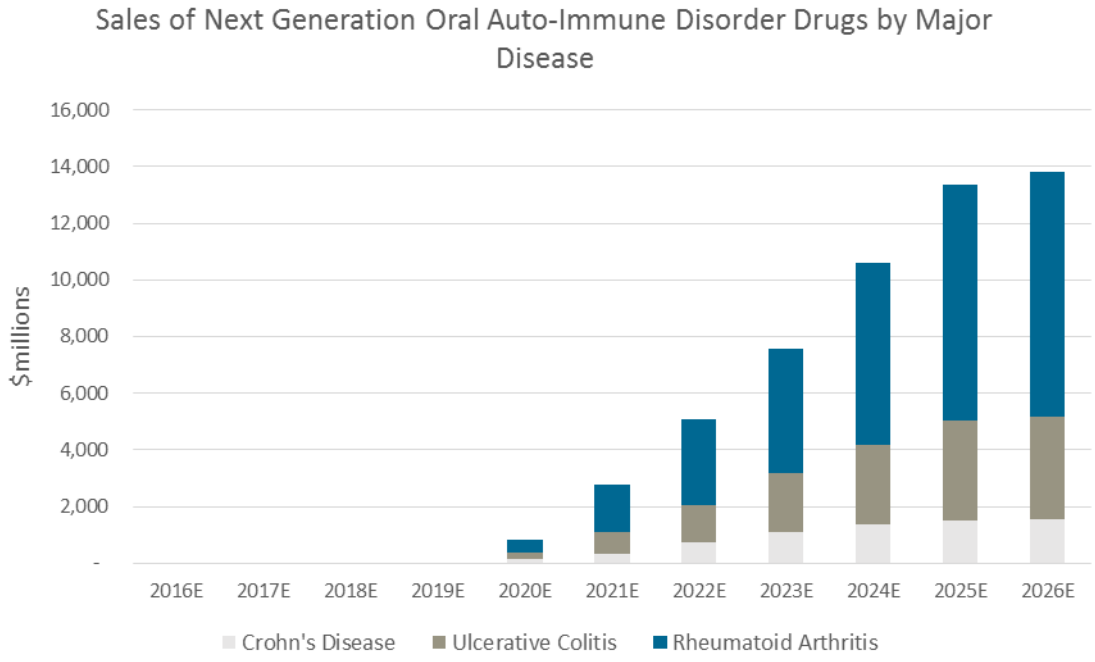
Consensus Estimates Underestimate the Next Gen JAKs

Filgotinib and upadacitinib are both selective JAK-1 inhibitors (relative to JAK-2 and JAK-3), and have demonstrated good clinical results to-date while avoiding toxicity that has limited use of earlier JAK-inhibitors such as tofacitinib. We find it difficult to delineate whether one drug is demonstrably better than the other, but do think that leadership in RA and a relatively strong Phase II dataset in Crohn's Disease gives upadacitinib a sentiment edge with investors near term. Our market model has filgotinib reaching ~$1.8bn in sales by 2022 and upadacitinib reaching ~$2.8bn in sales, with market share of both drug currently differentiated upon estimated time-to-market from the current clinical efforts. **Overall we estimate that the next generation of oral drugs for auto-immune disorders (including Mongersen) could surpass +$5bn in total sales by 2022 (Figure 7).**

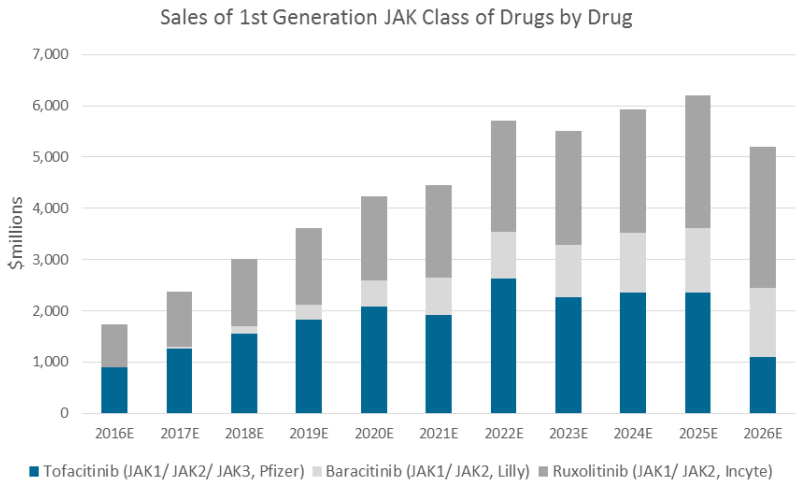
Figure 7. We forecast sales of next generation oral auto-immune drugs to surpass +$5bn by 2022E



