily pulmonary therapies being effective at clearing airway secretions and slowing the decline of lung function. This includes inhaled medications, antibiotics and airway clearance techniques (ACT) taught by a specialist physiotherapist to the parent, carer and/or patient. These therapies can take a significant amount of time to perform (up to four hours per day) and compliance is poor – only ~50% of patients adhere to chest physical therapy (link). Inhaled medications can include bronchodilators to open the airways, nebulised antibiotics to fight infections, mucus thinners (e.g, dornase alfa, branded Pulmozyme, Roche), expectorants to clear sputum and steroids to reduce inflammation.

Managing exacerbations is critical. Several treatments have been shown to reduce the frequency of exacerbations, including dornase alfa, inhaled antibiotics (tobramycin, colistin, aztreonam), inhaled levofloxacin, hypertonic saline (an expectorant), mannitol, and oral azithromycin. These treatments are each associated with a small (typically 3% to 5%) improvement in FEV_1 and a substantial reduction in the frequency of exacerbations.

When they occur, exacerbations are treated with antibiotics and increased airway clearance. Oral antibiotics are usually used for *S. aureus* and *H. influenza* infection, but once a patient first tests positive for *P. aeruginosa* (or other Gram-negative bacteria) treatment is typically aggressive in an attempt to achieve clearance: oral ciprofloxacin and inhaled colistin for 3 months. Chronic infections are treated for 14 days with extended action penicillin, third generation cephalosporin, or carbapenem in combination with an aminoglycoside or polymyxin.

Lung transplantation is typically offered to patients with respiratory failure who exhibit declining lung function, frequent exacerbations and an $FEV_1 < 30\%$ predicted. In developed countries it is very uncommon for children to present with this level of disease progression. Lung transplantation has good survival (60-70% at 5 years) but a shortage of organs can mean patients die waiting for transplant.

Symptoms affecting organs other than the lungs also require treatment. Pancreatic insufficiency is a problem at birth in patients with Class I to III disease, but can also develop later in life in patients with Class IV to VI disease. Digestive enzymes can be taken at each meal to improve digestion; however this requires careful dose titration to align with energy intake. In general, the increased metabolic rate present in patients with CF (due to the mutation, as well as the increased energy expenditure from breathing, and as a consequence of chronic infection) should be managed with support from a specialist dietician.

Vertex changed this with the launch 3 products to target the underlying disease. These products work by modulating the CFTR protein and there are now three treatment options currently approved by the FDA (Exhibit 68) which have expanded their patient base dramatically (Exhibit 69).

+ **Ivacaftor** (marketed as Kalydeco) is a potentiator that increases the probability of CFTR channel opening that addresses patients with specific 'responsive' mutations within Class III and IV (~6k patients). Kalydeco is associated with slowed decline in lung function and has the potential to modify the course of CF. Note that in patients with F508del mutations it is not sufficient to improve the activity of defective CFTR (as Kalydeco does) as this doesn't address the underlying issue with processing and trafficking that lead to insufficient CFTR reaching the cell surface membrane.

+ **Lumacaftor** (marketed as Orkambi, a combination lumacaftor-ivacaftor therapy) is a corrector that improves processing and trafficking of CTFR (which is a significant problem in patients who are homozygous for the F508del, ~45% to 50% of CF patients). Orkambi is also associated with slowed decline in lung function, however ~30% of eligible patients were not on Orkambi due to side effects (e.g., chest tightness, although this is an early AE that tends to ease) or due to concerns about drug-drug interactions with hormonal contraceptives.

+ **Tezacaftor** (marketed as Symdeko, a combination tezacaftor-ivacaftor therapy) is another corrector that was developed in an attempt to overcome the shortcomings of lumacaftor. Unlike Orkambi, Symdeko is not associated chest tightness nor does it interact with hormonal contraceptives. Vertex intends to target patients that previously tried Orkambi but discontinued it as these are likely to be motivated early adopters. It has been approved by the FDA and is being considered by the EMA having received a positive recommendation from CHMP in July 2018.

At the start of 2018, Vertex reported that treatment had been initiated in ~12.5k patients. We estimate that at that time there were about ~9k patients on treatment, which given high discontinuation rates due to adverse events (~30% for Orkambi) and/or lack of efficacy, is not inconsistent with Vertex's disclosure.

EXHIBIT 68: **Vertex disease modifying therapies**

Brand	Drug	US approval	Type	CF class	Mutation	Effect on sweat chloride	FEV1*	Pumonary exacerbations
Kalydeco	Ivacaftor	2012	Potentiator	Class III	G551D**	50% decrease	10% increase	40% decrease
				Class IV	F117H	25% decrease	3% increase	Unknown
Orkambi	Lumacaftor-Ivacaftor	2015	Corrector & Potentiator	Class II	F508del	8% decrease	3% increase	30% decrease
Symdeko	Tezacaftor-Ivacaftor	2018	Corrector & Potentiator	Class II	F508del	10% decrease	4% increase	35% decrease

Source: FDA, Taylor-Cousar et al (2017) N Engl J Med (link); Bernstein analysis
* forced expiratory volume in 1 second; ** for other class III mutations there is similar efficacy, but impact on exacerbations not known

EXHIBIT 69: **Vertex patient targets**

	Kalydeco (ivacaftor)	Orkambi (lumacaftor /ivacaftor)	Tezacaftor/ivacaftor	Triple combination regimens	Gene editing mRNA
Eligibility	Gating and residual function mutations	F508del homozygotes	F508del homozygotes or residual function mutations	F508del/ minimal CTFR function heterozygotes	Potential to treat all CF patients
Number of eligible patients (cumulative)	6,000	31,000	44,000*	68,000	75,000

Source: Vertex, Bernstein analysis. * includes other growth drivers in 2018: Orkambi EU reimbursement and label expansion to younger children

What is next from Vertex?

We would typically introduce the Galapagos assets at this point but given Vertex future development is ahead and core to the outlook for Galapagos' franchise, we discuss here first.

In modulator therapies, Vertex dominates for multiples reasons.

+ *First to market advantage.* The only modulator therapies currently approved were developed by Vertex. They have the best understanding of the market and an established relationship with prescribers and payers.

+ *Solid base from which to innovate.* Vertex already has a potentiator and two connectors, giving it an obvious advantage in the race to find a triple combination therapy that incorporates a next generation connector. Other companies must develop each of the individual components or accept that any successful candidates might only be efficacious when prescribed in combination with one or more of Vertex's molecules.
+ *Many prospective next-generation connectors.* Of four molecules undergoing recent phase 2 testing, all four met their primary end points. Vertex has chosen to focus on two for further development, but they have a deep base of high potential candidates.
+ *Potential to improve dosing.* Vertex has been testing a deuterated form of ivacaftor. If successful, this modified molecule is hoped to be more stable than ivacaftor, and potentially suitable for once daily dosing.

