Jefferies

Gilead Sciences

CRL on Filgo is Disappointing, We Predict Even More Pivot and Focus to Cancer

August 18, 2020

Key Takeaway

CRL for filgotinib is a setback given it was a key growth driver and $2B+ peak consensus. On the other side, we don't think expectations were super high for GILD against leader ABBV anyway and we've been saying there was some risk around 200mg high dose all along in reports/videos. We predict GILD will await more safety data in H1-21 but ultimately GILD could make tough decisions on FILG and will continue to increase focus on oncology (5 deals this year).

Filgo now in question....GILD received a CRL for filgotinib in rheumatoid arthritis and FDA has requested the full datasets from the ongoing MANTA and MANTA-RAy male toxicity studies. The FDA had access to blinded interim data, but it has requested the full data in H1-21 (so we est and re-filing would be mid-21 and PDUFA YE:21 or early 2022). GILD emphasized FDA had questions on risk/benefit for 200mg including the male tox signal at 200mg and other higher AEs vs lower 100mg dose - despite the fact overall JAK safety class issues are in fact lower for filgotinib than competitors...in our prior notes and videos we highlighted 200mg as a risk factor given MANTA 200mg data had not finished yet and the FDA is extremely conservative on the JAK class given lots of other RA drugs are available....we lowered our 2021-22 estimates and removed USA sales for now.

Source: Goldman Sachs Global Investment Research

Pipeline review

Jyseleca (filgotinib)

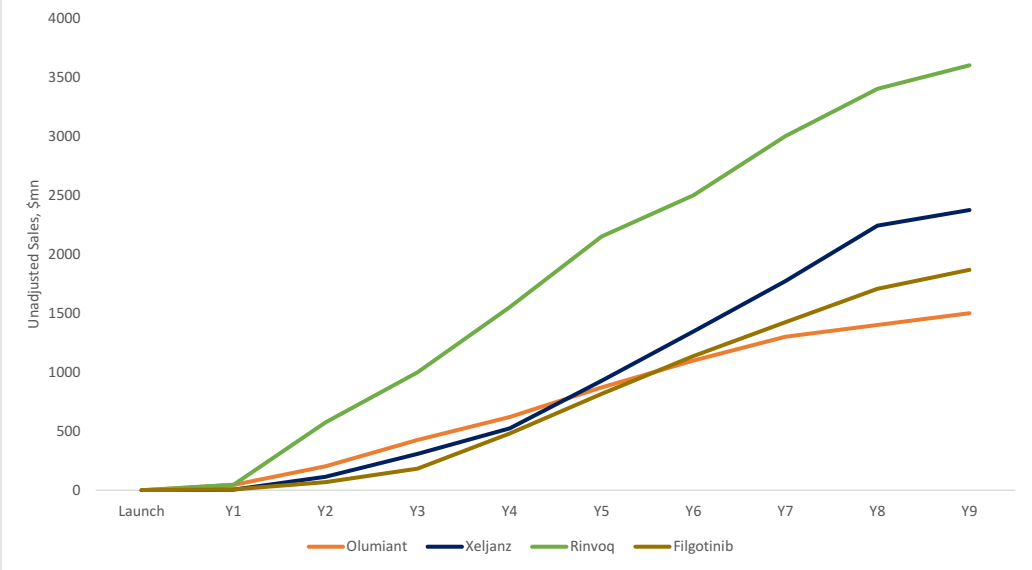
What is it and the market opportunity?

Filgotinib is a small molecule inhibitor of JAK1, a member of the JAK (Janus kinase) family of cytoplasmic tyrosine kinases. The family of receptors (JAK1, JAK2, JAK3 and TYK2) are broadly responsible for the modification of specific proteins within cells and control a diverse array of biological functions. JAKs are an important therapeutic target in a variety of diseases, particularly auto-immune diseases, as they up regulate a wide variety of cytokines (responsible for immune system signaling). Drugs that target JAK dampen the pro-inflammatory effects of cytokine signaling, thus providing therapeutic benefit in inflammatory diseases. Filgotinib is currently in development for rheumatoid arthritis (RA), ulcerative colitis (UC), psoriatic arthritis (PsA), Crohn's disease (CD) and ankylosing spondylitis (AS). According to prior GS research, we estimate that the global inflammation market will grow to ~$65bn by 2027.

Competitive landscape: Filgotinib represents the fourth JAK inhibitor (JAKi) to come to the market (currently approved in Japan and Europe, pending approval in the US). Others include Xeljanz (approved in 2012 for RA, PSA and UC), Olumiant (approved in 2018 for RA), and Rinvoq (approved in 2019 for RA), which are marketed by Pfizer, Eli Lilly, and AbbVie, respectively (all companies covered by Terence Flynn). That said, with respect to Rinvoq, ABBV has submitted supplemental new drug applications (sNDAs) for Rinvoq in PsA, AS and more recently, atopic dermatitis (AtD). Other trials underway include those for Rinvoq in CD, UC, axial spondyloarthritis, giant cell arteritis, and Takayasu arteritis.

Although, filgotinib has shown a favorable safety profile vs. the other JAKi's, we believe there is a risk that like for the other three JAKi's, a black box warning around safety could be applied to filgotinib (this of course assumes final approval by FDA). Thus, were this to be the case, we believe any potential safety advantages previously communicated by GLPG for filgotinib may ultimately be neutralized, with all four JAKi's potentially on a similar playing field with respect to safety. In terms of commercialization, we believe that GLPG/GILD are at a relative disadvantage vs. other immunology players, which have at least two drugs in their portfolio (ABBV, JNJ and LLY) and in some cases a longer, established presence in the space. Also, the potential launch of biosimilar versions of Humira in 2023 in the US market could become another disadvantage to filgotinib, which we currently expect to launch in US in 2022.

Exhibit 8: JAK inhibitor launch trajectories



The reported sales for Olumiant, Xeljanz and Rinvoq is till Y3,Y8 and Y1 respectively, beyond which we use GS estimates

Source: Company data, Goldman Sachs Global Investment Research

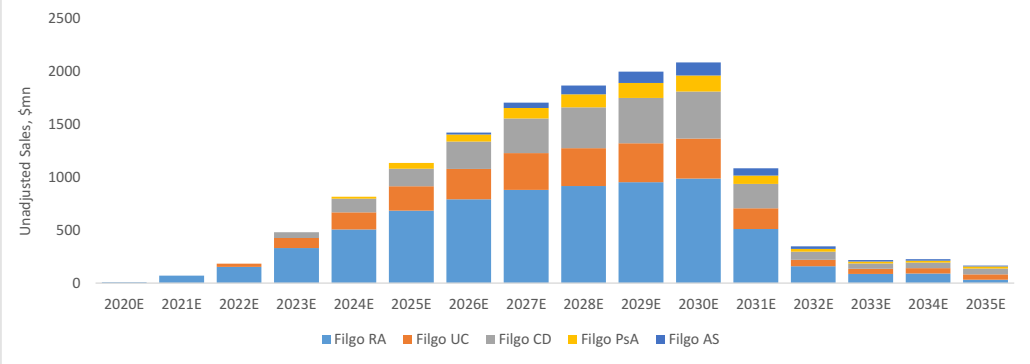
Our assumptions

- **RA —** Our model assumes US approval and subsequent launch in 2022 from 4Q20 prior (EU and Japan launch in 4Q20). We assign a PoS of 85% (US) and forecast peak risk unadjusted sales of $990mn in 2030, after which we expect patent

expiration and thus, a decline in sales due to generic erosion. (As filgotinib is a small molecule-based drug, any patent cliff in the post-2030 LOE period for the product could be steep.) We further assume an average annual price of c.$65k based on Rinvoq pricing, 25% GTN adjustment and 4% annual growth rate. In Europe, where filgotinib was recently approved as Jyseleca, we assume a 30% discount to the US price (c.$45k/year) and keep the price constant (i.e., we assume no annual price increases) throughout our forecast period.

- **UC —** Our model assumes US approval and subsequent launch in 2022, given the possibility of a parallel filing for RA and UC. Recall that filing timeline for filgotinib has been made uncertain given (1) mixed Phase 3 data in UC (LINK) and (2) the FDA CRL in the lead indication of RA, with GLPG stating that filing in the US for UC is dependent on the ultimate timing of resolution for filgotinib in RA. We currently assume an EU and Japan launch in 2022. In terms of our forecasts, we assign a PoS of 70% and project peak year risk unadjusted sales of $380mn in 2030, after which we expect patent expiration. We make the same pricing assumptions as filgotinib in RA, adjusted according to year of launch.
- **CD/PsA/AS —** Our model assumes US, EU and Japan launch in 2023/2024/2026 for CD/PsA/AS respectively. We assign a PoS of 60/50/50% and forecast peak risk unadjusted sales of ~$440/$150/$120 mn in 2030 for CD/PsA/AS after which we expect patent expiration. We make the same pricing assumptions as filgotinib in RA, adjusted according to year of launch.

Exhibit 9: Filgotinib risk-unadjusted sales summary in different indications



Source: Goldman Sachs Global Investment Research

Current status: GLPG received an approval in RA on September 25, 2020 in Japan and Europe and a complete response letter from the US FDA in August 2020 (LINK) for filgotinib in RA. As stated previously, positive Phase 3 data are in hand (specifically at the higher 200mg dose, but not the lower 10mg dose) and it is in Phase 3 clinical trials in Crohn's disease (CD) and psoriatic arthritis (PsA), with a Phase 3 in ankylosing spondylitis (AS) expected to start by YE2020. In addition, GILD is running Phase 2 trials for filgotinib in uveitis, small bowel Crohn's disease, and fistulizing Crohn's disease (indications we do not currently model).

#1 - Filgotinib risk/reward negative near-term

There is still plenty to debate (label, efficacy inferiority, 2 dose approval, CLE and Sjogren's). We briefly discuss each in turn with clinical data to support where needed.

We expect filgo to get a thrombosis warning. There is no doubt that post the FINCH data in totality, we think filgotinib can be considered best in class. We present the key safety data in Exhibits 4-8, but briefly comment that thrombosis is where Filgotinib really stands out:

+ With only 3 thrombosis events seen (2 from FINCH) we see a PE/DVT rate of 0.1/100PY across all key RA trials (we include retinal vein occlusion from FINCH 2 and confirmed there were no such events in FINCH 1 & 3). This compares vs. 0.4/100PY for upad. Using p3 data only, skews the difference even higher.
+ In other safety areas, Filgo fares well, including (i) Herpes zoster rate >2x lower vs. all peers, (ii) serious infection rates of 1.8/100PY, significantly below upad (2.7/100PY), (iii) MACE rate of 0.3/100PY vs. 1/100PY for upad. (iv) Death event rate of 0.3/100PY vs. 0.5/100PY for upad. There will certainly be some debate on the death that occurred in the 200mg + MTX arm and we will need to wait for details. However, given the death rate was similar across the FINCH trials vs. placebo/csDMARD (0.2%), we are not overly concerned and the 0.3/100PY event rate is in-line or below all JAK peers.

GLPG's previous expectations were for Filgo to get a black box warning for malignancies and infections, as is typical of the class, but avoid a warning for thrombotic events. Following the Upad label (link) which included a black box warning - "*Thrombosis, including deep vein thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated with Janus kinase inhibitors used to treat inflammatory conditions*", our base assumption is that filgo receives a similar class effect label. More importantly, our commercial view would change very little if filgo did not receive the label (see comments below).