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

The current class of JAK inhibitors, which we argue are generally inferior to the next generation, are expected to surpass +$4bn in sales by 2021 (Figure 8).

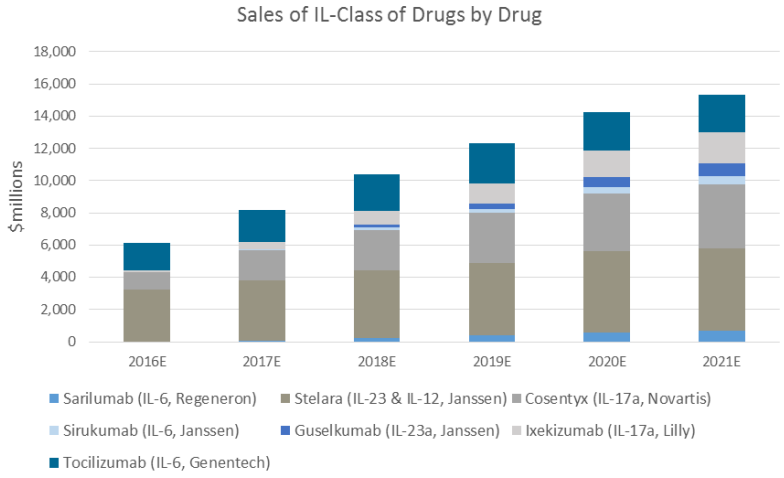
Figure 8. Consensus estimates project +$4bn in 2021E sales for the current JAK class



Source: Company Reports, Bloomberg, June 2017

Based upon current clinical results of the next generation JAK inhibitors, along with the potential to differentiate against the IV and subcu delivery of the current interleukin-target class of drugs, we think that consensus estimates for the current IL-targeted class of drugs to exceed ~$15bn in sales by 2021 may be overly-optimistic (Figure 9).

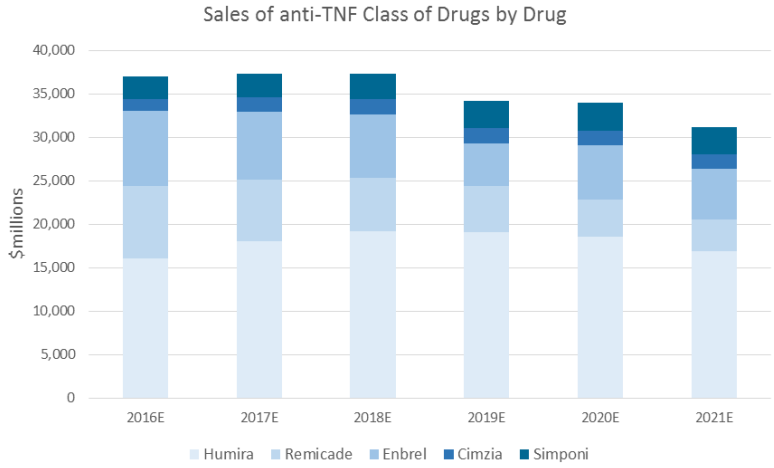
Figure 9. The interleukin-target class is expected to surpass +$15bn in sales by 2021E



Source: Company Reports, Bloomberg, June 2017

Furthermore, the current consensus sales expectations for the anti-TNF class does not seem to accurately factor in adoption of either the IL-class or next-generation JAK inhibitors, as sales of the anti-TNF class are only expected to fall by ~$5bn to ~$30bn by 2021 (Figure 10).