All about the triple. The strength of Vertex is particularly apparent when you consider that they are developing almost all the candidate modulators of CF that are in late stage development (Exhibit 70, we discuss the rest of the competitor pipeline later). Older dual therapies included a corrector to enable CFTR to be trafficked to the cell surface and a potentiator to enhance the flow of anions through those trafficked CFTR proteins. With triple therapy a 'next generation' or 'second generation' modulator is added to further improve CFTR folding. These later binding correctors enhance CFTR trafficking and/or function. With this portfolio they hope to be able to effectively treat 90% of CF patients (given 90% of patients have one or more copy of the F508del mutation).

Vertex has already progressed to p3 testing of two triple combinations which combine a next generation connector (they've prioritised VX-445 and VX-659) with their already approved combination of ivacaftor and tezacaftor. These studies, which cover both F508del homozygotes and F508del/min heterozygotes, are expected to complete in early 2019. This is important for one main reason, that is significantly ahead of the GLPG program which we will discuss next.

EXHIBIT 70: **Competitor pipeline for modulator molecules in CF**

Candidate	Company	Type	Mutation	Combined with…	Phase	Comments on progress	Study IDs
PTI-428	Proteostasis Therapeutics	Amplifier	F508del / F508del	Orkambi	Phase 2 completed	FEV1 improved 5.2% (p<0.05); FDA granted breakthrough therapy designation; Progressing to triple therapy studies with PTI-801 (C) and PTI-808 (P)	NCT02718495
VX-561 (was CTP-656)	Vertex	Potentiator	At least one gating mutation (i.e., Class III)	Monotherapy Orkambi	Phase 2	Terminated monotherapy study ("by sponsor") but has since been tested in combination therapies with Vertex corrector candidates Deuterated form of ivacaftor; may be more stable allowing for once daily dosing	NCT02971839 NCT03224351
VX-659	Vertex	Corrector	F508del / F508del or F508del / Min	Orkambi	Phase 2 completed, Phase 3 recruiting	FEV1 improved 10.2% to 13.3% (F508del/min); studies in F508del/F508del ongoing as of Feb 2018 Progressing to triple therapy studies with TEZ/IVA (est SC Apr 2019)	NCT03224351 NCT03447249 NCT03447262 NCT03460990
VX-445	Vertex	Corrector	F508del / Min	TEZ / V-561	Phase 2, moving into Phase 3	FEV1 improved 7.8% to 13.8% (p<0.0001 for all doses); moving into Phase 3 studies in patients homozygous for F508del or het F508del/min	NCT03227471 NCT03525548 NCT03525444 NCT03525574
VX-152	Vertex	Corrector	F508del / F508del or F508del / Min	Orkambi	Phase 2 completed	Favourable safety profile, rapid and significant increases in FEV1 (9.7% in F508del/min, 7.3% in F508del/F508del) Deprioritised in favour of VX-659 and VX-445	NCT02951195
VX-440	Vertex	Corrector	F508del / F508del or F508del / Min	Orkambi	Phase 2 completed	FEV1 improved 10.0% to 12.0% (F508del/min); 9.5% (F508del/F508del) Deprioritised in favour of VX-659 and VX-445	NCT02951182

Source: clinicaltrials.gov, press reports, company press releases, Bernstein analysis

Galapagos in CF – hard to get excited but unfair to dismiss

Galapagos (with AbbVie), like Vertex, are aiming to create a portfolio of potentiator and corrector molecules that can be used in triple combination therapy (i.e., one potentiator, two correctors). Galapagos has prioritised seven molecules for clinical development (Exhibit 71), with three molecules (GLPG2451, GLPG2222 and GLPG2737) progressing to a triple combination therapy study (FALCON).

EXHIBIT 71: **Galapagos' CF modulator candidates prioritised for clinical studies**

Candidate	Type	Stage	Comments	In triple therapy trial?
GLPG1837	Potentiator	Phase 2	Comparable efficacy to ivacaftor in patients with the G551D or S1251N mutation	Not yet
GLPG2451	Potentiator	Phase 1	Safety and tolerability studies completed (as monotherapy and in combination with GLPG2222)	Yes
GLPG3067	Potentiator	Phase 1	Safety and tolerability study completed (as monotherapy and in combination with GLPG2222)	Not yet
GLPG2222	C1 corrector	Phase 2	Incremental efficacy comparable to adding tezacaftor to ivacaftor	Yes
GLPG2851	C1 corrector	Pre-clinical	GLPG announced an intention to enter phase 1 trials by the end of 2016 but no trials have been registered	Not yet
GLPG2737	C2 corrector	Phase 2	Small positive incremental efficacy (on top of Orkambi)	Yes
GLPG3221	C2 corrector	Phase 1	GLPG announced start of P1 in Nov 17 but no trials registered with FDA	Not yet

Source: clinicaltrials.gov, company website, press reports, Bernstein analysis

Hard to know if the products are safe. A key challenge in the development of drug candidates in CF is safety. The small molecules tend to have non-specific action, leading to safety signals that may only become apparent in late stage trials. Some therapies also have drug-drug interaction issues that will only become apparent when they are trialled in combination. Vertex's Orkambi is a good example of this. Together, lumacaftor and ivacaftor induce CYP liver enzymes that reduce drug exposure and hence efficacy. While none of Galapagos' molecules have been tested in large scale trials yet, there are early data from pre-clinical, p1 and p2a studies (Exhibit 37). Treatment emergent AEs were typically mild or moderate, but they were also common and impacted diverse body systems (e.g., headache, abdominal pain, dry skin/rash, fatigue). CF patients can be severely affected, and this can translate into high rates of TEAE reporting (as evidenced by the placebo groups), but similar TEAEs were reported in those studies which dosed healthy volunteers. It is too early to read too much into the results (these are small studies), but having so many TEAEs feels like a lot.