EXHIBIT 4: **Filgotinib thrombo event rate analysis**

Study name	Total enrolment	739	Treatment regimen	Estimated PYE	PE/DVT	PE + DVT	PE/DVT / 100 PYE	PE + DVT / 100 PYE
DARWIN-3 (p2) interim (wk 156)	739	MTX-inadequate		2,203	1	2	0.0	0.1
FINCH-1	1,759	MTX-inadequate	+MTX	441	1	1	0.2	0.2
FINCH-2	448	bDMARD-inadequate	+csDMARD	138	1	1	0.7	0.7
FINCH-3	1,252	MTX-naïve	+MTX / monotherapy	384	0	0	0.0	0.0
P2 + P3 trials	**4,183**			**3,167**	**3**	**4**	**0.1**	**0.1**
P3 only (FINCH 1-3)	**3,459**			**964**	**2**	**2**	**0.2**	**0.2**

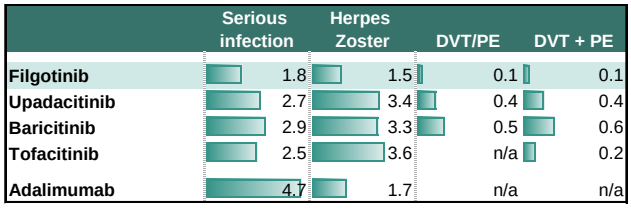
Source: Company disclosure, Bernstein analysis and estimates. Filgotinib DARWIN LT follow-up (link), FINCH-1 (link), FINCH-2 (link) and FINCH-3 (link)

EXHIBIT 5: **Filgotinib vs. updacitinib thrombo event rate analysis (p3 only, all doses – negative entries indicate Filgotinib superiority)**

Patient profile	Treatment regimen	Filgotinib vs. Upadacitinib	PE/DVT per 100 PYE	PE + DVT per 100 PYE
MTX-inadequate	+MTX	FINCH-1 vs. SELECT-COMPARE	-0.4	-0.4
bDMARD-inadequate	+csDMARD	FINCH-2 vs. SELECT-BEYOND	-1.6	-2.1
MTX-naïve	'+MTX / monotherapy	FINCH-3 vs. SELECT-MONO* & SELECT-EARLY	-0.5	-0.5

Source: Company disclosure, Bernstein analysis and estimates
FINCH-1 (link), FINCH-2 (link) and FINCH-3 (link); SELECT-EARLY (link), SELECT-BEYOND (link, link), SELECT-COMPARE (link), SELECT-MONOTHERAPY (link).
* Note SELECT-MONO was in MTX-inadequate patients, not MTX naïve as per FINCH-3, but this remains the closest comparator. Also note that SELECT-MONO was only 14 weeks.

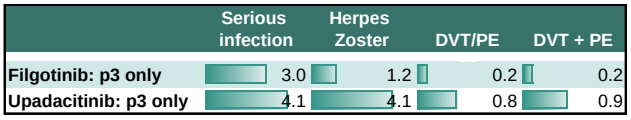
EXHIBIT 6: **JAK-specific safety signals – RA (per 100 pt year exposure)**



Source: Tofacitinib LT safety update (link); baricitinib long term safety update (link) and CV safety update (link); upadacitinib BALANCE-1 (link) and BALANCE-2 (link), BALANCE LTE (link), SELECT-EARLY (link), SELECT-NEXT (link), SELECT-BEYOND (link, link), SELECT-COMPARE (link), SELECT-MONOTHERAPY (link); filgotinib DARWIN LT follow-up (link), FINCH-1 (link), FINCH-2 (link) and FINCH-3 (link); adalimumab LT safety (link); company disclosure, Bernstein analysis and estimates

Note: where patient years of drug exposure have not been provided, these are estimated (# patients on drug x study duration). Filgotinib DARWIN LT follow-up data excludes patient groups with <10 patients and patients on doses <200mg/day

EXHIBIT 7: **JAK-specific safety signals – RA p3 only (per 100 pt year exposure)**



Source: Upadacitinib SELECT-EARLY (link), SELECT-NEXT (link), SELECT-BEYOND (link, link), SELECT-COMPARE (link), SELECT-MONOTHERAPY (link); FINCH-1 (link), FINCH-2 (link) and FINCH-3 (link); company disclosure, Bernstein analysis and estimates

Note: where patient years of drug exposure have not been provided, these have been estimated (# patients on drug x study duration)

EXHIBIT 8: **Safety data summary: RA clinical studies (incidence rate per 100 patient years)**

	Tofacitinib		Baricitinib		Upadacitinib		Filgotinib	
	Events	IR (/100PY)	739	IR (/100PY)	Events	IR (/100PY)	Events	IR (/100PY)
Patients	*7,061*		*2,203*		*3,230*		*2,827*	
Patient years (est)	*22,875*		*7,860*		*2,203*		*3,167*	
Deaths	59	0.3	5	0.4	10	0.5	9	0.3
Serious infections	576	2.5	27	2.9	59	2.7	56	1.8
Pneumonia	124	0.5			2	0.1	3*	0.1
Herpes zoster	782	3.6	34	3.3	74	3.4	46	1.5
Opportunistic infections	90	0.4			20	0.9	0	0.0
Tuberculosis	38	0.2	11	0.1	0	0.0	0	0.0
Malignancies (ex NMSC)	117	0.6	11	0.8	20	0.9	12	0.4
GI perforations	28	0.1	3	0.0	5	0.2	0	0.0
MACE	85	0.4	3	0.5	22	1.0	8	0.3
DVT/PE		0.0	42	0.5	8	0.4	3	0.1
DVT + PE	55	0.2	49	0.6	9	0.4	4	0.1
DVT	27	0.1	30	0.4	3	0.1	3	0.1
PE	28	0.1	19	0.2	6	0.3	1	0.0

Source: Tofacitinib long term safety update (link); baricitinib long term safety update (link) and cardiovascular safety update (link); upadacitinib BALANCE-1 (link) and BALANCE-2 (link), BALANCE LTE (link), SELECT-EARLY (link), SELECT-NEXT (link), SELECT-BEYOND (link, link), SELECT-COMPARE (link), SELECT-MONOTHERAPY (link); Filgotinib DARWIN LT follow-up (link), FINCH-1 (link), FINCH-2 (link) and FINCH-3 (link); Bernstein analysis and estimates

Note: where patient years of drug exposure have not been provided, these have been estimated (# patients on drug x study duration). Filgotinib DARWIN long-term follow-up data excludes patient groups with <10 patients and patients on doses <200mg/day

* DARWIN data only

Grey shading = Data not provided in FINCH-1, FINCH-3 and Darwin updates on 28 March 2019. These figures are therefore based on FINCH-2 and Darwin 132-week data (1024 pts, 2180 patient years)

We do not see efficacy as a debate – at least not one that will drive prescribing. We present the key efficacy endpoints from FINCH 1-3 in Exhibits 6-9 and a summary of the ACR 20 efficacy vs the competition in RA in Exhibit 13. Efficacy had never been a focus for investors, but after the FINCH 1 & 3 data came out, question marks were initially raised as (i) In FINCH 1, superiority vs. Humira was not achieved across most efficacy metrics. Whilst this was not a concern in itself, upadacitinib was able to achieve superiority (the Humira arm in FINCH 1 looked exceptionally strong vs. historical data). (ii) In FINCH 3, the mono arm was not convincing vs. MTX (unusually high).

Firstly, when comparing vs. upadacitinib using updated data post EULAR-19 (Exhibits 14-16), you could argue filgotinib is inferior using placebo adjusted rates, but on an absolute basis, filgotinib actually looks a little better. In addition, comparing Humira adjusted outcomes, yes Filgo is a little worse off, but the differences are not significant. Also worth remembering that upad will not have a Humira superiority claim on label. Secondly, and more broadly, in FINCH-2 (biological DMARD-inadequate patients), on ACR20 (primary), filgo appears to trump the competition, with Kezvara and upad coming closest.

In short, we do not consider efficacy a debate for Filgotinib. Yes, looking across the data sets and metrics, you could make an argument that upad is superior on efficacy, but there is very little in it and more importantly we do not see this impacting prescribing of the drug. We expect physicians to view the efficacy vs. upad as comparable.

EXHIBIT 9: **FINCH-1 efficacy data (MTX-inadequate pts, +MTX)**

	Week 12				Week 24			
	Placebo + MTX (n=475)	Humira + MTX (n=325)	100mg + MTX (n=480)	200mg + MTX (n=475)	Placebo + MTX (n=475)	Humira + MTX (n=325)	100mg + MTX (n=480)	200mg + MTX (n=475)
Proportion of patients achieving:								
ACR20	49.9%	70.8%	69.8%***	76.6%***	59.2%	74.5%	77.7%	78.1%
ACR50	19.8%	35.1%	36.3%***	47.2%***	33.3%	52.6%	52.7%	57.9%
ACR70	6.7%	14.2%	18.5%***	26.3%***	14.9%	29.5%	29.4%	36.2%
DAS28(CRP)≤ 3.2 (low disease activity)	23.4%	43.4%	38.8%***	49.7%***^	33.7%	50.5%	53.1%	60.6%
DAS28(CRP)< 2.6 (clinical remission)	9.3%	23.7%	23.8%***^	33.9%***^^	16.2%	35.7%	35.2%	48.4%

Source: EULAR 2019 presentation, Bernstein analysis

* p<0.05 versus placebo, ** p<0.01 versus placebo, *** p<0.001 versus placebo, ^ non-inferior to adalimumab, ^^ superior to adalimumab

EXHIBIT 10: **FINCH-2 efficacy data (bDMARD-inadequate pts)**

	Week 12			Week 24		
	Placebo (n=148)	100mg (n=153)	200mg (n=147)	Placebo (n=148)	100mg (n=153)	200mg (n=147)
Proportion of patients achieving:						
ACR20	31.1%	57.5%***	66.0%***	34.5%	54.9%***	69.4%***
ACR50	14.9%	32.0%***	42.9%***	18.9%	35.3%**	45.6%***
ACR70	6.8%	14.4%*	21.8%***	8.1%	20.3%**	32.0%***
DAS28(CRP)≤ 3.2 (low disease activity)	15.5%	37.3%***	40.8%***	20.9%	37.9%**	48.3%***
DAS28(CRP)< 2.6 (clinical remission)	8.1%	25.5%***	22.4%***	12.2%	26.1%**	30.6%***

Source: ACR 2018 (link), Bernstein analysis

* p<0.05 versus placebo, ** p<0.01 versus placebo, *** p<0.001 versus placebo.

EXHIBIT 11: **FINCH-3 efficacy data (MTX-naïve pts, +MTX arm)**

	Week 12			Week 24		
	MTX (n=416)	100mg + MTX (n=207)	200mg + MTX (n=416)	MTX (n=416)	100mg + MTX (n=207)	200mg + MTX (n=416)
Proportion of patients achieving:						
ACR20		**	***	71.4%	80.2%*	81.0%***
ACR50		***	***	45.7%	57.0%**	61.5%***
ACR70		***	***	26.0%	40.1%***	43.8%***
DAS28(CRP)≤ 3.2 (low disease activity)	28.6%	50.2%***	55.8%***	46.2%	62.8%***	68.8%***
DAS28(CRP)< 2.6 (clinical remission)	17.1%	31.9%***	39.7%***	29.1%	42.5%***	54.1%***

Source: EULAR 2019 presentation, Bernstein analysis

* p<0.05 versus placebo, ** p<0.01 versus placebo, *** p<0.001 versus placebo

Note that as at 12 weeks, the ACR20, 50 and 90 significance but not percentages of patients were specified in the detailed 2019 EULAR presentation

EXHIBIT 12: **FINCH-3 efficacy data (MTX-naïve pts, +monotherapy arm)**

	Week 12		Week 24	
	MTX (n=416)	200mg once daily (n=210)	MTX (n=416)	200mg once daily (n=210)
Proportion of patients achieving:				
ACR20		**	71.4%	78.1%
ACR50		***	45.7%	58.1%**
ACR70		***	26.0%	40.0%***
DAS28(CRP)≤ 3.2 (low disease activity)	28.6%	48.1%***	46.2%	60.0%***
DAS28(CRP)< 2.6 (clinical remission)	17.1%	29.5%***	29.1%	42.4%***

Source: EULAR 2019 presentation, Bernstein analysis

* p<0.05 versus placebo, ** p<0.01 versus placebo, *** p<0.001 versus placebo

Note that as at 12 weeks, the ACR20, 50 and 90 significance but not percentages of patients were specified in the detailed 2019 EULAR presentation

EXHIBIT 13: **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 (P3)	Gilead & Galapagos		71% 78%	50% 77%	59% 78%	31% 66%	35% 69%	
	upadacitinib 30 mg	AbbVie	41% 71%		36% 66%		28% 56%		

Legend	
Control	15%
Target	60%

Source: Company disclosure, medical literature, USPI, ClinicalTrials.gov, Bernstein analysis

Note that FINCH-3 data has been used for cDMARD inadequate monotherapy comparison purposes here, although whilst the data used from FINCH-3 is mono, patient background is actually MTX-naïve.