Figure 10. Sales of the anti-TNF class are only expected to fall to ~$30bn by 2021E

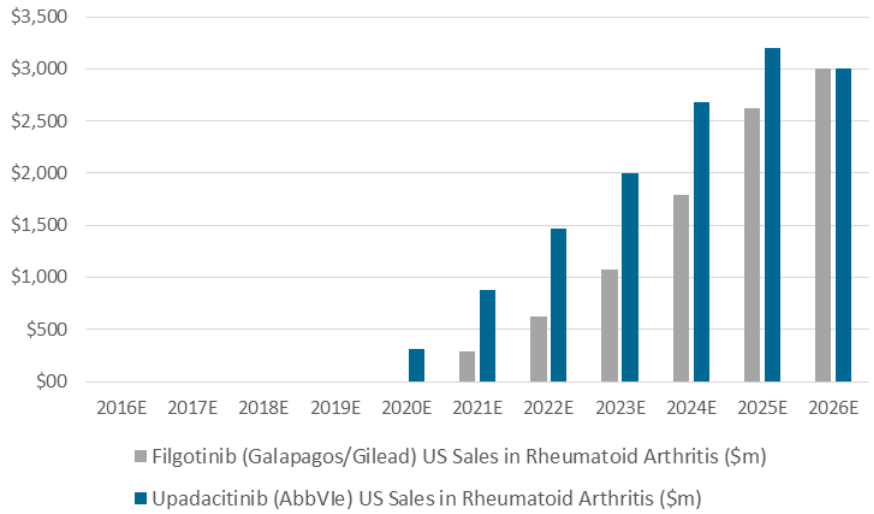


Source: Company Reports, Bloomberg, June 2017

Next Gen JAKs competing within Rheumatoid Arthritis (RA) is Promising but Complicated

Upadacitinib will likely be first approved for use in the treatment of Rheumatoid Arthritis (RA) by YE2019, while filgotinib could reach the market by 2021 (approval YE2020). The current datasets for both drugs look promising, but we are concerned about the shifting landscape of the anti-TNF and IL class drugs within the RA setting. The indication is competitive, and biosimilars may erode tolerance for the pricing of new drugs. That said, effective oral drugs provide convenience and maintenance dosing that should support adoption relative to injectables. We forecast both filgotinib and upadacitinib each reaching ~$3bn of sales within the US RA market by 2026 (Figure 11).

Figure 11. We forecast the next generation of JAK inhibitors to reach ~$3bn in US RA sales by 2026E



