Background on JAKs

What is the science behind the JAK? Inflammatory cytokines specifically bind to Type I and II receptors and rely upon the JAK-STAT pathway to transmit their signal from the cell surface into the cell nucleus. Such receptors associate with different JAKs (JAK1, JAK2, JAK3 and Tyk2), and dysregulation of this relationship has been associated with a number of diseases, including RA, psoriasis and IBD suggesting that highly selective therapies aimed at blocking the JAK mediated transmission of the pro-inflammatory message from ever entering the cell could provide clinicians with a powerful tool in treating autoimmune diseases.

Why does selectivity matter? Inhibition of JAK1 is of therapeutic benefit for a range of inflammatory conditions. Off-target JAK inhibition owing to reduced selectivity has been linked to anemia (JAK2 inhibition), increase risk for opportunistic infections (JAK3 inhibition) such as tuberculosis and herpes zoster, and clinically meaningful increases in LDL and liver enzymes. Therefore, assets with a higher selectivity for JAK1 are likely to be best-in-class given their cleaner safety and strong clinical profile.

Why are we excited about the 2nd generation JAK inhibitors in RA? We note that the first JAK to be approved was PFE's Xeljanz in 2012. However, Xeljanz is the least selective JAK and is considered a first-generation pan-JAK because it expresses inhibitory activity across the entire JAK family with selectivity for JAK3>JAK1>JAK2. We believe this has driven a number of safety concerns, including a boxed warning for malignancies such as lymphoma and increased risk of infections, and as such generated less excitement in the community. Among the 2nd generation JAKs, LLY's Baricitinib is selective for JAK1≈JAK2>>JAK3 while Upadacitinib (~10x more selective for JAK1 than JAK2 in whole blood assays) and GLPG's Filgotinib (~28x more selective for JAK-1 than JAK-in whole blood assays) are the most selective in the class. Filgotinib, the most selective in the class, is likely to confer a cleaner safety profile although this needs to be borne out still in phase 3 studies. Based on the data we have seen so far from LLY's Baricitinib, ABBV's Upadacitinib and GILD/GLPG's Filgotinib, we believe these 2nd generations JAKs have shown cleaner safety profiles and are even more efficacious than Xeljanz. Despite the inferior profile, Xeljanz has ~9% market share in naive RA patients and ~20% share in the switch patient population driving optimism for the uptake potential of these second-generation JAKs with superior profiles.

PFE's Xeljanz: A first-generation oral JAK inhibitor, Xeljanz was approved in 2012 (XR approved in 2016) for patients with RA who have experienced inadequate response or intolerance to MTX. Xeljanz is approved as a monotherapy treatment with dosing of 5mg twice daily and in an extended release form of 11mg once daily. We note that the newer JAKs have all demonstrated better efficacy than Xeljanz based on ACR scores and better durability as shown by the DAS28 scores. More importantly, the broader JAK specificity drives several side effects resulting in an inferior safety profile for Xeljanz that has limited commercial uptake. This includes reduced hemoglobin levels, anemia, and elevated liver and lipid levels as well as a

boxed warning for malignancies such as lymphoma and serious infections including tuberculosis on the label. We would expect Xeljanz to lose share once the 2nd generation JAKs get on the market in early 2019.

LLY's Bari: Bari has demonstrated good efficacy as a once-daily oral JAK1/2 inhibitor relative to Xeljanz on both the 2mg and 4mg dose across its four phase 3 studies. The drug is currently approved in RA for 2mg and 4mg once daily use in the EU and Japan, while not expected to launch in the US until late 2018/2019 following a CRL from the FDA taking away its potential lead vs. competitors. The CRL was issued due to an imbalance seen during the placebo-controlled studies where 5 patients reported events of DVT/PE in two out of seven completed phase 2/3 RA trials. We note that the precaution for DVT and PE were included in the EU and Japan labels (exhibit 9). PE/DVT are inherent risks that are characteristic of the RA population with published rates of DVT and PE for patients with RA in the range of approximately 0.3 to 0.8 per 100 patient years. While the overall rate of these events in the bari program seem consistent with the background rate, the concern for LLY appears to be with the higher 4mg dose (exhibit 9). Following discussions with the FDA, LLY now plans to re-submit its NDA with additional safety and efficacy data by the end of January 2018 along with a new clinical study subject to a six-month additional review—roughly a year earlier than originally expected—with extended Phase 3 safety data and a possible phase 2 interim trial. With this updated timeline, it's possible to assume a commercial launch in early 2019, likely ahead of Upadacitinib. However, we expect the label will contain the same precautions as in the EU and Japan and with less compelling efficacy than the other two second generation JAKs, we could anticipate a more modest commercial opportunity for Bari.

