Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C 646-789-5173

JAK2 has also manifested itself in Xeljanz's emerging clotting concerns at higher dose

Mar 20: PRAC first raises questions on higher clot risk at 10 mg vs 5 mg in a study among >50 y.o. w/ heart issues

Increased risk of blood clots in lungs and death with higher dose of Xeljanz (tofacitinib) for rheumatoid arthritis

Share

Press release 20/03/2019

EMA is advising healthcare professionals and patients not to exceed the recommended dose of Xeljanz (tofacitinib) when treating rheumatoid arthritis. The advice follows early results from an ongoing study (study A3921133) in patients with rheumatoid arthritis which showed an increased risk of blood clots in the lungs and death when the normal dose of 5 mg twice daily was doubled.

In the EU, 5 mg twice daily is the authorised dose for rheumatoid arthritis and psoriatic arthritis. The higher dose of 10 mg twice daily is approved for the initial treatment of patients with ulcerative colitis.

EMA is assessing the early results and will consider if any regulatory action is needed. In the meantime, patients with rheumatoid arthritis who are receiving Xeljanz at 10 mg twice daily in study A3921133 will have their dose reduced to 5 mg twice daily for the remaining duration of the study.

The aim of the study was to look at the risks of heart and circulatory problems with Xeljanz in patients 50 years of age or older who were already at higher risk of these, and to compare its safety with that of another medicine called a TNF inhibitor.

While full results are awaited, EMA is recommending that healthcare professionals monitor patients for signs and symptoms of blood clots in the lungs. Patients should not stop or change their dose of Xeljanz without talking to their doctor. Patients should seek medical attention immediately if they experience symptoms such as difficulty breathing, pain in the chest or upper back and coughing up blood.

Healthcare professionals are being informed in writing of the preliminary results of the study and the current treatment recommendations.

There are other ongoing clinical trials in the EU with Xeljanz at a dose of 10 mg twice daily. Patients taking part in clinical trials with Xeljanz should speak to the doctor giving it to them if they have any questions or concerns.

https://www.ema.europa.eu/en/news/increased-risk-blood-clots-lungs-death-higher-dose-xeljanz-tofacitinib-rheumatoid-arthritis

May 17: in a f/u, PRAC restricted pts from taking Xeljanz 10 mg in pts who are at high risk of clots in lung

Restrictions in use of Xeljanz while EMA reviews risk of blood clots in lungs

Share

Press release 17/05/2019

EMA's safety committee (PRAC) is recommending that doctors must not prescribe the 10 mg twice daily dose of Xeljanz (tofacitinib) in patients who are at high risk of blood clots in the lungs. These include patients who have heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients who take combined hormonal contraceptives, are receiving hormone replacement therapy or are undergoing major surgery.

In addition, doctors should consider other factors that may increase the risk of blood clots in the lungs including age, obesity, smoking or immobilisation.

Xeljanz is currently authorised for the treatment of rheumatoid arthritis, psoriatic arthritis and severe ulcerative colitis.

The PRAC's recommendation follows results from an ongoing study (study A3921133) in patients with rheumatoid arthritis. This study showed an increased risk of blood clots in the lungs and death when the 10 mg twice daily dose was used, which is double the recommended dose for rheumatoid arthritis.

The new advice means that, since 10 mg is the only recommended starting dose for ulcerative colitis, patients with this condition who are at high risk of blood clots must not be started on Xeljanz. Patients at high risk currently taking this dose for any condition must be switched to alternative treatments.

Patients should not stop or change their dose of Xeljanz without talking to their doctor. They should seek medical attention immediately if they experience symptoms such as difficulty breathing, pain in the chest or upper back and coughing up blood, which could indicate the presence of a blood clot in the lungs.

The new recommendations are temporary and follow previous PRAC advice not to exceed the recommended 5 mg twice daily dose when treating rheumatoid arthritis. The PRAC will now carry out a review of all available evidence, and updated guidance will be provided to patients and healthcare professionals once the review is concluded.