EXHIBIT 72: **GLPG candidate pre-clinical and P1 data: efficacy, PK/PD, and safety**

Candidate	Type	Efficacy / function	Safety
GLPG1837	Potentiator	In patients with S1251N mutation (paired with F508del for all but one subject) drug reduced sweat chloride, and FEV1 was stable or increased when drug plasma concentrations exceeded the target. No induction of CYP. Improved efficacy and potency compared to ivacaftor when tested in F508del/G551D cells	Drug was well tolerated when dosed up to 4 weeks, with all TEAEs mild or moderate (inc headache) except for one case of severe abdominal pain
GLPG2451	Potentiator	Potent in vitro activity in cells from patients with F508del / F508del. Has an active metabolite M31 with similar potency and efficacy as GLPG2451. Pharmacokinetic profile is dose-dependent and allows once daily low dose maintenance treatment.	Drug was well tolerated when administered for 14 days, and all TEAEs were mild or moderate (inc nasopharyngitis, headache, dry skin, diarrhoea, oropharyngeal pain, musculoskeletal stiffness, migraine, back pain).
GLPG3067	Potentiator	Only preliminary P1 results available. Suitable for once or twice daily dosing. Pharmacokinetics not impacted by combination with GLPG2222. Less that dose-proportional increases in exposure at higher dose ranges.	Drug was well tolerated when dosed for 14 days. All TEAEs were mild or moderate (inc headache, fatigue, back pain and diarrhoea). One patient temporarily discontinued treatment due to elevated liver enzymes, another (subject also treated with GLPG2222) discontinued due to macropapular rash
GLPG2222	C1 corrector	Potent in vitro activity, partially restoring cell surface expression of F508del CFTR. Rapidly absorbed. Once daily dosing achieves steady state with minimal accumulation. No induction of CYP3A4 - a liver enzyme thought to reduce the efficacy of Orkambi	In phase 1 studies subjects reported mild TEAEs (inc headache, asthenia, diarrhea, abdominal pain/discomfort, gastroentertitis, conjunctivitis, nasopharyngitis, pruritis). When tested in combination with GLPG2451 subjects reported mild to moderate TEAEs (inc diarrhoea and headache).
GLPG2851	C1 corrector	No phase 1 trials yet	No phase 1 trials yet
GLPG2737	C2 corrector	Potent in vitro activity in cells from patients with F508del / F508del. Rapid absorption and pharmacodynamics support once daily dosing. Unlikely to be an inducer of CYP.	Drug well tolerated when dosed up to 14 days. All TEAEs mild or moderate (inc oropharyngeal pain, dry throat, dry skin, acne, dry mouth, catheter site reaction, fatigue, nasopharyngitis, headache).
GLPG3221	C2 corrector	No phase 1 trials yet	No phase 1 trials yet

Source: Galapagos, Bernstein analysis

Early stage data is not bad, it's just not great (Exhibit 73). What is most notable is that for all of the studies, molecules delivered improvements in lung function (FEV_1 % predicted) that were seemingly comparable to or weaker than the improvements reported for Vertex molecules. Although there have been no head-to-head trials, the incremental activity seen when GLPG2222 is added to ivacaftor puts it at a similar efficacy to tezacaftor. Similarly, when GLPG2737 (a C2 corrector) is tested in triple combination therapy with Orkambi, the results were positive but not as impressive as other C2 molecules being tested by Vertex (link).

On the back of these disappointing clinical trial results, AbbVie has backed away from plans to conduct a second triple therapy study (which would have included GLPG3067, GLPG2222 and GLPG2737, Exhibit 74), and Galapagos is said to be considering the future of their partnership with AbbVie (we suspect it is dead and they will either look for a partner or go it alone). In the meantime, Galapagos' only triple combination therapy trial is FALCON, testing GLPG2451, GLPG2222 and GLPG2737, which is expected to give interim results in Q3 2018 with full study completion in 2020.

At best we can say that Galapagos will deliver a triple combination therapy that is good enough, but not better than, a triple combination developed by Vertex, but it is too early to say with more certainty.

EXHIBIT 73: **Recent clinical studies of Galapagos' correctors: GLPG2222 (C1) and GLPG2737 (C2)**

Study	Candidate	Type	Mutation	Dosing	Combined with…	# patients	Effect on sweat chloride	ppFEV1	Comments on results
ALBATROSS	GLPG2222	C1 corrector	F508del / G551D	150mg or 300mg or placebo, once daily for 28 days	Kalydeco	14 on each treatment, 7 placebo	Decreased 6mmol/L	Increased by 2.2%	All patients were on long term stable Kalydeco; Drug well tolerated at 150mg and 300mg/day; Incremental activity in line with that seen when adding tezacaftor to Kalydeco
FLAMINGO	GLPG2222	C1 corrector	F508del / F508del	50mg, 100mg, 200mg or 400mg, or placebo once daily for 4 weeks	N/A (monotherapy)	48 on treatment, 11 placebo	Decreased 18mmol/L (200mg group)	No significant change	Lack of decrease in ppFEV1 suggests is does not induce chest tightness; Drug well tolerated; Dose-dependent decrease in sweat chloride demonstrates modulation of CFTR activity
PELICAN	GLPG2737	C2 corrector	F508del / F508del	XXmg treatment or placebo, twice daily for 28 days	Orkambi	14 on treatment, 8 placebo	Decreased 19.6mmol/L	Positive trend but not sig (3.4% increase)	Results below market expectations; lung function certainly not as good as the 8%-12% improvements seen in Vertex's various triple combination trials

Source: clinicaltrials.gov, press reports, Bernstein analysis

EXHIBIT 74: **Proposed phase 1 triple combination trials**

Study	Potentiator	C1 corrector	C2 corrector	Mutation	Dosing	# patients	Comments
FALCON	GLPG2451	GLPG2222	GLPG2737	F508del homozygotes; F508del/min	Dual combo for 14 days then triple combo for 14 days	Total 24 patients	First interim results expected Q3 2018, study completion expected Q2 2020
TBA	*GLPG3067*	*GLPG2222*	*GLPG2737*	*F508del homozygotes; F508del/min*	*TBA*	*TBA*	*AbbVie decided not to proceed with this triple combination study*

Source: clinicaltrials.gov, Galapagos, Bernstein analysis. TBA: to be announced, min: minimal function mutation.

Early data may not be representative. In early stage development for CF much emphasis is placed on the in vitro studies showing increased cell surface expression of CFTR as an indicator of potential clinical efficacy. One KOL we spoke to said that those pre-clinical data points needed to be considered with caution – for the obvious reason that what happens in vitro might not in vivo, but also for the reason that more CFTR might not always mean disease improvement. There is high variability between patients and what might be a clinically meaningful increase in CFTR for one patient might bring virtually no benefit to another. The same caution applies for combination therapy, with a view that at some point there must be diminishing returns for increases in functional CFTR protein. So, until we see data in patients, and in large numbers of patients, it is not sensible to get too caught up in efficacy data in small P2 studies.

The rest of the competitor pipeline

Proteostasis is another interesting player in this space. They have an amplifier (PTI-428) which has a different and complementary function to the molecules being developed by Vertex: an amplifier will enhance protein expression, providing more CFTR proteins for the potentiators and correctors to act on. Phase 2 data was promising (Exhibit 76) and they are moving to further studies in combination with their own corrector (PTI-801) and potentiator (PTI-808). Proteostasis are seeking a broad label for their amplifier, and are simultaneously conducting studies on differing treatment backgrounds (e.g., in combination with Symdeko) in an effort to provide clinicians with prescribing flexibility to choose the combination that works best in each patient. Although the initial phase 2 trial was in F508del homozygotes, the amplifier could be used much more widely – one KOL we spoke to said it had the potential to be generally mutation agnostic, and that some patients with type III or IV mutations (those typically treated with Kalydeco) might do well when treated by an amplifier. There's also promising (but very early) data for their potentiator and corrector molecules.

