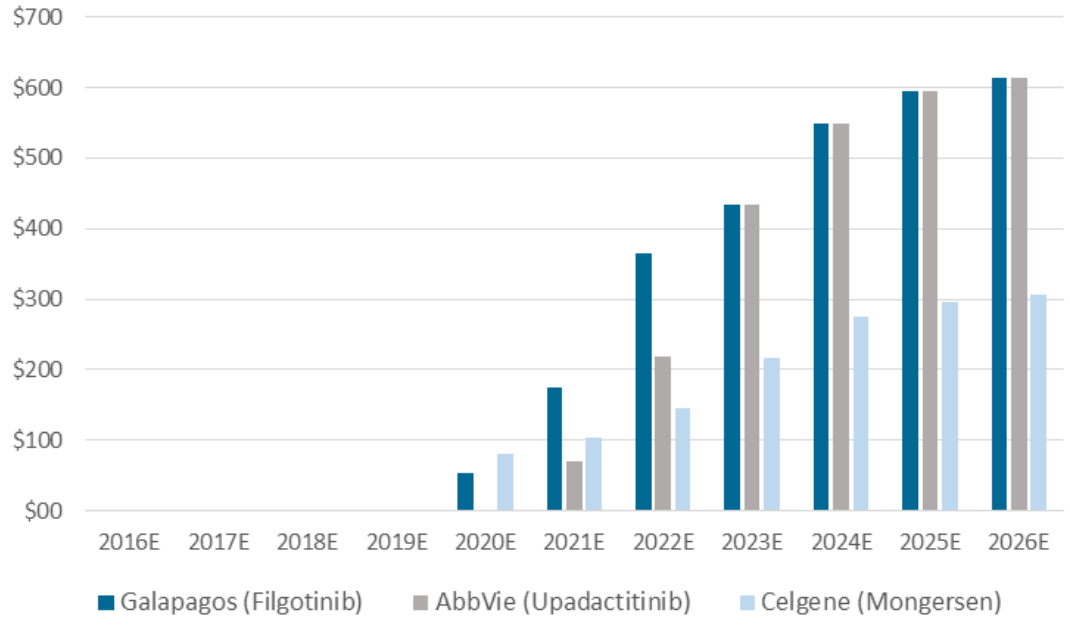
Crohn's is a Leading Opportunity for Filgotinib

Filgotinib is ahead of upadacitinib on a development timeline for Crohn's Disease (CD), with a pivotal read-out likely during 2019, versus a pivotal dataset from upadacitinib during 2020 at the earliest (Phase 3 studies have not yet been initiated). The recent Phase 2 dataset for upadacitinib within the moderate to severe Crohn's disease population has increased the competitive pressure on filgotinib, and the respective datasets of FITZROY (filgotinib) and CELEST (upadacitinib) seem to directionally support upadacitinib as the better drug within Crohn's, but a Completer's Analysis makes any superiority less clear. Phase 2 data for mongersen has been reported, but the data set appears far less robust relative to filgotinib and upadacitinib. **We currently forecast filgotinib and upadacitinib both reaching ~$600mm of sales within Crohn's Disease by 2026, with mongersen trailing at ~$300mm (Figure 18).**

Figure 18. Global sales of filgotinib in Crohn's Disease are expected to reach ~$600mm by 2026



Source: Company Reports, BTIG Research Estimates, June 2017

Our current CD timeline is for FDA approval of filgotinib during 2H2020, which may coincide with mongersen's approval. The first patient in filgotinib's pivotal phase 3 study (DIVERSITY) was dosed during November 2016, while the first patient for mongersen's pivotal studies (REVOLVE AND DEFINE) was dosed during June 2016. Although GLPG management has not disclosed a timeline for the data readout for filgotinib, we would expect to have a readout during 2019.

Celgene's (CELG, Buy, $138 PT) management has guided towards a data readout for mongersen during 2018. Mongersen's full-data readout and NDA may ultimately precede that of filgotinib's, but Gilead does have a priority review voucher that could be used to result in a similar approval time. Phase 2 results for upadacitinib in Crohn's were recently announced, supporting initiation of a Phase 3 trial, which is expected to start during 4H2017.