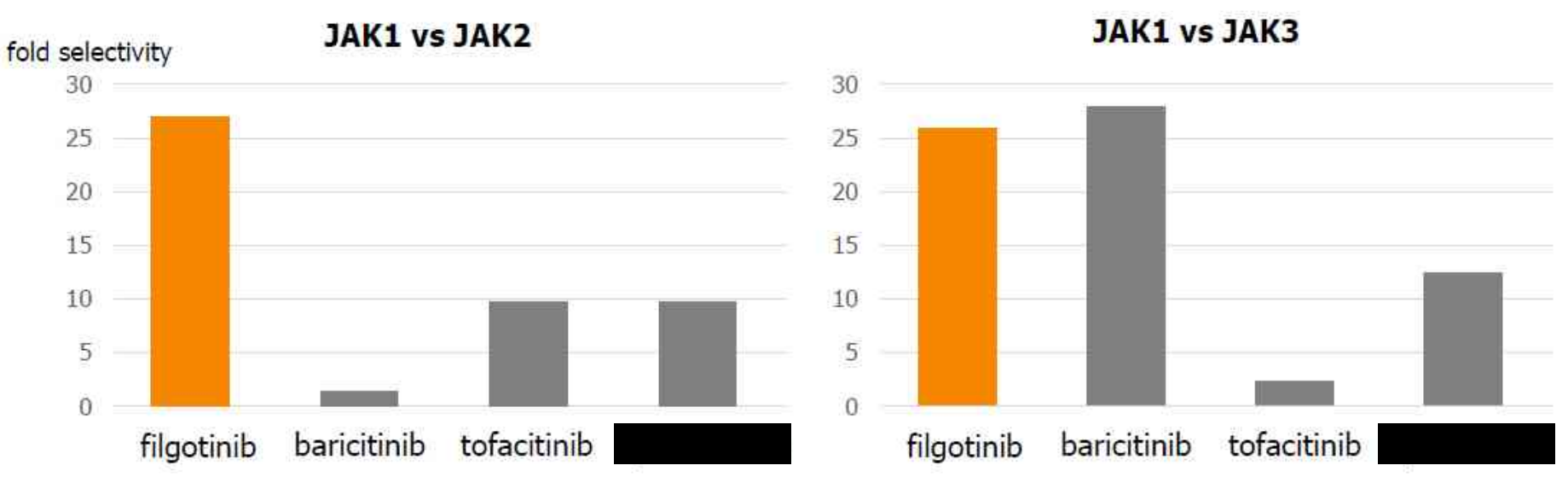
Information for patients

- An ongoing study in patients with rheumatoid arthritis showed that when Xeljanz was given at a dose of 10 mg twice daily there was an increased risk of dangerous blood clots in the lungs and death.
- This dose is higher than the approved dose of 5 mg twice daily for rheumatoid arthritis. However, this dose is used for the initial treatment of patients with ulcerative colitis (for up to 16 weeks) and may also be used in some patients when continuing treatment.

https://www.ema.europa.eu/en/news/restrictions-use-xeljanz-while-ema-reviews-risk-blood-clots-lungs

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C 646-789-5173

For reference, here is a Galapagos disclosure on JAK selectivity of filgotinib:



*"Ex Vivo Comparison of Baricitinib, Upadacitinib, Filgotinib, and Tofacitinib for Cytokine Signaling in Human Leukocyte Subpopulations," McInnes *et al*, ACR 2017

Sources: Company documents, Conference Presentations, FDA, EMA, Evercore ISI Estimates, Medical Journals, Pubmed, USPTO, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C 646-789-5173

Finally, what do we know about DVT data on filgotinib?

