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JAK inhibitor safety deep dive

Jul 2019

**See the last page of this report for important disclosures regarding these stocks and this report*

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

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This morning, FDA just announced a black box for Pfizer's Xeljanz

FDA approves Boxed Warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib (Xeljanz, Xeljanz XR)

FDA Drug Safety Communication

Safety Announcement

[7-26-2019] The U.S. Food and Drug Administration has approved new warnings about an increased risk of blood clots and of death with the 10 mg twice daily dose of tofacitinib (Xeljanz, Xeljanz XR), which is used in patients with ulcerative colitis. In addition, the approved use of tofacitinib for ulcerative colitis will be limited to certain patients who are not treated effectively or who experience severe side effects with certain other medicines. We approved these changes, including adding our most prominent *Boxed Warning*, after reviewing interim data from an ongoing safety clinical trial of tofacitinib in patients with rheumatoid arthritis (RA) that examined a lower and this higher dose of the medicine.

The 10 mg twice daily dose of tofacitinib is not approved for RA or psoriatic arthritis (PsA). This dose is only approved for ulcerative colitis for initial treatment and for long-term use in limited situations. While the increased risks of blood clots and of death were seen in patients taking this dose for RA, these risks may also apply to those taking tofacitinib for ulcerative colitis.

Tofacitinib works by decreasing the activity of the immune system; an overactive immune system contributes to RA, PsA, and ulcerative colitis. Tofacitinib was first approved in 2012 to treat adult patients with RA who did not respond well to the medicine methotrexate. In RA, the body attacks its own joints, causing pain, swelling, and loss of function. In 2017, we approved the medicine to treat patients with a second condition that causes joint pain and swelling, PsA, who did not respond well to methotrexate or other similar medicines. In 2018, we approved tofacitinib to treat ulcerative colitis, which is a chronic, inflammatory disease affecting the colon.

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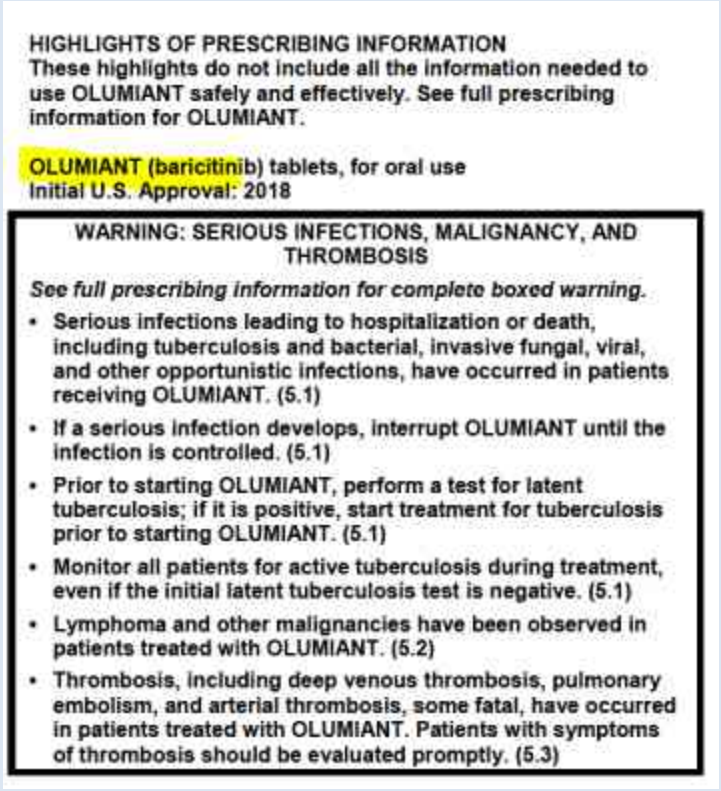
We've all previously gone through this with another JAK inhibitor: baricitinib



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OLUMIANT safely and effectively. See full prescribing information for OLUMIANT.

OLUMIANT (baricitinib) tablets, for oral use
Initial U.S. Approval: 2018

WARNING: SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS

See full prescribing information for complete boxed warning.

- Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving OLUMIANT. (5.1)
- If a serious infection develops, interrupt OLUMIANT until the infection is controlled. (5.1)
- Prior to starting OLUMIANT, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting OLUMIANT. (5.1)
- Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)
- Lymphoma and other malignancies have been observed in patients treated with OLUMIANT. (5.2)
- Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, some fatal, have occurred in patients treated with OLUMIANT. Patients with symptoms of thrombosis should be evaluated promptly. (5.3)

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… and there are several JAK inhibitors in late stage development … including GILD's recent announcement of filgotinib NDA filing this fall

July 01, 2019

Gilead Announces Intent to Submit New Drug Application for Filgotinib to U.S. Food and Drug Administration This Year

FOSTER CITY, Calif.--(BUSINESS WIRE)--Jul. 1, 2019-- Gilead Sciences, Inc. (NASDAQ: GILD) today announced that at a recent pre-New Drug Application (NDA) meeting with the U.S. Food and Drug Administration (FDA), the company provided an update about the investigational, oral, selective JAK1 inhibitor filgotinib. The company discussed with the agency the Phase 3 FINCH studies, as well as the ongoing Phase 2 MANTA safety study assessing semen parameters with filgotinib treatment in men with moderately to severely active ulcerative colitis or Crohn's disease. As a result of this discussion, a path forward has been established to submit the NDA for filgotinib as a treatment for rheumatoid arthritis in 2019.

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

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What are the biggest safety observations for the JAK class?

I'll only focus on MAJOR MAJOR observations … deal-breakers

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The first sign of a safety setback on JAK inhibitors we saw was on Xeljanz back in 2012

Summary of Malignancy

- Malignancy rates in tofacitinib-treated patients increased:
  - In a dose-related manner
  - With increasing exposure in LTE studies

Summary of Infections

- Infections in tofacitinib-treated patients were the most common cause of:
  - Deaths
  - Serious Adverse Events (SAEs)
  - Adverse Events (AEs) leading to discontinuation
- Rates for SIE increased in 10 mg group in LTE
- Opportunistic infections, dose-dependent

+

Malignancy

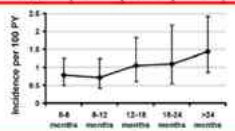
Phase 2, 3, and LTE studies (excluding NMSC):

- PBO: no cases
- ADA: 2 cases (lung and renal cell carcinoma)
- Tofacitinib: 66 solid and hematologic malignancies
  - Most common: Lung, Breast, Gastric and Prostate
  - Dose dependent increased incidence in RCT
  - Dose and exposure dependent increased incidence in LTE studies

	RCT Pooled Safety				Long-Term Extension (LTE)			
	PBO	ADA	CP5	CP10	CP5	CP10	All CP	All CP Update
Rate per 100 PY	0	0.6	0.6	0.9	1.0	1.4	1.1	1.1

Malignancy Rates Over Time

Non-Cumulative Incidence Rates of Malignancy (Excluding NMSC) in RA Program	0-6 months	6-12 months	12-18 months	18-24 months	>24 months
Incidence per 100 PY	0.79	0.72	1.06	1.09	1.43



Summary

- There is evidence that CP 10 mg and CP 5 mg may have some activity on radiographic progression. However, there is uncertainty associated with the results for the following reasons:
  - The effect in CP 10 mg group is sensitive to outliers
  - Data are not consistent with respect to dose
  - The evidence for an effect in radiographic progression is from a single study

=

Higher dose (10 mg) was NOT approved in RA

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FDA did approve Xeljanz's higher 10 mg dose in ulcerative colitis setting

Ulcerative Colitis

- XELJANZ 10 mg twice daily for at least 8 weeks; then 5 or 10 mg twice daily. Discontinue after 16 weeks of 10 mg twice daily, if adequate therapeutic benefit is not achieved. Use the lowest effective dose to maintain response. (2.3)
- Recommended dosage in patients with moderate and severe renal impairment or moderate hepatic impairment: half the total daily dosage recommended for patients with normal renal and hepatic function. (2, 8.7, 8.8)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203214s020,208246s006lbl.pdf

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However, clotting concerns on Xeljanz 10 mg have emerged:

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.

