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

However, JAK2 acts uniquely in this cascade:

****JAK2 uniquely forms a homodimer which is impt in hematopoiesis via signal transduction associated with EPO and TPO → THIS IS V V IMPT**

Steps:

1. Cytokine binds to receptor subunits →
2. causes formation of dimer (or higher complex) of receptor subunits →
3. recruits a pair of JAK enzymes to receptor subunit →
4. JAKs become phosphorylated, and phosphorylate the receptor subunit →
5. phosphorylated residues serve as binding site for STAT proteins →
6. enable STAT dimerization and translation to nucleus

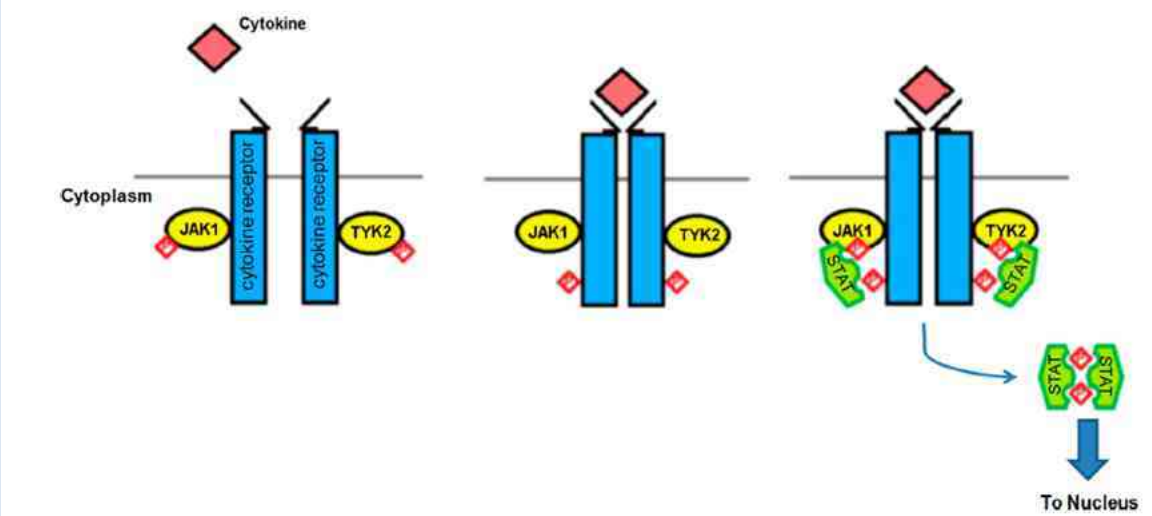


Figure 2. Basic mechanism of JAK/STAT mediated cytokine signaling.

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

There is mechanistic rationale for JAK2 involvement in platelet increases

- Steps:
  1. Liver makes a hormone called TPO →
  2. binds to Mpl (homodimer) on HSC →
  3. differentiates HSC into megakaryocytes →
  4. migrate towards bone marrow sinusoidal cells →
  5. extend pseudopodial projections through endothelial layer →
  6. shed platelets into bloodstream

- JAK2 knockout in HSC/progenitor cells induces anemia and thrombocytopenia (low platelets)

- Selective deletion of Mpl in mature platelets in mice leads to thrombocytosis (high platelets)

Under normal conditions, Mpl expressed on circulating platelets bind to and internalize circulating TPO for subsequent degradation via a JAK2 dependent mechanism.
In this way, circulating TPO levels are maintained at an appropriate level. With the loss of JAK2 function in mature platelets in this animal model, Mpl are not able to effectively remove TPO from the blood, resulting in elevated circulating TPO levels. JAK2 function is maintained in HSCs and MK progenitors in this model.

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

If TPO levels in bone marrow are not maintained, HSC expansion results in platelet increase (thrombocytosis)

- Under normal conditions, Mpl expressed on circulating platelets bind to and internalize circulating TPO for subsequent degradation via a JAK2 dependent mechanism.
- **In this way, circulating TPO levels are maintained at an appropriate level.**
- **With the loss of JAK2 function in mature platelets** in this animal model, Mpl are not able to effectively remove TPO from the blood, resulting in elevated circulating TPO levels. JAK2 function is maintained in HSCs and MK progenitors in this model

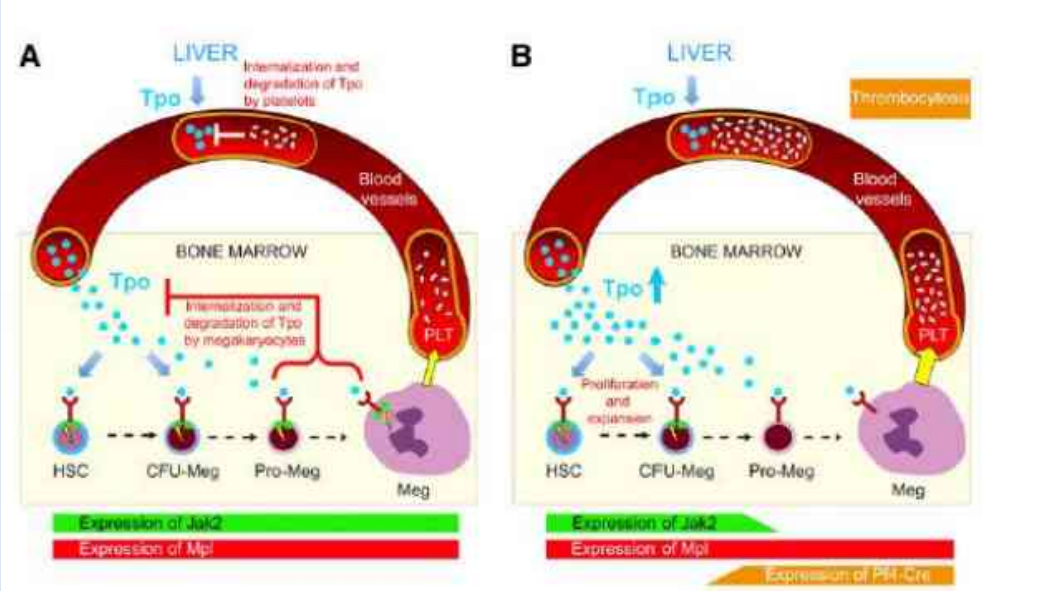


Figure 3. From Skoda (2014)[11]. *Left panel*: Under normal conditions, TPO produced in the liver reaches the bone marrow and stimulates MK differentiation via activation of Mpl (shown in red) on HSCs and MK progenitors. Note that JAK2 enzymes are represented as green circles associated with the intracellular portion of Mpl. *Right panel*: Selective deletion of *Jak2* in megakaryocytes and mature platelets as described in Meyer et al. (2014) leads to increased circulating TPO levels because Mpl is unable to remove and degrade TPO. JAK2 function is maintained in HSCs and MK progenitors in this animal model. Elevated TPO levels in bone marrow lead to expansion of HSCs and MK progenitors resulting in thrombocytosis.

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

Guess where FDA discussed this JAK2's involvement in platelet increase?