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C 646-789-5173

We've seen pooled safety data for FINCH Ph 3 program in RA (through week 24):

N (%)	PBO/MTX	ADA 40 mg EOW	FIL 100 mg + MTX/cDMARDs	FIL 200 mg + MTX/cDMARDs	FIL 200 mg monotherapy	FIL total
	N=1039	N=325	N=840	N=1038	N=210	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)

Note: FINCH 1, 2, and 3 events up to week 24
*Excludes retinal vein occlusion observed in FINCH 2
FIL: filgotinib; **ADA**: adalimumab; **MTX**: methotrexate; **PBO**: placebo;
csDMARD: conventional synthetic disease-modifying antirheumatic drug;
DVT: deep vein thrombosis; **PE**: pulmonary embolism; **NMSC**: nonmelanoma

Sources: Company documents, Conference Presentations, FDA, EMA, Evercore ISI Estimates, Medical Journals, Pubmed, USPTO, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C 646-789-5173

Safety data from each Ph 3 FINCH trial:

- FINCH-1

Table 2. Safety Events of Interest through Week 24

Patient with event, n (%)	FIL 200 mg (N = 475)	FIL 100 mg (N = 480)	ADA 40 mg Q2W (N = 325)	PBO (N = 475)
Serious AEs	21 (4.4)	24 (5.0)	14 (4.3)	20 (4.2)
Serious infections	8 (1.7)	8 (1.7)	8 (2.5)	4 (0.8)
Herpes zoster	2 (0.4)	2 (0.4)	2 (0.6)	2 (0.4)
Adjudicated MACEs	0	1 (0.2)	1 (0.3)	2 (0.4)
Venous thrombotic events	1 (0.2)	0	0	2 (0.4)
Malignancies	0	1 (0.2)	1 (0.3)	3 (0.6)
Deaths	2 (0.4)	1 (0.2)	0	2 (0.4)

AE, adverse event; MACE, major adverse cardiovascular event

http://scientific.sparx-ip.net/archiveeular/?c=a&view=2&searchfor=FILGOTINIB&item=2019LB0001

- FINCH-2

Table 1

TEAEs and Key Safety Outcomes Week 0-24 by Age Group, n (%)

Regimen	<65 yrs (n=335) FIL 200(n=112)	<65 yrs (n=335) FIL 100(n=117)	≥65 yrs (n=113) PBO(n=106)	FIL 200(n=35)	FIL 100(n=36)	PBO(n=42)
TEAE	72 (64.3)	81 (69.2%)	70 (66.0%)	30 (85.7%)	16 (44.4%)	30 (71.4%)
Serious AE	4 (3.6)	7 (6.0%)	4 (3.8%)	2 (5.7%)	1 (2.8%)	1 (2.4%)
TEAE leading to study drug discontinuation	4 (3.6)	6 (5.1%)	1 (0.9%)	1 (2.9%)	0	2 (4.8%)
Infection	39 (34.8)	47 (40.2%)	27 (25.5%)	14 (40.0%)	5 (13.9%)	11 (26.2%)
Herpes Zoster (uncomplicated)	2 (1.8)	2 (1.7)	0	0	0	0
Serious infection	1 (0.9)	3 (2.6)	2 (1.9)	0	0	0
MACE	0	1 (0.9)	1 (0.9)	0	0	0
Retinal vein occlusion	1 (0.9)	0	0	0	0	0

http://scientific.sparx-ip.net/archiveeular/?view=1&c=a&searchfor=phase&item=2019FRI0154

Technically, FINCH-2 has a second thrombotic event across FINCH program … but its NOT deep vein (i.e., not DVT)

- FINCH-3

Table 2. Safety Events of Interest through Week 24

Patients with event, n (%)	FIL 200 mg + MTX (N = 416)	FIL 100 mg + MTX (N = 207)	FIL 200 mg Monotherapy (N = 210)	MTX Monotherapy (N = 416)
Serious AEs	17 (4.1)	5 (2.4)	10 (4.8)	12 (2.9)
Serious infections	4 (1.0)	2 (1.0)	3 (1.4)	4 (1.0)
Herpes zoster	2 (0.5)	1 (0.5)	1 (0.5)	2 (0.5)
Adjudicated MACEs	2 (0.5)	0	1 (0.5)	2 (0.5)
Venous thrombotic events	0	0	0	1 (0.2)
Malignancies	0	0	0	1 (0.2)
Deaths	1 (0.2)[a]	0	0	0

[a]Cause of death was lupus myocardiopathy.
AE, adverse event; MACE, major adverse cardiovascular event

http://scientific.sparx-ip.net/archiveeular/?c=a&view=2&searchfor=FILGOTINIB&item=2019LB0003