ABBV's Upadacitinib: Upadacitinib is highly selective for JAK1 having showed 10x more selectivity toward JAK1 than JAK2 in whole blood assays. Upadacitinib has demonstrated an impressive efficacy and safety profile which appears to be best in class and more efficacious than LLY's bari based on phase 3 data from SELECT NEXT and SELECT BEYOND, likely de-risking the RA opportunity to a large extent. Both studies reported strong positive topline results meeting both the primary (ACR20 and low disease activity) and secondary endpoints (ACR50, ACR70 and clinical remission) across 15mg and 30mg doses (ACR70 in 15mg arm from SELECT-BEYOND was numerically but not statistically higher). However, we believe the data in totality compares very favorably to LLY's Baricitinib across both studies and comparable to Filgotinib's phase 2 DARWIN-1 trial (see exhibit 7 and 8). We note ACR 20 and ACR 70 scores look better on a placebo adjusted basis in SELECT NEXT vs. DARWIN-1. We were particularly encouraged by Upadacitinib's safety profile in the context of LLY's experience with Baricitinib, which has demonstrated to date no increases in platelet levels. We recognize that data from ABBV's Upadacitinib is still limited and incomplete, however from the data made available, treatment-emergent events of DVT/PE have been reported in the SELECT-BEYOND study and no events in SELECT-NEXT (exhibit 9). It is important to highlight that in SELECT-BEYOND 2 events (2 PE, no DVT) were seen in the placebo controlled portion of the study and 5 additional events (4 with PE, 1 with DVT) in the non-placebo controlled portion of the study. Until we have complete and final exposure data, it is difficult to characterize the events reported (particularly in the non placebo controlled portion), however this is something we will continue to watch closely as this competitive landscape evolves. There are currently four other ongoing clinical trials

evaluating Upadacitinib in different RA patient populations (SELECT-EARLY, SELECT-COMPARE, SELECT-MONO and SELECT-CHOICE). We look forward to readouts from SELECT-MONO (in MTX-IR patients) later this year, with the rest following in 2018.

Fligotnib is a highly selective second generation JAK1 which will be a strong competitor to Upadacitinib. GLPG's Filgotinib, which is being developed in collaboration with GILD, has shown impressive efficacy data during its phase 2 DARWIN program. On a placebo-adjusted basis, Filgotinib demonstrated a strong response on both ACR 20 and 70 scores, though less than Upadacitinib, albeit based on phase 2 data vs. ABBV's phase 3 (exhibit 7 and 8). We expect the phase 3 trial to start reading out in 2H18. In regards to safety, GLPG did highlight that hemoglobin and platelet levels increased and infection rates decreased over time across DARWIN 1, 2 and 3 which if maintained in phase 3 would confer better safety (consistent with the more selective for JAK1 profile). During the 84-week DARWIN-3 extension study, one case of treatment-emergent, serious DVT leading to PE with fatal outcome was reported, as well as 3 additional deaths (total deaths, n =4), however there was no placebo-control during this period. During pre-clinical testing the FDA flagged testicular toxicity as a safety concern with the 200mg dose based on preclinical tests that showed Filgotinib affected the production of sperm cells, after which Galapagos excluded males from this arm during the DARWIN studies. After further testing and negotiations with the FDA, GLPG will include males into the 200mg dosing arm for the phase 3 FINCH program, which will be monitored closely with a dedicated male patient testicular study. We note this as a risk factor to watch closely across indications, as any dose limitations imposed for male patients could drive a less potent efficacy profile.

Background on IL-Inhibitors

Which is the science behind the new biologics? New treatments selectively targeting the IL-17 and IL-23 pathways are seen as a refinement on inhibition of IL-12/23 (Stelara) and have shown promising results by achieving greater efficacy in the treatment of plaque psoriasis vs. current biologics.

- **IL-17mAb** (*Taltz and Cosentyx*): The IL-17 cascade is directly responsible for the pro-inflammatory effects triggering uncontrolled skin cell differentiation and proliferation resulting in the psoriatic profile. Selective therapies targeting the IL-17A cytokine have shown promising efficacy in both clinical trials and real world settings. Agents within this class have warnings for inflammatory bowel disease, and infections.
- **IL-23mAb** (*Tremfya, Risankizumab, Tildrakizumab*): The cytokine IL-23 serves as the *main gas pedal* for the secretion of the pro-inflammatory cytokine IL-17. Such therapies aimed at selectively targeting IL-23 act via the inhibition of its unique p19 subunit, which has shown to provide a more complete inhibition of IL-23 activity affecting the pathway that leads to IL-17, potentially producing a much better clinical response than targeting IL-17 itself. Current warnings in this class include risk of infection.