EXHIBIT 14: **Filgotinib (200mg) vs. Upadacitinib (15mg) efficacy in RA (positive entries indicate Filgotinib superiority)**

Patient profile	Treatment regimen	Filgotinib vs. Upadacitinib	ACR20	ACR50	ACR70	DAS28(CRP)≤ 3.2 (low disease activity)	DAS28(CRP)< 2.6 (clinical remission)
MTX-inadequate	+MTX	FINCH-1 vs. SELECT-COMPARE	11%	4%	2%	6%	8%
bDMARD-inadequate	+csDMARD	FINCH-2 vs. SELECT-BEYOND**	8%	3%	10%	-4%	-2%
MTX-naïve	+MTX arm	FINCH-3 vs. SELECT-EARLY	2%	1%	-1%	9%	6%
	monotherapy arm	FINCH-3 vs. SELECT-MONO*	n/a	n/a	n/a	n/a	n/a

Source: Company disclosure, Bernstein analysis and estimates.
FINCH-1 (link), FINCH-2 (link) and FINCH-3 (link); SELECT-EARLY (link), SELECT-BEYOND (link, link), SELECT-COMPARE (link), SELECT-MONOTHERAPY (link).
Note that data is 24 weeks unless stated.
* Note that there is no true comparator from the upad trials for the mono arm in FINCH-3. The closest comparator, SELECT-MONO was in MTX-inadequate patients, not MTX naïve as per FINCH-3, and we currently only have 24wk FINCH-3 data vs 14 wk from SELECT-MONO.

EXHIBIT 15: **Placebo or MTX adjusted efficacy of Filgotinib (200mg) vs. Upadacitinib (15mg) in RA (positive entries indicate Filgotinib superiority)**

Patient profile	Treatment regimen	Filgotinib vs. Upadacitinib	Adjusted vs	ACR20	ACR50	ACR70	DAS28(CRP)≤ 3.2 (low disease activity)	DAS28(CRP)< 2.6 (clinical remission)
MTX-inadequate	+MTX	FINCH-1 vs. SELECT-COMPARE	Placebo + MTX	-13%	-8%	-4%	-10%	1%
bDMARD-inadequate	+csDMARD	FINCH-2 vs. SELECT-BEYOND**	Placebo	2%	-4%	8%	-11%	-4%
MTX-naïve	+MTX arm	FINCH-3 vs. SELECT-EARLY	MTX	-11%	-11%	-8%	-5%	-5%
	monotherapy arm	FINCH-3 vs. SELECT-MONO*	n/a	n/a	n/a	n/a	n/a	n/a

Source: Company disclosure, Bernstein analysis and estimates.
FINCH-1 (link), FINCH-2 (link) and FINCH-3 (link); SELECT-EARLY (link), SELECT-BEYOND (link, link), SELECT-COMPARE (link), SELECT-MONOTHERAPY (link).
Note that data is 24 weeks unless stated.
* Note that there is no true comparator from the upad trials for the mono arm in FINCH-3. The closest comparator, SELECT-MONO was in MTX-inadequate patients, not MTX naïve as per FINCH-3, and we currently only have 24wk FINCH-3 data vs 14 wk from SELECT-MONO.
** SELECT BEYOND placebo patients switched to Upa post week 12, therefore 12-week placebo data is used here from SELECT BEYOND trial vs 24 week FINCH-2 data

EXHIBIT 16: **Humira adjusted efficacy of Filgotinib (200mg) vs. Upadacitinib (15mg) in RA (positive entries indicate FINCH-1 %'s are higher)**

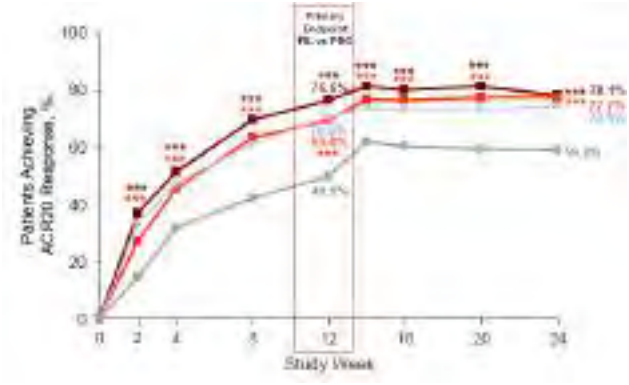
	FINCH-1			SELECT-COMPARE			FINCH-3 vs SELECT COMPARE		
	Filgo + MTX (n=475)	Humira + MTX (n=325)	Filgo adjusted	Upad + MTX (n=651)	Humira + MTX (n=327)	Upad adjusted	Filgo / Upad	Humira	Adjusted
ACR20	78.1%	74.5%	3.6%	67.4%	57.2%	10.2%	11%	17%	-7%
ACR50	57.9%	52.6%	5.3%	53.9%	41.9%	12.0%	4%	11%	-7%
ACR70	36.2%	29.5%	6.7%	34.7%	22.9%	11.8%	2%	7%	-5%
DAS28(CRP)≤ 3.2 (low disease activity)	60.6%	50.5%	10.1%	54.7%	38.5%	16.2%	6%	12%	-6%
DAS28(CRP)< 2.6 (clinical remission)	48.4%	35.7%	12.7%	40.9%	26.9%	14.0%	8%	9%	-1%

Source: Company disclosure, Bernstein analysis and estimates.
FINCH-1 (link), SELECT-COMPARE (link) at 24 and 26 weeks, respectively.

Both filgo doses should be approved. The FINCH 1-3 trials assessed both the 100mg and 200mg doses. In terms of efficacy, and looking to FINCH-1 and FINCH-3, we can see a dose-response curve (more apparent in the more stringent ACR70), highlighting that whilst the magnitude is not significant, higher doses are more efficacious (Exhibits 17-20), something that other JAKs have not achieved and hence the lack of multiple doses. Importantly, and what drives our confidence in approvals for both doses, is that from a safety perspective, there was no real differences between the two doses (Exhibit 21). *In short*, with a

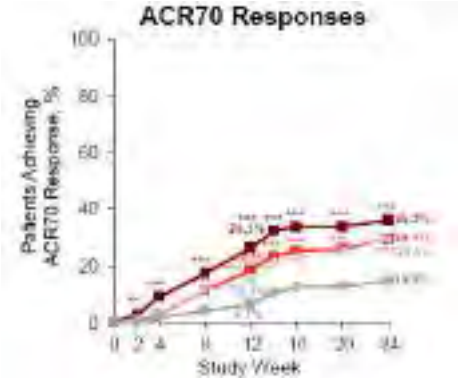
fraction more efficacy for no apparent detrimental effect, we would expect both doses to be approved, allowing for flexibility of incremental dosing (start most patients on 100mg and go from there).

EXHIBIT 17: **FINCH 1 – ACR20 dose response**



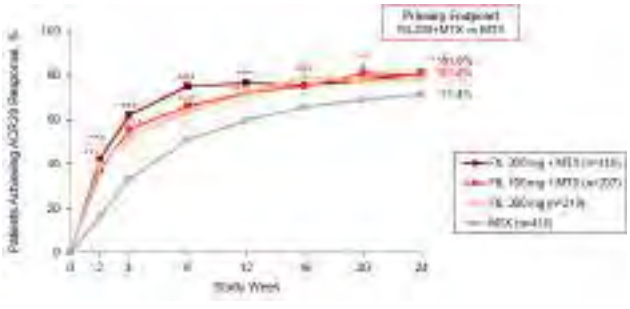
Source: EULAR 2019 presentation. Note: Maroon – Filgo 200mg, red – Filgo 100mg, light grey – ADA, dark grey - pbo

EXHIBIT 18: **FINCH 1 – ACR70 dose response**



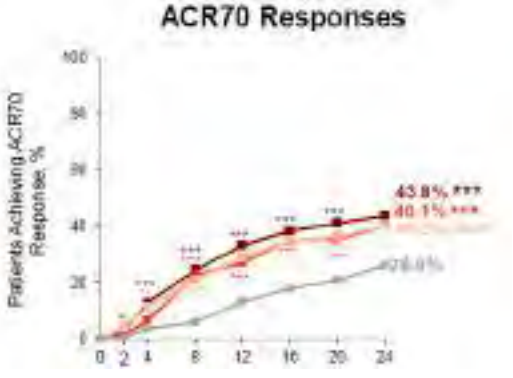
Source: EULAR 2019 presentation. Note: Maroon – Filgo 200mg, red – Filgo 100mg, light grey – ADA, dark grey - pbo

EXHIBIT 19: **FINCH 3 – ACR20 dose response**



Source: EULAR 2019 presentation. Note: Maroon – Filgo 200mg, red – Filgo 100mg, light grey – ADA, dark grey - pbo

EXHIBIT 20: **FINCH 3 – ACR70 dose response**



Source: EULAR 2019 presentation. Note: Maroon – Filgo 200mg, red – Filgo 100mg, light grey – ADA, dark grey - pbo

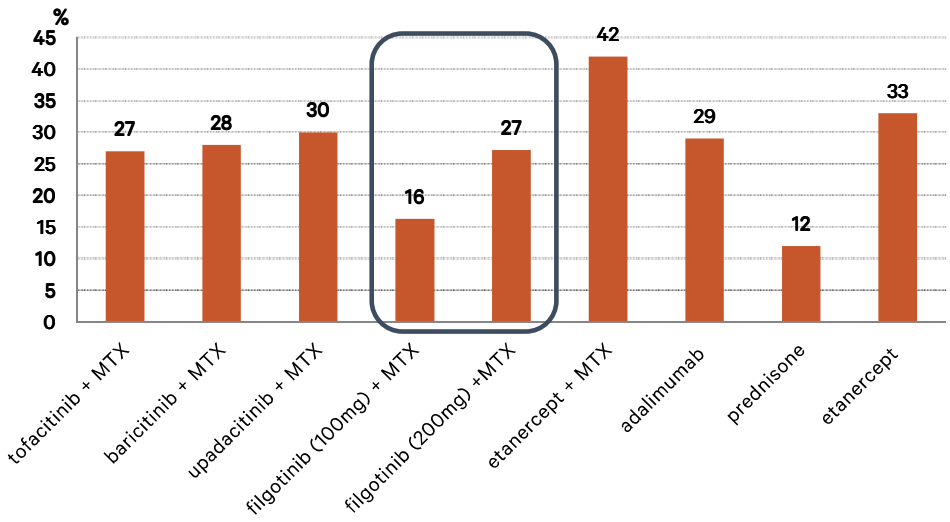
EXHIBIT 21: **Comparative safety summary of 100mg and 200mg doses across FINCH trials**

	FINCH-1		FINCH-2		FINCH-3	
	100mg *n = 480*	200mg *n = 475*	100mg *n = 153*	200mg *n = 147*	100mg + MTX *n = 207*	200mg + MTX *n = 416*
Any TEAE	**(59.6%)**	**(60.4%)**	**(63.4%)**	**(69.4%)**	**(69.6%)**	**(65.9%)**
TEAE leading to drug discontinuation	(1.7%)	(2.9%)	(3.9%)	(3.4%)		
TEAE leading to study discontinuation	(1.0%)	(1.7%)			(1.4%)	(1.9%)
Serious TEAE	(5.0%)	(4.4%)	(5.2%)	(4.1%)	(2.4%)	(4.1%)
Serious infections	(1.7%)	(1.7%)	(2.0%)	(0.7%)	(1.0%)	(1.0%)
Herpes zoster	(0.4%)	(0.4%)	(1.3%)	(1.4%)	(0.5%)	(0.5%)
Adjudicated MACEs	(0.2%)	(0.0%)	(0.7%)	(0.0%)	(0.0%)	(0.5%)
Thrombotic events	(0.0%)	(0.2%)	(0.0%)	(0.7%)	(0.0%)	(0.0%)
Malignancies excluding NMSC	(0.2%)	(0.0%)	(0.0%)	(0.0%)	(0.0%)	(0.0%)
Deaths	(0.2%)	(0.4%)	(0.0%)	(0.0%)	(0.0%)	(0.2%)

Source: FINCH-1 (EULAR 2019 presentation), FINCH-2 (link), FINCH-3 (EULAR 2019 presentation), Bernstein analysis

