BERNSTEIN

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Coverage Initiation

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European Specialty Pharma & Biotech

Galapagos NV

Rating

Outperform

Target Price

GLPG.NA **100.00**

Galapagos: Buy now for filgotinib but own long-term for IPF - Initiate Outperform

We are initiating coverage of Galapagos with an Outperform rating and a PT of €100.

Filgotinib should be differentiated but the market is tough. JAKs will continue to penetrate in RA (25% in 2030) and there is appetite to use the class earlier in the paradigm. IBD is mixed with higher unmet need but alternative orals exist (20% share). We expect filgotinib, driven by safety, to be considered best in class but not enough for dominance (30% in RA/UC given Xeljanz generic entry, higher in CD). Pricing at best will remain flat and we model declines given challenges ahead (ABBV use Humira to push upad, payors only need 1 JAK at preferred level, generic Humira/ Xeljanz). The net result, sales of €2.3B in 2030 (€1.8B risk-adj.), we suspect at the low end of expectations. If we get a clean safety label, our numbers will rise.

IPF is the game changer. Under-analysed and under-appreciated, GLPG have a broad IPF portfolio of assets with GLPG1690 p3 start shortly. The unmet need is high, pricing favourable and commercialisation simple - a nice set up. Initial data suggests the product should do well although this is a very high-risk program and trial certainty is limited (patient outcomes highly variable). With full ownership, our sales estimates of €1.3B in 2030 (at 30% prob.) suggest IPF is as important as filgotinib. The way we see it, get an approval and the drugs will sell.

CF is unlikely to matter but it is not a zero. AbbVie's lack of appetite for the partnership is not encouraging particularly when so far behind Vertex. However, we should not consider the program dead. CF patients and physicians have an appetite for alternatives in patient failures. Unlikely to be a major value driver (depends on asset ownership) and worth €5/share in DCF.

Investment Implications

We know what investors must be thinking, another GLPG buy to the list. However, we are not super bullish on filgotinib like many of our peers. We like the stock for the under-appreciated IPF assets (and the platform). If these assets alone work, GLPG is a doubler. O/P PT €100.

Close Date	10-Sep-2018
GLPG.NA Close Price (EUR)	84.34
Target Price (EUR)	100.00
Upside/(Downside)	19%
52-Week Low	70.64
52-Week High	98.82
MSDLE15	1,547.73
FYE	Dec
Indicated Div Yield	NA
Market Cap (EUR) (M)	4,330
EV (EUR) (M)	3,263

Performance	YTD	1M	6M	12M
Absolute (%)	6.8	(11.5)	1.4	1.7
MSDLE15 (%)	(4.3)	(3.3)	(1.4)	(0.9)
Relative (%)	11.0	(8.3)	2.8	2.6

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EPS Adjusted	F17A	F18E	F19E
GLPG.NA (EUR)	(2.34)	(2.50)	(3.72)
MSDLE15	101.41	110.07	120.25

Financials	F17A	F18E	F19E	CAGR
Revenues (M)	156	217	189	10.1%
EBIT (M)	(90)	(137)	(196)	NA
Net Earnings (M)	(116)	(128)	(193)	NA

Valuation Metrics	F17A	F18E	F19E
P/E Adjusted (x)	(36.04)	(33.80)	(22.64)

DETAILS

In this note we provide an Executive Summary of the key controversies including valuation, bull/bear scenarios and catalysts. The core of the note focuses on each of the key controversies in more detail. For those familiar with the stock, the IPF section of our report may be of most interest given the debates for filgotinib and cystic fibrosis have been around for some time.

EXECUTIVE SUMMARY

Introduction

Galapagos seemed like a simple company from the outside, but it is a little more complex than we first thought (Exhibit 1) and is one that is at an important juncture. The market is focused primarily on a royalty/partnership with Gilead on one key product, filgotinib in key autoimmune indications of rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). Expectations for filgotinib are high and key RA data is due any day, which will be followed by several additional read-outs across multiple indications for the product. With Gilead paying tiered royalties of 20-30% outside of co-promotion regions (EU-5 plus Benelux), filgotinib will be the main revenue generator. However, more importantly, Galapagos have a platform for drug discovery (see details) and a pipeline to match.

Looking at the revenue trajectory to 2030 (Exhibit 2) you can see that whilst filgotinib is important, IPF contributes similar revenues to 2030 (we appreciate filgotinib is all profit). The IPF assets are wholly owned by Galapagos and our modelled contribution is heavily risk-adjusted given the high-risk, high reward nature of the indication.

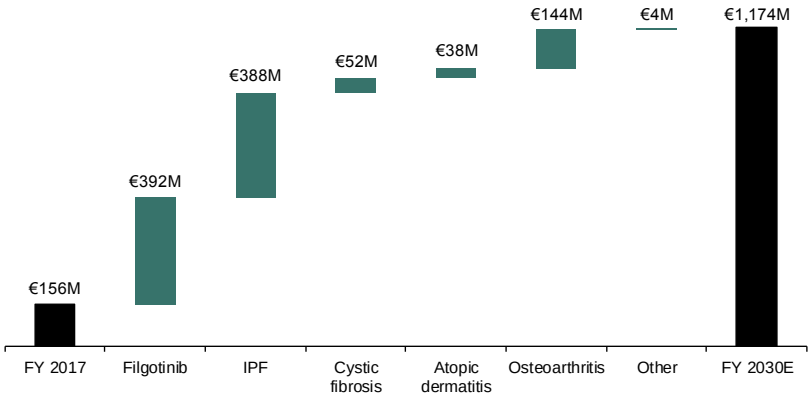
The product controversies as we see them - (i) Sales potential for filgotinib across multiple indications given the evolving treatment landscape and pricing environment. (ii) Strength of IPF portfolio, challenges to success and product potential. (iii) Viability of the cystic fibrosis program following recent "negative" updates (AbbVie not pursuing second triple combination).

EXHIBIT 1: **Galapagos overview**

	I&I (Filgotinib)	IPF	Cystic fibrosis	Atopic Dermatitis	Osteoarthritis
Candidates	Filgotinib	GLGP1690 GLPG1205 GLPG3499 GLPG2384(?)	Many: 2x potentiators, 2x C1 correctors, 2x C2 correctors	MOR106	GLPG1972
Partner	Gilead	Full rights retained by GLPG	AbbVie (for now)	Novartis (all milestones/ royalties split 50:50 with MorphoSys)	Servier
Financial terms:					
Upfront payments	$300m licence fee; $425m equity	n/a	$45m	€95m*	€6m license fee
Total milestones	$755m dev & reg; $600m sales	n/a	$360m total (dev, reg & sales)	€850m total (dev, reg & sales)*	€290m total
Royalties	Tiered: 20% to 30%	n/a	Tiered: mid-teens to 20%	Tiered: low-teens to low-twenties*	Low single-digit
Co-promotion regions	EU5 + Benelux	n/a	Benelux	n/a	n/a
Regions with full rights retained by GLPG	n/a	Global	China, S Korea	n/a	USA
Milestones already received	$85m	n/a	$78.5m	None	None relating to GLPG1972**
Peak product sales (2030), not probability adjusted	$2.8b	$1.5b	$1.3b	$1b	$0.8b
Assumed probability of success	RA, UC - 80%; PsA, CD - 70%; AS - 60%	GLPG1690 - 30%	CF triple therapy - 30%	MOR106 - 30%	GLPG1972 - 20%