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

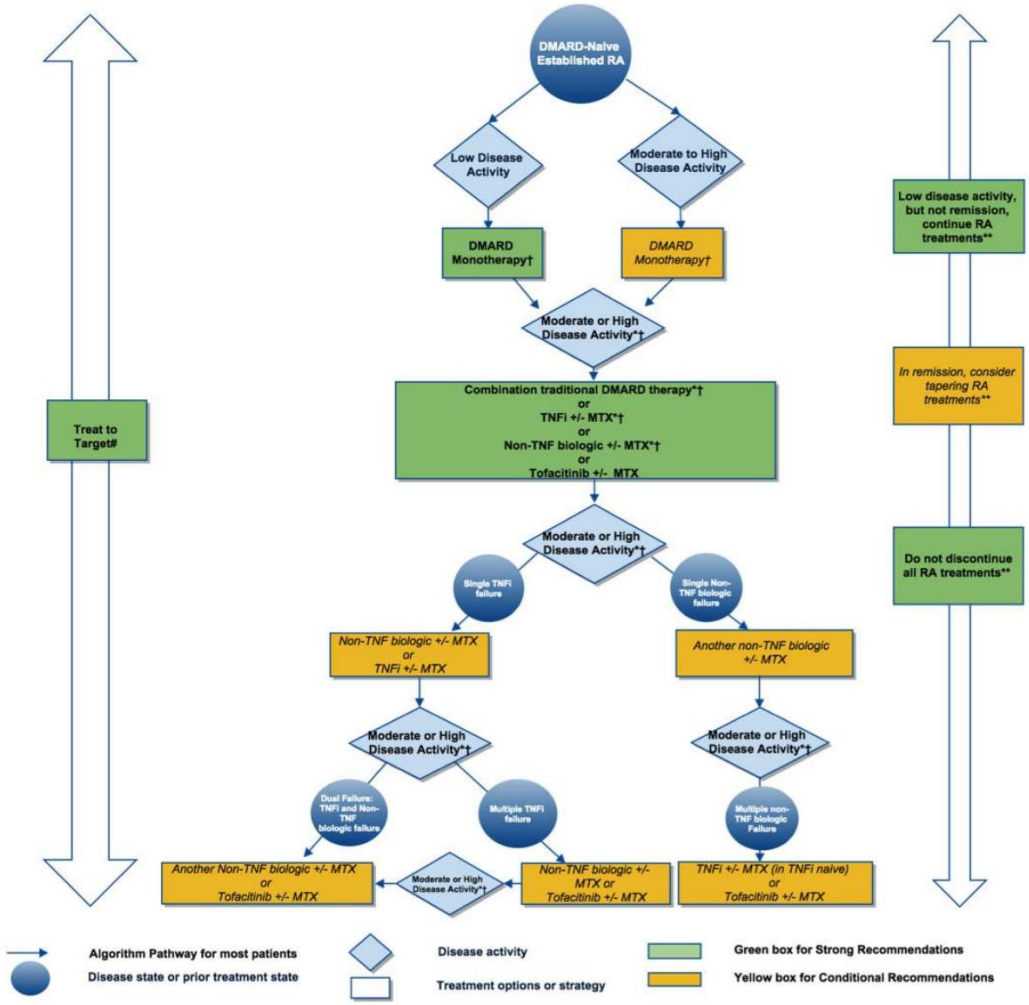
Rheumatoid Arthritis (RA) is one of the most common auto-immune disorders, and has been estimated to affect roughly ~1% of the global population. The incidence of RA varies by ethnic population, and is generally considered to be a disease that occurs as a mixed function of genetic susceptibility (50 – 60% of cases) and environmental factors. The pathology is complex, and although classical presentation occurs through destruction of the joints, with swelling, bone erosion and synovitis, the disease has a systemic effect through constituative activation of the immune system and a general loss for 'tolerance of self'. For example, when controlling for other variables, patients with active RA carry a 1.5x higher risk of cardiovascular mortality when compared to the general population. **The disease burden of RA is significant, as 1/3 of patients become work-disabled post 2-years of onset and 50% by 10-years[1].**

As the direct cause of RA is currently unknown and the pathology is complex, treatment is generally designed on a 'treat-to-target' basis, whereby goals are targeted on a patient basis for reduction of disease burden. Biologic therapies

[1] *Overview of Epidemiology, Pathophysiology, and Diagnosis of Rheumatoid Arthritis;* Gibofsky; *Am J Manag Care,* 2012, 18:S295-S302

are generally used second line to low-dose methotrexate (relative to utilization in oncology), and the leading biologic therapies used to treat RA focus on reducing the intercellular signaling processes of TNF-α and IL-6 – as both immune signaling pathways are thought to be central to active RA. **That said, as a result of having no 'cure', and high patient variability regarding therapeutic response, the current clinical treatment algorithm for RA involves many patient specific considerations (Figure 12).**

Figure 12. American College of Rheumatology (ACR) recommendations for the treatment of RA



Source: 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis; Singh and McAlindon et al.; *Arthritis Care & Research,* DOI 10,1002/acr.22783

Janus kinase inhibitors (JAK) differ from the major classes of anti-TNF and IL-antagonist therapies in that they focus on blocking the internal signalling (intracellular) pathways that cause constituative activation of the immune system, which in a complicated systemic auto-immune disease such as RA, may confer a broader effect on downregulation of the disease. They are also orally delivered versus IV infusion or subcutaneous injection for the anti-TNF and IL therapies. Tofacitinib (Xeljanz) was the first JAK inhibitor to be both approved and included within clinical treatment protocols for RA. A pooled analysis of

tofacitinib for use in the treatment of RA did not find substantial differences with adverse event rates relative to controls or biologic agents, but regulatory agencies did note serious concerns regarding long-term use associated with serious infections, cancers, and structural impairments such as heart disease. Furthermore, **long-term withdrawal rates for tofacitinib were estimated to be ~21%, which would generally put it around the range of the anti-TNF biologic agents.**