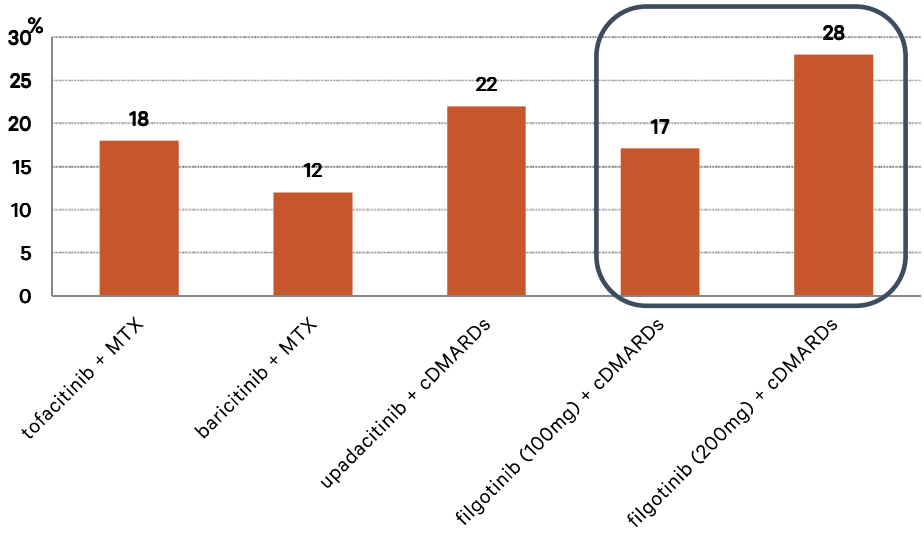
The efficacy of the JAK inhibitors in RA is well established. As shown in the Exhibits that follow, the first generation JAK inhibitors, tofacitinib (Xeljanz, Pfizer), and baricitinib (Olumiant, Incyte/Eli Lilly), as well as the next-generation JAK inhibitors, upadacitinib (Rinvoq, AbbVie), and filgotinib (Galapagos/Gilead) have demonstrated improvements in ACR20/50/70 that are comparable to standard of care biologics such as etanercept (Enbrel, Amgen) and adalimumab (Humira, AbbVie). In the Exhibits that follow, we show placebo-adjusted efficacy based on ACR50 for the JAKi, biologics, and prednisone. Additional details regarding the JAKs in RA is presented in Appendix B of our note entitled *Disruptive Discussion Part III: Inflammatory Conditions.*

Exhibit 6: Placebo-adjusted ACR50 in patients who have an inadequate response to methotrexate (MTX-IR)



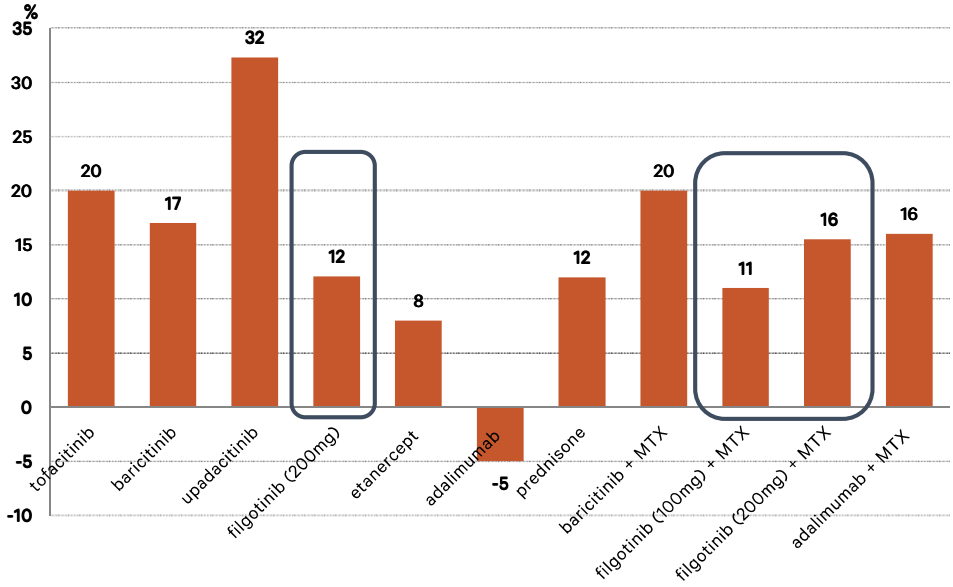
Note: 1. the baricitinib data is for the 4 mg high dose, which is not approved by FDA; all other data are for the approved dose; 2. The adalimumab data is at Week 24 while all other data are at Week 12
Source: NEJM (tofacitinib), NEJM (baricitinib), USPI (upadacitinib, etanercept, adalimumab, prednisone), British Society for Rheumatology, Company filings, Berenberg Capital Markets

Exhibit 7: Placebo-adjusted ACR50 in patients who have an inadequate response to biologic DMARDs (bDMARDs)



Note: 1. All data are for the approved dosage; 2. all data are at Week 12
Source: USPI (tofacitinib, upadacitinib), PubMed (baricitinib), British Society for Rheumatology, Company filings, Berenberg Capital Markets

Exhibit 8: Placebo-adjusted ACR50 in patients who are methotrexate naïve (MTX-naïve)



Note: 1. The baricitinib data is for the 4mg high dose which is not approved by FDA, all other data are for the approved dose; 2. All data (tofacitinib, baricitinib, upadacitinib, and filgotinib) data are at Week 24, while prednisone data are at Week 12 and adalimumab data are at Week 52.
Source: NEJM (tofacitinib), PubMed (baricitinib), USPI (upadacitinib, etanercept, adalimumab, prednisone), British Society for Rheumatology, Company filings, Berenberg Capital Markets

To us, safety is the key consideration for the JAKi in inflammatory conditions. Clinical trials to date have shown that filgotinib is well-tolerated, with atherogenic index improvement, absence of anemia, low infection rates, and low incidence of deep venous thrombosis (DVT) and pulmonary embolisms (PE). This is important because Olumiant (baricitinib) was at first rejected by FDA owing to concern regarding the risk/benefit profile across various doses, specifically the rate of thromboembolic events, diagnosed as DVT and PE, which were reported in five patients who received baricitinib during the controlled period of two of seven completed Phase II or Phase III trials in RA. The FDA eventually approved only the lower dose of baricitinib in RA. Pfizer's Xeljanz was also only approved at the low doses (5 mg twice daily; 11 mg once daily) as the FDA decided the modest incremental benefit at the high doses was not enough to offset apparent incremental toxicity. Finally, AbbVie's Rinvoq (upadacitinib) was recently approved for RA at the low dose (15 mg once daily); AbbVie did not even submit for approval at the high dose. Importantly, in long-term safety data generated by DARWIN 3, filgotinib appears to have demonstrated a differentiated safety profile.

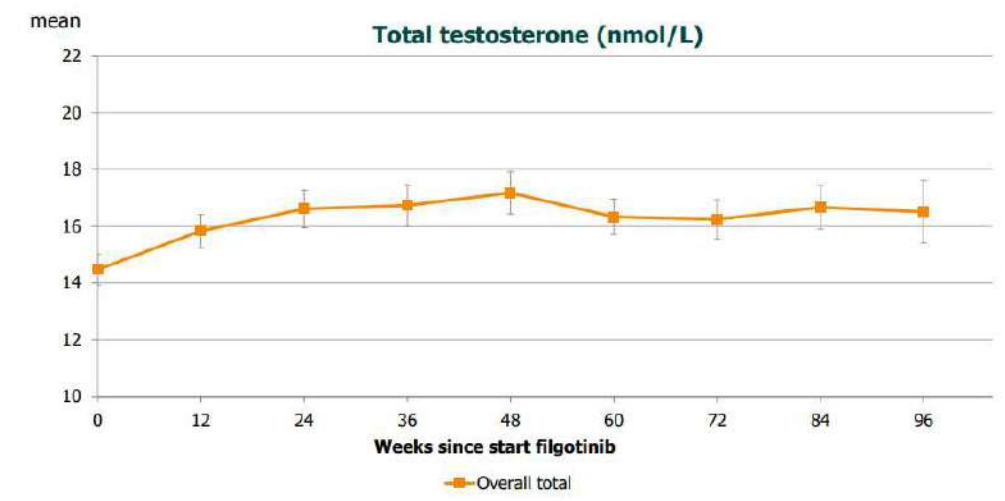
Exhibit 9: Filgotinib's long-term safety data compares well to other JAKs and biologics for RA

Event per 100 PYE	Filgotinib 50 - 200 mg	Baricitinib 2 and 4 mg	Tofacitinib 5 mg	Upadacitinib 6 and 12 mg	Tocilizumab 4 and 8 mg/kg	Adalimumab
PYE	**2,042**	6,637	5,278	725	14,994	23,943
Serious infection	**1.0**	2.9	2.4	2.3	4.5	4.6
Herpes zoster	**1.5**	3.2	3.8	3.7	ND	ND
DVT/PE	**0.1**	0.5	0.2	0.7	ND	ND
Deaths	**0.2**	0.3	0.6	0.3	0.6	0.8
Source	**DARWIN3**	ACR2017	ACR2017	ACR2017	ACR2012	Burmester 2011

Note: PYE = patient year experience; DARWIN 3 was the long-term open-label extension portion of the Phase II DARWIN program evaluating filgotinib in RA patients
Source: Company filings, Berenberg Capital Markets

One area of controversy unique to filgotinib is potential testicular toxicity. The concern was first raised during the Phase II trials (DARWIN) where the FDA enforced a maximum daily dose of 100 mg among men at U.S. clinical trial sites primarily as pre-clinical tests suggested the 200 mg dose of filgotinib affected the production of sperm cells. Galapagos has noted that the testosterone levels of males in the DARWIN program were stable.

Exhibit 10: Testosterone levels measured in males in the DARWIN program were stable



Note: Normal ranges (nmol/L) males: 8.40 – 28.70 (≥18y); Gilead is conducting a male safety study in Ph3
Source: Company filings

Encouragingly, following the end of Phase II meetings with FDA, Galapagos/Gilead confirmed the pivotal program (FINCH) would include arms that give the 100 mg and 200 mg daily doses to both men and women. In addition, a Phase II trial (MANTA + MANTA-RA) designed to evaluate the sperm count of filgotinib in men with moderate-to-severe UC (MANTA), as well as other inflammatory conditions (MANTA-RA) is underway. At its R&D Day on November 14, Galapagos confirmed that the MANTA trial readouts will not act as a gating factor for the submission of filgotinib in RA in the U.S., though it remains unclear to us how much if any of the data from the testicular toxicity studies will be available for the Gilead medical affairs and marketing teams at the time of the potential U.S. launch.

However, the FDA views the risk of thrombosis as a class effect for the JAK inhibitors. This was evident in the summary document regarding Rinvoq's approval, and also clearly stated at ACR2019 during an FDA safety update presentation we attended. Thus, we doubt filgotinib's label will look different from Rinvoq's from a safety perspective; we think this is in line with investors' expectations.

Areas of differentiation for filgotinib: safety, dosing, indications, and pricing. Galapagos/Gilead presented several abstracts at ACR2019 (see Appendix C of our note entitled *Disruptive Discussion Part III: Inflammatory Conditions*) that we think are an effort to 1) distinguish the safety profile of filgotinib compared to other JAK inhibitors; 2) demonstrate the persistence of efficacy of filgotinib; and 3) demonstrate the risk-benefit of filgotinib 200 mg, which appears to have improved efficacy without a concurrent increase in the rate of adverse events vs. placebo. The case will have to be made to the FDA that filgotinib 100 mg and 200 mg are both safe and effective options and that having a high dose on the market would increase the potential benefits for patients without increasing the risk of serious adverse events.

We think investor expectations are mixed regarding the prospect for the high dose receiving FDA approval in RA. Some believe the submission of the high dose in a New Drug Application (NDA) could lead to an advisory committee, which could be received negatively by the Street; others view the prospect of an advisory committee as being positive, as this will give Galapagos/Gilead a chance to make the case to the expert panel regarding the short and long-term safety data generated to-date for filgotinib at both the low and high doses.

To us, the number of indications on filgotinib's label will be a more significant driver of long-term value creation. Perhaps the biggest differentiator will be having more than one, and possibly up to five or six indications on the filgotinib label, which we believe could ease the path for reimbursement with payors, something which will be critical for commercial success, particularly in the U.S., in our view. This will be particularly true if payors move to a more indication-focused regime for reimbursement, something which the president of a major think tank told us is likely in the years ahead (see Disruptive Discussions: Part II, here, for additional details).

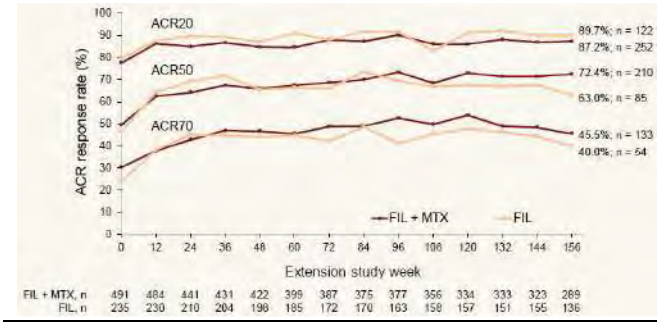
Finally, there is the pricing for filgotinib, which if priced at a discount to Rinvoq could provide an incentive to payors. We discuss our pricing assumptions in greater detail later on in this section of this report.