Source: Company disclosure, Bernstein analysis and estimates
* Jointly to GLPG and MorphoSys
** Ongoing collaboration agreement in osteoarthritis, from which GLPG has previously received milestones relating to pre-clinical candidate discovery

EXHIBIT 2: **Galapagos revenue bridge by product/franchise highlights the contribution from IPF**



Source: Company disclosure, Bernstein analysis and estimates

Our view on key controversies

#1 - We are not overly bullish on filgotinib potential but we like it. This will matter most in the near-term and clearly where investors are most focused ahead of the FINCH-2 RA data (any day now). We expect a positive outcome (efficacy in-line with peers and competition) and the stock to react accordingly (double digit upside). The key will be a clean safety profile so watch for thrombosis, herpes zoster and lymphocyte/neutrophil counts. Our longer-term view for Filgotinib is straightforward – (i) JAKs will continue to penetrate in RA (25% in 2030 vs. 5% today), taking a greater share of the 1L population over-time but still significantly behind the TNFs. KOL discussions suggest a real appetite to use the class earlier in the treatment paradigm. IBD (CD and UC) is the tougher opportunity, given alternative oral competition (20% share by 2030) but the lack of TNF dominance in 1L is an advantage. Safety is likely to continue to be a headwind for the class (thrombosis, herpes zoster, lower lymphocyte/neutrophil counts), but oral administration and decent efficacy will prevail particularly given the ability to prescribe the drug as monotherapy (without MTX). (ii) We expect filgotinib to be considered best in class, driven by safety (only just) that

will help differentiate the asset from JAK competitors but not enough for the product to have a dominant role (30% in RA and UC given Xeljanz generic entry but higher in CD). The idea of JAK cycling supports our forecasts (much like we see in the TNFs today). Ultimately, if one JAK fails, there is no reason another will also, particularly given different receptor affinities. (iii) Pricing at best will remain flat and we model declines longer-term. Ultimately, formulary coverage will remain a challenge in an environment where ABBV use Humira to push upadacitinib into earlier coverage (payors will like this), a need to give discounts for preferred status (payors only need 1 JAK at that level), and biosimilar Humira entry in 2023 followed by Xeljanz in 2025. It is hard to see how pricing remains flat in such a competitive environment in what is now the 3rd largest category for payors (after oncology and diabetes).

The net result – global peak sales of €2.3B in 2030 ($2.8B), we suspect somewhere in the lower end of the pack vs. consensus (no specific estimates available that far out). For now, we risk adjust each program (RA 80%, CD 70%, UC 80%, PsA 70%, AS 60%) resulting in modelled peak sales of €1.8B in 2030. If the safety label is very clean vs. peers, we will be too low. We place no value on the multiple additional indications for now and leave as upside. Filgotinib catalysts will keep coming and this will support the share price once efficacy and safety in RA is confirmed.

#2 - IPF is the real game changer. Surprisingly an area of limited focus for investors. Galapagos have a broad IPF portfolio of assets with differing mechanisms but only one asset (GLPG1690) has demonstrated proof of concept and that is where we focus our attention.

IPF is a severe, progressive lung disease marked by a highly variable clinical course which makes a confident diagnosis challenging to achieve. The track record of products in IPF is pretty poor and the only curative therapy for IPF remains lung transplantation. Drug treatment changed in 2014 with the approval of 2 drugs for the treatment of IPF (Esbriet and Ofev). However, tolerability is an issue, with substantial discontinuation rates for both medicines.

GLPG1690 is a selective autotaxin (ATX) inhibitor (increased ATX activity has been detected in a range of inflammatory and fibroproliferative diseases in the lung, kidney and skin). Earlier clinical and pre-clinical data demonstrated dose-dependent reductions of several pro-fibrotic mediators and dose dependent reductions in biomarkers for autotaxin inhibition. The p2a FLORA efficacy results were encouraging, demonstrating a stabilisation of FVC at 12 weeks, which KOLs suggest is a very good outcome. Cross trial comparisons in IPF are a challenge. Even more so given the fact that the GLPG1690 study was so short (12wks vs. peers of 52wks) and only recruited 17 drug treated patients. We must take data with a pinch of salt but looking at the 12-week data for both Esbriet and Ofev, (i) neither were able to demonstrate any form of improvement in FVC, which GLPG1690 did, (ii) both have inferior tolerability profiles, particularly GI, and (iii) both have inferior dosing schedules (once daily vs. multiple pills a day).

Whilst the addressable population is large (~125k patients in the US), diagnosis and thus treatment rates are low (our estimates suggest less than 20% in the US). Physicians suggest if their patients are diagnosed with the disease, they would typically use one of the 2 approved products. Importantly, Galapagos have designed the ISABELA p3 trials (to begin shortly) to include arms on top of SoC. Important, given KOLs suggest use on top of existing products is the most likely outcome for pipeline assets. 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. We must also acknowledge the competitor pipeline in IPF. Promedior and Fibrogen have 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. 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.

With Galapagos owning full rights for the IPF portfolio, our peak sales estimates of €1.3B in 2030 (very realistic for an efficacious product, 2 existing products already approaching $1B) can be a big contributor to GLPG value. 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 that GLPG1690 will demonstrate superiority (hence our 30% probability of success). 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. The way we see it, get an approval (late 2021 launch) and the drug will sell.

#3 - CF will be tough but do not write if off just yet. First off, we suspect the ABBV partnership is over but the challenge we have in modelling the assets is that we do not know the eventual structure of the franchise. Putting that to one side, the Galapagos strategy is aggressive, moving forward with the triple combination without testing the double first is a risky strategy for multiple

reasons – (i) if there is a problem, they will not know which component of the triple drove the negative outcome and (ii) FDA typically would like to see proof that the combination is superior to the individual components. We appreciate why this is the strategy. Vertex already has a double therapy (Symdeko), which it knows to be safe and efficacious, as a base for building a triple therapy. Whilst Galapagos is soon expecting preliminary p1 results for its first triple therapy studies (using component molecules that have not yet been comprehensively tested), 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, as 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.

Importantly for the outlook we expect pricing will come under pressure, particularly in non-US markets. 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. 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 vs. closer to $250k today) in the US, with declines longer term to $150k. The net result - peak sales of $1.3B (€1.1B) globally in 2030, 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 thus assuming $1.3B in global sales is not aggressive. At 30% probability, this only adds €5/share to our DCF but we appreciate should GLPG go it alone, whilst costs will go up, the economics become much more attractive.

Valuation, catalysts, scenarios and consensus

We take a four-step approach to thinking about Galapagos fair value – we look at valuation, upside/downside scenarios, catalysts and, finally, consensus.

DCF suggests upside. In terms of valuation, given a multiple based approach is of less value for a company in Galapagos' current position (no positive earnings until 2022), we use our SOTP DCF which suggests a value of €100 (Exhibit 3). For our DCF we assume a -2% terminal post 2030 (and WACC of 8.25%), reasonable given our assumption that filgotinib patents expire in 2033 and the rest of the pipeline will go beyond that period (GLPG1690 in 2034, GLPG1972 in 2035, MOR106 in 2037). One could argue that this could be higher or lower and it's hard to disagree when thinking about the company in 10 years' time. In addition, we include €1B in value for the platform (see details).

