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Xeljanz DSMB PE w/ High-Dose; Good for GLPG

Quick Note

Monday, PFE announced DSMB's findings in an open-label post-marketing study (A3921133 / NCT02092467), in which RA patients being treated with Xeljanz (tofacitinib) 10 mg BID (the highest approved dose) had a statistically and clinically meaningful difference in PE rates vs. those being treated with TNF inhibitors (Humira or Enbrel). The study was designed to assess CV risk and required subjects to be at least 50 years old with at least one CV risk factor and on a stable dose of background MTX. DSMB believes however, Xeljanz 5mg BID's risk-benefit profile is appropriately balanced vs. TNFi group. The study is fully enrolled and will continue through completion (March 3, 2020 estimate). Accordingly, PFE is taking steps to transition rheumatoid arthritis study patients who were on Xeljanz 10mg BID to the lower (and cheaper) 5mg dose. DSMB's observations further validate the view that GLPG's selective-JAK1 inhibitor, safety profile is best-in-class – a profile that may lead to an edge at higher dose levels, in the more difficult to treat RA patient subpopulations and in IBD where higher doses appear to be required for efficacy.

We view this as a positive development for GLPG's filgotinib, which has consistently delivered best-in-class therapeutic profile – including PE/DVT's under 1% (see FINCH 1 data here and LTE data here) – supporting chronic dosing at the highest dose level across treatment lines and indications (here).

We anticipate positive, de-risking data from the final filgotinib Ph 3 FINCH 1& 3 readouts in RA - expected in 1Q19 (preview here). Competitive safety concerns also give GLPG/GILD's filgo some "breathing room" even should PE rates tick up in the high dose arm. We anticipate an earlier-than-consensus NDA submission in 2Q19 (with PRV, 6mos review) setting up for a potential YE19 launch. *Reiterate Buy, $140 TP.*

- **ABBV Low Dose Moves to NDA, PE a Concern.** Recall, FDA accepted for Priority Review, ABBV's NDA for upadacitinib (JAK1/JAK2 inhibitor) in mod-sev RA. ABBV filed the NDA with a Priority Review voucher, pulling forward the anticipated launch time to 3Q19 (from our 4Q19 est., note here). However, we question whether the PRV was worth the use - noting the advantage of earlier approval for long-term market uptake is likely minimal in the saturated, beachhead RA indication. We believe IBD is the more lucrative opportunity with higher unmet need (and in UC, filgo is ahead of Upa; see here). We also note ABBV filed Upa for mod-sev RA on only the low dose (15mg QD), which had a 0.6 thrombotic events per 100 patient years exposure in controlled period (Fig. 3) – higher than Olumiant's VTE rate of 0.5 in all RA trials (note here). FDA placed a black-box label on Olumiant for thrombosis including DVT/PE. We believe ABBV may face a similar label, clouding Upa's competitive market opportunity – we look for color at the likely ADCOM meeting for Upa, expected ~one month prior to PDUFA (2Q19/early 3Q19) of this year.
- **Thrombotic Events - Is It a Class Effect or JAK 1/JAK2 Selectivity? Xeljanz Hits JAK2 Too!** Xeljanz is frequently described as a JAK1/JAK3

Instinet, LLC, Equity Research

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Rating Remains	**Buy**
Target Price Remains	USD 140.00
Closing price 19 February 2019	USD 101.70

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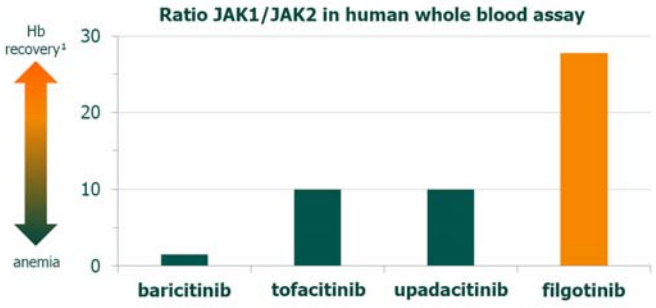
inhibitor, however the drug also inhibits JAK2 to some extent (more at higher doses). It has been long hypothesized that JAK1 and JAK2 activation leads to thrombotic events – DSMB's post-marketing findings for Xeljanz (tofacitinib) may support that filgo's higher JAK1 selectivity (see Fig. 1) is responsible for the superior safety profile (see note "ACR JAK Data Highlight Filgo Selectivity"). The DSMB finding, may trigger concerns of a "class effect", however, we note filgo's selectivity for JAK1 over JAK2 (by human whole blood essay) is multiple fold higher than Xeljanz (tofacitinib) or upadacitinib – and the clinical safety data appears to bear that out (Fig. 2, 3). W*e believe filgo's selectivity-driven therapeutic profile, if confirmed in FINCH 1 & 3, will allow GILD/GLPG to include both low and high doses in their NDA – providing another potential advantage over its earlier competitors.* Further, SGLT2 inhibitors would be a prime example of a class of drugs with an early-line, large market opportunity (T2DM) and a black-box taint that was misconceived as a class effect (Invokana's amputation risk) – turns out it wasn't. We expect clean and consistent safety results (i.e. <0.1 PYE) from filgo's final Phase 3 readouts.