Why are we excited about these new therapies? In general, the new agents have demonstrated superior overall skin clearance with a good safety profile compared to current biologic agents whose efficacy has been known to be more modest in this setting (see exhibit 17-21). Safety is consistent, but given the immunosuppressive nature of the class, not surprisingly, there is an elevated risk of infection with both IL-17's and IL-23's and a warning for IBD specific to IL-17's. Through long-term extension studies, these agents have succeeded at achieving the highest PASI-90 and PASI-100 scores demonstrating their enhanced durability and ability to achieve maintenance. Given the low biologic penetration in this setting (only 10% vs. 40% in RA) likely due to physician concern over long term durability and biologic impact on the immune system resulting from use of broad acting immunosuppressants (such as TNF-inhibitors) especially for those physicians looking only to achieve skin clearance, we expect significant uptake of the newer agents. We believe there is a room for market expansion in this setting particularly driven by greater biologic penetration off a low base. We note that with multiple agents with a competitive profile, dosing can be a competitive advantage and a determinant of market share. Specifically, therapies adhering to a 12 week dosing schedule (like Stelara and ABBV's Risankizumab among the new agents), consistent with how dermatologists prefer to see their patients, could experience more rapid adoption into the market.

The Incumbent biologics *(Humira and Stelara):* Humira is the most widely used TNF inhibitor in psoriasis (followed by a big margin by Enbrel and Remicade) with superior data, more convenient subcutaneous formulation (vs. IV for Remicade) and every other week dosing (vs. once/twice weekly Enbrel). The other widely used biologic is Stelara, an IL-12/23 inhibitor that has a similar clinical profile to Humira (PASI 90/100 scores of 42%/13% and 45%/20%, respectively) and has a convenient

dosing profile of once every 3 months dosing over the TNFs. By virtue of mechanism, TNFs are used more in patients where the physician's focus is beyond skin clearance as TNFs are highly effective on broader immune imbalances while Stelara is used more by physicians/patients focused specifically on skin clearance.

New agents *(IL-17: Taltz, Cosentyx, IL-23: Tremfya,* Risankizumab, *Tildrakizumab):* The IL-17s have been approved and on market for nearly two years and have seen strong uptake in this setting. Cosentyx launched in early 2016 and had already gaining 8%/12% share in US/OUS in year 1 and Taltz is ramping up well, with a more compelling efficacy profile amongst the IL-17s. While the IL-17s demonstrated superior efficacy to Stelara/Humira with PASI90/100 scores, the data from the IL-23 since have demonstrated the greatest efficacy at competitive dosing profiles, i.e. Q8W/Q12W vs. Q4W/Q2W for the IL-17s. Among the IL-23s, Tremfya was recently approved and recently, Risankizumab toplined phase 3 data and we expect it to be on market in 2019. So far, Risankizumab has shown better efficacy than all the other agents with the best dosing schedule of quarterly dosing (aligned with dermatologists), which we believe lends it the most differentiated profile. In terms of durability, Risankizumab has demonstrated strong PASI-90 and PASI-100 scores at 1-year and has a longer half life (20-28 days vs. 15-18 days with Tremfya and 13 days with Taltz) but we still need to see longer term responses to compare to other incumbents (eg. Taltz). A 3rd IL-23mAb is SunPharma's Tildrakizumab, which utilizes a favorable quarterly dosing schedule but falls short on efficacy and is unlikely to stand up to the stronger assets in the space such as Tremfya, Risankizumab and Taltz.

In terms of comparing data for efficacy, we use the following data sets -

Exhibit 17: Risankizumab (IMMhance), Tremfya (weighted avg. VOYAGE-1,2), Tildrakizumab (reSURFACE-2,200mg), Taltz (weighted avg. UNCOVER-1,2,3), Cosentyx (weighted avg. FIXTURE/ERASURE,300mg), Humira (REVEAL), Stelara (PHOENIX-1)

Exhibit 18: Risankizumab (weighted avg. UltiMMa-1,2 & IMMvent, IMMhance), Guselkumab (weighted avg. VOYAGE-1,2), Tildrakizumab (reSURFACE-2,200mg), Taltz (weighted avg. UNCOVER-1,2,3), Cosentyx (weighted avg. FIXTURE/ERASURE, 300mg), Humira (REVEAL), Stelara (PHOENIX-1)

Exhibit 19: Risankizumab (weighted avg. UltiMMa-1,2 & IMMvent, IMMhance), Guselkumab (weighted avg. VOYAGE-1,2), Tildrakizumab (reSURFACE-2,200mg), Taltz (weighted avg. UNCOVER-1,2,3), Cosentyx (weighted avg. FIXTURE/ERASURE,300mg), Humira (REVEAL), Stelara (PHOENIX-1).