Platelets are anucleated cells that are released into the blood from megakaryocytes present in the bone marrow. Megakaryocytes are formed through the process of megakaryopoiesis (Figure 1). Megakaryopoiesis involves the differentiation and maturation of hematopoietic stem cells (HSCs) residing in the bone marrow into megakaryocyte progenitors and ultimately into mature megakaryocytes (MKs)[6]. Megakaryopoiesis is primarily mediated by thrombopoietin (TPO), a

Reviewer: Matthew Whittaker, Ph.D. NDA 207924

glycoprotein hormone produced mainly in the liver. TPO binds to TPO receptors (myeloproliferative leukemia protein, Mpl) expressed on HSCs and megakaryocyte progenitors and stimulates the differentiation of HSCs to megakaryocytes. Mpl is a homodimeric cytokine receptor that associates with JAK2. Downstream effects of JAK2 activation are mediated by STAT, MAPK and PI3K.

Megakaryocytes migrate toward bone marrow sinusoidal endothelial cells, and extend pseudopodial projections termed protoplatelets through or between the cells of the sinusoidal endothelial layer and shed platelets into the bloodstream.

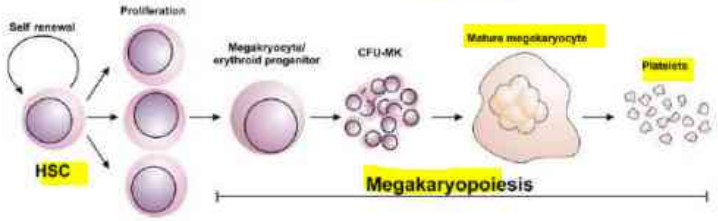


Figure 1. From Geddis (2010). Megakaryopoiesis (differentiation and maturation of hematopoietic stem cells to megakaryocytes in bone marrow) is mediated by thrombopoietin.

- LLY's baricitinib review

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

FDA has actually opined on a possible mechanistic link between JAK2 and platelet increases (and hence the DVT risk)

FDA briefing on baricitinib

- The initial spike in peripheral blood platelets observed after 14 days of treatment may be due to inhibition of Mpl-associated JAK2 in peripheral platelets and a subsequent increase in circulating TPO.
- During this early time period of treatment, bone marrow concentrations of baricitinib may not be sufficient to inhibit Mpl-associated JAK2 function in HSCs and MK progenitors. These conditions would allow for TPO-induced expansion of these cell types resulting in increased peripheral blood platelets.
- The peak platelet level occurred at a time point that correlates approximately with the platelet lifespan in humans of 10 – 14 days. At later time points, bone marrow baricitinib concentrations are likely to be sufficient to inhibit JAK2 in HSCs and MK progenitors.
- A new steady-state would be reached whereby the potential stimulatory effects of elevated circulating TPO would be mitigated by the inhibitory effect of baricitinib on JAK2 function in HSCs and MK progenitors

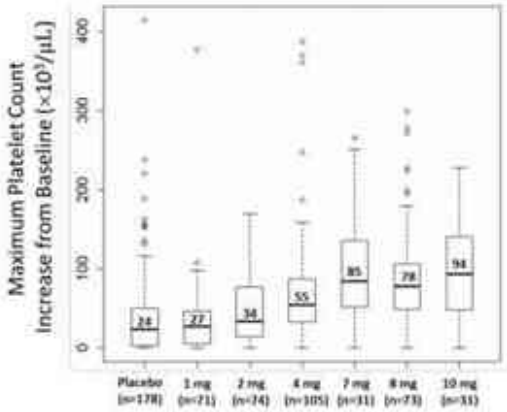
Sources: Company documents, Conference Presentations, FDA, EMA, Evercore ISI Estimates, Medical Journals, Pubmed, USPTO, Court documents

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

For JAK2, this looks particularly concerning since baricitinib is a selective JAK2 inhibitor with evidence of platelet increases

Summary of Resubmission and DPARP/OND Recommendations — NDA 207924 Baricitinib, a JAK inhibitor for RA

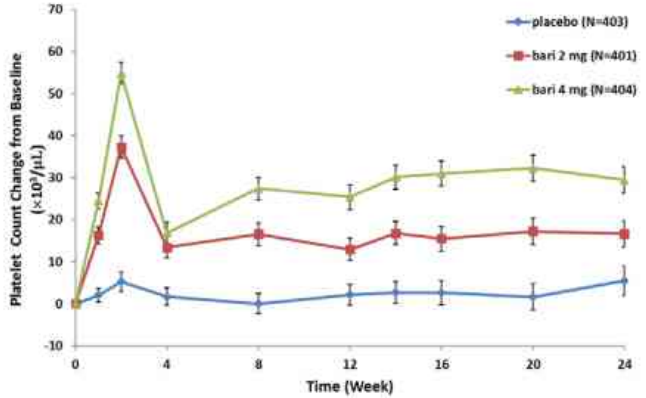
Figure 3. Maximal Platelet Count Increase from Baseline by Baricitinib Dose.



Source: platelet.xpt dated on 2/15/2018

The same dose-dependent trend was observed in two phase 3 studies (JADX and JADW) which investigated both 2 mg and 4 mg doses of baricitinib (Figure 4). The elevation of mean platelet count peaked around Week 2 following baricitinib once daily treatment and was 37×10^3/μL and 55×10^3/μL higher than the baseline in the 2 mg group and 4 mg group, respectively. After Week 8, the mean platelet count remained stable in the baricitinib groups with an approximately 15×10^3/μL and 30×10^3/μL increase from baseline in the 2 mg group and 4 mg group, respectively. Figure 4 shows mean platelet count change from baseline over time by placebo (blue), baricitinib 2 mg (red) and baricitinib 4 mg (green) groups from pooled results from Studies JADX and JADW.

Figure 4. Pooled JADX and JADW: Mean Platelet Count, Change from I 24



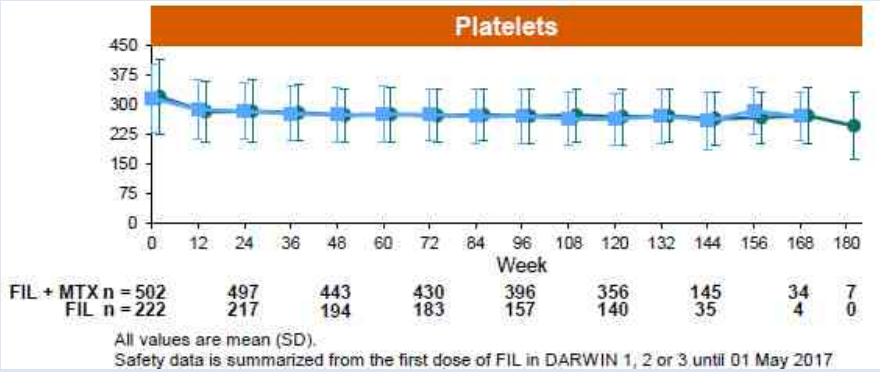
Source: Study JADW and Study JADX

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

Filgotinib does look like a selective JAK1 inhibitor – see this platelet data:

GILD's filgotinib



Incidence rate (Events)		FIL 200 mg + MTX n=502 PYE=1189	FIL 200 mg n=222 PYE=486
Platelets	Grade 1	2.2 (26)	0.4 (2)
	Grade 2	0.3 (3)	0
	Grade 3	0.1 (1)	0
	Grade 4	0.1 (1)	0

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

Thinking through safety risk on various JAKs:

JAK-STAT biology & role of JAK2 in platelet increases (DVT risk)

Comparing chemical structures of various JAK inhibitors

IC50s for JAK inhibitors + assay types

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

So far:

- We've seen lots of evidence for JAK2 being a bad actor
- We've also seen some JAK inhibitors call themselves "JAK1" etc.
- However, this JAK1 vs JAK2 specificity is a scale … and NOT absolute

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

Let's start with a (overly) simple table

	Brand Name	Company	JAK1	JAK2	JAK3	Tyk2
Tofacitinib	Xeljanz	Pfizer	XX	X	XX	X
Baricitinib	Olumiant	Lilly	X	XX		
Ruxolitinib	Jakafi	Incyte	X	XX		
[redacted]			XX			
Filgotinib		Gilead	XX			
BMS-986165		Bristol				XX
PF-04965842		Pfizer	XX	X		
PF-06651600		Pfizer			XX	
PF-06700841		Pfizer	XX			XX
CTP-543		Concert	XX	XX		
ATI-502		Aclaris	XX		X	

– The JAK selectivity above is overly simplified … in reality, its much more nuanced, and often varies depending on assay selectivity … we'll discuss on next few slides

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

JAK family members have a very high sequence homology … e.g., check out the blue (JAK3) vs magenta lines (JAK2)

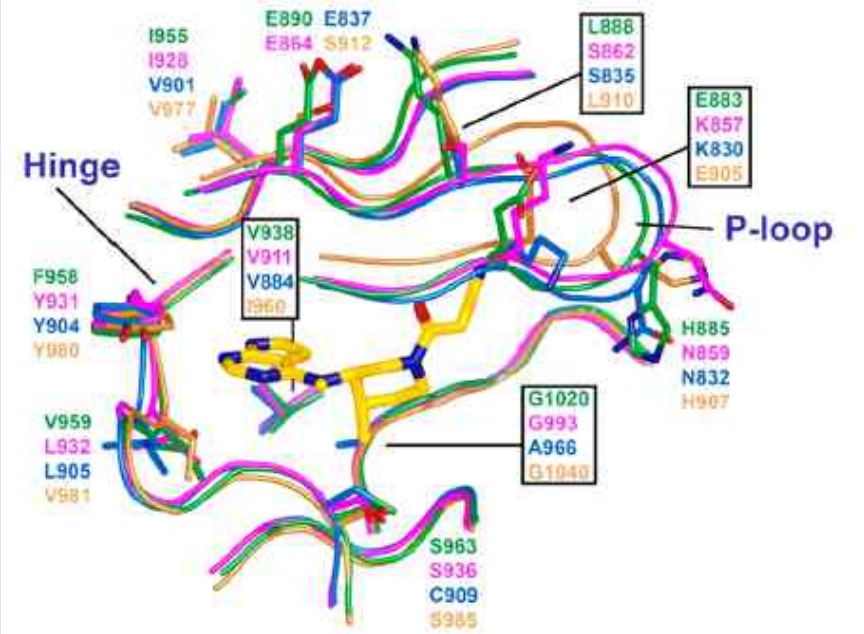


Figure 4. X-ray cocrystal structures with sequence alignment for JAK1 (green, 3EYG), JAK2 (magenta, 3FUP), JAK3 (blue, 3LXK), and TYK2 (orange, 5WAL).[5,21,32,33]

- Very subtle amino acid differences across JAK family in regions where various JAK inhibitors bind

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

If we look at chemical structures of most JAK inhibitors of interest, they all share one common theme: pyrrolo(2,3-d)pyrimidine

Tofacitinib **Baricitinib** **Ruxolitinib**

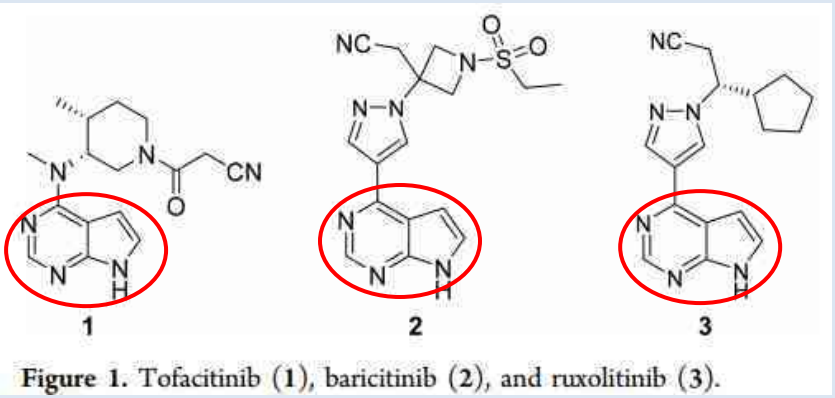
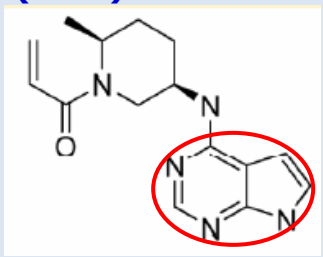
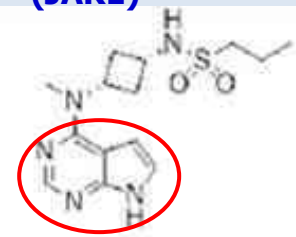


Figure 1. Tofacitinib (1), baricitinib (2), and ruxolitinib (3).

PF-06651600 (JAK3)

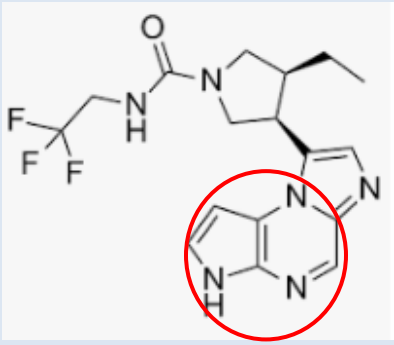


PF-04965842 (JAK1)



PF-04965842
(Compound 25)
JAK1 selective

[redacted]