Scenarios - A wide band skewed to the upside. With respect to upside / downside cases, we flex filgotinib, IPF, CF and the 2 other early stage partnered products. We summarise these in Exhibit 4. Our bear case gets to a DCF valuation of €50 and our bull case €205 (note that we do not include any changes in our terminal value as part of our scenario analysis). Very clearly, the risk/reward is to the upside and this is without the possibility of filgotinib sales above and beyond our forecasts in not only the core modelled indications, but across the multiple additional indications in development. Get a clean safety profile and the upside scenario will be closer to €250.

Catalysts – Multiple read-outs over the next 18-24 months across all franchise. Catalyst rich is putting it lightly and importantly, good outcomes will lead to removal of risk adjustments and/or upgrades (Exhibit 5). We of course await the near-term RA read-out (FINCH-2) but this will be followed by detailed presentation (potential at ACR in 4Q) and data from the FALCON CF study.

Consensus – We have highlighted where we are different in Exhibit 6. The reality is that earnings do not matter for Galapagos in the near-term and timing of milestones across the portfolio is uncertain thus we place little value on comparisons vs. peers at this point. Sourcing an accurate filgotinib forecast is of more relevance but just as frustrating. The company suggest peak sales estimates range from €2.5-6.5B but we find the top end of that range a little hard to believe (although ABBV have guided to upadacitinib peak sales of $6.5B). It also suggests our €2.3B is at the very low end of the range.

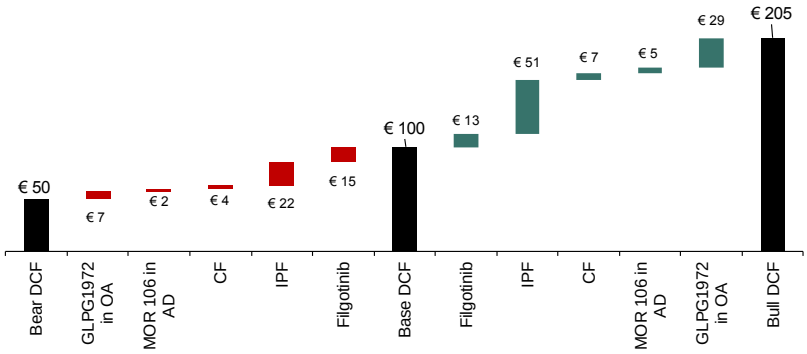
In short, we come away from our review of Galapagos reasonably positive. We are less bullish than some of our peers on the potential for filgotinib but appreciate the catalysts for the product will drive sentiment and with it, stock price. The risk reward for our estimates are to the upside. The upcoming FINCH-2 data will be big with respect to stock movement and we would be buyers in to the data, particularly given the recent pullback. We own longer-term for IPF potential and Galapagos' ability to develop pipeline assets from their platform. Outperform PT €100.

EXHIBIT 3: **DCF values Galapagos at €100/share**

	US	OUS	Milestones	Total	% of Total	Probability
Filgotinib - I&I						
Rheumatoid arthritis	*€ 9.1*	*€ 6.9*		*€ 16.0*	*16%*	80%
Ankylosing spondylitis	*€ 0.9*	*€ 0.7*		*€ 1.6*	*2%*	60%
Psoriatic arthritis	*€ 1.3*	*€ 1.6*		*€ 2.9*	*3%*	70%
Crohn's disease	*€ 4.1*	*€ 2.6*		*€ 6.7*	*7%*	70%
Ulcerative colitis	*€ 3.1*	*€ 1.6*		*€ 4.7*	*5%*	80%
Sjogren's						0%
Cutaneous lupus erythematosus						0%
Lupus membranous nephropathy						0%
Uveitis						0%
Milestone payments			*€ 13.6*	*€ 13.6*		
Filgotinib total	€ 18.5	€ 13.3	€ 13.6	€ 45.4	45%	
GLPG1690 - IPF	€ 12.1	€ 6.2	n/a	€ 18.3	18%	30%
Triple combo - CF	€ 1.9	€ 1.1	€ 1.8	€ 4.7	5%	30%
MOR106 - AtD*	€ 0.5	€ 0.1	€ 2.2	€ 2.9	3%	30%
GLPG1972 - OA	€ 3.5	€ 0.2	€ 0.7	€ 4.5	4%	20%
Target discovery platform/technology				€ 22.5	22%	
Reimbursement revenue				€ 0.7	1%	
Services revenue				€ 1.3	1%	
Other income				€ 5.0	5%	
Total				**€ 105.4**	**105%**	
Terminal (-2%)				**€ 66.2**	**66%**	
General & admin; sales & marketing				€ 0.6	1%	
Capex				-€ 3.4	-3%	
R&D				-€ 89.3	-89%	
Other Non-Op Items				€ 1.6	2%	
Total Other				**-€ 90.6**	**-90%**	
Net Debt				**€ 19.5**	**19%**	
TOTAL GROUP (SOTP)				**€ 100.4**	**100%**	
TOTAL GROUP (Group DCF)				**€ 100.4**		

Source: Company disclosure, Bernstein analysis and estimates

EXHIBIT 4: **Galapagos scenario analysis suggests an upside of €205**



	Base	Bear	Bull
Filgotinib	80% success in RA, 60% in AS, 70% in PsA, 70%, CD, 80% in UC. Total sales of €1.8B	Failure of all indications outside of RA	100% success across all indications (€2.3B in 2030 sales)
IPF	30% probability of $1.5B in 2030 revenues	Failure	100% probability of $1.5B in 2030 revenues
CF	30% probability of $1.3B in 2030 revenues (assuming ABBV deal structure)	Failure	100% probability of $1.3B in 2030 revenues (assuming ABBV deal structure)
MOR 106 in AD	30% probability of $0.8B in 2030 revenues (14-22% royalty)	Failure	100% probability of $0.8B in 2030 revenues (14-22% royalty)
GLPG1972 in OA	20% probability of $1B in 2030 revenues (7% royalty on OUS sales)	Failure	100% probability of $1B in 2030 revenues (7% royalty on OUS sales)
DCF	€ 100	€ 50	€ 205

Source: Company disclosure, Bernstein analysis and estimates. Note we do not account for changes in terminal value and only include value to 2030

EXHIBIT 5: **Galapagos catalysts**

Timing	Drug/Franchise	Comments
Q3 2018	**Filgotinib**	**FINCH2 results in RA (patients with inadequate response to DMARDs)**
Q4 2018	Filgotinib	Data from PsA, AS (and RA?) likely to be presented at ACR
H2 2018	IPF	ISABELA 1 & 2 P3 trials to start with GLPG1690
H2 2018	IPF	PINTA P2 trial to start with GLPG1205
H2 2018	**CF**	**FALCON P1b proof of concept data from first clinical study of a triple combination**
Q3 2019	**Filgotinib**	**Data from FINCH 1 and FINCH 3 in RA (combination therapy with MTX in MTX inadequate responders and MTX naïve patients respectively; FINCH 1 includes adalimumab arm)**
H2 2019	Filgotinib	File for regulatory approval in RA: seeking full label (e.g., monotherapy, combination therapy with MTX) using data from all three FINCH studies
Q4 2019	**Atopic dermatitis**	**Data from IGUANA P2 trial of MOR106**
Q4 2019	Filgotinib	Data from P2 study in cutaneous lupus erythematosus (CLE)
late 19/early 20	**IPF**	**Data from PINTA P2 trial with GLPG1205**
Q1 2020	Filgotinib	Data from SELECTION1 P3 trial in ulcerative colitis
Q1 2020	**Filgotinib**	**Data from DIVERSITY1 P3 trial in Crohn's disease**
Q1 2020	Filgotinib	Data from P2 study in Sjogren's Syndrome
Q3 2020	Filgotinib	Data from CD sub-studies (perianal fistulising CD and small bowel CD)
2020	**IPF**	**Data from ISABELA P3 trials with GLPG1690**
Q1 2021	**Osteoarthritis**	**Data from ROCCELLA P2 trial in US of GLPG1972**
Q3 2021	Filgotinib	Data from P2 study in lupus membranous nephropathy (LMN)
Q4 2022	Filgotinib	Data from P2 study in uveitis