There are also some prospective treatments for CF that are not in the modulator class. **ProQR's Eluforsen** (previously QR-010) is in very early stages of development but has shown promising action. It is an inhaled oligonucleotide drug designed to bind defective CFTR RNA and restore the function of the CFTR protein. Development is focused on patients with F508del homozygotes or heterozygotes, but they are also considering therapeutics for other CFTR mutations (including those with Class I stop-codon mutations) – thus far only in early discovery stage. Two clinical trials have suggested eluforsen is safe and well-tolerated, and showed promising action (but only in F508del homozygotes): improvement in CFQ-R RSS (mean 13.0 to 19.2 point improvement over 4 weeks, with 4.0 point change considered clinically significant) and improvement in $ppFEV_1$ (mean 4.0%, with a stronger effect of 10.9% in those subjects with lower lung function). Eluforsen has FDA fast track designation and orphan drug designation in the US and Europe. A phase 2 study is expected to start in 2018 subject to a potential partnership.

PTC Therapeutics' Ataluren (branded Translarna) had been a promising candidate for Class I CF. This therapy, which is approved in the EU for nonsense mutation Duchenne muscular dystrophy, allows ribosomal read through of nonsense mutations which otherwise create a premature stop signal in the translation of DNA into mRNA. It was hoped that Ataluren would allow ribosomes to ignore the nonsense mutations found in patients with Class I CF, leading to production of full length and functional CFTR. This drug failed in phase 3 when it didn't meet the primary endpoint: change in FEV1 % predicted from baseline to week 48 was just 0.6%. Ataluren did reduce the rate of pulmonary exacerbations (14%) but this was not significantly different from placebo.

Beyond that, Vertex expects **gene editing mRNA therapies** could be a game changer in cystic fibrosis. If it can be made to work, it could effectively cure all patients, regardless of the mutations that they carry. But this type of treatment is entirely hypothetical so we don't expect it to have an impact within our forecasting time horizon. Vertex has a longer-term goal of developing customised treatments to suit the individual mutations present in each patient – effectively opening up therapy to the entire population of patients with cystic fibrosis. The recent announcement of a collaboration with Genomics (link) suggests this is no idle dream. The deal allows Vertex to leverage Genomics' genetic analysis 'engine', essentially a database of over 100 billion data points, to link genetic mutations with their molecular, cellular, physiological and disease outcomes. Cystic fibrosis isn't explicitly listed as a disease of interest, but the deal seems an ideal way to address Vertex's aspirations in this area.

Final thoughts - Uncertain how this will play out (€1.1B by 2030 at 30% probability)

We suspect the ABBV partnership is over. Galapagos seem somewhat "fed-up" with AbbVie and whilst not official yet, we suspect the partnership is over. Of the $360M in milestones potentially owed to Galapagos, AbbVie have paid $78M (in addition to the $45M upfront). The challenge we have in modelling the assets is that we do not know the eventual structure of how Galapagos intend to move forward and if they would even need to pay AbbVie for the right to do so. For now, we assume a similar structure to the AbbVie deal and assume Galapagos find a new partner. Should they go it alone, the royalty structure (mid-teens to 20%) in our model will be removed but with it, increased R&D and S&M costs.

The Galapagos strategy is risky. The challenge Galapagos will have is that moving forward with the triple without testing the double first is a risky strategy for multiple reasons. First, if there is a problem, they will not know which component of the triple drove the negative outcome. Secondly, FDA typically would like to see proof that the combination is superior to the individual components. Potentially, this can be proven in the p3 study but it would need to be big to have enough patients in each arm. Highly prospective CF candidates often fail on safety, and issues may only be uncovered when tested in larger patient groups (larger than the p1b FALCON trial).

Galapagos is playing catch up and being first does matter (but it is not over). Vertex already has a double therapy (Symdeko), which it knows to be safe and efficacious, as a base for building a triple therapy. Galapagos is soon expecting preliminary p1 results for its first triple therapy studies, but using component molecules that have not yet been comprehensively tested. Meanwhile Vertex has p3 trials in progress for two triple combinations, and if those fail, it has back-up molecules to which it can quickly pivot. Given these triples are expected to target patients who previously had no option, if the Vertex drug works, there will be no need to switch. Even if efficacy is better than we expect, Galapagos will probably still struggle to displace Vertex. However, one KOL we spoke to put it – "there is no phenomenal brand loyalty for Vertex, there will always be people who are not doing well on drug so physicians would like an alternative". In short, demonstrate efficacy (ideally non-inferiority vs. Vertex) and you may not be the market leader but you will capture share, especially with the right price).

Pricing will come under pressure, particularly in non-US markets. These are high cost drugs, with list prices in the US of ~$300k. For now, Vertex has a monopoly on disease modifying treatments, but any new entrants could disrupt the pricing structure (e.g. HCV with Gilead). There's already signs of pricing trouble in the US and uptake of Orkambi has been particularly slow in the EU because of price. Vertex highlights France/UK as significant markets for which it is yet to negotiate reimbursement despite drug approval being achieved more than two years ago. If/when Symdeco is approved in EU, Vertex is likely to face similar pressure to reduce prices. As new drugs expand the treatable patient target, this becomes a significant burden on payors. A Galapagos triple, even if not quite as good, will allow payors to squeeze prices across the board. The net result, we hit pricing hard assuming a Galapagos triple will sell at $180K (realised price) in the US, with declines longer term to $150k upon generic entry of competitors (Kaldeco/Symdeko 2027), although we appreciate these will not be direct threats to a GLPG triple at that point in time.

The net result - peak sales of $1.3B (€1.1B) globally in 2030 (Exhibit 75), with GLPG capturing a peak share of 20% in the US (5.8k patients of a total target population of 30k class II). For context, Vertex is already achieving CF sales of $2.5B and expectations are for this to increase towards $6B by 2022 but assuming $1.3B in global sales is not aggressive.

The net result is CF is worth only €4.7/share in our DCF (30% probability of success). Not a big driver of upside in our minds but if the economics change (if GLPG go it alone), things could be different.