Adding uncertainty to the development timelines for both filgotinib and upadacitinib has been the review delays for Eli Lilly's JAK inhibitor baracitinib, which after ~2.5yrs of clinical trials was submitted for a New Drug Approval to the FDA during January 2016, and was issued a Complete Response Letter during April 2017 asking for additional dosage data. As such, **we would not anticipate upadacitinib achieving FDA approval until YE2019 and filgotinib achieving FDA approval until YE2020.**

Since we are expecting several JAK inhibitors to be on the market for RA by the time filgotinib is approved (YE2020), the key question will be whether filgotinib can legitimately demonstrate best-in-class or differentiating attributes. **Cross-study comparisons are difficult, but using common clinical endpoints, the DARWIN 1 dataset for filgotinib compares favorably to the current class of biologics on standard American College of Rheumatology scoring. Specifically, filgotinib scored higher on the number of patients that were able to achieve a 50% reduction and 70% reduction in active disease (ACR50 and ACR70, Figure 13).**

Figure 13. Filgotinib efficacy looks favorably versus the current class of anti-TNF therapies

	Filgotinib (DARWIN 1, 200mg QD)*	Adalimumab (ADA)**	Entanercept (ETN)**	Infliximab (IFX)**	Secukinumab (150mg)***	Abatacept***
Time Period	24 week Data	24 week Data	24 week Data	24 week Data	24 week Data	24 week Data
Number of patients (ACR)	86	519	383	852	137	138
ACR 50	50%	45%	40%	31%	17%	28%
ACR 70	29%	24%	21%	14%	10%	12%
DAS28 remission	26%	32%	26%	21%	-	-
EULAR Response						
Good	51%	52%	42%	34%	-	-
Moderate	38%	33%	39%	38%	-	-
No Response	11%	15%	19%	29%	-	-

*Biologic experienced, data from the Phase iib study of Filgotinib versus Placebo, *Filgotinib (GLPG0634/ GS-6034), an oral JAK1 selective inhibitor, is effective in combination with methotrexate (MTX) in patients with active rheumatoid arthritis and insufficient response to MTX: results from a randomised, dose-finding study (DARWIN 1); W* esthovens and Harrison et al.; *Ann Rheum Dis;* 2016, *0:1-11*

**Biologic naïve w/ ~76% on concomitant MTX, *Direct Comparison of Treatment Responses, Remission Rates, and Drug Adherence in Patients with Rheumatoid Arthritis Treated with Adalimumab, Etanercept, or Infliximab,* Hetland and Ostergaard et al.; *Arthritis & Rheumatism;* January 2010, Vol. 62, No. 1, pp 22 - 32

***Biologic experienced patients, data from the Phase 3 study of Secukinumab versus Abatacept, *Secukinumab in Active Rheumatoid Arthritis: A Phase III Randomized, Double-Blind, Active Comparator - and Placebo-Controlled Study;* Blanco and Richards et al.; *Arthritis & Rheumatology* ; June 2017, Vol 69, No 6

Source: R Westhovens and Harrison et al. Ann Rheum Dis: 2016,0:1-11, Hetland and Ostergaard et al.; Arthritis & Rheumatism; January 2016, 62(1):22-32

Beyond comparison to the current landscape of disease modifying biologic agents for RA, filgotinib will also need to differentiate within the new JAK inhibitor class, which includes baracitinib and upadacitinib. **Regarding efficacy, filgotinib looks comparable to both agents, with filgotinib and upadacitinib looking numerically stronger compared to baracitinib on an ACR50 and ACR70 basis at 12weeks (Figure 14).**