Background on CD and UC

Which are the new biologics we are excited about? Given the concern around systemic (and broad) immunosuppression in the body with current therapies (mainly TNFs), the new wave of treatments take a more targeted approach to reduce inflammation in the gut, and provide increased efficacy and reduced adverse effects, most notably on infections and anemia. As the only approved next-generation biologic in IBD, Stelara (IL-12/23) has had rapid uptake and quickly gained share in CD. However, in our view we recognize IL-inhibitors that specifically target IL-23 as likely to provide a more favorable risk/benefit profile. Particularly, we are also interested in the highly selective JAK-1 inhibitors (Filgotinib and Upadacitinib) given their anemia sparing profile and ability to interfere with a number of key pro-inflammatory cytokines involved in the pathogenesis of IBD.

Why don't IL-17s work here? Specifically within IBD, IL-17mAb's have shown to provide no clinical benefit and in fact can even exacerbate the disease, as seen with the failure of Cosentyx in this setting. Despite IL-17's potential to drive inflammation as in other auto-immune conditions (i.e. psoriasis), a dichotomy exists between IL-17 and IL-23 in IBD suggesting IL-17 signaling may differ on intestinal epithelia compared to other epithelial surfaces as anti IL-17 agents don't seem to have the same anti-inflammatory effect in the gut.

Why are we excited about these new therapies? Within CD, we have seen phase 2 data from the two JAKs, Upadacitinib and Filgotinib and the IL-23, risankizumab. Upadacitinib and risankizumab have demonstrated the best efficacy in biologic-IR patients and Filgotinib has shown promise in biologic naive patients (we have not seen data from Upadacitinib or risankizumab in bio-naive). JAK dosing is most favorable across all assets with a once-daily oral dosing vs. current biologic therapy and the IL-inhibitors offering an IV induction regimen followed by subcutaneous maintenance therapy. We note that within CD, it is particularly challenging to compare data across trials since almost every trial uses a different criteria for remission, endoscopic response and has varying proportions of bio-naïve to bio-IR patients. However, in order to assess the competitive landscape, we try and assess the safety and, on efficacy, look at induction responses for CDAI remission and endoscopic response which are more suggestive of a drugs performance in this setting.

The Incumbents *(Humira, Entyvio and Stelara):* Humira is the most widely used TNF inhibitor in IBD, and quickly replaced Remicade as first line therapy given Humira's ease of use—self injection vs. IV infusion with Remicade although both together have a meaningful share of the market (combined 75-80% share in IBD). In 2014, Entyvio, a cell adhesion molecule (CAM) inhibitor, became the first non-TNFi approved for treatment in IBD after showcasing encouraging results in the Phase 3 GEMINI-2 and 3 trial for CD. Nevertheless, the agent has been unable to trump the TNF's position and is currently used in TNF-refractory patients for both indications. In CD, Stelara has demonstrated a superior clinical profile and offers more convenient dosing (subQ vs. IV with Entyvio), and is now used as the first switch option for patients who have failed their

initial anti-TNF therapy (~36% market share). We expect Stelara to gain more share in 2L and potentially 1L until the newer agents make it to market in 2021/2022.

New agents *(Filgotinib, Upadacitinib, Risankizumab):* Among the next-gen assets, on a placebo-adjusted basis in bio-IR patients, we saw best in class efficacy from ABBV's Upadacitinib (phase 2 CELEST trial) in totality on the two endpoints—CDAI remission and endoscopic response. The data is particularly impressive since the trial included a population which represented the most refractory CD patients studied in a clinical trial to date (~96% of the patients had failed or were intolerant to TNFs). In a similarly refractory population (~95% Bio-IR), Risankizumab showed almost as good efficacy (demonstrated similar improvements in clinical remission CDAI<150, 21% vs. 23%, respectively) although less compelling than Upadacitinib on the endoscopic endpoint. In comparison, Filgotinib does not look as good in the bio-IR patients as Upadacitinib and Risankizumab. We note that in the bio-naive population which are less severe, Filgotinib has demonstrated good efficacy (47% placebo-adjusted clinical remission). While we have yet to see data in this population of patients for Risankizumab and Upadacitinib (unlikely until phase 3), given the better data in a sicker population, we would expect them to demonstrate better activity in the naive population as well. However, we will have to wait for phase 3 data to make that determination in the naive population. In terms of maintenance, we have seen phase 2 data from Risankizumab which showed patients who achieved clinical remission at the end of induction therapy maintaining clinical and endoscopic remission through week 52.