EXHIBIT 75: **Galapagos cystic fibrosis market model**

		2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
US market												
Patient population												
CF patients		31,098	31,357	31,628	31,909	32,200	32,500	32,809	33,125	33,449	33,780	34,118
New diagnoses		1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000
Average age at death		42	43	44	45	46	47	48	49	50	51	52
Deaths		740	729	719	709	700	691	684	676	669	662	656
Ending CF patients		31,357	31,628	31,909	32,200	32,500	32,809	33,125	33,449	33,780	34,118	34,462
Of which are older than 12	69.0%	21,457	21,636	21,823	22,017	22,218	22,425	22,638	22,856	23,080	23,308	23,541
Of which are between 6-11	15.5%	4,820	4,860	4,902	4,946	4,991	5,038	5,085	5,134	5,185	5,236	5,288
Of which are between 1-5	13.0%	4,043	4,076	4,112	4,148	4,186	4,225	4,265	4,306	4,348	4,391	4,435
Patient sub-populations (%, and total CF patients):												
Class I	10.0%	3,110	3,136	3,163	3,191	3,220	3,250	3,281	3,313	3,345	3,378	3,412
Class II - F508del homozygotes	45.8%	14,243	14,362	14,486	14,614	14,748	14,885	15,026	15,171	15,320	15,471	15,626
Class II - F508del heterozygotes	40.7%	12,657	12,762	12,873	12,987	13,105	13,228	13,353	13,482	13,614	13,748	13,886
Class III	5.0%	1,555	1,568	1,581	1,595	1,610	1,625	1,640	1,656	1,672	1,689	1,706
Class IV	5.0%	1,555	1,568	1,581	1,595	1,610	1,625	1,640	1,656	1,672	1,689	1,706
Class V	3.0%	933	941	949	957	966	975	984	994	1,003	1,013	1,024
Patients treated by GLPG triple combo												
Class III and IV mutations (adults and children)		0	0	0	0	0	0	0	0	0	0	0
Class II - F508del homozyotes - adults		0	0	400	605	814	1,027	1,244	1,466	1,691	1,922	2,156
Class II - F508del homozyotes - children		0	0	0	0	84	170	257	432	655	882	891
Class II - F508del heterozyotes - adults		0	0	178	448	723	1,004	1,290	1,581	1,691	1,802	1,916
Class II - F508del heterozyotes - children		0	0	0	0	75	188	381	576	776	784	791
Total		**0**	**0**	**577**	**1,053**	**1,696**	**2,389**	**3,172**	**4,056**	**4,813**	**5,389**	**5,755**
Price per patient per year		0	0	180,000	180,000	180,000	180,000	180,000	180,000	160,000	150,000	150,000
GLPG triple combo US sales ($M)		**$0M**	**$0M**	**$104M**	**$190M**	**$305M**	**$430M**	**$571M**	**$730M**	**$770M**	**$808M**	**$863M**
OUS market (Europe, Canada, Australia)												
Patient population												
CF patients		46,646	47,036	47,442	47,864	48,300	48,750	49,213	49,688	50,173	50,670	51,176
New diagnoses		1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500
Average age at death		42	43	44	45	46	47	48	49	50	51	52
Deaths		1,111	1,094	1,078	1,064	1,050	1,037	1,025	1,014	1,003	994	984
Ending CF patients		47,036	47,442	47,864	48,300	48,750	49,213	49,688	50,173	50,670	51,176	51,692
Of which are older than 12	69.0%	32,186	32,455	32,735	33,026	33,327	33,638	33,957	34,284	34,620	34,962	35,312
Of which are between 6-11	15.5%	7,230	7,291	7,353	7,419	7,487	7,556	7,628	7,702	7,777	7,854	7,932
Of which are between 1-5	13.0%	6,064	6,115	6,167	6,222	6,279	6,338	6,398	6,459	6,523	6,587	6,653
Patient sub-populations (%, and total CF patients):												
Class I	16.0%	7,463	7,526	7,591	7,658	7,728	7,800	7,874	7,950	8,028	8,107	8,188
Class II - F508del homozygotes	42.5%	19,825	19,990	20,163	20,342	20,528	20,719	20,915	21,117	21,324	21,535	21,750
Class II - F508del heterozygotes	41.0%	19,125	19,285	19,451	19,624	19,803	19,988	20,177	20,372	20,571	20,775	20,982
Class III	4.0%	1,866	1,881	1,898	1,915	1,932	1,950	1,969	1,988	2,007	2,027	2,047
Class IV	3.3%	1,539	1,552	1,566	1,580	1,594	1,609	1,624	1,640	1,656	1,672	1,689
Class V	3.0%	1,399	1,411	1,423	1,436	1,449	1,463	1,476	1,491	1,505	1,520	1,535
Patients treated by GLPG triple combo												
Class III and IV mutations (adults and children)		0	0	0	0	0	0	0	0	0	0	0
Class II - F508del homozyotes - adults		0	0	278	421	567	715	866	1,020	1,177	1,337	1,501
Class II - F508del homozyotes - children		0	0	0	0	117	177	238	301	365	430	496
Class II - F508del heterozyotes - adults		0	0	268	677	1,093	1,379	1,671	1,968	2,129	2,150	2,172
Class II - F508del heterozyotes - children		0	0	0	0	113	399	690	755	821	888	897
Total		**0**	**0**	**547**	**1,098**	**1,890**	**2,670**	**3,465**	**4,044**	**4,492**	**4,805**	**5,065**
Price per patient per year		0	0	110,000	110,000	110,000	100,000	100,000	90,000	90,000	90,000	90,000
GLPG triple combo OUS sales ($M)		**$0M**	**$0M**	**$60M**	**$121M**	**$208M**	**$267M**	**$347M**	**$364M**	**$404M**	**$432M**	**$456M**
GLPG triple combo global sales ($M)		**$0M**	**$0M**	**$164M**	**$310M**	**$513M**	**$697M**	**$917M**	**$1,094M**	**$1,174M**	**$1,241M**	**$1,319M**

Source: FactSet, IMS, Company reports, Bernstein estimates and analysis; note percentage split of patient genotypes does not add to 100% because there is some overlap between F588del heterozygotes and other classes

OTHER PARTNERED PRODUCTS A LITTLE TOO EARLY TO HAVE CONFIDENCE

MOR106 recently got more interesting

Investors had given little consideration for the product until the recent licensing deal from Novartis. The economics are less favourable than other pipeline assets but MOR106 must still be a consideration in valuing Galapagos. We provide a summary below.

Atopic dermatitis is a chronic pruritic inflammatory skin disorder. Atopic dermatitis is the most common form of eczema. It can develop in any age group but is more common in children: prevalence is always hard to pinpoint but 15-20% in children and 5-15% in adults (lifetime prevalence) is a fair reflection. Of those patients with childhood AD, 10-30% will have disease that persists into adulthood. The term 'atopic' refers to the fact that it tends to be related to an increased sensitivity to environmental antigens, with potential triggers including soaps, detergents, stress, weather, or food. There is a genetic component, as AD tends to occur in families (along with other inflammatory conditions such as asthma and hay fever).