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C 646-789-5173

If anything, FINCH-1 shows platelet decrease

- FINCH 1 Ph3 RA Filgo + MTX – Platelet decrease should decrease DVT risk

Safety Through Week 24
Safety Analysis Set
FINCH1

Patients with TEAE, n (%)	FIL 200 mg (N = 475)	FIL 100 mg (N = 480)	ADA (N = 325)	PBO (N = 475)
Any TEAE	287 (60.4)	286 (59.6)	185 (56.9)	253 (53.3)
TEAE leading to study drug discontinuation	14 (2.9)	8 (1.7)	13 (4.0)	16 (3.4)
TEAE leading to study discontinuation	8 (1.7)	5 (1.0)	5 (1.5)	9 (1.9)
Serious TEAEs	21 (4.4)	24 (5.0)	14 (4.3)	20 (4.2)
Serious infections	8 (1.7)	8 (1.7)	8 (2.5)	4 (0.8)
Herpes zoster	2 (0.4)	2 (0.4)	2 (0.6)	2 (0.4)
Adjudicated MACEs	0	1 (0.2)	1 (0.3)	2 (0.4)
Venous thrombotic events	1 (0.2)	0	0	2 (0.4)
Malignancies excluding NMSC	0	1 (0.2)	1 (0.3)	3 (0.6)
Deaths[a]	2 (0.4)	1 (0.2)	0	2 (0.4)

[a]Includes all deaths (including TEAE)
ADA, adalimumab; FIL, filgotinib; NMSC, nonmelanoma skin cancer; MACE, major adverse cardiovascular event; PBO, placebo; TEAE, treatment-emergent adverse event

Treatment-Emergent Laboratory Abnormalities Through Week 24
Safety Analysis Set
FINCH1

Patients with Grade of event, %		FIL 200 mg n=475	FIL 100 mg n=480	ADA n=325	PBO n=475
Hemoglobin decreased:	Any grade	19.6	21.1	15.7	25.1
	Grade 3	0.4	0.6	0.6	0.9
	Grade 4	0	0	0	0
Neutrophils decreased:	Any grade	16.0	9.8	20.4	6.4
	Grade 3	1.1	0.8	0.3	0.4
	Grade 4	0	0.2	0	0
Lymphocytes decreased:	Any grade	15.2	10.3	7.4	13.4
	Grade 3	2.1	1.3	0.6	0.6
	Grade 4	0.2	0	0	0
Platelets decreased:	Any grade	3.6	4.0	2.2	2.8
	Grade 3	0	0	0	0
	Grade 4	0	0	0	0
ALT increased:	Any grade	28.9	26.2	31.8	24.7
	Grade 3	0.6	0.8	1.9	1.1
	Grade 4	0	0	0	0
AST increased:	Any grade	27.4	24.1	24.7	19.4
	Grade 3	0.6	0.4	0.6	0.2
	Grade 4	0	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIL, filgotinib; MTX, methotrexate; n, number of patients with result; N, number of patients with laboratory data available

- FINCH 3 Ph3 RA naïve to MTX, Filgo +/– MTX

Safety Summary Through Week 24
Safety Analysis Set
FINCH3

Patients with TEAE, n (%)	FIL 200 mg + MTX n=416	FIL 100 mg + MTX n=207	FIL 200 mg n=210	MTX n=416
Any TEAE	274 (65.9)	144 (69.6)	113 (53.8)	261 (62.7)
Serious TEAE	17 (4.1)	5 (2.4)	10 (4.8)	12 (2.9)
TEAE leading to study DC	8 (1.9)	3 (1.4)	4 (1.9)	4 (1.0)
Serious infection	4 (1.0)	2 (1.0)	3 (1.4)	4 (1.0)
Herpes zoster	2 (0.5)	1 (0.5)	1 (0.5)	2 (0.5)
Adjudicated MACE	2 (0.5)	0	1 (0.5)	2 (0.5)
Venous thrombotic event	0	0	0	1 (0.2)
Malignancy	0	0	0	1 (0.2)
Death	1 (0.2)[a]	0	0	0