Fig. 1: Filgotinib Has the Highest JAK1 Selectivity vs. Competing JAK Inhibitors a Potential Factor Contributing to Lower PV Rates



Source: Company data

- **GILD Notes MANTA Progress.** MANTA trial (NCT03201445) now enrolling at 114 sites (up vs. 94 sites on Jan 30). We believe MANTA as a gating factor to the filgo NDA, may see 1) more rapid data availability than Street expectations or 2) future flexibility that could facilitate a faster-than-anticipated approval for filgo.

Fig. 2: Upa vs. Filgo Phase 3 Safety Summary (bDMARD-IR moderate to severe RA)

Drug (Name of Pivotal Trial)	Upadacitinib (P3 SELECT-BEYOND)					Filgotinib (P3 FINCH 2)		
Assessment Period	Weeks 0-12			Weeks 12-24*		Week 24		
Trial Arm	PBO	Low Dose	High Dose	Low Dose	High Dose	PBO	Low Dose	High Dose
n	169	164	165	228	223	148	153	147
Serious AE	**0 (0.0%)**	**8 (4.9%)**	**12 (7.3%)**	**10 (4.4%)**	**10 (4.5%)**	**5 (3.4%)**	**8 (5.2%)**	**6 (4.1%)**
PE/DVT	**0 (0.0%)**	**1 (0.6%)**	**1 (0.6%)**	**3 (1.3%)**	**1 (0.4%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
Deaths	**0 (0.0%)**	**0 (0.0%)**	**1 (0.6%)**	**1 (0.4%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)^**
Herpes Zoster	1 (0.6%)	1 (0.6%)	4 (2.4%)	2 (0.9%)	3 (1.3%)	0 (0.0%)	2 (1.3%)	2 (1.4%)
Serious Infections	0 (0.0%)	1 (0.6%)	4 (2.4%)	3 (1.3%)	3 (1.3%)	2 (1.4%)	3 (2.0%)	1 (0.7%)
Opportunistic Infections	0 (0.0%)	1 (0.6%)	2 (1.2%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Malignancy	1 (0.6%)	1 (0.6%)	2 (1.2%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MACE	0 (0.0%)	1 (0.6%)	1 (0.6%)	0 (0.0%)	1 (0.4%)	1 (0.7%)	1 (0.7%)	0 (0.0%)

** Week 12-24 Includes PBO switches to Upa 15 or Upa 30mg*
^ 1 case of retinal vein occlusion, non-serious

Source: Company data, Instinet research

Fig. 3: Upadacitinib Pooled DVT/PE Rates

VTE rates are the same as Olumiant - LLY/INCY's marketed JAK1/JAK2 inhibitor (approved only in the US at the lower 2mg dose with black box warning for thrombotic events)

Exposure-adjusted Incidence Rate of VTEs from SELECT-NEXT, SELECT-BEYOND, SELECT-MONOTHERAPY, SELECT-COMPARE and SELECT-EARLY[26] Number of patients with events/100 patient years exposure					
Controlled Period	Any Adjudicated VTE – Controlled Period				
	Placebo (PBO)/MTX	Adalimumab 40 mg EOW	Upadacitinib 15 mg	Upadacitinib 30 mg	Upadacitinib Total
	0.5	3.5	0.6	0.4	0.5
Long-term Period	Any Adjudicated VTE – Long-term Period				
	PBO	Adalimumab 40 mg EOW	Upadacitinib 15 mg	Upadacitinib 30 mg	Upadacitinib Total
	N/A	1.2	0.5	0.3	0.4

Source: Company data

Fig. 4: Filgotinib in RA – Estimated Timeline to Approval and Launch

Development Timeline	1Q19	2Q19	3Q19	4Q19	1Q20
Clinical Timelines					
FINCH 1 (MTX-IR, P3)	Topline Readout	Possible Presentation at AACR or EULAR			
~~FINCH 2 (bDMARD-IR, P3)~~					
FINCH 3 (MTX-Naiive, P3)	Topline Readout	Possible Presentation at AACR or EULAR			
MANTA (Testicular Tox, P2)	Enrollment Complete	Testicular Safety Data			
~~NCT03417778 (PK, P1)~~					
Regulatory Timelines					
Filgotinib		Regulatory Filing (Possible PRV for 6mo review)		Approval & Launch	
Upadacitinib	~~FDA Accepts NDA for Review w/ PRV~~		Approval & Launch		

Source: Company data, Instinet research