Source: Company disclosure, clinicaltrials.gov, Bernstein analysis

EXHIBIT 6: **Bernstein vs consensus – key financial metrics**

		FY 2018E	FY 2019E	FY 2020E	FY 2021E	FY 2022E
Sales	BERNe	217.4	189.1	205.9	305.2	445.8
	Consensus	207.9	212.8	217.5	267.3	432.8
		5%	*-11%*	*-5%*	*14%*	*3%*
EBIT	BERNe	-136.8	-196.2	-244.1	-167.2	-39.2
	Consensus	-150.4	-136.8	-181.8	-191.3	-25.6
		-9%	*43%*	*34%*	*-13%*	*53%*
Net income	BERNe	-128.1	-193.1	-241.7	-166.0	-38.8
	Consensus	-143.5	-139.8	-182.8	-184.7	-23.1
		-11%	*38%*	*32%*	*-10%*	*68%*
EPS	BERNe	-2.50	-3.72	-4.62	-3.14	-0.73
	Consensus	-2.63	-2.56	-2.97	-3.95	-0.49
		-5%	*46%*	*55%*	*-20%*	*49%*

Source: Factset Consensus, Bernstein analysis and estimates

Final thoughts

Where we could be wrong? First off, if the near-term FINCH-2 RA study fails on efficacy, the stock will be down big and likely un-investible in the near-term. If we see the same safety concerns as with the other JAKs, sales potential will likely be lower than our estimates but not dramatically (we have not been aggressive on share capture for the class or product specifically). Second, IPF fails (which is not unrealistic) and investors need to wait beyond the early 2020s for the first wholly owned launch from the company. This will then raise the debate of whether the platform can produce additional success stories.

Takeover by Gilead is realistic. Investors will ask why have Gilead not done so already considering they already have a ~13% share ownership. Our answer is simple – they want to see the filgotinib p3 data demonstrating the superior safety profile before doing so. The obvious pushback here is that Gilead's history suggests they are not afraid of taking earlier bets (Pharmasset and Kite are 2 recent examples) but we point to the challenges facing filgotinib should the product be considered a "me-too" JAK. We think a very clean label and Gilead will consider the deal not just for filgotinib, but for the IPF assets which will complement Gilead's NASH portfolio nicely.

FILGOTINIB SAFETY SHOULD BE A DIFFERENTIATOR BUT THE MARKET IS NOT EASY

Filgotinib remains the key focus of investors. It is the most advanced, with progressing p2 and p3 studies in the large I&I indications plus a few extras. The debates are simple – (i) Do the JAKs have a major role to play in the increasingly competitive I&I space and within which indications and (ii) How differentiated is Filgotinib vs. peers?

We state upfront that some of the exhibits from this section have been modified from US Spec Pharma and Biotech analyst Ronny Gal's previous research on the JAK class - JAK Inhibitors: Class review.

Introduction (skip if familiar)

Filgotinib is Galapagos' most advanced candidate. It was identified using Galapagos' target discovery platform, and then initially developed in partnership with AbbVie, who exited the alliance in Sept 2015 to focus on the development of their own candidate, then known as ABT-494 (i.e., upadacitinib, which has a similar mechanism of action to filgotinib). Galapagos' shares fell 25% on news of AbbVie's departure but a new partner was found quickly – the deal with Gilead included an upfront fee of $300m, a 15% ($425m) stake in Galapagos, and potential future royalty payments of $1.35B.

Through Gilead, the drug is under investigation for a range of autoimmune conditions (Exhibit 7), with studies most advanced in rheumatoid arthritis, Crohn's disease and ulcerative colitis (all in Phase 3 studies). Phase 2 studies have been completed in psoriatic arthritis and ankylosing spondylitis. Further Phase 2 studies are recruiting patients for small bowel Crohn's disease, fistulizing Crohn's disease, Sjorgen's syndrome, cutaneous lupus erythematosus, lupus membranous nephropathy, and uveitis.

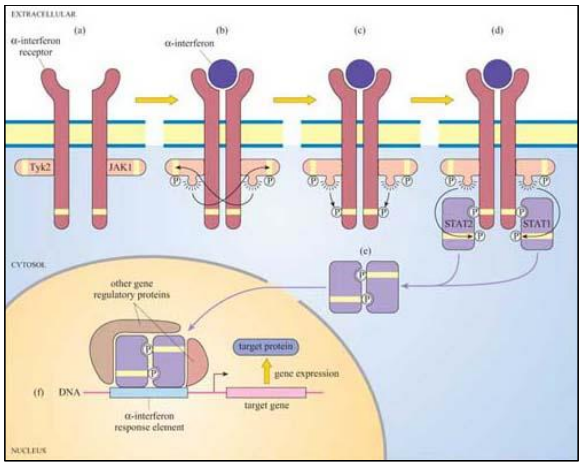
EXHIBIT 7: **Filgotinib clinical trials programme**

	Rheumatoid arthritis	Crohn's disease	Ulcerative colitis	Ankylosing spondylitis	Psoriatic arthritis	Small bowel CD	Fistulizing CD	Sjogren's	Cutaneous lupus erythematosus	Lupus membranous nephropathy	Uveitis
Phase	Phase 3	Phase 3	Phase 3	Phase 2	Phase 2	Phase 2	Phase 2	Phase 2	Phase 2	Phase 2	Phase 2
Primary completion	Mono Jun 18	Nov 19	Nov 19	Completed	Completed	Mar 20	Apr 21	Mar 19	Oct 18	Jul 20	Dec 20
Secondary completion	Mono Sep 18	Dec 19	Dec 19	Completed	Completed	Mar 20	Apr 21	Dec 19	Jul 19	Apr 21	Jul 22

Source: www.clinicaltrials.gov

Filgotinib is a type of janus kinase (JAK) inhibitor. This class of medications functions by inhibiting intracellular signalling via the JAK-STAT (signal transducer and activator of transcription) pathway. Cytokines typically signal by binding to type I and type II cytokine receptors. These integral membrane receptors rely on JAKs for signal transduction to STATs, which then regulate gene transcription (Exhibit 8). The enzymatic activity of JAKs is essential for cytokine signal transduction, therefore medications that inhibit the activity of JAK block cytokine activity.