ACR2019 showcased filgotinib's compelling attributes in RA

Galapagos/Gilead maintained a strong presence at ACR2019, including with several abstracts highlighting the robust long-term efficacy, as well as the safety of filgotinib in RA. We think the efficacy data presentation for DARWIN 3 and the pooled safety analysis of FINCH 1-3 in particular highlight the compelling risk-benefit profile of filgotinib 100 mg and 200 mg in RA. Moreover, the persistency of efficacy and the benign safety profile demonstrated in the ACR abstracts could point to potentially fewer drug discontinuations for filgotinib in the real-world setting, in our view. For additional details, refer to Appendix C of our note entitled *Disruptive Discussion Part III: Inflammatory Conditions*.

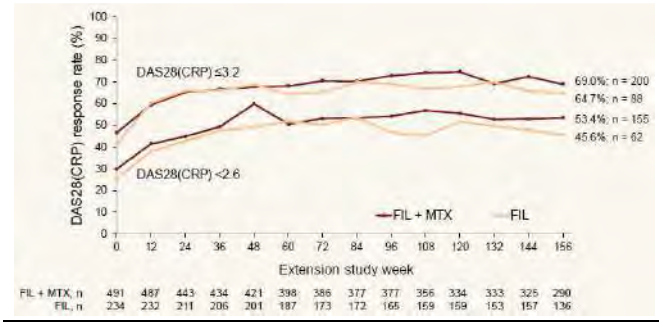
- The DARWIN 3 trial is an ongoing, open-label, long-term extension study of earlier Phase IIb trials evaluating the longer-term safety and efficacy of filgotinib in RA.
- The Phase IIb DARWIN 1 and 2 trials (core studies) evaluated filgotinib with and without methotrexate (MTX), respectively, for 24 weeks in patients with moderate to severely active RA and inadequate response to methotrexate (MTX-IR).
- All patients completing DARWIN 1 and 2 were eligible to roll over to DARWIN 3.
- All patients in DARWIN 3 received filgotinib 200 mg/day with the exception of 15 males in the U.S. who received 100 mg/day.
- The week 156 (extension 156) interim data cutoff was May 30, 2018.
- Exposure was calculated up to the data cutoff date for patients continuing the study at the time of analysis.

Exhibit 11: Robust, durable rates of ACR20/50/70 improvement demonstrated by both filgotinib monotherapy and FIL + MTX



ACR, American College of Rheumatology; FIL, filgotinib; MTX, methotrexate.
Source: ACR

Exhibit 12: Robust, durable rates of disease activity improvement demonstrated by both filgotinib monotherapy and FIL + MTX



DAS28(CRP), Disease Activity Score 28 C-reactive protein; FIL, filgotinib; MTX, methotrexate.
Source: ACR

- The safety and efficacy of FIL has been investigated in the FINCH clinical program that includes four Phase III, randomized, multicenter studies in patients with moderate to severely active RA.
- The studies were designed to characterize the efficacy and safety of FIL in several key patient populations following the typical RA treatment pathway.
- These included: 1) patients who had an inadequate response (IR) to methotrexate (MTX) (FINCH-1); 2) patients with difficult-to-treat RA and an IR to biological disease-modifying antirheumatic drugs (bDMARDs) (FINCH-2); and 3) MTX-naïve patients (FINCH-3).
- Instances of DVT/PE with FIL 200 mg + MTX/csDMARD were less than placebo. No instances of DVT/PE were reported for FIL 200 mg monotherapy (n=210).

Exhibit 13: Incidence of treatment-emergent AEs and all deaths across FINCH 1-3 (weeks 0-24)

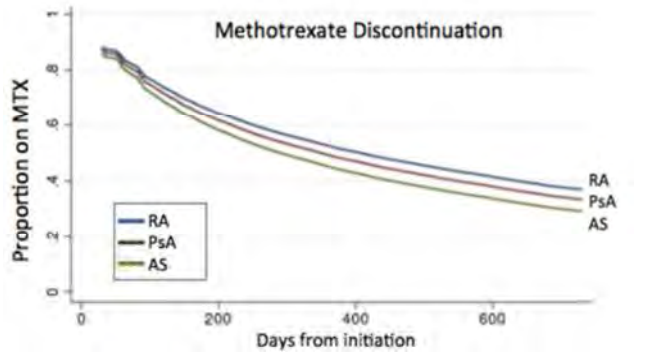
n (%)	Placebo + MTX/ csDMARD N = 1,039	ADA 40 mg + MTX N = 325	FIL 100 mg + MTX/ csDMARD N = 840	FIL 200 mg + MTX/ csDMARD N = 1,038	FIL 200 mg Monotherapy N = 210	FIL Total N = 2,088
Treatment-emergent AE	614 (59.1)	185 (56.9)	527 (62.7)	663 (63.9)	113 (53.8)	1303 (62.4)
Treatment-emergent serious AE	37 (3.6)	14 (4.3)	37 (4.4)	44 (4.2)	10 (4.8)	91 (4.4)
Treatment-emergent AE of interest						
Infectious AE	244 (23.5)	88 (27.1)	229 (27.3)	283 (27.3)	53 (25.2)	565 (27.1)
Serious Infectious AE	10 (1.0)	8 (2.5)	13 (1.5)	13 (1.3)	3 (1.4)	29 (1.4)
Herpes Zoster	4 (0.4)	2 (0.6)	5 (0.6)	6 (0.6)	1 (0.5)	12 (0.6)
Hepatitis B or C	1 (< 0.1)	1 (0.3)	0	2 (0.2)	0	2 (< 0.1)
Opportunistic Infections	0	1 (0.3)	0	1 (< 0.1)	0	1 (< 0.1)
Active TB	0	0	0	0	0	0
MACE*	5 (0.5)	1 (0.3)	2 (0.2)	2 (0.2)	1 (0.5)	5 (0.2)
DVT/PE†	3 (0.3)	0	0	2 (0.2)	0	2 (< 0.1)
Malignancy Excluding NMSC	4 (0.4)	1 (0.3)	1 (0.1)	0	0	1 (< 0.1)
NMSC	0	0	0	1 (< 0.1)	0	1 (< 0.1)
Gastrointestinal Perforations	0	0	0	0	0	0
Treatment-emergent AE leading to premature discontinuation of study drug	29 (2.8)	13 (4.0)	19 (2.3)	34 (3.3)	4 (1.9)	57 (2.7)
Treatment-emergent AE leading to premature discontinuation of study	16 (1.5)	5 (1.5)	13 (1.5)	19 (1.8)	4 (1.9)	36 (1.7)
Death	2 (0.2)	0	1 (0.1)	3 (0.3)	0	4 (0.2)

Rates of cardiovascular and thrombotic events at high dose FIL similar to or less than placebo and ADA

*Note: *Only positively adjudicated MACEs were included; †Unadjudicated events. Adverse events were coded using the Medical Dictionary for Regulatory Activities. All reports of hepatitis B and C occurred in subjects who were at risk and were monitored during the study and none were associated with clinically significant liver enzyme elevation or clinical disease. Opportunistic infections included one case of serious PCP pneumonia (ADA 40 mg + MTX) and one case of non-serious esophageal candidiasis (FIL 200 mg + MTX/csDMARD) ADA, adalimumab; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; DVT, deep vein thrombosis; FIL, filgotinib; MACE, major adverse cardiac event; MTX, methotrexate; NMSC, Nonmelanoma Skin Cancer; PBO, placebo; PE, pulmonary embolism; TB, tuberculosis*
Source: ACR

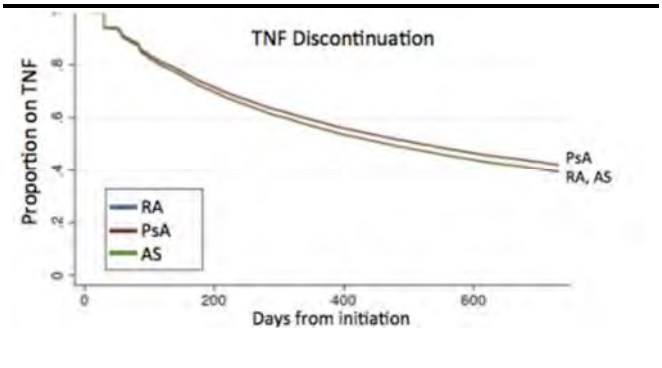
Persistence of efficacy and benign safety profile of filgotinib could predict fewer discontinuations in the real-world setting. We note that RA patients typically discontinue their therapy owing to loss of efficacy and/or safety/tolerability issues or concerns; thus, filgotinib's persistent efficacy and differentiated safety profile could help it stand out. In long-term extension (LTE) studies of bDMARDs in RA patients, the proportion of patients remaining on treatment after five years ranges from 40-66%. In a retrospective study, persistence of RA therapy (2-year drug survival) was higher for TNF inhibitors than csDMARDs at 38.7% vs. 29.5%, respectively. In a longitudinal observational study of patients with RA receiving bDMARDs between 1999 and 2013, discontinuations were mainly due to adverse events (45.8%) and lack of efficacy (40.8%). In 4,967 tofactinib-treated patients entering LTE studies, mean (maximum) treatment duration was 3.5 (9.4) years. Median drug survival was 4.9 years; overall, 50.7% of patients discontinued tofacitinib; of these, 47.2% were owing to adverse events and 7.1% for lack/loss of efficacy. An increased risk of discontinuation was associated with baseline diabetes, hypertension, negative anticyclic citrullinated peptide (anti-CCP), negative rheumatoid factor (RF), and inadequate response to tumor necrosis factor inhibitors (TNFi-IR). See here and here for details.

Exhibit 14: Patients with rheumatic disease tend to discontinue MTX over time



Note: The above chart represents the time to methotrexate discontinuation in rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS).
Source: The Journal of Rheumatology

Exhibit 15: Patients with rheumatic disease tend to discontinue TNFi over time



Note: The above chart represents the time to TNFi discontinuation in rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS).
Source: The Journal of Rheumatology

Filgotinib has also generated compelling data in other indications

Inflammatory bowel disease (IBD) – Phase III data expected in 2020

Filgotinib generated very compelling Phase II data in anti-TNF naïve CD patients. The FITZROY Phase II trial evaluated once-daily filgotinib in 174 patients versus placebo in patients with moderate-to-severely active Crohn's disease (CD) and mucosal ulceration. Patients recruited were either anti-TNF naïve or anti-TNF failures. We note that FITZROY was the first trial in CD to require endoscopic confirmation of lesions at entry, and also to include a placebo control on endoscopy.

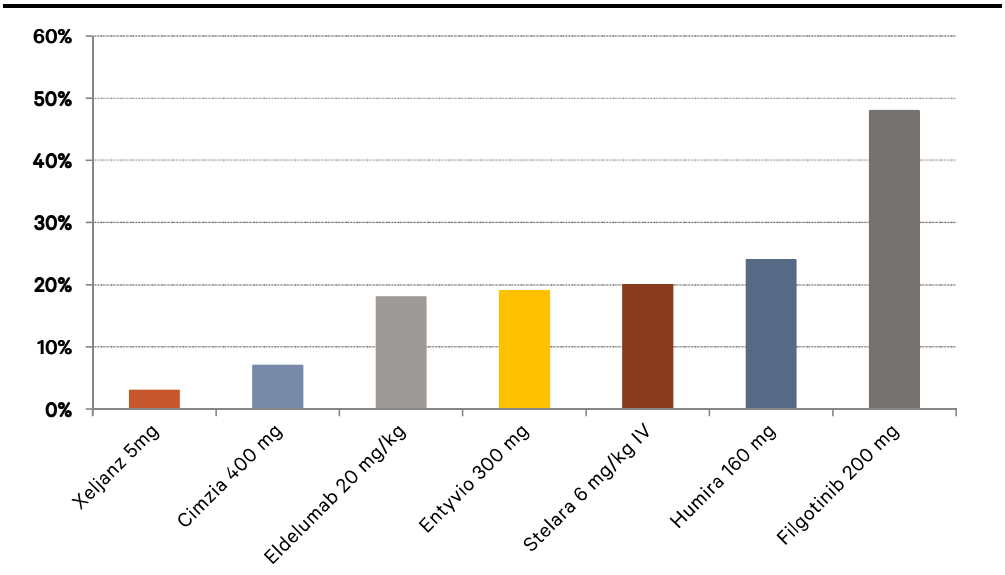
The trial comprised two parts, each of 10 weeks duration: the first part investigated the safety and efficacy of filgotinib 200 mg once daily versus placebo, while the second part of the trial investigated continued treatment through 20 weeks in an observational exploratory design.