Our current timeline estimates approval for both filgotinib and mongersen during 2020, but with a ~12-month later approval for upadacitinib (Figure 19). We have also noted estimated approval dates for two other competing drugs that are further behind in clinical development (Ozanimod and SHP647), as their eventual approval could also affect our sales estimates.

Figure 19. FDA approval of filgotinib in Crohn's could occur during 2H2020

Drug	Manufacturer	Target	Current Phase	Data Readout	Approval	Delivery	Frequenc
Filgotinib	**Galapagos/Gilead**	**JAK 1**	**3**	**1Q2019**	**2H2020**	**Oral**	**QD**
Upadacitinib	AbbVie	JAK 1	2	1H2017	2H2021	Oral	QD/BID
Mongersen	Celgene	Smad7	3	YE2018	2H2020	Oral	QD
Ozanimod	Celgene	S1-P	2	2H2017	2H2021	Oral	QD
SHP647	Shire	MAdCAM-1	2	-	-	SC	Q4W

Source: Company Reports, BTIG Research Estimates, June 2017

Current Data is Supportive of Filgotinib's Efficacy in Crohn's

We have accounted for greater maximum penetration within the anti-TNF non-responders versus the overall moderate-severe patient population (22% vs 16%) (Figure 20), which is supported by the sales trends of the currently marketed IBD drug, vendolizumab. Also, as presented at the 2017 ECCO conference, a majority of anti-TNF-naive patients for the FITZROY study were recruited in Eastern Europe relative to anti-TNF non-responder patients in the US and Western Europe (UK, Germany, etc.), so we think that it is likely for a majority of sales within the US and Western Europe to be based upon penetration of the non-responder population. **However, positive data from the pivotal trials expected during 2019 could further support clinical use of filgotinib within the anti-TNF naïve, and the anti-TNF intolerant patient populations.**

Figure 20. Opportunity for greater penetration within the anti-TNF non-responder patient population

Crohn's Disease	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E
# of Moderate to Severe Crohn's Patients (TNF-Non responders	0	0	1305	4017	6847	10840	12879	13162	13452
% Patients Treated	0%	0%	2%	7%	12%	19%	22%	22%	22%
# of Moderate to Severe Crohn's Patients (TNF-Experienced)	0	0	2453	6025	14383	19936	25725	28499	29126
% Patients Treated	0%	0%	2%	4%	9%	12%	15%	16%	16%

Source: Company Reports, BTIG Research Estimates, June 2017

The induction of remission rates achieved within moderate to severe Crohn's patients' naïve or intolerant to anti-TNFs may prove highly competitive (Figure 21). Patients taking 200 mg of filgotinib within the FITZROY study achieved a ~60% (Δ47% vs PBO) remission rate, making it highly competitive relative to marketed drugs like ustekinumab (40%, Δ21% vs PBO), vendolizumab (35%, Δ19% vs PBO), and adalimumab (36%, Δ24% vs PBO).

In a Phase II study of patients taking mongersen (160mg for 2 weeks) there was no breakdown of the response based on prior anti-TNF use. Overall, 72% (Δ58% vs PBO) of all patients achieved clinical remission, which is higher than that observed with filgotinib, but this was within a more moderate patient population (Figure 21). A Phase 2b exploratory/non-placebo controlled study evaluating mongersen in a more comparable patient population (mean CDAI ~294 vs ~243 in the previous study), showed an overall lower remission rate of 48% at 12 weeks. Although a lack of a data on the split between anti-TNF experienced and naïve patients was not provided, we would estimate the remission rates in the naïve population to be ~65% (n=21), which could be in line with filgotinib depending on the placebo remission rate. The phase 2 study for upadacitinib only included 4% of patients intolerant or naïve to anti-TNFs, but we would assume that the drug would also be highly efficacious in this patient population making it another strong competitor to filgotinib.

Filgotinib's efficacy (Δ8% remission vs PBO) in anti-TNF experienced/non-responsive patients is low, but the results are promising (Figure 21). In FITZROY, anti-TNF experienced patients taking filgotinib achieved a 37% remission rate (Δ8% vs PBO). The remission rate is lower than the rate for marketed drugs like vendolizumab (Δ14% vs PBO) and adalimumab (Δ14% vs PBO), but not ustekinumab (Δ5% vs PBO). This low rate of remission could have been a result of the high rate of remission in the placebo arm, and the study was also under powered to show differentiation between anti-TNF naïve and anti-TNF experienced patients.