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

… except Gilead's filgotinib & fedratinib

Tofacitinib **Baricitinib** **Ruxolitinib**

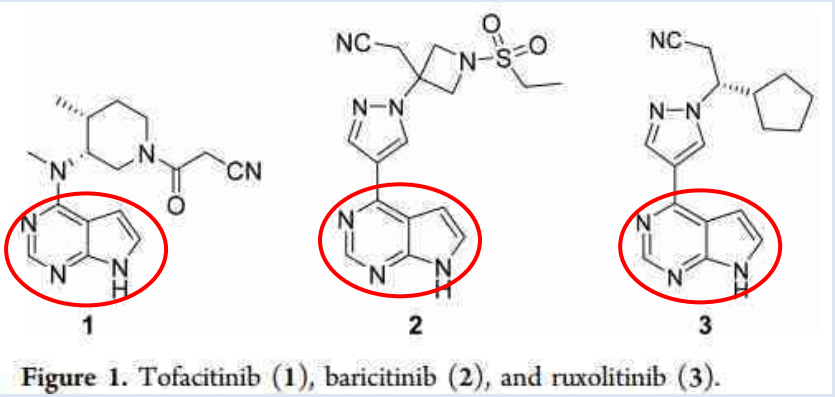
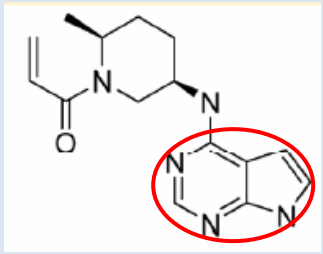
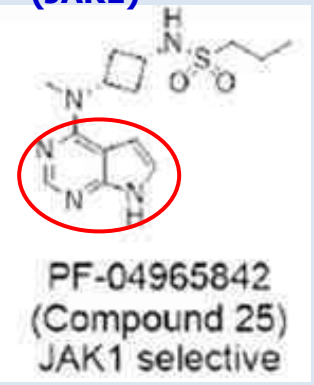


Figure 1. Tofacitinib (1), baricitinib (2), and ruxolitinib (3).

PF-06651600 (JAK3)



PF-04965842 (JAK1)



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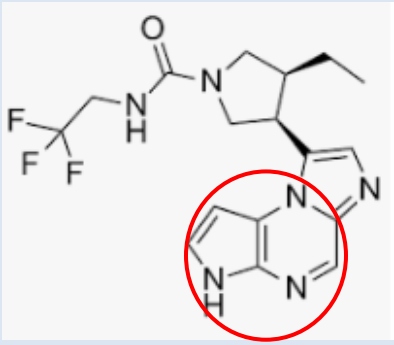
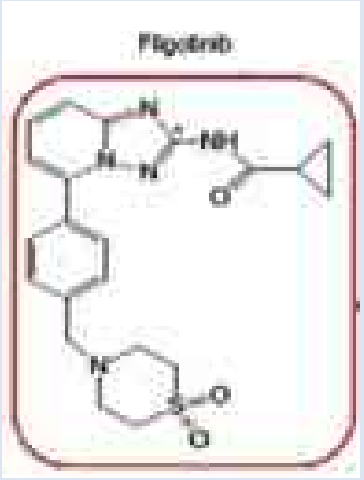
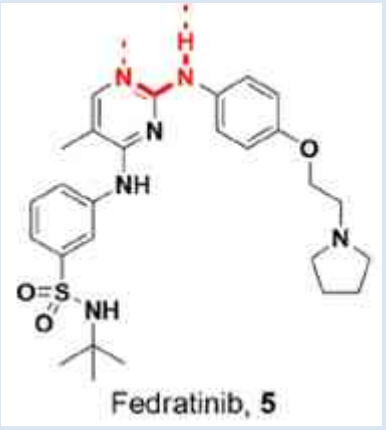


Gilead filgotinib >>





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

Significance of pyrrolo(2,3-d)pyrimidine

- Hinge binding is through a 2-pronged interaction between **pyrole NH** and **pyrimidine N1**

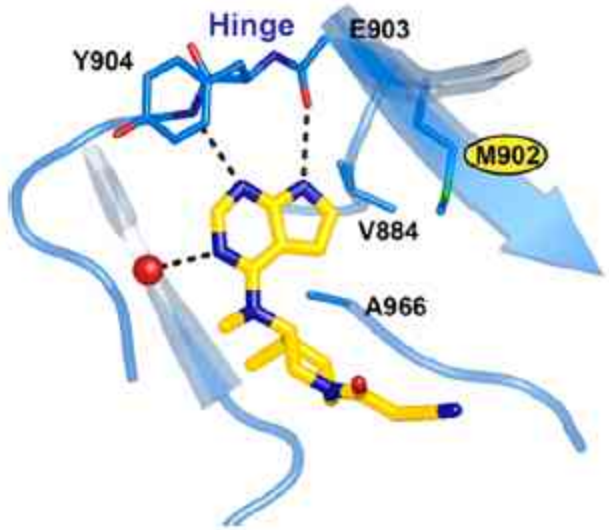


Figure 3. Tofacitinib (1) cocrystallized with JAK3 (3LXK).[21] Hydrogen bonds to hinge residues Tyr904 and Glu903 and a conserved water are presented as black dashes. In addition, gatekeeper residue Met902 is highlighted.

previously.[3] Briefly, hinge binding is through a two-pronged interaction between the pyrole NH and the pyrimidine N1 with the backbone of hinge residues Tyr904 and Glu903 in JAK3.[21,22] This is a common motif among JAK inhibitors. The C6 hydrogen points back toward gatekeeper residue Met902 and a Met for all members of the JAK family. The aminopiperidine presents the acyl nitrile under the P-loop cleft while the piperidine methyl groups helps maximize interaction with a hydrophobic pocket.

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

Here's the hinge binding for pyrole NH and pyrimidine N1 in play:

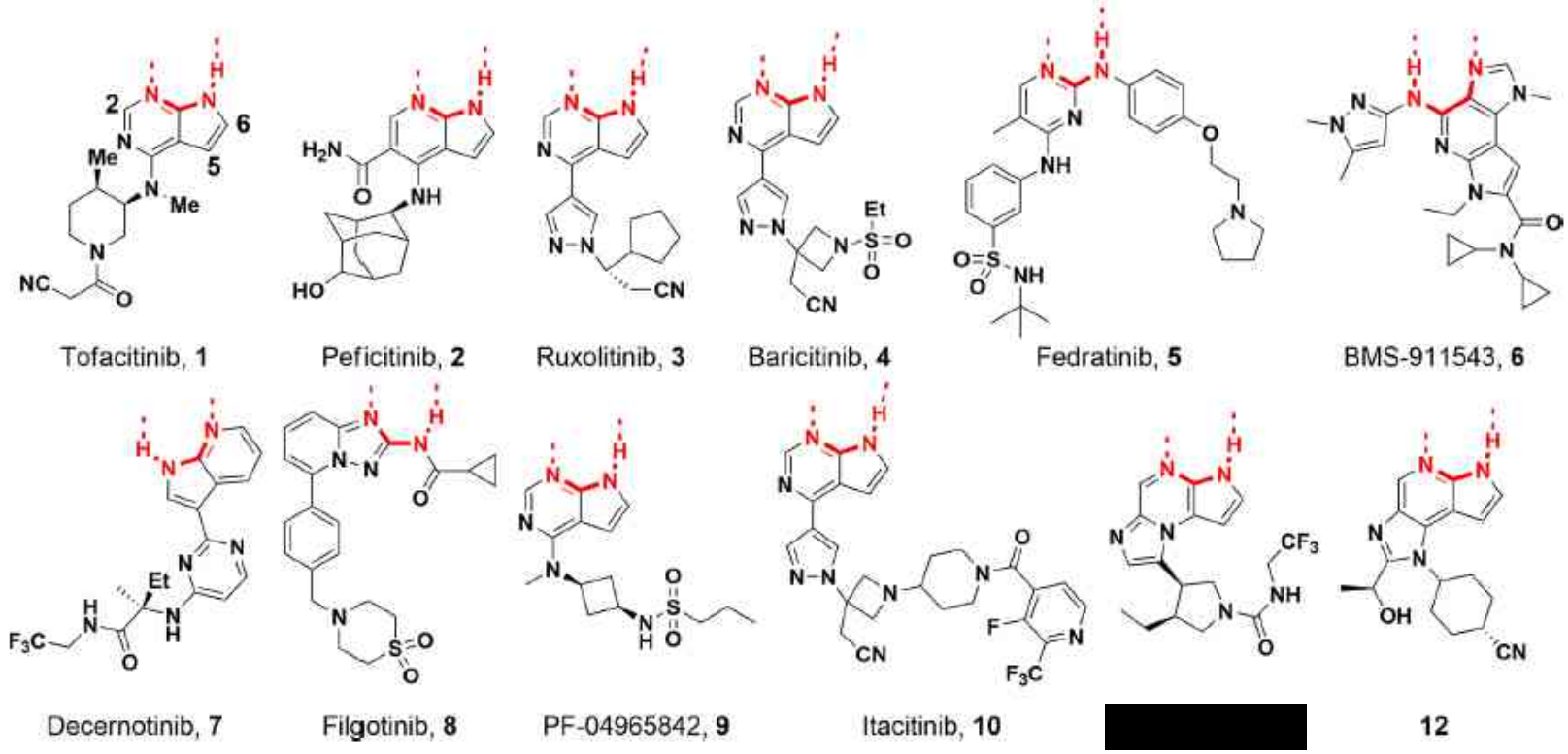


Figure 2. Example inhibitors of the JAK/STAT pathway in the clinic for the treatment of immunological diseases or approved by the FDA. Atoms participating in binding to the hinge region of the active site are shown in red with dashed lines for putative hydrogen bonds.

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

Thinking through safety risk on various JAKs:

JAK-STAT biology & role of JAK2 in platelet increases (DVT risk)

Comparing chemical structures of various JAK inhibitors

IC50s for JAK inhibitors + assay types

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

Let's start by looking at JAK1 vs JAK2 vs JAK3 on a kinase map:

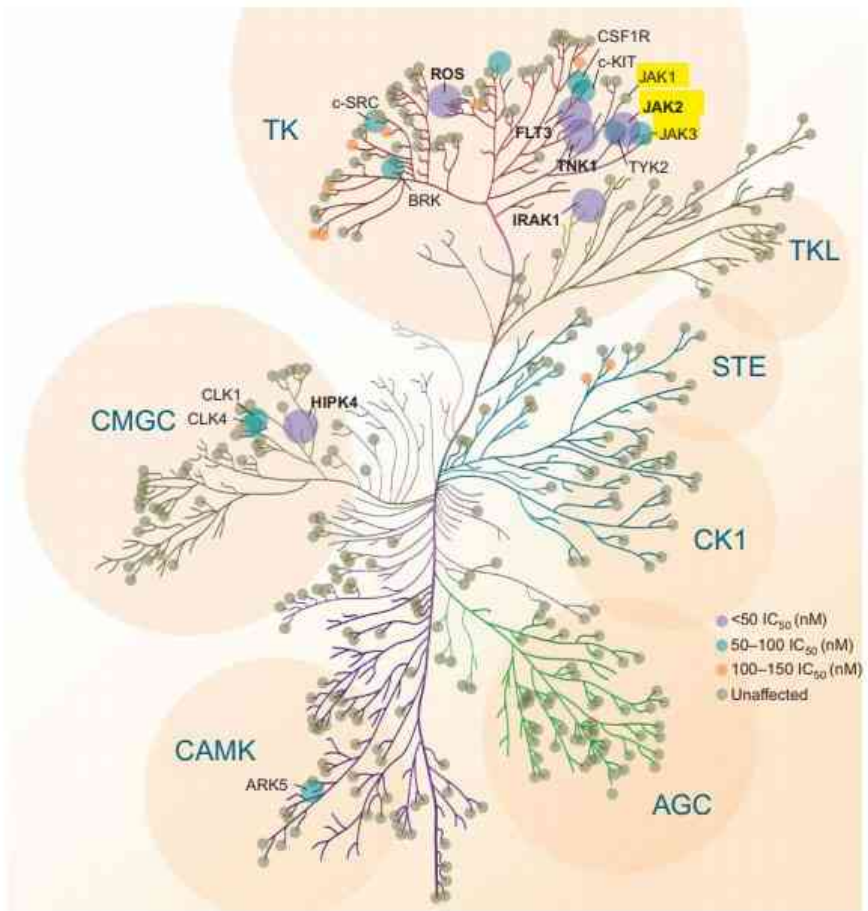
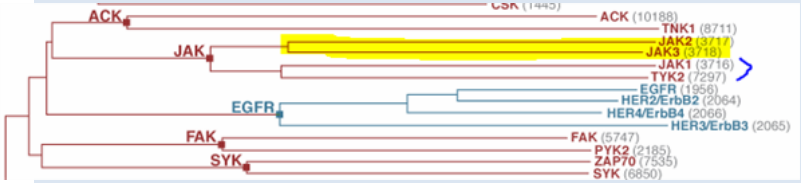


Figure 2 Pacritinib activity kinome map.
Abbreviations: AGC, protein kinase A, G, C group; ARK, Beta-adrenergic receptor kinase; BRK, breast tumor kinase; CK1, casein kinase; CLK, CDC Like Kinase 1; CSF1R, colony-stimulating factor 1 receptor; FLT3, fms-like receptor tyrosine kinase 3; HIPK4, homeodomain-interacting protein kinase 4; IC_{50}, half maximal inhibitory concentration; IRAK1, interleukin-1 receptor-associated kinase 1; JAK, Janus kinase; STE, homolog of sterile; TK, tyrosine kinase; TKL, tyrosine kinase-like group of kinases; TNK1, tyrosine kinase nonreceptor 1; TYK2, tyrosine kinase 2.



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

Perhaps this JMC image makes the point in a more direct way: look at the high sequence homology among JAK family members in the ATP binding domain

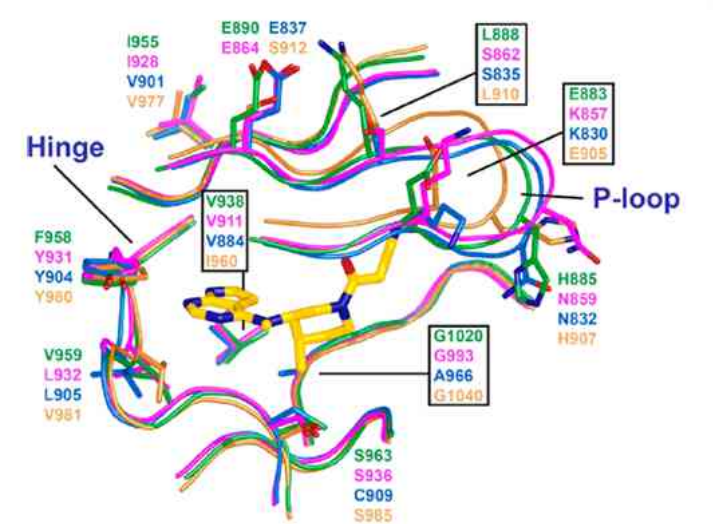


Figure 4. X-ray cocrystal structures with sequence alignment for JAK1 (green, 3EYG), JAK2 (magenta, 3FUP), JAK3 (blue, 3LXK), and TYK2 (orange, 5WAL).[5,21,32,33]