The FITZROY trial achieved the primary endpoint of clinical remission at 10 weeks: the percentage of patients overall achieving a Crohn's Disease Activity Index (CDAI) score lower than 150 was statistically significantly higher in patients treated with filgotinib (47%) versus patients receiving placebo (23%). The share of patients achieving 100 points clinical response (60%) also was significant versus those receiving placebo (41%). Clinical responses were maintained from week 10 to week 20. Non-responders in the placebo arm from the first ten weeks received filgotinib 100 mg in the second ten weeks and showed improvement in clinical remission during the second part of the trial.

Overall, in the FITZROY trial at 20 weeks of treatment, filgotinib demonstrated a favorable safety profile consistent with the DARWIN trials in RA. An increase in hemoglobin was also observed in FITZROY, without difference between filgotinib and placebo. No clinically significant changes from baseline in neutrophils or liver function tests were observed.

Exhibit 16: Filgotinib performs very well in anti-TNF naïve patients

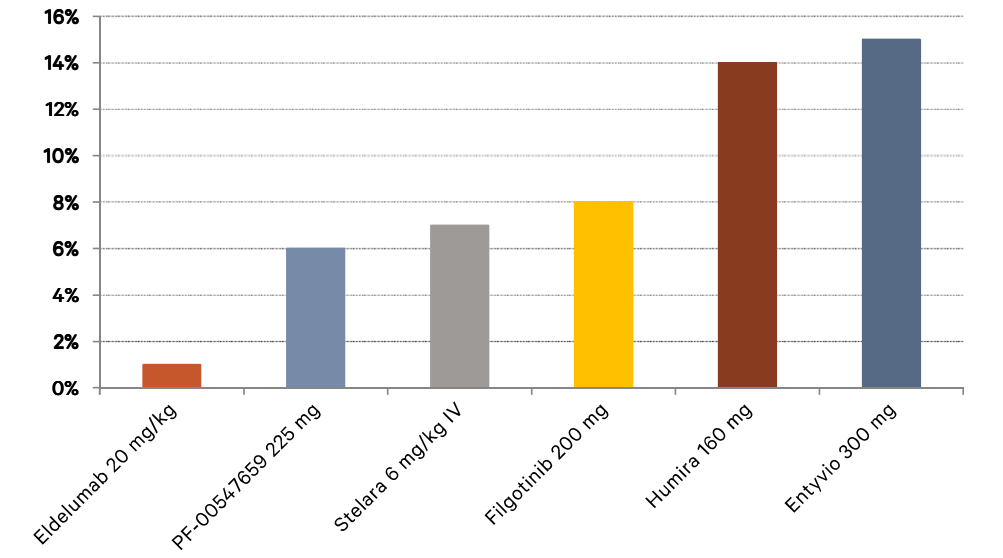
Expressed as % remission, induction study, placebo-adjusted



Source: Company filings, Berenberg Capital Markets

Exhibit 17: Filgotinib's efficacy is comparable to Stelara in patients who failed anti-TNF therapy

Expressed as % remission, induction study, placebo-adjusted



Source: Company filings, Berenberg Capital Markets

Gilead initiated a Phase III trial (DIVERSITY) with filgotinib in CD in November 2016. DIVERSITY will investigate efficacy and safety of 100 mg and 200 mg filgotinib once-daily compared to placebo in patients with moderately to severely active disease, including those with prior antibody therapy failure. Gilead will recruit approximately 1,300 patients from the United States, Europe, Latin America, Canada, and Asia/Pacific regions. Men and women in the DIVERSITY trial will be randomized to receive placebo, 100 mg, or 200 mg filgotinib. In the United States, males may receive 200 mg if they failed at least one anti-TNF and vedolizumab, a monoclonal anti-integrin antibody sold by Takeda. Gilead expects to complete recruitment for DIVERSITY in H220. Refer to details, here.

Gilead initiated the SELECTION Phase IIb/III trial in UC in December 2016. SELECTION investigates efficacy and safety of 100 mg and 200 mg filgotinib once-daily compared to placebo in patients with moderately to severely active disease, including those with prior

antibody therapy failure. Gilead will recruit approximately 1,300 patients from the United States, Europe, Latin America, Canada, and Asia/Pacific regions. SELECTION included a futility analysis, serving as the Phase IIb part of this integrated Phase II/III trial. Men and women in SELECTION will be randomized to receive placebo, 100 mg, or 200 mg filgotinib. In the United States, males may receive 200 mg if they failed at least one anti-TNF and vedolizumab. Refer to details, here.

Filgotinib advanced to Phase III in UC in 2018. On May 30, 2018, Galapagos/Gilead announced that the independent Data Monitoring Committee (DMC) conducted a planned interim futility analysis after 350 patients completed the induction period in the Phase IIb portion of the study. The DMC recommended that the study proceed into Phase III as planned at both the 100 mg and 200 mg once-daily dose level in biologic-experienced and biologic-naïve patients. Galapagos received a $15m payment from Gilead for this progression from Phase II to Phase III in the SELECTION trial. **SELECTION is fully recruited, which implies top-line data should be available around Q220.**

Separately, we note that in March 2017, Gilead initiated a Phase II trial in small bowel CD and a Phase II trial in fistulizing CD. These trials are currently recruiting.

Psoriatic arthritis (PsA) – Phase III study started enrollment in H219

Galapagos/Gilead announced positive Phase II data (EQUATOR) in April 2018. EQUATOR was a multi-center, randomized, double-blind, placebo-controlled trial that assessed the safety and efficacy of filgotinib 200 mg once-daily treatment in adult patients with moderately to severely active PsA. The primary goal of EQUATOR was to evaluate the effect of filgotinib compared to placebo on the signs and symptoms of PsA as assessed by the ACR20 at Week 16. The trial also explored the effects of filgotinib on the skin manifestations (psoriasis), as well as other domains like fingers (dactylitis), tendon insertions (tendinitis), spine involvement (spondylitis), and nail involvement.

Between March 9 and September 27, 2017, 191 patients in eight European countries were screened and 131 were randomly allocated to treatment (65 to filgotinib 200 mg and 66 to placebo); 60 (92%) patients in the filgotinib group and 64 (97%) patients in the placebo group completed the study; five patients (8%) in the filgotinib group and two patients (3%) in the placebo group discontinued treatment.

Filgotinib met the primary endpoint in EQUATOR; 52 (80%) of 65 patients in the filgotinib group and 22 (33%) of 66 in the placebo group achieved ACR20 at week 16 (treatment difference 47%, p<0.0001). In terms of safety, 37 (57%) patients who received filgotinib and 39 (59%) patients who received placebo had at least one treatment-emergent adverse event. Six participants had an event that was grade 3 or worse. The most common events were nasopharyngitis and headache, occurring at similar proportions in each group. One serious treatment-emergent adverse event was reported in each group (pneumonia and hip fracture after a fall), one of which (pneumonia) was fatal in the filgotinib group. The full results were published in *The Lancet*.

Ankylosing spondylitis (AS) – Phase III study start expected H120

Galapagos/Gilead announced positive Phase II data (TORTUGA) in September 2018. TORTUGA was a multi-center, randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of filgotinib in adult patients with moderate to severely active AS. The primary goal of TORTUGA was to evaluate the effect of filgotinib compared to placebo on the signs and symptoms of AS, as assessed by the Ankylosing Spondylitis Disease Activity Score (ASDAS) at Week 12. The trial also explored signs and symptoms of AS, physical function, spinal mobility, enthesitis, spinal and sacroiliac joint inflammation, and safety.

Between March 7, 2017, and July 2, 2018, 263 patients in eight European countries were screened and 116 randomly assigned to filgotinib (n=58) or placebo (n=58); 55 (95%) patients in the filgotinib group and 52 (90%) in the placebo group completed the study; three (5%) patients in the filgotinib group and six (10%) in the placebo group discontinued treatment.

TORTUGA met the primary endpoint; the mean ASDAS change from baseline to week 12 was −1.47 in the filgotinib group and −0.57 in the placebo group (p<0.0001). In addition, approximately 76% of patients who received filgotinib achieved an ASAS20 (Assessment in Ankylosing Spondylitis response, at least 20% improvement), versus 40% of patients who

received placebo (p<0.0001).

Treatment-emergent adverse events were reported in 18 patients in each group, the most common being nasopharyngitis (in two patients in the filgotinib group and in four patients in the placebo group). Treatment-emergent adverse events led to permanent treatment discontinuation in two patients, including a case of grade 3 pneumonia in the filgotinib group and of high creatine kinase in the placebo group. No deaths were reported during the study. The full results were published in *The Lancet*.

Clinician view

Broadly, clinicians we spoke to at ACR and afterward (including one who attended ACR) report to us that they believe the current treatment armamentarium for RA is the strongest it has ever been. Methotrexate (MTX) is the preferred conventional synthetic disease modifying anti-rheumatic drug (csDMARD) for RA. From here, if patients are still demonstrating disease activity, the clinicians move on to the biologic DMARDs (bDMARDS) with the anti-TNF antibodies being preferred, particularly Enbrel (Amgen) and Humira (AbbVie). Some reported to us their desire to move from a csDMARD directly to a JAK inhibitor, typically Xeljanz, with payor hurdles being the primary barrier to more usage; payors may require a patient to fail at least one biologic before covering a JAK inhibitor.

Additional takeaways:

- The JAK inhibitor sessions were among the most well attended of the sessions we went to during ACR2019.
- Few clinicians we spoke to had experience with Rinvoq (AbbVie) though all were curious about it; we were hard pressed to walk to a part of the convention center in Atlanta that did not include a massive wall-to-wall Rinvoq advertisement.
- Clinicians we caught up with afterward and during the poster tours tell us their experience has been mostly positive with the JAK inhibitors in their RA patients.
- At the upper end, some clinicians reported moving more advanced disease stage patients to biologics and JAKs in a 50/50 split.
- The biggest concern regarding the JAK inhibitors is regarding safety, specifically thrombosis and potential cardiovascular disease events, particularly given the impact on cholesterol.
- The topic of JAK specificity continues to be of high interest among rheumatologists; generally, those we spoke to place this in the to-be-determined category; clinicians want to see how their patients respond to the next generation JAKs (Rinvoq and filgotinib) and to see more long-term data before making a final determination.
- Galapagos/Gilead and AbbVie's abstracts regarding the short and long-term safety and efficacy of filgotinib and Rinvoq, respectively, was helpful. However, both assets appear to have a long way to go in the view of many clinicians in terms of distinguishing safety of their JAK1 selective compounds.

Additional details regarding the clinician views on rheumatic diseases can be found in Appendix D of our note entitled: *Disruptive Discussion Part III: Inflammatory Conditions*.

Our view

Filgotinib could generate peak revenues of €4.5bn (or $5bn) in all indications. We think filgotinib in RA will be approved at both doses in major markets; we also are viewing the potential in additional indications incrementally more favorably. As a result, we are now modeling approvals in RA, IBD, AS, and PsA at probabilities of success (POS) of 75-95% (vs. prior 70%-90%); we continue to model additional indications at a 50% POS (unchanged). Overall we view the number of indications as being the most important determinant of success for filgotinib, both in terms of patient population and payor coverage.

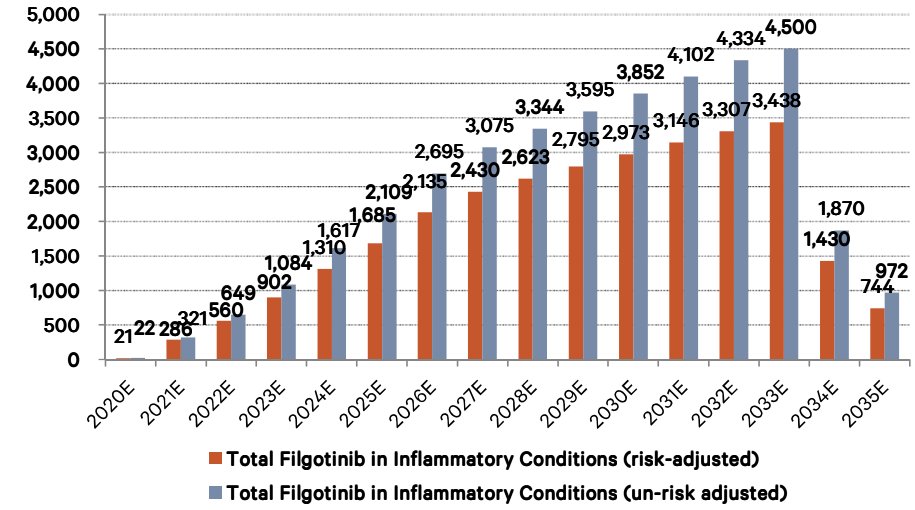
In terms of U.S. pricing at launch in late 2020, we think the Street will be very focused on Gilead's commercial strategy; we are modeling a gross price of $45,000 with a gross-to-net (i.e., GTN, the differential between the gross price and net price, which primarily represents the payments to payors in the form of rebates and discounts) of 25%, implying a net price $33,750 in 2020. This would represent more than a 20% discount to Humira and Rinvoq based on a recently released ICER report (see here).