EXHIBIT 8: **Schematic: IFN-alpha signalling via JAK-STAT pathway**



Source: The Open University (link)

There are four members of the JAK family of enzymes: JAK1, JAK2, JAK3 and TYK2. Each of these enzymes is associated with specific types of cytokine receptors (Exhibit 9), which in turn drive differentiation, activation and proliferation of different lymphocyte types (Exhibit 10). It should be noted that each JAK is associated with multiple cytokines, so any inhibition of a JAK will interfere with multiple signalling pathways. This could mean that a JAK inhibitor is more likely to be efficacious because it has broad activity against several cytokines involved in a particular disease. It could also mean JAK inhibitors are likely to work across different diseases each with different cytokine dysregulation patterns. It might also mean that JAK inhibitors, by acting on multiple pathways, carry a higher risk of adverse events and side effects – a problem that might be compounded in JAK inhibitors that act on multiple JAKs. As discussed more below, side effects are a concern for the class. Mutation studies provide a hint to potential safety concerns (link):

+ JAK3 mutations can result in no T or NK cells and B cells with impaired function. Theoretically, JAK3 inhibition might be associated with higher frequency and/or severity of infections.
+ TYK2 deficiency is associated with viral and intracellular infections.
+ JAK2 mutations are associated with hematologic malignancies. The JAK2 homodimer is involved in erythropoietin (EPO) and thrombopoeitin (TPO) signalling, which are essential for hematopoiesis, so theoretically JAK2 inhibition might lead to blood disorders such as anemia and thrombocytopenia.

+ No JAK1 mutations in humans have been reported, and lack of JAK1 is embryonically lethal in mice and associated with deficiencies in the generation of lymphocytes and erythrocytes.

EXHIBIT 9: **Mapping JAKs to cytokines**

	JAK1	JAK2	JAK3	TYK2
JAK1	IL-10 IL-6 IL-11 OSM LIF CNTF IL-22	IFN-γ G-CSF	IL-2 IL-4 IL-7 IL-9 IL-15 IL-21	IFN-α/β
JAK2		EPO TPO IL-3 IL-5 Leptin GM-CSF Prolactin GH		IL-12 IL-23
JAK3				
TYK2				

Source: Murray (2007) J Immunol (link), Bernstein analysis

EXHIBIT 10: **Mapping JAKs to lymphocyte response**

	JAK1	JAK2	JAK3	TYK2
JAK1	Th17 (IL-6)	*Th1* *(IFN-γ;* *less potent)*	Th2 (IL-4) Cytotoxic T cells (IL-7) B cells (IL-4, IL-21)	*Th1* *(IFN-α/β;* *less potent)*
JAK2				Th1 (IL-12)
JAK3				
TYK2				

Source: Seif et al (2017) Cell Commun Signal (link), Bernstein analysis

The JAK inhibitor class is expanding. A summary of approved and late stage candidates is provided in Exhibit 11. Xeljanz has demonstrated attractiveness in rheumatology and gastroenterology, and this success has been followed by approval for Olumiant (albeit with some concerns from the FDA regarding safety and dosing). The JAK inhibitor class has attracted multiple developers, with many candidates in late stage development and typically targeting more than one indication. Where the JAKi class has found attraction just recently has been in atopic dermatitis, where early positive results by Pfizer and Eli Lilly have led to a race to be the first to this emerging indication. Of these JAKs, filgotinib faces the most competitive pressure from upadacitinib, which is likely be first to secure approval in RA (we estimate end of 2019 vs. 2020 for filgotinib) and is also well advanced in the other indications being targeted by filgotinib.

EXHIBIT 11: **Approved and late-stage JAK inhibitors by I&I indication**

		Rheumatology			Gastroenterology		Dermatology		
Name	**Company**	**RA**	**PsA**	**AS**	**UC**	**CD**	**PsO**	**AD**	**Comments**
Tofacitinib (Xeljanz)	Pfizer	Approved	Approved	P3	Approved	On Hold	Denied	P2	Suspended trials:ERSD, dry eye, kidney transplant rejection
Baricitinib (Olumiant)	Lilly/Incyte	Approved	P1	-	-	-	On Hold	P3	Pursuing SLE; suspended trials in diabetic nephropathy
Filgotinib	**Gilead/ Galapagos**	**P3**	**P2**	**P2**	**P2/3**	**P3**	**-**	**-**	**Pursuing cutaneous lupus, Sjogren's, uveitis, lupus nephritis**
Upadacitinib	Abbvie	P3	P3	P2/3	P2/3	P3	-	P2b	
Peficitinib	Astellas	P3	-	-	P2	-	On Hold	-	Suspended trials in transplant rejection
PF-04965842	Pfizer	-	-	-	-	-	On Hold	P3	Suspended trials in SLE
PF-06651600	Pfizer	P2	-	-	P2b	P1	-	-	Pursuing alopecia
PF-06700841	Pfizer	-	-	-	P2b	-	P2	-	Pursuing alopecia & SLE
Ruxolitinib (Jakafi)	Lilly/Incyte	-	-	-	-	-	-	P2	Approved for myelofibrosis & polycythemia vera
Delgocitinib	LEO	-	-	-	-	-	-	P2	Pursuing alopecia

Source: clinicaltrials.gov, BioMed Tracker, company websites, Bernstein analysis

JAK specificity is likely to matter. As mentioned above, it is expected that JAK specificity will be relevant both for efficacy and for side effects. We show JAK specificity for the approved and late stage JAK inhibitors in Exhibit 12. The two already approved medicines in I&I both have broad specificity: Xeljanz has highest specificity for JAK3 and JAK1, but can also inhibit JAK2, while

Olumiant has specificity for JAK1 and JAK2. By contrast, Filgotinib has high specificity for JAK 1, as do other pipeline candidates from Pfizer and AbbVie.

JAK inhibitor selectivity by filgotinib has been measured in two ways which have unexpectedly yielded differing results: in biochemical assays (which measure the ability of filgotinib to compete with ATP to bind recombinant JAK proteins) and in cellular assays (which measure the ability of filgotinib to inhibit specific signally pathways in cultured cells). At a biochemical level filgotinib exhibits selective inhibition of JAK1 *and* JAK2 over JAK3 and TYK2 (Exhibit 13). It is surprising, given approximately equivalent potency for JAK1 and JAK2 in biochemical assays, that at a cellular level filgotinib has high specificity for pathways involving JAK1 over JAK2:

+ Filgotinib is 28-fold more selective for JAK1 than JAK2 in whole blood assays (note that tofacitinib and baricitinib were included for comparison, these were 10-fold and 2-fold more selective for JAK1 than JAK2 respectively).
+ When tested for potency with JAK1 heterodimer combinations and JAK2 homodimers, filgotinib inhibition is most potent for JAK1/JAK3 and JAK1/TYK2 signalling pathways and weakest for JAK2/JAK2 signalling pathways (results of tests in different cell types and with different stimuli summarised in Exhibit 13).

The specificity hypothesis is interesting from filgotinib's perspective but we make 2 comments – (i) specificity is never 100% and in-vitro assays are imperfect. Cellular assay for the same drugs are not always in agreement and (ii) because JAK receptors tend to work in tandem (notably JAK1 and JAK3), inhibiting one will by default inhibit signalling through the others to some extent. In short, clinical evidence and experiential clinical data are much more important.