Figure 14. Filgotinib efficacy looks competitive to other JAK inhibitors

Drug/ Study	Filgotinib (DARWIN 1, 200mg QD)	Upadacitinib (SELECT-NEXT, 30mg QD)	Baracitinib (RA-BUILD, 4mg QD)
Time Period	12 week Data vs Placebo	12 week Data vs Placebo	12 week Data vs Placebo
Number of patients (ACR)	86 vs 86	219 vs 221	227 vs 228
ACR 50	43% vs 15%	43% vs 15%	33% vs 13%
ACR 70	24% vs 8%	27% vs 6%	18% vs 3%
DAS28 (CRP) remission	22% vs 7%	28% vs 10%	26% vs 9%

Source: R Westhovens et al. Ann Rheum Dis 76(6), 998-1008. 2016 Dec 19. AbbVie Company Reports, June 2017, Kuriya B. et al. The Adv Musculoskelet Dis. 201 Feb;9(2):37-44

Differentiation on toxicity remains too early to call, but on the basis of overall discontinuation rates, filgotinib looks balanced with placebo and inline with the other JAK inhibitors on a 12 week dataset (Figure 15). We would note that there did seem to be a higher rate of Grade 3+ hemoglobin declines within the upadacitinib Phase IIb study.

Figure 15. Filgotinib safety looks compelling relative to other JAK inhibitors

Drug/ Study	Filgotinib (DARWIN 1, 200mg QD)	Upadacitinib (Phase II, 18mg BID)*	Baracitinib (RA-BUILD, 4mg QD)
Time Period	12 week Data vs Placebo	12 week Data vs Placebo	12 week Data vs Placebo
Serious TEAEs	3.6% vs 7.1%	2% vs 2%	2% vs 4%
TE Infections	8.3% vs 1.8%	38% vs 23%	29% vs 23%
TE Serious Infections	1.2% vs 1.8%	0% vs 2%	<1% vs 1%
Discontinuations	3.6% vs 3.6%	4% vs 4%	4% vs 4%
Haemoglobin AEs (Grade 3+)	1.2% vs 0%	15% vs 0%	0% vs 0%

**A Phase Iib Study of ABT-494, a selective JAK-1 Inhibitor, in Patients with Rheumatoid Arthritis and an Inadequate Response to Anti-Tumor Necrosis Factor Therapy;* Kremer and Keystone et al.; *Arthritis & Rheumatology;* December 2016, Vol 68, No 12, pp 2867 - 2877

Source: R Westhovens et al. Ann Rheum Dis 76(6), 998-1008. 2016 Dec 19. AbbVie Company Reports, June 2017, Kuriya B. et al. The Adv Musculoskeletal Dis. 2017 Feb;9(2):37-44; Kremar and Keystone et al.; Arthritis & Rheumatology; December 2016;68(12):2867-2877

Galapagos/ Gilead (filgotinib) and AbbVie (upadacitinib) are in a race to the market with their respective next generation JAK inhibitors for RA, with **AbbVie's SELECT trials likely to support a NDA filing approximately 12-months ahead of Galapagos' FINCH studies. We estimate that the FINCH-1 and FINCH-2 studies will have pivotal datasets available during 2H2019 (Figure 16).**

Figure 16. FINCH-1 and FINCH-2 studies will have pivotal datasets available during 2H2019