We think our pricing assumption could be conservative, though with filgotinib being the fourth JAKi on the market in RA, a significant price discount to existing compounds is possible, in our view. We model modest pricing going forward, except in 2023 and 2025 when biosimilars of Humira and generics of Xeljanz could be introduced, respectively. We assume sharper expansions of GTN percentages in those years, something which may not be fully appreciated by the Street, based on consensus estimates for the JAKi and also for the anti-TNFs on the market.

Request our Excel model for the complete details regarding our modeling assumptions.

Exhibit 18: Filgotinib could generate peak sales of €4.5bn in all indications

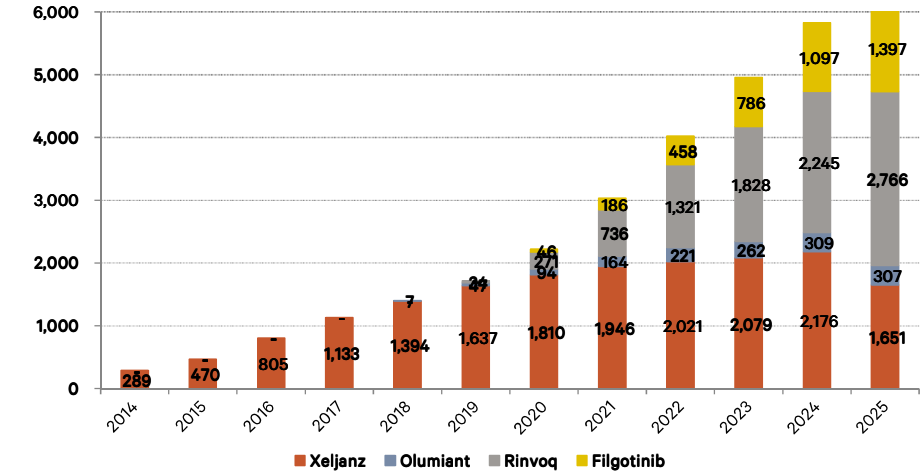
€ in millions



Source: Company filings, BCM estimates

Exhibit 19: By 2025, JAKinibs for inflammation could reach sales of $6bn (or €5.5bn)

$ in millions



Source: Company filings, First Order Analytics, BCM estimates

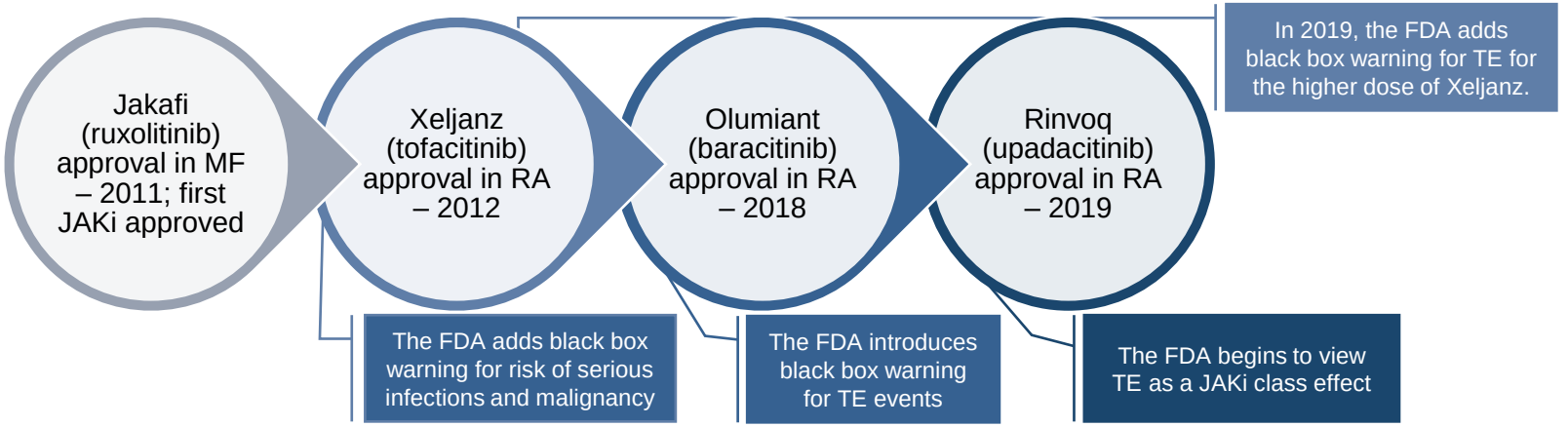
The Evolution of JAK Inhibitor Labeling, Which Includes a Black Box Warning, and What It Could Mean For Filgotinib

Multiple JAKi's Have Had Thromboembolic (TE) Adverse Events And The FDA's View On This Safety Risk Has Evolved Over Time

Stifel Commentary

JAK inhibitors have a history of TE adverse events at higher doses and the FDA's approach to this risk has changed over time – most recently demonstrated by the "class" black box applied to ABBV's upadacitinib (Rinvoq). GLPG believes filgotinib's safety profile is differentiated from competitor profiles, which could be manifested in labeling or approval of a higher dose and offer a commercial competitive advantage. In our KOL checks, physicians have noted comfort with the safety of the JAKi class is growing, and a black box warning wouldn't slow adoption, though a higher approved dose with differentiated efficacy could be a meaningful advantage. We would also note that regulators globally have taken varied approaches (i.e. the same drug can have different labeling between FDA, EMA, Japan).

JAKi Class Approval History



*Our **base case** is that both doses of filgotinib will be approved with a black box warning. We believe that in a **bull case** scenario, filgotinib is approved without a black box at both dose levels after showing a satisfactory benefit-risk profile. Our **bear case** assumes that filgotinib is approved at its lower dose with a black box warning and limited/onerous label or meaningful novel safety concerns.*

Sources: FDA label information, Company information and Stifel Research

STIFEL

The Evolution In The FDA's Labeling For The JAKi Class Drives Our Base Case That Filgotinib Will Receive A Class Black Box Similar To Upadacitinib's

2012 - PFE's Xeljanz (tofacitinib)

XELJANZ® (tofacitinib) tablets, for oral use
XELJANZ® XR (tofacitinib) extended-release tablets, for oral use
Initial U.S. Approval: 2012

WARNING: SERIOUS INFECTIONS AND MALIGNANCY
See full prescribing information for complete boxed warning.

- Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving XELJANZ. (5.1)
- If a serious infection develops, interrupt XELJANZ/XELJANZ XR until the infection is controlled. (5.1)
- Prior to starting XELJANZ/XELJANZ XR, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting XELJANZ/XELJANZ XR. (5.1)
- Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)
- Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications. (5.2)

- PFE's tofacitinib was approved in 2012 for the treatment of RA along with a black box warning for serious infections (tuberculosis and other opportunistic infections) and malignancy (lymphoma).

2018 - LLY's Olumiant (baricitinib)

OLUMIANT (baricitinib) tablets, for oral use
Initial U.S. Approval: 2018

WARNING: SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS
See full prescribing information for complete boxed warning.

- Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving OLUMIANT. (5.1)
- If a serious infection develops, interrupt OLUMIANT until the infection is controlled. (5.1)
- Prior to starting OLUMIANT, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting OLUMIANT. (5.1)
- Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)
- Lymphoma and other malignancies have been observed in patients treated with OLUMIANT. (5.2)
- Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, some fatal, have occurred in patients treated with OLUMIANT. Patients with symptoms of thrombosis should be evaluated promptly. (5.3)

- LLY/INCY's baracitinib was only approved at the lower 2mg dose after an FDA advisory panel voted against the safety profile of the 4mg dose due to serious venous thromboembolic events, which made it on to its label.

2019 - ABBV's Rinvoq (upadacitinib)

RINVOQ™ (upadacitinib) extended-release tablets, for oral use
Initial U.S. Approval: 2019

WARNING: SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS
See full prescribing information for complete boxed warning.

- Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving RINVOQ. (5.1)
- If a serious infection develops, interrupt RINVOQ until the infection is controlled. (5.1)
- Prior to starting RINVOQ, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting RINVOQ. (5.1)
- Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)
- Lymphoma and other malignancies have been observed in patients treated with RINVOQ. (5.2)
- Thrombosis, including deep vein thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated with Janus kinase inhibitors used to treat inflammatory conditions. (5.3)

- ABBV's upadacitinib – approved for RA – received a black box warning for infections, malignancies, and thromboembolic events despite rates in both the placebo-controlled and OLE remaining consistent with the background rate in the RA population. We note the language to include "Janus kinase inhibitors" instead of Rinvoq specifically, highly suggests the FDA views this as a class effect.

Sources: FDA label information, Company information and Stifel Research

STIFEL

In 2017, INCY/LLY Received A CRL For Baracitinib After The 4mg Dose Demonstrated An Increased Risk For TE Versus The 2mg Dose

LLY submits NDA for Olumiant – Jan. 2016

Olumiant receives a CRL – April 2017

The FDA concluded that the benefit-risk assessment of baracitinib 2mg and 4mg was not favorable given the potential serious risk of thrombosis, coupled with the lack of a consistent efficacy advantage of the 4mg dose over the 2mg dose.

Safety Data From The Original Submission

Table 6. Update of VTE (DVT and PE) in Baricitinib Clinical Program in RA

	BARI 4	BARI 2	Placebo
Original Submission, August 10, 2015 Data Lock			
0-16 weeks			
Number of patients	1265	403	892
Total exposure in patient years	387	123	267
Patients with thromboses, n (rate)	5* (1)	0	0
0-52 weeks			
Total exposure in patient years	1695	305	365
Patients with thromboses, n (rate)	9* (0.5)	2 (0.7)	0
> 52 weeks			
Total exposure in patient years	1301	210	NA
Patients with thromboses, n (rate)	8 (0.6)	0	
0-any duration			
Total exposure in patient years	2996	515	NA
Patients with thromboses, n (rate)	17* (0.5)	2 (0.4)	

Efficacy Data Submitted For Approval of Olumiant

Table 10. JADX: Proportion of ACR20 Responders

Week	% Responders (Responders/Total)			Odds Ratio (p-value) (95% CI)		
	BARI 4	BARI 2	Pbo	BARI 4:Pbo	BARI 2:Pbo	BARI4:BARI2
12	62 (140/227)	66 (151/229)	39 (90/228)	2.5 (<.001) (1.7, 3.7)	3.0 (<.001) (2.0, 4.4)	0.8 (.4) (0.6, 1.2)
24	65 (148/227)	61 (140/229)	42 (96/228)	2.6 (<.001) (1.8, 3.9)	2.2 (<.001) (1.5, 3.2)	1.2 (0.3) (0.8, 1.8)

Source: FDA statistical reviewer
Abbreviations: BARI=baricitinib; Pbo=placebo; CI=confidence interval

Table 11. JADW: Proportion of ACR20 Responders

Week	% Responders (Responders/Total)			Odds Ratio (p-value) (95% CI)		
	BARI 4	BARI 2	Pbo	BARI 4:Pbo	BARI 2:Pbo	BARI 4:BARI 2
12	55 (98/177)	49 (85/174)	27 (48/176)	3.4 (<.001) (2.2, 5.4)	2.7 (<.001) (1.7, 4.2)	1.3 (0.3) (0.8, 2)
24	46 (82/177)	45 (78/174)	27 (48/176)	2.4 (<.001) (1.5, 3.7)	2.3 (<.001) (1.5, 3.6)	1.0 (.9) (0.7, 1.6)

Source: FDA statistical reviewer
Abbreviations: BARI=baricitinib; Pbo=placebo; CI=confidence interval

Source: FDA Summary Review for baricitinib, Company information and Stifel Research

STIFEL

The FDA Advisory Panel Ended Up Recommending Approval Of Only The Baricitinib 2mg Dose In Rheumatoid Arthritis And Not The 4mg Due To These Safety Concerns

Stifel Commentary

Although members of the advisory committee agreed the data presented by LLY for baracitinib supported efficacy at both doses, the TE signal at the 4mg dose compared to 2mg led to the recommendation to approve only the 2mg with the inclusion of a black box warning for TE. While the panel also noted uncertainty with regard to TE risk at the 2mg dose due to the limited safety database, the panel highlighted other data pointing to a dose response in terms of its safety profile, which could translate into a lower risk of SAEs of interest, such as serious infection, at lower doses.