From a safety standpoint, the JAKs have a higher infection rate than the IL-23 which is consistent with the class effect and as such Risankizumab screens with a cleaner safety profile. Amongst the JAKs, we are unable to compare safety across the trials given ABBV's trials included a more refractory population (no bio-naive patients) and GLPG breaks out efficacy but not safety by subpopulation of Bio-IR and Bio-naive patients. However, in isolation both the JAKs demonstrated no new safety signals and safety is consistent with what we have seen in other indications (exhibit 30 and 31). We do note that based on PK studies, Filgotinib shows the least likelihood of drug interactions lending a profile more suited for combination therapy. For Risankizumab, there was no dose dependent safety signals and on worsening of CD, which is a common AE for the IL class (normal in a highly refractory CD population), Risankizumab seems to have cleaner profile over Stelara (lower infections, AE, and CD exacerbation). Risankizumab is positioned to be the first IL-23mAb to market in this indication, while we are aware of phase 3 studies planned in CD for JNJ's Tremfya but have not seen any data so far.

Things to monitor in the space

Exhibit 45: Development Status of Emerging Therapeutics

Drug	Mechanism of Action	Rheumatoid Arthitis	Psoriatic Arthritis	Crohn's Disease	Ulcerative Colitis	Psoriasis	Atopic Dermatitis
Xeljanz	JAK-Inhibitor	Approved 2012/2016	PDUFA Dec 2017	--	PDUFA March 2018	--	--
Upadacitinib	JAK-Inhibitor	SELECT-Program Phase 3	SELECT-PsA Phase 3	Phase 3 Planned	Phase 2	--	Phase 2
Filgotinib	JAK-Inhibitor	FINCH-Program Phase 3	Phase 2	DIVERSITY-1/2 Phase 3	SELECTION-1/2 Phase 3	--	--
Baricitnib	JAK-Inhibitor	US: CRL EU: Approved 2017	Phase 3 Planned	--	--	--	Phase 3 Planned
Risankizumab	IL-23	--	Phase 2	Phase 2	Phase 3 Planned	ultIMMa/IMMvent Phase 3	--
Tremfya	IL-23	--	DISCOVER-1/2 Phase 3	Phase 3 Planned	--	Approved 2017	--
Taltz	IL-17	--	Approved 2017	--	--	Approved 2016	--
Cosentyx	IL-17	--	Approved 2016	--	--	Approved 2015	--
Stelara	IL-12/23	--	Approved 2013	Approved 2016	UNIFI-Trial Phase 3	Approved 2017	--

Source: Company data, Goldman Sachs Global Investment Research

Exhibit 46: Other developmental biologics to watch

Other Next-Gen Biologics in Development					
Drug	**Company**	**Class**	**Indication**	**Status**	**Approved**
Peficitinib (ASP015K)	Astellas	JAK-1/3	RA	Phase 3 (Japan, Asia) & Phase 2 (US, EU)	--
Jakafi (US)/ Jakavi (EU)	INCY/NVS	JAK-1/2	Acute & Chronic GvHD, Thrombocythemia	Pivotal Studies	Myelofibrosis and Polycythemia
Itacitinib	INCY	JAK-1	GvHD & NSCLC	Privotal Studies	--
TD-1473	Theravance	Pan-JAK	IBD	Phase 1	--
CTP-543	Concert Pharma	JAK-1/2	Alopecia Areata	Phase 2a	--
Topical Jakafi/Jakavi	INCY	JAK-1/2	Atopic Dermatitis & Vitiligo	Phase 2	--
Mirikizumab	LLY	IL-23	Psoriasis/CD/UC	Phase 2	--
Brazikumab	MedImmune/AGN	IL-23	CD	Phase 2	--
Otezla	CELG	PDE4-Inhibitor	UC	Phase 2	--

Source: Company data, Goldman Sachs Global Investment Research

Contributing Author

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