Diagnosis typically requires a recent itchy skin condition plus three or more of the following: visibly irritated red skin in the creases of your skin (e.g., inside elbows, back of knees), or a history of this, generally dry skin, a history (or family history) of hay fever or asthma, and early onset prior to two years of age (this last factor not being relevant for children aged under four).

Existing therapies typically ease symptoms rather than treating the underlying disease: avoiding things that might make it worse (e.g., exposure to triggers, scratching), emollients (moisturising treatments), topical corticosteroids to reduce symptoms during a flare, and antihistamines to reduce severe itching. Topical tacrolimus can be used for sensitive sites not responding to other treatment. Topical therapies have limited efficacy for patients with moderate-to-severe disease, and long term topical corticosteroid use has a risk of side effects. Systemic immunosuppressants are more effective, but have greater toxicity and may be associated with rebound effects when treatment is discontinued. The alternative in more severe patient is phototherapy (ultraviolet light three times weekly) but is inconvenient, could increase skin cancer risk, and is of unclear efficacy (much of use is driven by familiarity with use in psoriasis).

Dupixent (dupilumab) is the only approved disease modifying therapy in AD. Dupixent is an agonist of the shared IL-4Rα subunit which inhibits signalling by IL-4 and IL-13. These cytokines are critical to the initiation and maintenance of the Th2 immune response that occurs in allergic immune diseases. In clinical trials Dupixent improved many indicators of disease activity including IGA (Investigators' Global Assessment) response and EASI (Eczema Area and Severity Index) score (link). However, it isn't effective in all patients. It also has significant side effects: serious allergic reactions, eye problems (e.g., conjunctivitis, keratitis, swollen and/or itchy eyes), and herpes simplex outbreaks.

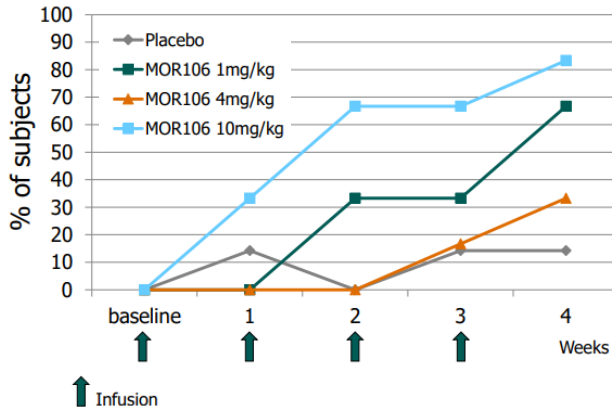
Importantly, multiple additional DMDs (in p3) are on the horizon across various MOA. We have the JAKs (AbbVie's upadacitinib, Lilly's baricitinib, and Pfizer's PF-04965842), Vanda's Tradipitant (an orally administered neurokinin 1 antagonist), and LEO Pharma's tralokinumab (IL-13 inhibitor).

MOR106 was jointly developed with Morphosys. MOR106 is a selective inhibitor of IL-17C, one of six members of the IL-17 family (IL-17A to IL-17F). The IL-17 market is already crowded, but the current therapies have different IL-17 targets: Cosentyx and Taltz both inhibit IL-17A, while Siliq inhibits IL-17A, IL-17F and IL-17E (also known as IL-25). MOR106 is the first publicly disclosed human monoclonal antibody with IL-17C as the target.

The role of IL-17C is not well characterised but is believed to induce the production of proinflammatory cytokines and also has a function in mucosal immunity and autoimmune responses. In experimental autoimmune encephalomyelitis, a model of T-cell-mediated autoimmune disease, mice lacking IL-17C were less likely to exhibit EAE symptoms and had much milder disease. Importantly, IL-17C is produced by keratinocytes where it acts locally to amplify inflammatory mediators, and IL-17C expression is increased in atopic dermatitis skin.

Early data is encouraging. Starting with the pre-clinical data, using two mouse models of atopic dermatitis, MOR106 neutralisation of IL-17C reduced skin inflammation (link). A phase 1b study in 25 patients tested three dosing regimens (1mg/kg, 4mg/kg and 10mg/kg) versus placebo over a 4-wk period of weekly IV infusions. Drug exposure was approximately dose proportional and the drug was well tolerated with only mild or moderate adverse events (Exhibit 77), although one patient did develop anti-drug antibodies. Skin efficacy was promising, with a fast onset of response which was maintained after stopping treatment for at least two months of follow up. Up to 83% of patients receiving the high dose achieved EASI 50 or better by week 4 (Exhibit 76) (link). Somewhat comparable to Dupixent p2 data.

EXHIBIT 76: **MOR106 P1 study: % patients with 50% EASI improvement**



Source: Galapagos, Bernstein analysis

EXHIBIT 77: **MOR106 P1 study: safety data**

Number (%)	Placebo (n=7)	1mg/kg (n=6)	4mg/kg (n=6)	10mg/kg (n=6)
TEAE	2 (28.6)	5 (83.3)	5 (83.3)	3 (50.0)
Serious	0	0	0	0
Death	0	0	0	0
Worst TEAE intensity				
Mild	0	2 (33.3)	2 (33.3)	1 (16.7)
Moderate	2 (28.6)	3 (50.0)	3 (50.0)	2 (33.3)
Severe	0	0	0	0
Treatment related	0	2 (33.3)	1 (16.7)	1 (16.7)
Permanently stopped	1 (14.3)	1 (16.7)	0	0

Source: Galapagos, Bernstein analysis

Phase 2 data should be expected before the end of 2019. The Phase 2 IGUANA study will recruit 180 patients with moderate to severe atopic dermatitis (NCT03568071). Five dosing regimens will be tested over a 12-week period with the primary outcome focused on EASI score. As a reference, Dupixent demonstrated EASI-75 scores in ~50% of patients across the SOLO-1 and 2 studies (vs. 12-15% for placebo) both with the weekly and biweekly dosing and 35-40% of patients achieving clearing or near clearing of skin lesions. With trial completion expected in Sep-19, we do not have to wait long for an update. Most importantly, the recent global licensing deal by Novartis for the asset, whilst limiting the economics for Galapagos, suggests we will get both an acceleration and expansion in program. In short, Novartis just made the asset real.