Global trials of Filgotinib and ABT-494 (Upadacitinib)	Trial Number	Trial Name	Drugs	Phase 3	Patient Enrollment Target	Expected Results
MTX Naïve						
SELECT-EARLY	NCT02706873	A Study to Compare ABT-494 Monotherapy to Methotrexate Monotherapy in Subjects With Rheumatoid Arthritis (RA) Who Have Not Previously Taken Methotrexate	Drug: ABT-494 | Drug: Methotrexate | Drug: ABT-494 matching placebo | Drug: Methotrexate matching placebo	Phase 3	975	3Q2018
FINCH-3	NCT02886728	Filgotinib Alone and in Combination With Methotrexate (MTX) in Adults With Moderately to Severely Active Rheumatoid Arthritis Who Are Naive to MTX Therapy	Drug: Filgotinib | Drug: Placebo to match filgotinib | Drug: MTX | Drug: Placebo to match MTX	Phase 3	1200	1Q2020
Head to Head Biologics						
SELECT-COMPARE	NCT02629159	A Study Comparing ABT-494 to Placebo and to Adalimumab in Subjects With Rheumatoid Arthritis Who Are on a Stable Dose of Methotrexate and Who Have an Inadequate Response to Methotrexate	Drug: ABT-494 | Drug: Placebo for ABT-494 | Drug: Adalimumab | Drug: Placebo for Adalimumab	Phase 3	1500	3Q2017
SELECT-CHOICE	NCT03086343	A Phase 3 Study to Compare ABT-494 to Abatacept in Subjects With Rheumatoid Arthritis on Stable Dose of Conventional Synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs) Who Have an Inadequate Response or Intolerance to Biologic DMARDs	Drug: ABT-494 | Drug: Abatacept | Drug: ABT-494 matching placebo | Drug: Abatacept matching placebo	Phase 3	550	3Q2019
MTX Inadequate Response + MTX						
SELECT-MONOTHERAPY	NCT02706951	A Study Comparing ABT-494 Monotherapy to Methotrexate (MTX) Monotherapy in Subjects With Rheumatoid Arthritis (RA) Who Have an Inadequate Response to MTX (SELECT-MONOTHERAPY)	Drug: ABT-494 | Drug: Methotrexate | Drug: ABT-494 matching placebo | Drug: Methotrexate matching placebo	Phase 3	600	3Q2017
FINCH-1	NCT02889796	Filgotinib in Combination With Methotrexate in Adults With Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate	Drug: Filgotinib | Drug: Placebo to match filgotinib | Drug: Adalimumab | Drug: Placebo to match adalimumab | Drug: MTX	Phase 3	1650	1Q2019
3rd Line Post Biologics						
SELECT-BEYOND	NCT02706847	A Study to Compare ABT-494 to Placebo in Subjects With Rheumatoid Arthritis on Stable Dose of Conventional Synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs) Who Have an Inadequate Response or Intolerance to Biologic DMARDs	Drug: ABT-494 | Drug: Placebo	Phase 3	450	2Q2017
FINCH-2	NCT02873936	Filgotinib Versus Placebo in Adults With Active Rheumatoid Arthritis (RA) Who Have an Inadequate Response to Biologic Disease-modifying Anti-rheumatic Drug(s) (DMARDs) Treatment	Drug: Filgotinib | Drug: Placebo to match filgotinib | Drug: csDMARDs	Phase 3	423	2Q2018
Hybrid (Conventional + Biologics)						
SELECT-NEXT	NCT02675426	A Study Comparing ABT-494 to Placebo in Subjects With Rheumatoid Arthritis on a Stable Dose of Conventional Synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs) Who Have an Inadequate Response to csDMARDs Alone	Drug: ABT-494 | Drug: Placebo	Phase 3	600	2Q2017
Long-Term Follow-up						
FINCH-4	NCT03025308	Long Term Extension Study to Assess the Safety and Efficacy of Filgotinib in Adults With Rheumatoid Arthritis	Drug: Filgotinib | Drug: Placebo to match filgotinib	Phase 3	2800	4Q2020

Source: Company Reports, Clinicaltrials.gov, June 2017

Our current RA market model for the next generation JAK inhibitors assumes an approval for upadacitinib by YE2019 and an approval for filgotinib by YE2020. We forecast market share balancing towards 50-50 by 2026 and overall penetration reaching ~15% for TNF-experienced and naïve patients within the United States (US) and ~4% ex-US. This equates to ~$3bn in annual US revenues and ~$1.3bn ex-US for filgotinib by 2026E (Figure 17).