No comparable data set is available for mongersen, since the data reported from the Phase II study did not differentiate between anti-TNF experienced and naïve patients. Although the non-placebo controlled exploratory Phase 2b study for mongersen did show remission rates in the anti-TNF experienced patients, the results were pooled from a variety of dosing regimens making it difficult to make a valid comparison. However, our calculations suggest a likely response rate of ~32% (n=21) similar to filgotinib's, although as stated above, the significance of the results could swing widely depending the remission rates in the placebo arm. Upadacitinib Phase 2 data (CELEST) did show a significant remission rate (Δ15% vs PBO) in this patient population, but this was after dosing for 6 weeks longer (16 weeks). The results could be very competitive since it was achieved in the difficult to treat, anti-TNF patient population with rapid tapering of corticosteroids.

Evidence of endoscopic responses further supports filgotinib's efficacy, and a potential role of JAK inhibition in Crohn's. In patients taking filgotinib, there was a 50% endoscopic response observed in 25% of patients (Δ11% vs PBO) at 10 weeks (Figure 21). The data is generally in line with what was achieved in clinical trials following continuous dosing of adalimumab at 4 weeks (Δ11% vs PBO) and at 52 weeks (Δ11% vs PBO), supporting filgotinib's efficacy. Vendolizumab was approved without data on endoscopic outcomes, because the evaluation is tedious and slow, however with phase 3 data from competing drugs on the horizon, Takeda's (TKPYY, Not Rated) management has decided to evaluate endoscopic outcomes since evidence of long term therapeutic benefits could sway payers in the face of competitive therapies. Preliminary data presented at 2017 ECCO meeting showed that 40% of patients achieved a 50% endoscopic response at week 16, and presentations at the 2017 DDW showed trends toward a decline in surgical rates following long term use of vendolizumab.

33% (Δ30% vs PBO) of patients taking upadacitinib achieved a 50% endoscopic response, generally in line with filgotinib, but this was in the difficult to treat anti-TNF experienced patient population. There is no placebo controlled dataset for mongersen since the study excluded patients with lesions in the proximal, transverse, and left colon or due to the complexity of acquisition of endoscopic data. However, the smaller exploratory Phase 1b/non-placebo controlled study showed 30% of patients treated with mongersen achieved a 50% endoscopic response. Again, without a control arm, it is difficult to determine the true effect, and its competitive positioning. Evidence of mucosal healing is certainly going to be a strong marker for differentiator in the in the view of payers, and we think the hurdle for newer drugs will be high in terms of showing better long-term efficacy.

Figure 21. Filgotinib induces remission in anti-TNF naïve and non-responder patients (Treatment vs PBO)

	Filgotinib (100-200mg QD Oral / 10 wks) FITZROY N = 128	Upadacitinib (24mg BID Oral/ 16 wks) CELEST N = 36	Mongersen (160mg QD Oral/4 wks) Phase II N = 43	Ustekinumab (6mg/kg IV /8 wks) UNITI-1,UNITI-2 N=	Vendolizumab (300mg IV/10 wks) GEMINI III N=	Adalimumab (160mg SC/4 wks) CLASSIC I, CLASSIC II N=
	JAK1	JAK1	Smad7	IL-12/23p40	$\alpha_4\beta_7$ integrin	TNF
CDAI remission (CDAI < 150)	47% vs 23%	-	72% vs 14%	20% vs 7%	28% vs 13%	-
Anti- TNF naive	60% vs 13%	-	-	40% vs 19%	35% vs 16%	36% vs 12%¥
Anti-TNF experienced	37% vs 29%	31% vs 15%	-	20% vs 15%	26% vs 12%	21% vs 7%¤
CDAI response (100-point reduction in CDAI)	59% vs 41%	-	72% vs 17%	33% vs 21%ɵ	47% vs 24%	-
Anti- TNF naive	67% vs 44%		-	47% vs 29%	51% vs 22%	50% vs 25%¥
Anti-TNF experienced	54% vs 39%	56% vs 16%	-	66% vs 44%	46% vs 24%	52% vs 34%¤
50% endoscopic response	25% vs 14%	-	-	-	-	-
Anti- TNF naive	28% vs 19%	-	-	-	-	-
Anti-TNF experienced	23% vs 11%	33% vs 3%	-	-	40% vs - *	-