[a]Cause of death was lupus myocarditis/pericarditis
DC, discontinuation; FIL, filgotinib; MACE, major adverse cardiovascular event;

Treatment-Emergent Laboratory Abnormalities Through Week 24
Safety Analysis Set
FINCH3

Patients with Grade of event, %		FIL 200 mg + MTX n=416	FIL 100 mg + MTX n=207	FIL 200 mg n=210	MTX n=416
Hemoglobin decreased:	Any grade	17.9	19.1	15.9	25.7
	Grade 3	1.0	0	0	1.0
	Grade 4	0	0	0	0
Neutrophils decreased:	Any grade	12.8	10.3	12.6	7.3
	Grade 3	0.2	1.0	0.5	0.2
	Grade 4	0	0	0.5	0
Lymphocytes decreased:	Any grade	13.6	9.3	10.6	10.9
	Grade 3	1.7	1.0	0	1.2
	Grade 4	0	0	0	0
Platelets decreased:	Any grade	4.4	3.9	3.4	2.7
	Grade 3	0.2	0.5	0	0
	Grade 4	0	0	0	0
ALT increased:	Any grade	28.1	30.9	15.9	27.4
	Grade 3	3.4	1.5	0.5	0.5
	Grade 4	0	0	0	0
AST increased:	Any grade	22.5	21.6	15.9	19.9
	Grade 3	1.2	0.5	1.0	0
	Grade 4	0	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIL, filgotinib; MTX, methotrexate; number of patients with laboratory data available

ons, FDA, EMA,
Evercore ISI Estimates, Medical Journals, Pubmed, USPTO, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C 646-789-5173

We have also seen long-term safety from DARWIN-3

event per 100 PYE	filgotinib 50-200 mg DARWIN 3 week 156
patient year exp.	2,203
serious infection	1.2
herpes zoster	1.5
DVT/PE	2/2,203* 0.1
deaths	0.2

Data on file; DVT/PE = deep venous thrombosis/pulmonary embolism
** one single patient experiencing DVT and PE*

Sources: Company documents, Conference Presentations, FDA, EMA, Evercore ISI Estimates, Medical Journals, Pubmed, USPTO, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C 646-789-5173

Additional data from DARWIN-1 and -2

- DARWIN 1 Ph2b RA, add-on to MTX 24 wk

TEAEs of special interest
Week 0-24

Subjects with:	placebo only (N=56)	filgotinib exposed (N=538)
All infections	17.9%	25.5%
All serious infections	1.8%	0.9%
Herpes zoster	1.8%	0.7%
Urinary tract infections	1.8%	3.7%
Upper RTI	1.8%	3.7%
Pneumonia	0.0%	0.4%
MACE*	0.0%	0.4%

* non fatal and not considered drug related
No cases of opportunistic infections, tuberculosis, malignancies or lymphoma

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Safety
Week 0-24, change versus baseline

Parameter	Measure
Hemoglobin	increase up to 4%
Platelets	decrease towards mid normal value
Lymphocytes	no effect
Neutrophils	decrease towards mid normal value
Creatinine	increase up to 11%
ALT	no CTCAE gr 3-4
Lipids	increase of HDL (up to 23%) > LDL (up to 13%)
Male reproductive hormones	no clinically meaningful changes; no discontinuations

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- DARWIN 2 Ph2b RA mono, 24 wk f/u

Safety – DARWIN 1 & 2
Week 0-24, change versus baseline

Parameter	Measure
Hemoglobin	increase up to 4%
Platelets	decrease towards mid normal value
Lymphocytes	no drop
Neutrophils	decrease towards mid normal value
Creatinine	increase up to 13%
ALT	no CTCAE gr 3-4 on treatment
Lipids	increase of HDL (up to 24%) & LDL (up to 17%)
Male hormones	no clinically meaningful changes

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Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C 646-789-5173