We forecast revenues of €0.65B by 2030 at 35% probability. This is the tricky part. Whilst prevalence rates are incredibly high, this will not be the population from which to consider market potential. Our KOL calls suggest 1/3 of current topical corticosteroids in the US are used for AD (~14M prescriptions). Assuming 2-4 per patient per year, this suggests ~5M patients in the US. Whilst ~20% of patients report their disease as "severe" (assuming 30-40M patients in the US and 20% treatment gets you close to the 5M number), KOLs suggest that no more than 5% would actually qualify as having disease that is severe enough to warrant biological treatment. We therefore assume a population of 250k is a realistic target for this market. Current IMS data suggests ~20k patients are currently on Dupixent treatment in the US. Assuming a 10% share of the US market at $25k per patient would result in peak sales of $625M in the US. With OUS revenues only 15% of US currently for Dupixent (later launch, lower price), we assume an incremental $150M for OUS revenues. This is by no means a stretch vs. Dupixent estimates although this includes additional indications unrelated to AD and thus consensus is not a good benchmark here. Our caution is driven by lack of additional data and what looks like a competitive pipeline.

Our forecasts account for the 50% of milestone payments (up to €850M) and low-teen to low-twenties royalties, with MorphoSys taking the other half. We assume milestones are split between sales ($200M/€175M, of which GLPG could take half) with regulatory/development milestones accounting for the remainder (~€670M). We assume GLPG receives €250M in regulatory/development milestones between now and approval. The remaining €170M will come from additional indications, possibly psoriasis (although this is already quite crowded), but inflammatory diseases of the joints, CNS and cardiovascular system are also potential options (link). We don't model other approvals within our 2030 time horizon and thus do not give credit for additional milestones.

GLPG1972 in Osteoarthritis has potential but not much to go on – we are less excited but it could be meaningful

Osteoarthritis is a degenerative disease leading to joint destruction and loss of cartilage. Symptoms include pain, swelling, and reduced motion in affected joints. Osteophytes (bone spurs) may develop at the joint edges, and fragments of bone or cartilage may detach and float in the joint space – causing more pain and damage. The knee, hip and small joints of the hands are most commonly affected. Osteoarthritis is the most common form of arthritis, affecting ~12% of the global population. Diagnosis typically involves ruling out other forms of arthritis. Osteoarthritis may be indicated in a patient over the age of 50 and for whom

the pain gets worse with increased use of the joints. Osteoarthritis typically manifests with joint stiffness in the morning that lasts less than 30 minutes (or not at all), while RA will typically have prolonged joint stiffness in the morning.

Currently available therapies treat the symptoms but are not disease modifying. For mild disease, therapy is focused on exercise, weight loss, supportive foot wear or other devices intended to minimise joint strain. Severe symptoms are treated with systemic painkillers (e.g., paracetamol, NSAIDs, cox-2 inhibitors, opioids) or topical painkillers (e.g., NSAIDs, capsaicin cream). Steroids may be injected into the joints to provide short-term relief. Platelet rich plasma, extracted from the patient's own blood for intraarticular injection, is a newer therapy that may enhance healing. In extreme cases, joint reconstruction, replacement or fusion surgery may be necessary.

The pipeline is not exactly full. Drugs are either focused on enhanced pain management or ultimately attempting to be disease modifying.

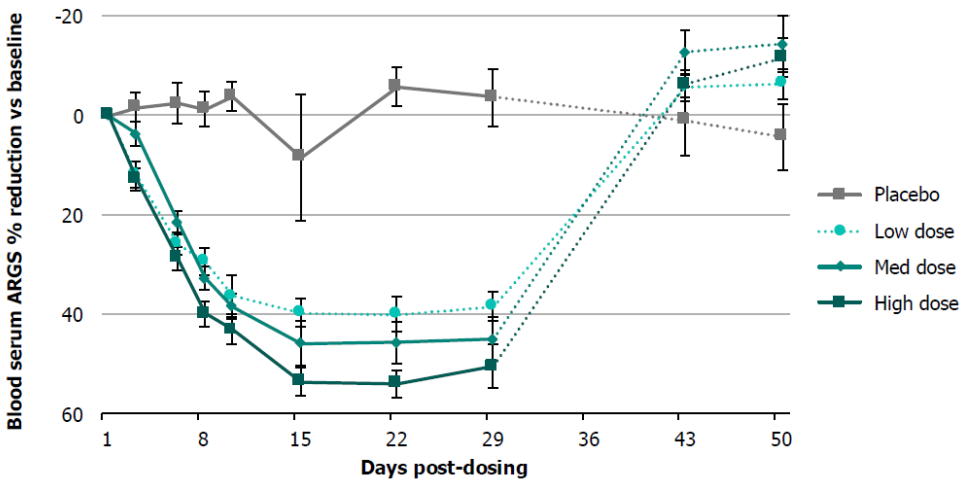
+ *Enhanced pain management.* (i) Tanezumab (Pfizer/Lilly), a nerve growth factor inhibitor that delivered positive p3 topline results in July 2018 with improvement to pain, physical function, and overall patient assessment of their OA. (ii) Fasinumab (Regeneron/Teva), also an inhibitor of NGF, which similarly reported positive p3 results in August 2018, although the market does seem overly excited by either.

+ *Potential disease modifying action.* (i) Invossa (TissueGene/Kolon), is a mixture of non-transduced allogeneic (i.e., donor) human chondrocytes and allogeneic human chondrocytes expressing transforming growth factor beta 1 (TGF-β1). Invossa is already approved in Korea on the basis of symptom relief only (not disease modifying activity), but TissueGene/Kolon expects to get FDA approval as a DMOAD by collecting evidence of disease modifying activity in the Korean market in a post-marketing study of 3,000 participants. On symptom relief alone Invossa's results are impressive: 84-88% symptom reduction lasting up to two years. (ii) JointStem (Nature Cell/Biostar) is an autologous adipose-derived mesenchymal stem cell technology currently undergoing phase 2 testing in the US and Korea. It recently suffered a set-back when it failed to get conditional approval from the Korean regulators who considered that their submitted study data included too few patients, demonstrated lack of efficacy in more than half of patients, demonstrated that stem cell therapy was not as effective as platelet-rich plasma therapy, and had an insufficient wash out period to exclude the possibility of corticosteroids contributing to the results. (iii) SM04690 (Samumed), a small molecule Wnt pathway inhibitor and potentially a disease modifying therapy, reported positive p2 results in terms of structural progression and patient reported pain/function.

GLPG1972 has an interesting MoA but data is limited. The product is an inhibitor of ADAMTS-5 (A Disintegrin and Metalloproteinase with Thrombospondin motifs). ADAMTS-5 is a secreted, extracellular enzyme which plays a role in extracellular matrix remodelling. In joints, it plays a role (along with ADAMTS-4) in breaking down the aggrecan in cartilage, which leaves the collagen matrix exposed and subject to degradation. Although both ADAMTS-4 and 5 are present in cartilage, ADAMTS-5 is 1000-fold more potent in vitro. ADAMTS-5 expression is induced by IL-1, TNF-α, IL-6, S100A8 and S100A9 – all known to be upregulated in inflammatory diseases (link). Data in several mouse models suggests a role for ADAMTS-5 in osteoarthritis: mice lacking ADAMTS-5 are protected from surgery induced osteoarthritis and antigen-induced arthritis models, and exhibit blockade of fibrosis and accumulation of aggrecan in the joints.