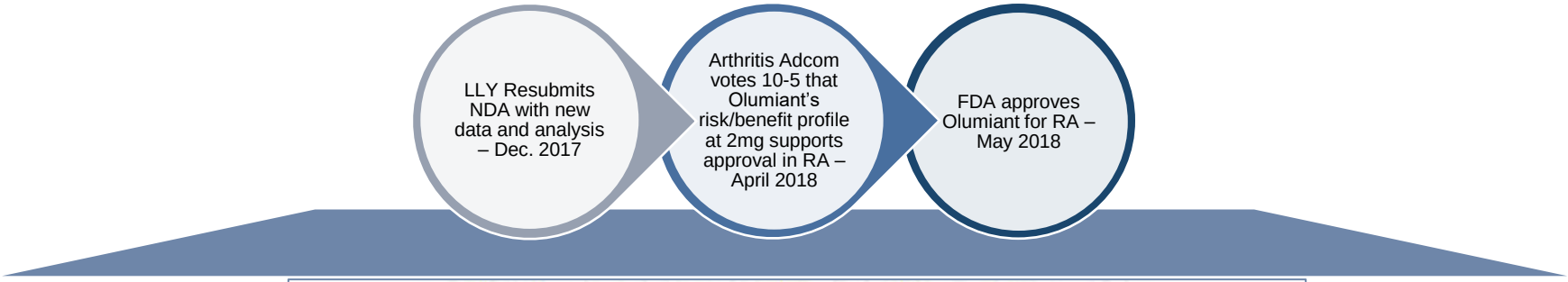


Table 1: Thromboembolic events from the baricitinib safety database update

	Exposure Weeks 0-16			Exposure of any duration	
	Placebo n (IR)	Baricitinib 2mg n (IR)	Baricitinib 4mg n (IR)	Baricitinib 2mg n (IR)	Baricitinib 4mg n (IR)
No. Patients	892	403	1265	929	2717
Patient-Years Exposure	267	123	387	1261	5820
Venous thromboembolism	0	0	5 (1.3)	5 (0.4)	34 (0.6)
Arterial thromboembolism	1 (0.4)	2 (1.6)	2 (0.5)	4 (0.3)	28 (0.5)

IR = Incidence rate per 100 patient-years
Source: FDA Briefing Document Arthritis Advisory Committee Meeting, April 23, 2018, p. 161-162; Information Request Response NDA 207924, March 19, 2018, p. 8.

Source: FDA Summary Review for baricitinib, Company information and Stifel Research

Similarly In 2019, PFE's Tofacitinib Received A Black Box After A Post-Marketing Study Showed The Higher 10mg BID Dose Was Associated With TE and All-Cause Death

Stifel Commentary

A post-marketing study in RA evaluating tofacitinib 5mg BID and 10mg BID compared to anti-TNF therapy demonstrated an increase rate of blood clots (19/3,884 patient years in the 10mg BID arm vs. 3/3,982 patient years for anti-TNF therapy and death (45/3,884 patient in the 10mg BID arm vs. 25/3,982 patient years for anti-TNF therapy). The DSMB advised PFE to transition all patients to 5mg BID.

Boxed Warning About Increased Risk Of Thrombosis And Death With Higher Dose Of Xeljanz In RA And Ulcerative Colitis

[7-26-2019] The U.S. Food and Drug Administration has approved new warnings about an increased risk of blood clots and of death with the 10 mg twice daily dose of tofacitinib (Xeljanz, Xeljanz XR), which is used in patients with ulcerative colitis. In addition, the approved use of tofacitinib for ulcerative colitis will be limited to certain patients who are not treated effectively or who experience severe side effects with certain other medicines. We approved these changes, including adding our most prominent *Boxed Warning*, after reviewing interim data from an ongoing safety clinical trial of tofacitinib in patients with rheumatoid arthritis (RA) that examined a lower and this higher dose of the medicine.

The 10 mg twice daily dose of tofacitinib is not approved for RA or psoriatic arthritis (PsA). This dose is only approved for ulcerative colitis for initial treatment and for long-term use in limited situations. While the increased risks of blood clots and of death were seen in patients taking this dose for RA, these risks may also apply to those taking tofacitinib for ulcerative colitis.

In 2019, the FDA added a new warning for the risk of blood clots and death for the 10mg BID dose of tofacitinib.

Source: FDA label information, Company information and Stifel Research

STIFEL

While Upadacitinib's Safety Was Clean, The FDA Only Approved The Lower Dose Due To Concerns About The Risk-Benefit Of Increasing JAKi Doses

- Recall, upadacitinib and filgotinib are similar in that they are both JAK1 specific and thereby should have improved safety.
- Data from five Phase 3 studies were submitted for upadacitinib's approval, which demonstrated ample evidence of efficacy for both the 15mg and 30mg doses.
- However, there was a minimal incremental benefit – in terms of efficacy – between the 15mg and 30mg doses.
- In short-term controlled studies, upadacitinib did not show higher incidence rates of venous TE compared to placebo, methotrexate, or adalimumab. However, the FDA noted that the short placebo-controlled period of the study limited definitive conclusions regarding the risks of TE event with upadacitinib.
- Long-term venous TE event data with upadacitinib did not show a dose-dependent relationship between upadacitinib treatment and venous TE.

In the upadacitinib summary review, the FDA first outlined its view of thrombosis as a JAKi class effect and determined that: "Given that two JAK inhibitor programs have identified thrombosis as a safety signal, thrombosis is now considered a class safety issue and the upadacitinib product label will include a Boxed Warning regarding VTE." In addition, the FDA concluded that the small incremental benefit of the 30mg dose does not outweigh the dose-related safety risks with the 30mg dose of upadacitinib.

Efficacy Data Of Phase 3 Studies With Upadacitinib In RA

Treatment Arm	N	Count(%)[1]	Diff (%) [95 % CI]; P-value[2]
MTX Add on Studies[3]			
M13-542			
Placebo	169	48 (28%)	
UPA 15 mg QD	164	106 (65%)	36.2% (26.2% - 46.2%); <0.001
UPA 30 mg QD	165	93 (56%)	28.0% (17.8% - 38.1%); <0.001
M13-549			
Placebo	221	79 (36%)	
UPA 15 mg QD	221	141 (64%)	28.1% (19.1% - 37.0%); <0.001
UPA 30 mg QD	219	145 (66%)	30.5% (21.6% - 39.4%); <0.001
M14-465			
Placebo	651	237 (36%)	
UPA 15 mg QD	651	459 (71%)	34.1% (29.0% - 39.2%); <0.001
ADA 40 mg EOW	327	206 (63%)	26.6% (20.2% - 33.0%); <0.001
MTX Monotherapy Studies[3]			
M15-555			
MTX	216	89 (41%)	
UPA 15 mg QD	217	147 (68%)	26.5% (17.5% - 35.6%); <0.001
UPA 30 mg QD	215	153 (71%)	30.0% (21.0% - 38.9%); <0.001
M13-545 (ACR50)			
MTX	314	89 (28%)	
UPA 15 mg QD	317	165 (52%)	23.7% (16.3% - 31.1%); <0.001
UPA 30 mg QD	314	177 (56%)	28.0% (20.6% - 35.4%); <0.001

Long-term Data For VTEs – Pooled Data Across Controlled Long-term Periods Of The Phase 3 Studies

	MTX[a] (N=314) n/PY (n/100 PY)	ADA [b] (N=579) n/PY (n/100 PY)	All UPA 15 mg [c] (N=2630) n/PY (n/100 PY)	Any UPA 15 mg [d] (N=1213) n/PY (n/100 PY)	Any UPA 30 mg [d] (N=1204) n/PY (n/100 PY)
VTE	2/314 (0.6)	5/468 (1.1)	16/2653 (0.6)	12/1409 (0.9)	5/1362 (0.3)

Source: Genovese, M.C. et al. 2018 Jun 23;391(10139):2513-2524, Burmester, G.R. et al. 2018. Jun 23;391(10139):2503-2512, FDA Summary Review for upadacitinib and Stifel Research

STIFEL

With That Said, The Safety Profile Of Both The 100mg And The 200mg Doses Of Filgotinib Look Good Compared To Other JAKs – But Will It Be Enough?

Stifel Commentary

The fact the FDA issued a black box warning for upadacitinib in RA despite demonstrating VTE events similar to the background rate in the RA population, may be a harbinger for filgotinib. Compared to its peers, filgotinib dosed between 50-200mg demonstrated lower rates of serious infection, deep vein thrombosis/pulmonary embolism events (DVT/PE), and deaths. Moreover, data from the FINCH studies (100-200mg) at 24 weeks, demonstrate low rates of both DVT and death compared to placebo/methotrexate and adalimumab, and also compares favorably to the safety data from its peers in the JAK class.

DARWIN3 Long Term Safety Data In Comparison To Peers

Event per 100 PYE	filgotinib 50-200 mg	baricitinib 2 and 4 mg QD	tofacitinib 5 mg BID	upadacitinib 6 and 12 mg BID	tocilizumab 4 and 8 mg/kg	adalimumab
Patient year exp.	2,203	6,637	5,278	725	14,994	23,943
Serious infection	1.2	2.9	2.4	2.3	4.5	4.6
herpes zoster	1.5	3.2	3.8	3.7	ND	ND
DVT/PE	2/2,203 0.1	31/6,754 0.5	3/1,849 0.2	5/725 0.7	ND	ND
Deaths	0.2	0.3	0.6	0.3	0.6	0.8
Malignancy excluding NMSC	0.5	-	-	-	-	-
MACE	0.1	-	-	-	-	-
Source	DARWIN3 wk156	Genovese *et al* ACR2017	Wollenhaupt ACR 2017	Genovese ACR2017	Genovese ACR 2012	Burmester 2011

FINCH Safety Data Up To Week 24

N (%)	PBO/MTX N=1039	ADA 40 mg EOW N=105	FIL 100 mg + MTX/cDMARDs N=840	FIL 200 mg + MTX/cDMARDs N=1038	FIL 200 mg monotherapy N=210	FIL total N=2088
serious infection	10 (1.0)	8 (2.5)	13 (1.5)	13 (1.3)	3 (1.4)	29 (1.4)
herpes zoster	4 (0.4)	2 (0.6)	5 (0.6)	6 (0.6)	1 (0.5)	12 (0.6)
DVT/PE	3 (0.3)	0 (0)	0 (0)	1 (0.2)*	0 (0)	1 (<0.1)
deaths	2 (0.2)	0 (0)	1 (0.1)	3 (0.3)	0 (0)	4 (0.2)
malignancy excl. NMSC	4 (0.4)	1 (0.3)	1 (0.1)	0 (0)	0 (0)	1 (<0.1)
MACE	5 (0.5)	1 (0.3)	2 (0.2)	2 (0.2)	1 (0.5)	5 (0.2)

GLPG will likely highlight these data and also argue that filgotinib's specificity for JAK1 makes it distinct from others in the class which could lead to differences in label language.

Source: Company information and Stifel Research

STIFEL

Could The Risk Of Testicular Toxicity Also Make The Filgotinib Label In Rheumatoid Arthritis?

- One point of concern for investors has been the potential for language in filgotinib's label warning for a risk of testicular toxicity. This signal was picked up in pre-clinical animal models and appeared to be dose dependent. While there has been no specific cases to-date in GLPG's human clinical trials, there is still not sufficient evidence to make a call on this.
- We think this concern is especially relevant for two reasons: (1) in ulcerative colitis, patients tend to be younger compared to the older population in RA and the higher 200mg dose performed the best in the recent Phase 2 ulcerative colitis study; (2) the testicular toxicity was seen at higher doses and could be another reason for the FDA to only approve the 100mg dose of filgotinib.
- To flesh out this signal, GILD/GLPG is conducting the MANTA (ulcerative colitis) - and MANTA-RAy (in rheumatoid arthritis) studies to evaluate testicular toxicity in adult males treated with filgotinib.
- We think it is unlikely the FDA will require data from the MANTA/MANTA-RAy studies, which were expected to read out in early 2021 but have been impacted by COVID19, before approving filgotinib in RA but its technically possible. Additionally, if it is approved, it is possible the FDA could add language on filgotinib's label warning of the potential for testicular toxicity.

Stifel Commentary

We think if the FDA requires the data from the MANTA/MANTA-RAy studies resulting in a CRL for filgotinib, it could push out a filgotinib launch in RA to late 2021 or 2022 depending on the delay from COVID19 and review timelines. If it is approved with specific label language for testicular toxicity before the read out of the MANTA/MANTA-RAy studies, this could lead to less uptake in the early part of launch until the read out of the studies.

Source: Company information, clinicaltrial.gov and Stifel Research

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