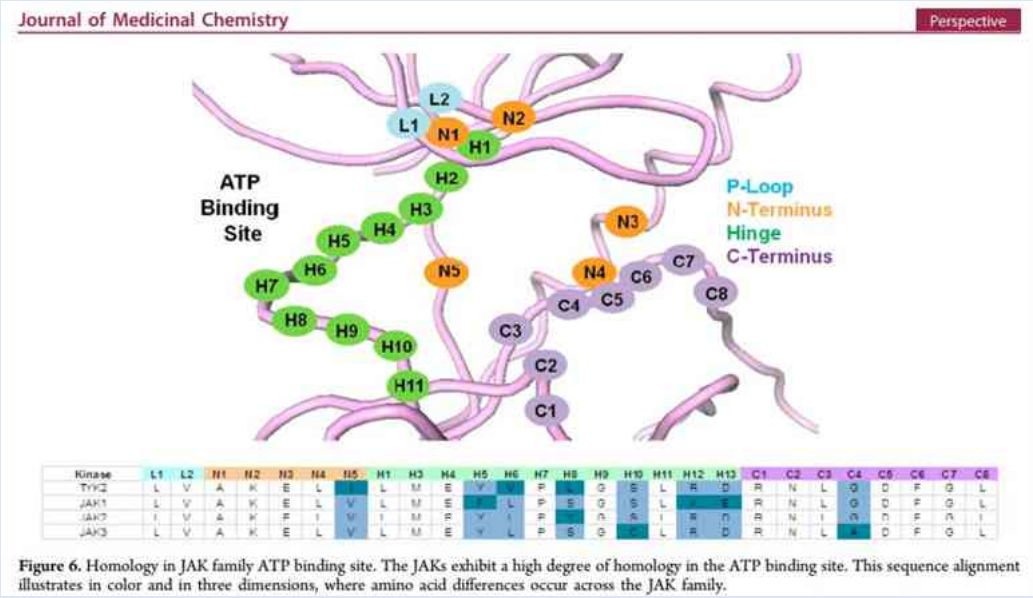


Figure 6. Homology in JAK family ATP binding site. The JAKs exhibit a high degree of homology in the ATP binding site. This sequence alignment illustrates in color and in three dimensions, where amino acid differences occur across the JAK family.

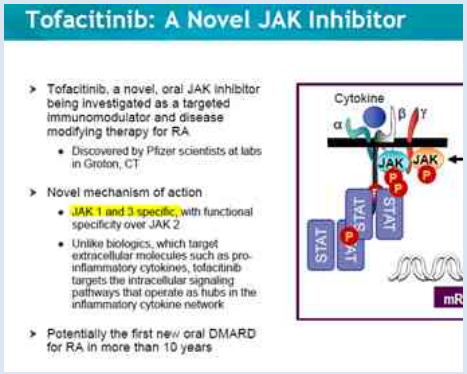
Sources: Company documents, Conference Presentations, FDA, EMA, Evercore ISI Estimates, Medical Journals, Pubmed, USPTO, Court documents

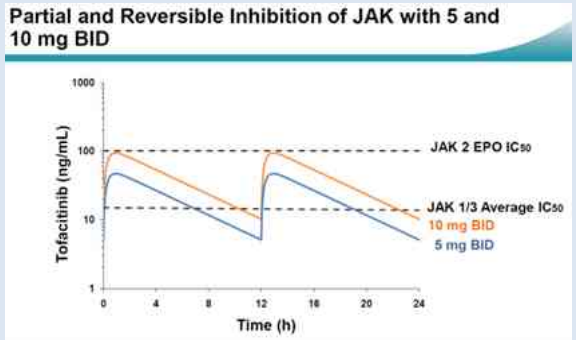
Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C 646-789-5173

We've often seen JAK inhibitors get characterized as JAK1 or JAK2 … and sometimes, the description keeps changing

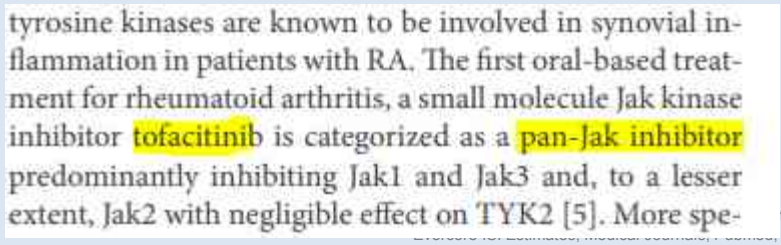
- PFE's 2009 slides called Xeljanz a **JAK3** inhibitor

- PFE's 2011 ACR slides and AdCom slides called it a JAK1 and JAK3 inhibitor





- More recent literature calls it a pan-JAK inhibitor



tyrosine kinases are known to be involved in synovial inflammation in patients with RA. The first oral-based treatment for rheumatoid arthritis, a small molecule Jak kinase inhibitor tofacitinib is categorized as a pan-Jak inhibitor predominantly inhibiting Jak1 and Jak3 and, to a lesser extent, Jak2 with negligible effect on TYK2 [5]. More spe-

tations, FDA, EMA, USPTO, Court documents

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

The reason JAK selectivity information varies is because of assay type being used

- I don't intend to bore you here, but I do wanna make an impt point
- E.g., look at this description of baricitinib & JAK3 in FDA review:

Eli Lilly designed baricitinib with the intention to be selective for JAK1 and JAK2. The rationale for sparing JAK3 inhibition was to reduce the immune suppressive effects associated with pan-JAK inhibition. In isolated enzyme assays comparable to those conducted with tofacitinib, baricitinib inhibited the function of JAK1, JAK2, and TYK 2 with a potency of 5.7 – 53 nM. Inhibitory potency at JAK3 was >400 nM. However, the JAK3-sparing selectivity of baricitinib was not recapitulated in cell-based assays conducted in human leukocyte preparations[4].