Figure 17. Our RA market model projects filgotinib achieving ~7.5% share (US) by 2026E

Rheumatoid Arthritis	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	202
Total US Sales in Rheumatoid Arthritis ($m)	**$00**	**$00**	**$00**	**$00**	**$314**	**$1,175**	**$2,095**	**$3,074**	**$4,465**	**$5,822**	**$6,0**
Filgotinib (Galapagos/Gilead) US Sales in Rheumatoid Arthritis ($m)	$00	$00	$00	$00	$00	$294	$629	$1,076	$1,786.09	$2,620	$3,0
Upadacitinib (AbbVIe) US Sales in Rheumatoid Arthritis ($m)	$00	$00	$00	$00	$314	$881	$1,467	$1,998	$2,679	$3,202	$3,0
Filgotinib	0%	0%	0%	0%	0%	25%	30%	35%	40%	45%	50
Upadacitinib (ABT-494)	0%	0%	0%	0%	100%	75%	70%	65%	60%	55%	50
						TRUE	TRUE	TRUE	TRUE	TRUE	TRU
Total US Sales ($m)	**$00**	**$00**	**$00**	**$00**	**$314**	**$1,175**	**$2,095**	**$3,074**	**$4,465**	**$5,822**	**$6,0**
# of Moderate to Severe Rheumatoid Arthritis Patients (TNF-Experienced)	410,687	419,723	428,957	438,394	448,038	457,895	467,969	478,264	488,786	499,539	510,52
% Patients Treated	0%	0%	0%	0%	3%	5%	8%	10%	15%	15%	15
# of Moderate to Severe Rheumatoid Arthritis Patients (TNF-Naïve)	684,479	699,538	714,928	730,656	746,730	763,158	779,948	797,107	814,643	832,565	850,88
% Patients Treated	0%	0%	0%	0%	0%	3%	5%	8%	10%	15%	15
Patients Treated	-	-	-	-	11,200.96	41,974	74,095	107,609	154,782	199,816	204,21
Cost of Therapy Per Patient	$28,000	$28,000	$28,000	$28,000	$28,000	$28,000	$28,280	$28,563	$28,848	$29,137	$29,4
Price Inflation %	0%	0%	0%	0%	1%	1%	1%	1%	1%	1%	1
Total Int'l Sales in Rheumatoid Arthritis ($m)	**$00**	**$00**	**$00**	**$00**	**$136**	**$511**	**$911**	**$1,336**	**$1,940**	**$2,530**	**$2,6**
Filgotinib (Galapagos/Gilead) EU Sales in Rheumatoid Arthritis ($m)	$00	$00	$00	$00	$00	$128	$273	$467	$776	$1,138	$1,3
Upadacitinib (AbbVIe) EU Sales in Rheumatoid Arthritis ($m)	$00	$00	$00	$00	$136	$383	$637	$868	$1,164	$1,391	$1,3
Filgotinib	0%	0%	0%	0%	0%	25%	30%	35%	40%	45%	50
Upadacitinib (ABT-494)	0%	0%	0%	0%	100%	75%	70%	65%	60%	55%	50
						TRUE	TRUE	TRUE	TRUE	TRUE	TRU
Total Int'l Sales in Rheumatoid Arthritis ($m)	**$00**	**$00**	**$00**	**$00**	**$136**	**$511**	**$911**	**$1,336**	**$1,940**	**$2,530**	**$2,6**
Moderate to Severe Rheumatoid Arthritis Patients (TNF-Experienced)	892,319	911,950	932,013	952,517	973,473	994,889	1,016,777	1,039,146	1,062,007	1,085,371	1,109,24
% Patients Treated	0%	0%	0%	0%	1%	1%	2%	3%	4%	4%	4
Moderate to Severe Rheumatoid Arthritis Patients (TNF-Naive)	1,487,199	1,519,917	1,553,355	1,587,529	1,622,455	1,658,149	1,694,628	1,731,910	1,770,012	1,808,952	1,848,74
% Patients Treated	0%	0%	0%	0%	0%	1%	1%	2%	3%	4%	4
Patients Treated	-	-	-	-	6,084.21	22,800	40,247	58,452	84,076	108,537	110,92
Cost of Therapy Per Patient	$22,400	$22,400	$22,400	$22,400	$22,400	$22,400	$22,624	$22,850	$23,079	$23,310	$23,5
Price Inflation %	0%	0%	0%	0%	0%	0%	1%	1%	1%	1%	1

Source: Company Reports, BTIG Research Estimates, June 2017