… and also, EQUATOR Ph2 PsA

	Filgotinib (n=65)	Placebo (n=66)
Treatment-emergent adverse events		
All	37 (57%)	39 (59%)
Nasopharyngitis	8 (12%)	10 (15%)
Headache	3 (5%)	5 (8%)
Blood cholesterol increased	5 (8%)	0
Diarrhoea	2 (3%)	2 (3%)
Dizziness	2 (3%)	2 (3%)
Drug-related	11 (17%)	9 (14%)
Serious	1 (2%)*	1 (2%)
Drug-related serious	1 (2%)*	0
Serious treatment-emergent infection	1 (2%)*	0
Grade 3 or worse	1 (2%)*	5 (8%)
Led to permanent discontinuation of study drug	1 (2%)†	0
Treatment-emergent adverse events of special interest		
Infections	14 (22%)	14 (21%)
All serious infections	1 (2%)*	0
Opportunistic infections	0	0
Herpes zoster	1 (2%)	0
Active tuberculosis	0	0
Urinary tract infections	1 (2%)	3 (5%)
Respiratory tract infections	10 (15%)*	10 (15%)
Malignancies	0	0
Deep venous thrombosis	0	0
Pulmonary embolism	0	0
Major adverse cardiovascular events	1 (2%)*	0
Deaths due to treatment-emergent adverse event	1 (2%)*	0

Data are n (%). The top five most common treatment-emergent adverse events are shown. *One patient died following onset of pneumonia (the same single case is represented in several categories). †Since treatment in the patient that died was not discontinued before, this patient is not included here.

Table 4: **Safety endpoints (full analysis set)**

Sources: Company documents, Conference Presentations, FDA, EMA, Evercore ISI Estimates, Medical Journals, Pubmed, USPTO, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C 646-789-5173

Meanwhile, FDA appears increasingly more comfortable with testicular safety

	MANTA-RAy	MANTA
Objective	Semen parameters in adult males **Results may be pooled with MANTA, total N in both trials ~250**	Testicular safety in adult males
Indications	Active RA, PsA, AS, nr-AxSpA	Mod-sev active UC
N	250	250
Design	Experimental x **13 wk** ->** OL Extension x 143 wk if sperm parameters OK. If sperm decline during OLE enter Monitoring; OR Monitoring x 39 wk (if >=50% decline in sperm conc., **motility, and/or morphology**)	Experimental x **26 wk** ->** LTE x 195 wk (if Sperm conc. OK); OR Monitoring (if >=50% decline in sperm conc.)
Arm	Experimental: Filgo 200 mg qD vs Pbo x 13 wk. OLE Filgo responder: Filgo 200 mg qD up to wk 156. OLE Filgo non-responder & Pbo pts: SOC. Monitoring: SOC up to wk 52 or until semen parameters reversibility	Experimental: Filgo 200 mg qD vs pbo x 26 wk. LTE responder: continue same blinded tx. LTE non-responder: OL filgo x add'l 195 wk. Monitoring: SOC.
Primary endpoint	% pts with >=50% decline in Sperm Conc. @wk 13	% pts with >=50% decline in Sperm Conc. @wk 13
Age	**21–65 y**	25–55 y
Inclusion	Active RA, PsA, AS, nr-AxSpA for >=12 wk	Endoscopic & histopathologic evidence of UC. UC for >= 4 mo && minimum disease extent of 15 cm from anal verge.
Exclusion	Prior male reproductive problem/infertility; Concomitant prohibited medications;	Prior male reproductive problem/infertility; Concomitant prohibited medications; Active TB; CD, other colitis, toxic mega-colon;
Clinical sites	1 in Estonia (more may likely be added on update)	US, Can, Aus, EU, India, Taiwan
Start	May 2019	Jul 2017
Primary completion	Jan 2021	Jan 2021

- It is my understanding that as GILD/GLPG generated more data, it is not seeing any changes on male hormones at 200 mg dose
- FDA has signed off on filing with interim data

Sources: Company documents, Conference Presentations, FDA, EMA, Evercore ISI Estimates, Medical Journals, Pubmed, USPTO, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C 646-789-5173

Summing it up

News

- FDA has issued black box on Xeljanz 10 mg
- We had previously seen Olumiant launch get affected by DVT warnings

Structural similarity

- Almost all JAK inhibitors share pyrrolo pyrimidine – except filgotinib, fedratinib and Aclaris JAK