Tables includes responses from the highest dose used vs placebo for the induction phase of the Studies at the Time-points Shown for the Various Dosages *Sourced from 2017 ECCO Abstract (Pauwel R.W.M. et al) ¥ Sourced from CLASSIC-I Trial in CD, and ¤ Sourced from GAIN Trial § Response based on >70 point reduction in CDAI, ɵ Response evaluated at 6 weeks

Source: Vermeire S. et al. Lancet. 2017; 389(10066):266-275, S Ardizzone et al. Therap Adv Gastroenterol. 2016 Jul;9(4):527-32, Sands BE et al. Gastroenterology. 2014 Sep;147(3):618-627, Pauwel RWM et al., ECCO. 2017; Clinical: Therapy and observation, Monteleone G. et al. N Engl J Med. 2015 Mar 19;372(12):1104-13, Cassinotti et al. Biologics. 2008 Dec; 2(4): 763–777

Long-term anti-TNF studies suggest that the current remission rates achieved with filgotinib during the induction phase could be durable (Figure 22). A meta-analysis of retrospective and prospective trials on long-term vs short-term study outcomes for mostly adalimumab treated patients following infliximab failure showed that remission rates do not decline significantly with time.[2] Following primary failure of infliximab, the 30% remission rate achieved in the short-term was sustained in the long-term (28%). Actually, in patients intolerant to infliximab, a mean increase was observed from 60% to 83% in the short to long-term (Figure 22). There are clearly a lot of factors at play, but these results suggest that current remission rates may likely be durable. This is encouraging as the results of the long-term studies could significantly affect the estimated PPPY of $38K, which is based upon drug usage as chronic maintenance therapy, and not only for induction, which is typically short (approximately, 3 months or 12 weeks). Based on these results from the meta-analysis, we would think the long-term maintenance efficacy hurdle for the new oral class would be ≥60% in anti-TNF native patients, ≥ 30% in patients with a primary failure, and ≥40% in patients with a secondary failure.

[2] Gisbert JP et al. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. Aliment Pharmacol Ther. 2015 Apr;41(7):613-23

Figure 22. Minimal decline in long-term versus short-term remission rates

		Overall	Short Term 4 – 8 weeks	Medium Term 9 - 40 weeks	Long Term 41 – 52 weeks
Primary Failure	Remission	30%	18%	30%	28%
	Response	53%	35%	67%	42%
Secondary Failure	Remission	45%	41%	38%	60%
	Response	82%	66%	42%	--
Intolerance	Remission	61%	50%	60%	83%
	Response	-	70%	77%	--

Source: Gisbert JP et al. Aliment Pharmacol Ther. 2015 Apr;41(7):613-23

Safety Profile Could Support Adoption Relative to First Generation JAKs

Filgotinib's selectivity for Jak1 could potentially allow it to circumvent some of the safety risks associated with broad JAK inhibition.[3] Over 1100 patient years of safety data based on studies across multiple clinical programs, including Phase 1 data in Osteoarthritis is now available. With one of the major concerns of JAK inhibition being infections as well as alterations to the kidneys, liver, and hemoglobin, it is encouraging that filgotinib's impact is relatively limited (Figure 23). These safety results have been reported generally following concomitant corticosteroid and antibiotic use, but in the absence of immunomodulators (e.g. thiopurines, methotrexate, etc.). **We think that the high selectivity for Jak1 could allow for combination therapies without significantly increasing the safety risk.**

Figure 23. Selectivity for Jak1 allows for potentially improved safety profile

	Filgotinib	Baricitinib	Tofacitinib
Target	JAK1	JAK1,JAK2	JAK1,JAK3
Lymphocyte number	↔	↔	↓
NK cell number	↔	↓	↓
Neutrophil number	↓	↓	↓
Haemoglobin level	↑	↓	↑
Platelet count	↓	↔	↓
Liver Transaminase	↓	↑	↑
Creatinine Phosphokinase	-	↑	↑
Creatinine	↑	↑	↑
HDL level	↑	↑	↑
LDL level	↔	↑	↑

General Reported Trends in Crohn's: In some cases, changes were seen at only certain doses, for certain studies with varying sample sizes. ↑: increase ↓: decrease ↔: no change

Source: Wintrop KL et al. Journal of Rhematology. Nat Rev Rheumatol. 2017 Apr;13(4):234-243

[3] Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol. 2017 Apr;13(4):234-243.