P1b studies support the notion of GLPG1972 as a DMOAD demonstrating significant reductions in circulating levels of ARGS neoepitope, a biomarker for cartilage breakdown (Exhibit 78).

EXHIBIT 78: **GLPG treatment reduces biomarker for cartilage breakdown (p1b)**



Source: Galapagos

Phase 2 study will not report data until early 2021 but time may not matter here. The large p2 ROCCELLA trial in 850 patients with knee osteoarthritis began recruitment a few months ago (NCT03595618), with the goal to demonstrate disease modifying efficacy, not just pain relief. The primary outcome measure will measure cartilage reduction (via quantitative MRI) after 52 weeks of treatment.

It can be debated whether GLPG1972 would be the "first" DMOAD to market but the product is dosed orally, an advantage over competitors in the clinic (IV) and the product would face fewer logistical challenges than Invossa (requires that live cells must then survive transport and storage, typically using cryopreservation, and requires a laboratory technician at the clinical centre to reconstitute the cells for injection into the patient). In a battle for patient share, convenience should be a huge advantage, and we expect Invossa would need vastly superior efficacy to become standard of care.

Big potential but little probability for now - €1B at 20% probability. First off, much like MOR106, the headline population of OA is large (120m total in US/EU and growing) and DMOADs are likely to be used only in the most severe population. That being said, pain prescriptions for OA patients alone are suggested to be $4B a year and we must also consider the costs of joint replacements.

Under the agreement for GLPG1972, Servier has ex-US rights and responsibility for further clinical development, registration and commercialisation. Galapagos retains US commercialisation rights, and is also eligible for milestone payments (up to €290M), as well as royalties ex-US (single digit – we assume 7%). In short, if it works, this will be big for the company.

THE PLATFORM HAS BEEN PROVEN – WORTH €1BN EVEN IF ALL ELSE FAILS

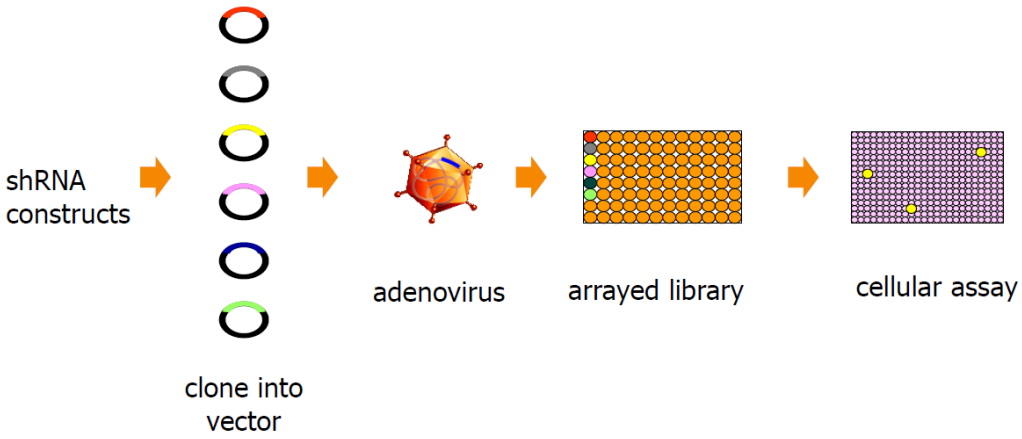
Galapagos has a target discovery platform which it uses on four R&D focus areas: inflammation, fibrosis (e.g., CF, IPF), metabolic disorders (type 2 diabetes) and anti-infectives (HepB).

How does it work? Galapagos is able to generate adenoviruses that carry shRNA sequences to knock out the expression of specific proteins. These viruses are able to infect human cells where they generate short hairpin RNA, specific to a particular protein, and each shRNA has been designed to specifically interfere with the expression of a single protein. Their library of viruses allows them to rapidly test more than 6,000 human genes for possible links to the disease of interest.

Testing is done using human primary cells taken from the diseased tissues (e.g., the joints of an RA patient) which are cultured in array plates. These cells are typically showing signs of distress (e.g., producing inflammatory markers). Each well of the cell culture array plate is then treated by a single unique gene-silencing adenovirus. The goal is to see whether loss of a specific protein resolves the disease state of the cultured patient cells. If cells in one of the wells appear to improve, then the adenovirus

is hypothesised to have knocked out a 'disease critical protein' – and that protein is considered a potential target. An overview of this process is provided in Exhibit 79.

EXHIBIT 79: **Galapagos' target discovery platform**



Source: Galapagos R&D Update Presentation (June 2017) (link)

Having identified a target, the next step is to screen chemical compounds (typically GLPG focus on small molecules) that inhibit the hypothesised 'disease critical protein' and those that are successful are potential candidates for further study.

Investors typically query whether this platform is truly differentiated: shRNA techniques are widely used and so too is the practice of studying primary cells. Where Galapagos believe they have an advantage is in the sophistication of their primary patient cell cultures. An example they provided at 2016's R&D update event was for the study of GI disease. They are able to take different cell types from different tissues/samples (e.g., dendritic cells from blood and mixed cell types from a gastrointestinal biopsy), grow organ-like structures (i.e., from the biopsy sample) and then add the dendritic cells. They believe this is a more powerful model that better mimics the interplay between organ and immune system. This might be expected to enhance the detection of targets if it is the interaction between the co-cultured cell types that is critical to the disease state.

Platform delivers high throughput. Whether sophistication in cell co-culture techniques is a genuine source of competitive advantage is uncertain, but regardless the platform gives Galapagos impressive throughput: at any one time there are 20+ candidates in pre-clinical development (derived from 7-8 new targets per year) in order to deliver 3 candidates to clinical trials each year. The R&D goal is to deliver one phase 3 start every two years – something they have achieved for filgotinib in three separate indications over the last 1-2 years.

Having a wide screening library enables Galapagos to look at protein targets that may not yet be identified as correlates of disease by the scientific community. This enables them to focus on novel mechanisms of action rather than 'me too' candidates that mimic other approved or pipeline therapies. This does mean that there might be a higher rate of failure, but a successful candidate might be expected to be differentiated.

Platform worth €22.50/share. Filgotinib entering phase 3 is arguably proof of the platform. We assume that even if all of Galapagos' current candidates were to fail, it would still be able to monetise the platform. The proof of course is in the numbers and based on deals and milestones (collected and future), we can at least say the platform is creating value. We assign a value of €1B (€22.5/share).