JAK selectivity, JAK2 & DVTs

- JAK2 knockout impairs Mpl's ability to remove TPO – increasing platelets – and thus clotting risk
- baricitinib's JAK2 selectivity and increased DVT risk as per FDA
- Cell based assays best way to assess selectivity

Filgotinib safety experience

- No DVT imbalance
- No platelet increase
- FDA comfortable filing on interim MANTA data on testicular tox

Sources: Company documents, Conference Presentations, FDA, EMA, Evercore ISI Estimates, Medical Journals, Pubmed, USPTO, Court documents

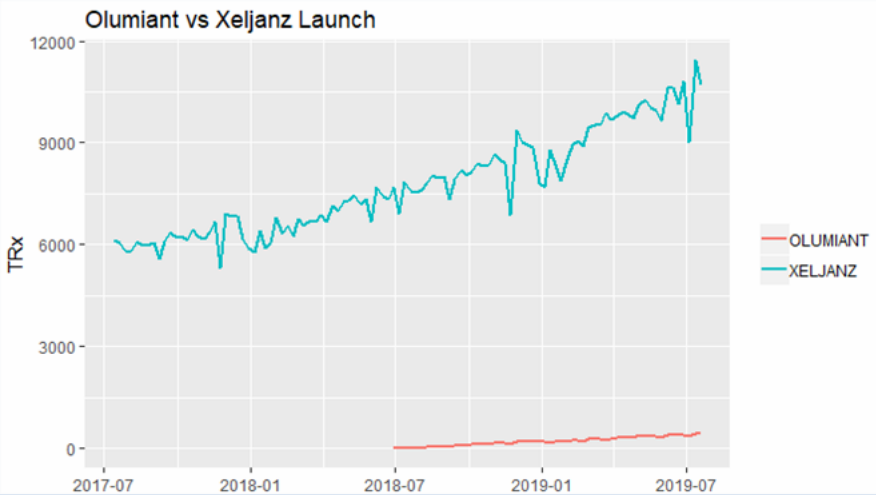
Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C 646-789-5173

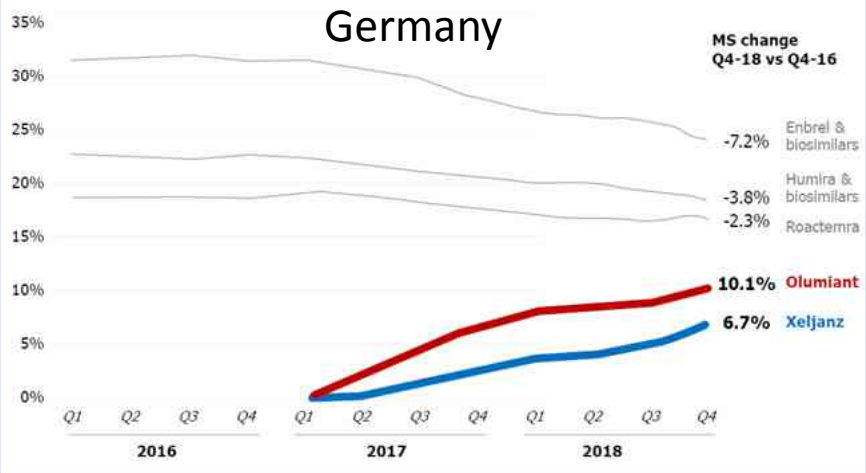
Appendix

Sources: Company documents, Conference Presentations, FDA, EMA, Evercore ISI Estimates, Medical Journals, Pubmed, USPTO, Court documents

Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C 646-789-5173

Olumiant (baricitinib) launch
US = ☹
EU = ☺





	1Q17	2Q17	3Q17	4Q17	2017	1Q18	2Q18	3Q18	4Q18	2018	1Q19
Olumiant (baricitinib)											
US	0	0	0	0	-	0	2	1	4	7	6
Europe	2	5	15	22	43	31	0	48	56	134	62

Sources: Company documents, Conference Presentations, FDA, EMA, Evercore ISI Estimates, Medical Journals, Pubmed, USPTO, Court documents