EXHIBIT 12: **JAK specificity of approved and/or candidate JAK inhibitors**

Name	Company	JAK1	JAK2	JAK3	TYK2
Tofacitinib (Xeljanz)	Pfizer	✓		✓	
Baricitinib (Olumiant)	Lilly/Incyte	✓	✓		
Filgotinib	**Gilead/ Galapagos**	✓			
Upadacitinib	Abbvie	✓			
Peficitinib	Astellas			✓	
PF-04965842	Pfizer	✓			
PF-06651600	Pfizer			✓	
PF-06700841	Pfizer	✓			
Ruxolitinib (Jakafi)	Lilly/Incyte	✓	✓		
Delgocitinib	LEO	✓	✓		

Source: Selleckchem, press reports, company websites, Bernstein analysis

EXHIBIT 13: **Biochemical and cellular specificity data for filgotinib**

	JAK	IC50 (nM)
Biochemical specificity	JAK1	10
	JAK2	28
	JAK3	810
	TYK2	116
Cellular specificity	JAK1/JAK3	~150-760
	JAK1/TYK2	~440-490
	JAK1/JAK2	~1,050-3,360
	JAK2/JAK2	~3,500 to >10,000

Source: Van Rompaey et al (2013) J Immunol (link), Bernstein analysis; note that lower IC_{50} values indicate higher potency of inhibition (i.e., inhibition at a lower concentration of filgotinib); cellular specificity was tested in different cell types under different stimulatory models and the indicated ranges cover all experiments relating to the specific JAK/JAK combination

Potentially large market across multiple indications in I&I

The registered clinical trials for filgotinib point to most of the large indications in I&I: rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis and Crohn's disease (as summarised in Exhibit 14). Missing is psoriasis, perhaps because it is crowded by the recent influx of IL-17 inhibitors (note that there is growing evidence that JAK inhibition is efficacious for psoriasis; JAKi indirectly reduces IL-17 by upstream blocking of IL-23). Filgotinib is also being explored in clinical studies for uveitis, Sjogren's syndrome, and specific skin and kidney manifestations of lupus (for a full list of key trials see Exhibit 84 in appendix).

We will go through each of the key indications in a little more detail but state upfront that even though the field of approved therapies is already pretty crowded (Exhibit 15), not every medication will work in every patient, and even in patients who initially

respond well to treatment there is a significant chance of becoming a secondary non-responder over time. In this context, clinical optionality has value. The question is which indications are likely to respond to the JAK inhibitor class, and how big is the opportunity for each, given competition from existing and pipeline therapies.

EXHIBIT 14: **Summary of key autoimmune diseases**

Indication	Description	Treatment	Prevalence/Incidence
Rheumatoid arthritis	A chronic disease in which various joints in the body are inflamed, leading to swelling, pain, stiffness and possible loss of function.	Less severe patients start on NSAIDs, adding steroids and immunomodulators (methotrexate) as the disease worsens and, finally, biologics where 2/3 lines of anti-TNFs (Remicade, Humira, Enbrel, Simponi, Cimzia) are the mainstay of treatment. Other options used typically after anti-TNF failure are IL-6s (Actemra), CTLA4 (Orencia) and JAK/STAT (Xeljanz, and very recently Olumiant).	Prevalence is estimated at around 0.5-1%, of which ~65% are considered 'moderate-to-severe' enough to require more than steroid treatment
Ankylosing spondylitis	A spectrum of types of chronic inflammatory arthritis involving the spine and/or sacroiliac joints	Similar to RA, less severe patients start on NSAIDs, adding steroids and immunomodulators as the disease worsens and, finally, biologic anti-TNFs are the mainstay of treatment. Other options are limited outside of Cosentyx.	Prevalence is estimated at around 0.35%, of which roughly 20% are considered severe enough to use biological DMARDs
Psoriatic arthritis	A form of arthritis affecting individuals with psoriasis. Like RA, joints become inflamed, which causes pain, swelling and stiffness.	Similar to RA, less severe patients start on NSAIDs, adding steroids and immunomodulators as the disease worsens, Finally biologics where 2/3 lines of anti-TNFs (Remicade, Humira, Enbrel, Simponi, Cimzia) are the mainstay of treatment. Cosentyx, Otezla and Xeljanz are other options used after anti-TNF failure.	Up to 30% of those with psoriasis may develop some form of arthritis but in most people (80%) the arthritis develops after the appearance of psoriasis.
Ulcerative colitis	Inflammatory disease of the bowel, generally the colon and rectum which can become ulcerated. Symptoms are primarily abdominal pain and diarrhea mixed with blood. The disease is characterised by flares and periods of remission.	Less severe patients are typically managed with 5-ASAs (aminosalicyclates). More severe patients typically receive steroids for induction therapy and then non-biologic immunomodulators for maintenance. The most severe are treated with biologics. Anti-TNFs (Remicade, Humira, Simponi) are the mainstay of treatment, but they have recently been joined by Takeda's Entyvio (a4ß7 integrin MAb) and Pfizer's Xeljanz (JAKi)	Prevalence is estimated at around 0.24% (~700k in the US), of which roughly 65% are in remission. Of the remaining 35%, roughly half have 'severe' disease that might be treated by biologics.
Crohn's disease	Inflammatory disease of the bowel, generally in the terminal ileum and the colon, but can affect the entire GI tract. Patients often develop fistulas (holes between adjacent areas of small bowel or small bowel and the skin) and strictures (narrowings of the gut).	Less severe patients are typically managed with 5-ASAs (aminosalicyclates). More severe patients typically receive steroids for induction therapy and then non-biologic immunomodulators for maintenance. The most severe are treated with biologics. Anti-TNFs (Remicade, Humira, Cimzia) are the mainstay of treatment, but they have recently been joined by J&J's Stelara (IL12/23 inhibitor) and Takeda's Entyvio (a4ß7 integrin MAb)	Prevalence is estimated at around 0.2% (~600k in the US), of which roughly 20% are considered 'moderate-to-severe' enough to require biological treatment