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

101 on cell based assays vs enzyme assays

Enzyme assays

- JAK always act in concert - except JAK2 (homodimer) … and as a result, enzyme to cell assay data is v hard in silo
- Thus, Enzyme assays don't tell the whole picture
  - Specific kinase domains are cloned, expressed in certain cells and the JAK kinase assays use a fluorescence assay with peptide substrate … and IC50 is simply the concentration required for 50% inhibition of fluorescent signal

Cell based assays

- Cell based assays: analyzes the full kinase
  - from structure of JAK kinases (which are large proteins)
  - it only involves catalytic kinase domains
  - in this assay, you interrogate all 7 domains of the protein
  - However, to be clear, there are no cell based assays purely driven by JAK1 or JAK3 … in cells, all receptors utilize 2 different kinases - either JAK1/2 or JAK1/3, or Tyk2

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

This paper has a very helpful analysis of JAK selectivity by enzyme vs human whole blood assay:

Journal of Medicinal Chemistry Perspective

Table 1. JAK Kinase and Whole-Cell Assays: Comparison of Enzymatic and Whole-Cell Activity for Experimental and Approved JAK Inhibitors for Inflammatory Indications

	enzyme assay IC_{50} (nM)[a]				human whole blood (HWB) IC_{50} (nM)[a,b,c,d,e,f,g]					
compd	JAK1	JAK2	JAK3	TYK2	IL-15[b] P-stat5	IL-6[c] P-stat1	IL-12[d] P-stat4	IFNα[e] P-stat3	IL-23[d] P-stat3	CD34+[g] cells EPO[f] P-stat5
1	15.1	77.4	55.0	489	55.8	75.4	409	35.0	229	302
5	6.4	8.8	487.0	30.1	1850	298	1090	194	818	677
6	4.0	6.6	787.0	61.0	259	21.1	149	28.7	81.9	87.8
7	112	619	74.4	>10K	932	1870	16400	1290	11200	>20K
8	363	2400	>10K	2600	2140	918	13362	1500	10123	13200

[a]Run in the presence of 1 mM ATP. [b]Signals through JAK1/JAK3. [c]Signals though JAK1/JAK2 or TYK2. [d]Signals through JAK2/TYK2. [e]Signals through JAK1/TYK2. [f]Signals through JAK2/JAK2. [g]CD34+ cells spiked into human whole blood (HWB). Data reported for tofacitinib (**1**), ruxolitinib (**5**), baricitinib (**6**), decernotinib (**7**), and filgotinib (**8**).

JMC paper - Clark et al - 2014

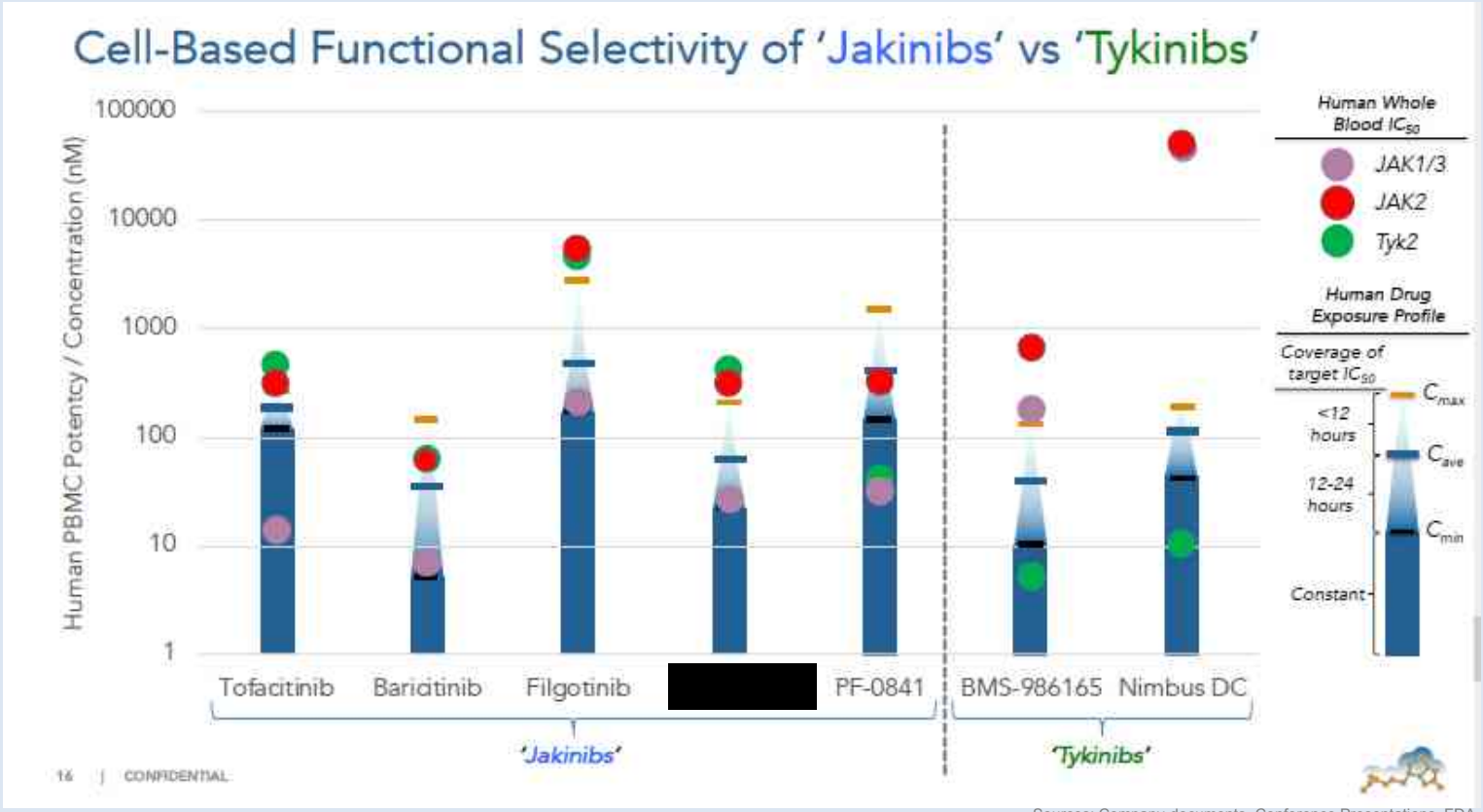
	enzyme assay					whole blood assay					
						IL-15 pSTAT5	IL-6 pSTAT1	IL-12 pSTAT4	IFN-alpha pSTAT3	IL-23 pSTAT3	CD34+ EPO pSTAT5
	JAK1	JAK2	JAK3	Tyk 2	*runs thru:*	JAK1/JAK3	JAK1/JAK2	JAK2/Tyk2	JAK1/Tyk2	JAK2/JAK2	
Tofacitinib	15	77	55	489		56	75	409	35	229	302
Ruxolitinib	6	9	487	30		1,850	298	1,090	194	818	677
Baricitinib	4	7	787	61		259	21	149	29	82	88
Decernotinib	112	619	74	10,000		932	1,870	16,400	1,290	11,200	20,000
Filgotinib	363	2,400	10,000	2,600		2,140	918	13,362	1,500	10,123	13,200
PF-06651600	10,000	10,000	33	10,000		51					
PF-04965842	29	803	10,000	125					1,890		7,180

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

So let's turn to a nice image on JAK selectivity from cell-based assays from a company slide:

The higher the red dot (JAK2) relative to other dots, the more selective AGAINST JAK2

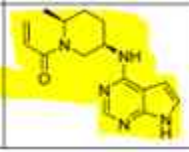


Sources: Company documents, Conference Presentations, FDA, EMA, Evercore ISI Estimates, Medical Journals, Pubmed, USPTO, Court documents

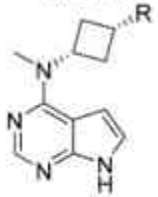
Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C 646-789-5173

Specific IC50 values we've found (1)

- PF-06651600:
  - JAK3

Cmpd #	Structure	JAK3 IC_{50} (nM) Km♦	JAK3 IC50 (nM)*	JAK1 IC50 (nM) Km#	JAK1 IC50 (nM)*	JAK2 IC50 (nM)*	TYK2 IC50 (nM)*	IL-15 PBMC (cell) IC50 (nM)	IL-15 HWB (cell) IC50 (nM)
11		0.3	33	1640	>10000	>10000	>10000	51	197

- PF-04965842
  - JAK1
  - JAK2?