Incidence rates of serious AEs are lower than upadacitinib, with a low rate of discontinuation that could generally be on par with 2nd generation biologics. Following 10 weeks of treatment, patients treated with filgotinib had common infections including urinary tract infections, nasopharyngitis, pneumonia, herpes zoster, and oral candiditis. Infection rates was 23%(Δ +7%), which was lower than upadacitinib 50%(Δ +18%) (Figure 24). Although these rates were higher than that reported for vendolizumab (Δ +2%) and ustekinumab (Δ +2%), there were no TAEs that lead to a permanent stop in therapy. This could allow filgotinib to remain competitive in earlier lines of therapy.

Figure 24. Low rate of study discontinuations could allow filgotinib to remain competitive

	Filgotinib (200mg QD Oral /10 wks) FITZROY N = 128	Upadacitinib (24mg BID Oral/16 wks) CELEST N = 36	Mongersen (160mg QD Oral/4 wks) Phase II N = 43	Ustekinumab (6mg/kg/8 wks) UNITI-1, UNITI-2	Vendolizumab (300mg/10 wks) GEMINI III	Adalimumab¥ (160mg/4 wks) CLASSIC I, CLASSIC II
Target	JAK1	JAK1	Smad7	IL-12/23p40	$\alpha_4\beta_7$ integrin	TNF
Adverse Events (Any)	74% vs 59%	83% vs 73%	49% vs 67%	65% vs 69%	56% vs 60%	21% vs 16%
Serious Adverse Events	9% vs 0%	8% vs 5%	2% vs 2%	7% vs 6%	6% vs 8%	4% vs 4%
Infections	30% vs 23%	50% vs 32%	-	25% vs 23%	19% vs 17%	21 vs 16%
Serious Infections	0% vs 0%	3% vs 0%	-	2% vs 1%	<1% vs 0%	3% vs 0%
Discontinuations	0% vs 0%	8% vs 14%	-		2% vs 2%	0% vs 3%

Tables includes responses from the highest dose used vs placebo for the induction phase of the Studies at the Time-points Shown for the Various Dosages. AEs are for the

Source: Source: Vermeire S. et al. Lancet. 2017; 389(10066):266-275, S Ardizzone et al. Therap Adv Gastroenterol. 2016 Jul;9(4):527-32, Sands BE et al. Gastroenterology. 2014 Sep;147(3):618-627, Pauwel RWM et al., ECCO. 2017; Clinical: Therapy and observation, Monteleone G. et al. N Engl J Med. 2015 Mar 19;372(12):1104-13, Cassinotti et al. Biologics. 2008 Dec; 2(4): 763–777.

Lab results also showed minimization in the percent change from baseline (%CFB) in some key risk indicators with time on filgotinib: Patients treated for 10 weeks with 200 mg filgotinib vs placebo had higher ALT (Δ +17%) levels relative to baseline, but lower ALT (Δ -17%) levels relative to patients treated for 20 weeks. This would suggest a potential minimization of the increase with time on filgotinib. Similarly, changes in CD4/CD8 ratio and the number of NK cells at 10 versus 20 weeks also showed an increase of Δ +7% and Δ +17%, respectively which may decrease susceptibility to infections. Mean changes in hemoglobin (Δ -4%), platelet (Δ +1%), and lymphocyte (Δ -3%) counts were also small suggesting a minimal impact on the liver and pancreas, and immune system. The analysis was done in a re-randomized patient population so the same group of patients were not evaluated at both time points, however since we have used mean parameters from a sample size of 20 – 77 patients, we think these results are still informative.