Source: Company disclosure, Bernstein analysis

EXHIBIT 15: **Approved treatment options by therapy area**

					US Approval						Europe Approval					
Brand	**Generic**	**Company**	**Target**	**Dosing**	**RA**	**AS**	**PsO**	**PsA**	**CD**	**UC**	**RA**	**AS**	**PsO**	**PsA**	**CD**	**UC**
Filgotinib		**GILD/GLPG**	**JAK/STAT**	**Oral**	**P3**	**P2**		**P2**	**P3**	**P3**	**P3**	**P2**		**P2**	**P3**	**P3**
Olumiant	Baricitinib	LLY	JAK/STAT	Oral	Jun '18	--	--	--	--	--	Feb '17	--	--	--	--	--
Xeljanz	Tofacitinib	PFE	JAK/STAT	Oral	Nov '12	--	--	Dec '17	--	Jun '18	Mar '17	--	--	Jun '18	--	Jul '18
Enbrel	Etanercept	AMGN	TNF	SC, Weekly	Nov '98	Jul '03	Jul '04	Jan '02	--	--	Feb '00	Jan '04	Sep '04	Dec '02	--	--
Remicade	Infliximab	JNJ	TNF	IV, Bimonthly	Nov '99	Dec '04	Sep '06	Oct '05	Aug '98	Sep '05	Jun '00	--	Nov '06	Oct '04	Aug '99	Mar '06
Humira	Adalimumab	ABT	TNF	SC, Biweekly	Dec '02	Jul '06	Jan '08	Oct '05	Feb '07	Sep '12	Sep '03	Jun '06	Dec '07	Aug '05	Jun '07	Feb '12
Simponi	Golimumab	J&J	TNF	IV/SC, Monthly	Apr '09	Apr '09	--	Apr '09	--	May '13	Oct '09	Oct '09	--	Oct '09	--	Sep '13
Cimzia	Certolizumab	UCB	TNF	SC, Monthly	May '09	Oct '13	May '18	Sep '13	Apr '08	P3 start '10	Oct '09	Oct '13	Apr '18	Dec '13	--	--
Kineret	Anakinra	SOBI	IL-1	SC, Daily	Nov '01	--	--	--	--	--	Mar '02	--	--	--	--	--
Actemra	Tocilizumab	ROG	IL-6	IV/SC, Monthly	Jan. '10	--	--	--	--	--	Jan '09	--	--	--	--	--
Kevzara	Sarilumab	REGN/SAN	IL-6R	SC, Biweekly	May '17	--	--	--	--	--	Jun '17	--	--	--	--	--
Stelara	Ustekinumab	JNJ	IL-12/23	SC, 4x/year	--	--	Sep '09	Sep '13	Sep '16	--	--	--	Jan '09	Sep '13	Nov '16	--
Cosentyx	Secukinumab	NOVN	IL-17A	IV/SC, Monthly	--	Jan '16	Jan '15	Jan '16	--	--	--	Nov '15	Jan '15	Nov '15	--	--
Taltz	Ixekizumab	LLY	IL-17A	SC, Monthly	--	--	Mar '16	Dec '17	--	--	--	--	Apr '16	Jan '18	--	--
Siliq	Brodalumab	VRX/LEO	IL-17A	SC, Biweekly	--	--	Feb '17	--	--	--	--	--	Jul '17	--	--	--
Tremfya	Guselkumab	JNJ	IL-23	SC, Bimonthly	--	--	Jul '17	--	--	--	--	--	Nov '17	--	--	--
Orencia	Abatacept	BMY	CTLA4-Ig	IV/SC Monthly	Feb '06	--	--	Jul '17	--	--	Jun '07	--	--	Jul '17	--	--
Otezla	Aprelimast	CELG	PDE4	Oral	--	--	Sep '14	Mar '14	--	P3 start '18	--	--	Jan '15	Jan '15	--	P3 start '18
Entyvio	Vedolizumab	TAK	α4β7 integrin	IV, Bimonthly	--	--	--	--	May '14	May '14	--	--	--	--	May '14	May '14

ource: FDA, EMA, press releases, Bernstein analysis. RA: rheumatoid arthritis, AS: ankylosing spondylitis, PsO: psoriasis, PsA: psoriatic arthritis, CD: Crohn's Disease, UC: ulcerative colitis.
lote Siliq is marketed as "Kyntheum" in the EU by LEO Pharma

#1 Rheumatoid arthritis

Although RA is considered a core market for disease modifying therapies, it is also among the most crowded. It is led by the TNF inhibitors (e.g. Humira, Remicade, Enbrel) and has options with a large number of alternative mechanisms of actions.

However, amongst many available options the JAKs are viewed positively by rheumatologists. Many KOLs see the class as very viable options for RA, including use in 1L and/or as a monotherapy. The challenge - reimbursement.

The major advantages of the JAK class are oral administration, the ability to use as monotherapy (many patients avoid using methotrexate), and the lack of antigenicity. We had hypothesised that daily oral administration might actually be more onerous than less frequent dosing (e.g., many of the alternative are administered by sub-cutaneous injection every 2-4 weeks), but feedback suggests (and our previous survey – see below) that is not the case. Moreover, because of the rapid effect of JAKs, a patient who misses a dose will very quickly notice a return of symptoms so compliance is not typically an issue.

Efficacy in RA is typically considered in three scenarios: (i) as monotherapy, or (ii) in combination with methotrexate – both of these having the potential to be first line treatments, or (iii) after TNF failure. In Exhibit 16 the efficacy data across these three clinical situations is summarised for the approved therapies and compared to the JAKs.

+ **Monotherapy data** for the JAKs is mixed: Xeljanz failed its monotherapy non-inferiority trial, while Olumiant and upadacitinib showed non-inferiority. Filgotinib demonstrated efficacy as a monotherapy in P2 (DARWIN 2) but we have to wait for P3 data (FINCH 3, due to finish mid-2019) to know if it can demonstrate non-inferiority.

+ **First line** use of JAKs relies on clinicians viewing these therapies as superior, or at least non-inferior, to conventional first line therapies (i.e., the anti-TNFs). Experience in both Germany (baricitinib) and the US (tofacitinib) suggests strong growth of JAKs - these are the fastest growing therapies in RA, and 40% of use is in biologic-naïve patients. The KOLs we spoke to consider it likely that the JAKs will continue to take share in RA, given patient preference and broadly comparable efficacy/safety.

  In clinical trials the JAKs have actually had mixed performance vs Humira. Xeljanz failed non-inferiority, and Olumiant (+ MTX) showed non-inferiority. By contrast, AbbVie's upadacitinib reported strong superiority data in patients on background MTX therapy, achieving significantly better results at week 12 for the proportion of patients achieving ACR20 (71% vs 63% for Humira, sig at p=0.05 level), ACR50 (45% vs 29% for Humira, sig at p=0.001 level), ACR70 (25% vs 13% for Humira, sig at p=0.001 level), as well as clinical remission (29% vs 18% for Humira) and low disease activity (45% vs 29%) (both measured using DAS28-CRP, both sig at p=0.001 level). If filgotinib is to be used first line then data from the phase 3 head-to-head study versus Humira (FINCH 1) will be important as competition within the JAK class increases.

+ **TNF-experienced patients** are an important target market, especially while clinicians remain in the habit of using TNFs (as well as reimbursement challenges associated with using JAKs first line). Xeljanz and Olumiant are both effective in these patients. Filgotinib's phase 2 data was not split by TNF response status so we have no data to go on. To quote one KOL we spoke to – "if filgotinib doesn't work in TNF failures, it's dead". We won't need to wait long to know as FINCH-2 will report soon.

What else will we be looking for in the filgotinib P3 data? The phase 2 dosing studies showed poor spread of dose response (especially in combination with MTX), so we'll want to see a clearer dose response at phase 3. There are also some concerns about the choice of dose that's been progressed to phase 3: at phase 2 the 200mg per day dose was typically not as efficacious as 100mg twice per day. Yet the phase 3 trials are testing 100mg and 200mg doses (both once per day) and not the 100mg twice per day regimen. This creates some concern about sustainability of response and it may also impact safety.

We expect filgotinib to be the fourth JAK to market but volumes will come across the entire treatment paradigm. AbbVie's upadacitinib will be ahead of filgotinib (Exhibit 17). Astella's peficitinib will also likely file before filgotinib, but it is focused on Asian markets and it is not clear if/when it will become a competitor in the US/EU (and even then, it has only been tested in combination therapy in clinical trials, not as monotherapy). Being later than upadacitinib is obviously a disadvantage for filgotinib – especially if AbbVie manages to secure a less restrictive label than Olumiant (which is limited to patients that have already failed TNFs, and has only been approved at a low dose that is less efficacious in this patient group). But as one KOL pointed out, timing isn't everything – what matters is access and safety. If Gilead gets that right, and perhaps can demonstrate a superior safety profile, then it is likely that filgotinib could take a significant part of the growing JAK share within the RA market.