Cmpd No.	Structure	JAK1[a] IC_{50} (μM)	JAK2[a] IC_{50} (μM)	JAK2/JAK1 ratio	HWB[b] IFN_{α} pSTAT3 IC_{50} (μM)	HWB[b] CD34+ EPO pSTAT5 IC_{50} (μM)	HLM[c] @ 1 uM CLint, app (μL/min/mg)	LogD[d] pH 7.4
1	 tofacitinib	0.015	0.077	5	0.035	0.302	<8	1.1
2	baricitinib	0.004	0.007	2	0.029	0.088	<8	1.2
3	ruxolitinib	0.006	0.009	2	0.194	0.677	17	2.7
25		0.029	0.803	28	0.189	7.18	<9	1.9

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

Specific IC50 values we've found (2)

	JAK1	JAK2	JAK3	Tyk2		Source:
Ruxolitinib	3.3	2.8	364		cell free assay	1. Quintas-Cardama A, et al. Blood, 2010, 115(15), 3109-3117.
Baricitinib	5.9	5.7	399	57	cell free assay	1. Norman P, et al. Expert Opin Ther Pat, 2012, 22(10), 1233-1249
Tofacitinib			1			1. Changelian PS, et al, Science, 2003, 302(5646), 875-878.
Filgotinib	10	28	810	116		1. Van Rompaey L, et al. J Immunol. 2013, 191(7), 3568-3577.

Enzyme assay:

Table 1. Reported Enzymatic Potency for JAK Family Members for Disclosed Molecules

compd	enzyme assay IC_{50} (nM) JAK1	JAK2	JAK3	TYK2
1[5]	15	77	55	489
2[26]	4	5	<1	5
3[5]	6	9	487	30
4[5]	4	7	787	61
5[27]	105[b]	3	1002[b]	405[b]
6[28]	360	1	75	66
7[5]	112	619	74.4	>10K
8[5]	363	2400	>10k	2600
9[29]	29	803	>10k	1253
11[30]	43	120	2300	4700
12[a,31]	2	68[b]	280	12

[a]k_i values reported. [b]Estimated k_i using reported JAK1 selectivity index.

DOI: 10.1021/acs.jmedchem.8b00667
J. Med. Chem. XXXX, XXX, XXX−XXX

JMC paper					JAK1:JAK	JAk2:JAK1
Tofacitinib	15	77	55	489	5.1x	0.2x
Peficitinib	4	5	1	5	1.3x	0.8x
Ruxolitinib	6	9	487	30	1.5x	0.7x
Baricitinib	4	7	787	61	1.8x	0.6x
Fedratinib	105	3	1,002	405	0.0x	35.0x
BMS-911543	360	1	75	66	0.0x	360.0x
Decernotinib	112	619	74	10,000	5.5x	0.2x
Filgotinib	363	2,400	10,000	2,600	6.6x	0.2x
PF-04965842	29	803	10,000	125	27.7x	0.0x
Itacitinib						
[redacted]	43	120	2,300	4,700	2.8x	0.4x
Genentech JAI	2	68	280	12	34.0x	0.0x

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

The reason I obsess over JAK2 selectivity is because of the LLY baricitinib experience and FDA's strong views

EVERCORE ISI – Biotech & Pharma Equity Research
Umer Raffat
umer.raffat@evercoreisi.com | W 212-888-3905 | C 646-789-5173

FDA has actually opined on a possible mechanistic link between JAK2 and platelet increases (and hence the DVT risk)

FDA briefing on baricitinib

- The initial spike in peripheral blood platelets observed after 14 days of treatment may be due to inhibition of Mpl-associated JAK2 in peripheral platelets and a subsequent increase in circulating TPO.
- During this early time period of treatment, bone marrow concentrations of baricitinib may not be sufficient to inhibit Mpl-associated JAK2 function in HSCs and MK progenitors. These conditions would allow for TPO-induced expansion of these cell types resulting in increased peripheral blood platelets.
- The peak platelet level occurred at a time point that correlates approximately with the platelet lifespan in humans of 10 – 14 days. At later time points, bone marrow baricitinib concentrations are likely to be sufficient to inhibit JAK2 in HSCs and MK progenitors.
- A new steady-state would be reached whereby the potential stimulatory effects of elevated circulating TPO would be mitigated by the inhibitory effect of baricitinib on JAK2 function in HSCs and MK progenitors

EVERCORE ISI – Biotech & Pharma Equity Research
Umer Raffat

Guess where FDA discussed this JAK2's involvement in platelet increase?

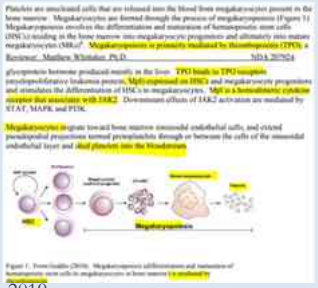
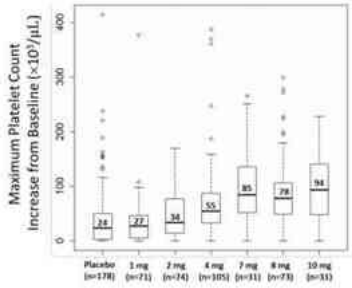


Figure 3. Maximal Platelet Count Increase from Baseline by Baricitinib Dose.



Source: platelet.xpt dated on 2/15/2018

The same dose-dependent trend was observed in two phase 3 studies (JADX and JADW) which investigated both 2 mg and 4 mg doses of baricitinib (Figure 4). The elevation of mean platelet count peaked around Week 2 following baricitinib once daily treatment and was 37×10^3/μL and 55×10^3/μL higher than the baseline in the 2 mg group and 4 mg group, respectively. After Week 8, the mean platelet count remained stable in the baricitinib groups with an approximately 15×10^3/μL and 30×10^3/μL increase from baseline in the 2 mg group and 4 mg group, respectively. Figure 4 shows mean platelet count change from baseline over time by placebo (blue), baricitinib 2 mg (red) and baricitinib 4 mg (green) groups from pooled results from Studies JADX and JADW.

5.3 Thrombosis

Thrombosis, including deep venous thrombosis (DVT) and pulmonary embolism (PE), has been observed at an increased incidence in patients treated with OLUMIANT compared to placebo. In addition, arterial thrombosis events in the extremities have been reported in clinical studies with OLUMIANT. Many of these adverse events were serious and some resulted in death. There was no clear relationship between platelet count elevations and thrombotic events. OLUMIANT should be used with caution in patients who may be at increased risk of thrombosis. If clinical features of DVT/PE or arterial thrombosis occur, patients should be evaluated promptly and treated appropriately.

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