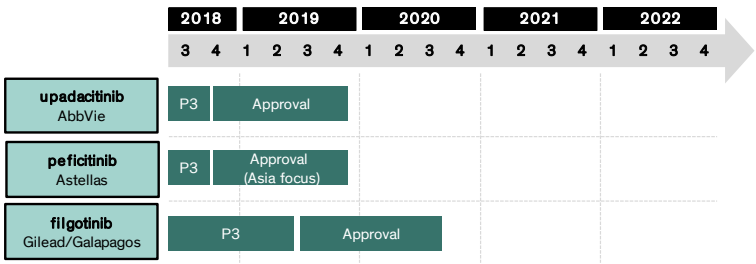
EXHIBIT 16: **Efficacy Benchmarking in RA, JAK inhibitors vs. Approved Drugs, ACR20 Data***

MOA	RA Agents	Company	Conventional DMARD-Inadequate				TNFi-Inadequate			
			Monotherapy		+DMARD		+DMARD			
			Wk 12-16	Wk 24-30	Wk 12-16	Wk 24-30	Wk 12-16	Wk 24-30		
anti-TNFα	Humira	AbbVie	19% / 46%		30% / 61%	63%				**TNF Inhibitors** are traditional 1L drugs, especially Humira, Enbrel and Remicade
	Enbrel	Amgen	23% / 62%	11% / 59%	33% / 66%	27% / 71%				
	Remicade 3 mg/kg q8w	J&J				20% / 50%				
	Cimzia	UCB		9% / 46%		14% / 59%				
	Simponi 50 mg	J&J			33% / 55%	28% / 60%	18% / 35%	16% / 31%		
	Simponi Aria	J&J			25% / 59%	32% / 63%				
anti-CTLA-4	Orencia	BMS	Similar retention as Orencia + MTX		37% / 62%	40% / 68%	18% / 46%	20% / 50%		**Other MOAs** have often shown efficacy in the TNFi-inadequate setting
anti-CD20	Rituxan	Biogen & Genentech						18% / 51%		
anti-IL6R	Actemra SC	Genentech	IV is superior to MTX at Wk 24 (70% vs. 53%)			32% / 61%	IV is Superior to Placebo at Wk 24 (30% vs. 10%)			
	Kevzara	Regeneron & Sanofi	Superior to Humira Mono (71% vs. 58%) at Wk 24		35% / 65%	33% / 66%	38% / 63%	34% / 61%		
anti-IL6	olokizumab (P2b)	UCB/R-Pharm	No planned trials		Ongoing P3 vs. MTX and Humira + MTX		30% / 55%			
anti-IL1R	Kineret	Sobi			24% / 34%	22% / 38%				
anti-JAK1/3	Xeljanz 5 mg bid	Pfizer	Inferior to Xel+MTX and Humira+MTX		27% / 55%	25% / 50%	24% / 41%	51%		**JAK inhibitors**, where newer agents have promising mono data
anti-JAK1/2	Olumiant 4 mg qd	Eli Lilly & Incyte	40% / 62%		40% / 70%		27% / 55%	27% / 46%		
anti-JAK1	filgotinib 200 mg (P2)	Gilead & Galapagos	29% / 73%		44% / 69%	42% / 73%				
	upadacitinib 30 mg	AbbVie	41% / 71%		36% / 66%					

Legend	
Control	15%
Target	60%

Source: USPI, medical literature, ClinicalTrials.gov; **peficitinib** not shown due to not stratifying by line of therapy (P2 data showed ACR20 66% by Wk12 vs. 10%); Modified from previous work by Ronny Gal (link).

EXHIBIT 17: **Anticipated JAK launch in RA**



Source: ClinicalTrials.gov, Bernstein analysis. Modified from previous work by Ronny Gal (link).

#2 IBD: Crohn's disease and Ulcerative colitis

The unmet medical need is arguably greatest in gastrointestinal indications, and there are early indications that the JAKi class could find a strong niche here given efficacy data so far has been strong. With the exception of J&J's Stelara, none of the anti-interleukins are approved for UC or CD (in fact, there has been some focus on the anti-IL-17s as potential triggers of IBD flares).

Crohn's disease and ulcerative colitis are both severe diseases with poor prognoses and limited clinical options. Even in UC, which is considered by clinicians to be more responsive to drug treatment than CD, >20%-25% of the population is not responding to current pharmacology. The treatment paradigms are similar: usually Humira first and then more potent, typically infused treatments like Remicade and Entyvio.

Xeljanz is currently the only JAK approved in IBD, in ulcerative colitis, where it has relatively strong efficacy (Exhibit 18). Interestingly both upadacitinib and filgotinib have leapfrogged phase 2 in ulcerative colitis, launching straight into P2b/3 trials – Gilead/Galapagos and AbbVie presumably took Xeljanz's efficacy as a sign of class effect and didn't want to delay market entry. In CD, Xeljanz has not progressed beyond phase 2 trials due to weak efficacy (Exhibit 20). In CD upadacitinib and filgotinib have both shown promising efficacy in phase 2 induction trials, although perhaps weaker than the TNFs. These P2 trials did not address maintenance. Both candidates are undergoing pivotal trials in UC and CD, with data expected in the first half of 2020 (except for upadacitinib in UC which will be later, see Exhibit 22).

One weak data point we would like to highlight is the lower efficacy in TNF-experienced patients for filgotinib (Exhibit 21).

EXHIBIT 18: **Efficacy Benchmarking in UC, JAK inhibitors vs. Approved and P3+ Pipeline Drugs**

MOA	UC Agent	Company	Initial Remission		Sustained Remission		Mucosal Healing		
			Rate	Time	Rate	Time	Rate	Time	
anti-TNFα	Humira	AbbVie	9% 17%	Wk8	4% 9%	Wk8 & 52			**TNF inhibitors**, traditional 1L biologics (esp. Humira, Remicade)
	Remicade 5 mg/kg	J&J	15% 39%	Wk8	7% 20%	Wk8, 30 and 54	18% 45%	Wk54	
	Simponi 100 mg	J&J	6% 18%	Wk6	16% 28%	Wk6, 30 and 54	29% 42%	Wk6	
anti-intα4β7	Entyvio	Takeda	26% 47%	Wk6	9% 21%	Wk6 & 52	20% 52%	Wk52	**Other MOAs**, mostly pipeline therapies, many of which are oral
anti-intα4β7/ αEβ7	etrolizumab 100mg (Ph2 result)	Roche	0% 21%	Wk10					
anti-intα4	AJM300 (Ph2 result)	EA /Kissei	4% 24%	Wk8			29% 59%	Wk8	
anti-S1P-R	ozanimod 1 mg (Ph2 result)	Ozanimod	6% 16%	Wk8	6% 21%	Wk32 (not sustained)	12% 33%	Wk32	
	etrasimod (Ph2 result)	Arena	8% 33%	Wk12					
anti-MAdCAM	PF-00547659 (Ph2 result)	Shire	3% 17%	Wk12	P2 data available, P3 has not begun				
anti-PDE4	Otezla (Ph2 result)	Celgene	14% 32%	Wk12	P2 not yet complete				
PC Substitute	LT-02 (Ph2 result)	Lipid / Nestlé	15% 27%	Wk12			40% 55%		
anti-JAK1/3	Xeljanz 5mg bid (Ph3 result)	Pfizer	8% 19%	Wk8	5% 22%		13% 37%	Wk52	**JAK inhibitors**

Legend	
Placebo	30%
Target	50%

Source: USPI, medical literature, ClinicalTrials.gov; Modified from previous work by Ronny Gal (link).