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Specifically, here is what was observed in the A3921133 trial:

- Design
  - Open label (Ph 4)
  - >50 y.o. with CV risk
  - N=4400

- As per PFE PR, DSMB observed that pts on Xeljanz 10 mg BID had statistically and clinically important difference in:
  - occurrence of pulmonary embolism, compared with patients in this study who were treated with a TNFi
  - increase in overall mortality in the 10 mg twice daily treatment group compared to the tofacitinib 5 mg twice daily and TNFi treatment arms

- Post DSMB update, PFE transitioned the RA pts from 10 mg BID arm to 5 mg BID arm

Study A3921133	Xeljanz 5 mg	Xeljanz 10 mg	TNF	
Patient Years		3,833	3,982	
PE		19	3	
%		0.50%	0.08%	6.6x
Deaths		45	25	
%		1.17%	0.63%	1.9x

PFE PR:
Similar results to study A3921133 have **not** been identified in Pfizer analyses of other tofacitinib RA clinical trials or routine monitoring of post-marketing safety data, including our statistical analyses of the FDA Adverse Event Reporting System database.

https://investors.pfizer.com/investor-news/press-release-details/2019/Pfizer-Announces-Modification-to-Ongoing-Tofacitinib-FDA-Post-Marketing-Requirement-Study-in-Patients-with-Rheumatoid-Arthritis/default.aspx

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Next steps on Xeljanz 10 mg:

- PRAC recommendation issued May 17
- CHMP will consider the PRAC recommendation at the following plenary meeting and will agree on the timeframe needed to issue an opinion.
  - This timeframe should not exceed 30 days after receipt of the PRAC recommendation.
  - Next CHMP mtg = May 27-29
- PFE response to committee due by Jun 20th
- CHMP decision likely in Aug 2019

6 July 2018
EMA/403287/2015 Rev.3
Human Medicines Evaluation

The timetables in this document may be subject to revision

Post-Authorisation Measures (PAMs) assessed by PRAC

	Deadline for Submission (*)	Start date	PRAC Rapporteur AR	Comments from PRAC (~)	Updated PRAC Rapporteur AR (#)	PRAC conclusion	CHMP adoption
A1	26/06/2018	09/07/2018	13/08/2018	28/08/2018	30/08/2018	06/09/2018	20/09/2018
A2	24/07/2018	06/08/2018	10/09/2018	24/09/2018	27/09/2018	04/10/2018	18/10/2018
A3	21/08/2018	03/09/2018	08/10/2018	22/10/2018	25/10/2018	31/10/2018	15/11/2018
A10	02/04/2019	15/04/2019	20/05/2019	03/06/2019	06/06/2019	14/06/2019	27/06/2019
A11	30/04/2019	13/05/2019	17/06/2019	01/07/2019	04/07/2019	11/07/2019	25/07/2019
A12							
A13	25/06/2019	08/07/2019	12/08/2019	27/08/2019	29/08/2019	05/09/2019	19/09/2019
A14	23/07/2019	05/08/2019	09/09/2019	23/09/2019	26/09/2019	03/10/2019	17/10/2019
A15	20/08/2019	02/09/2019	07/10/2019	21/10/2019	24/10/2019	31/10/2019	14/11/2019
A16	17/09/2019	30/09/2019	04/11/2019	18/11/2019	21/11/2019	28/11/2019	12/12/2019

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While EMA PRAC is pending, FDA has finalized a black box warning

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Meanwhile, perhaps the biggest setback in JAK space was LLY's JAK2 (baricitinib) @ FDA AdCom in 2017:

VOTE: Are the safety data adequate to support approval of baricitinib 4 mg once daily for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate (MTX)?

- If no, what data are needed?

Vote Result: **Yes: 5** **No: 10** **Abstain: 0**

Committee Discussion: *The majority of the committee voted "No", that the safety data are not adequate to support approval of baricitinib 4 mg once daily for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to methotrexate. These members agreed that although the study is not powered to answer the safety question, there was a clear signal for thromboembolic events since more patients were enrolled in the 4 mg trial. One committee member recommended a comparative trial between the two doses to look at safety in particular. The members who voted "Yes" noted that although there was a safety signal, the 4 mg dose would could be used in refractory population such as patients who failed biologic disease-modifying anti-rheumatic drugs (bDMARDs). Please see the transcript for details of the committee discussion.*

Overall Thrombosis

FDA

					IRD (95 % CI)	
	Placebo N=1070	BARI 2 N=479	BARI 4 N=997	BARI 2/4 N=1476	BARI 2/4 vs Placebo	BARI 4 vs BARI 2
0-16 weeks						
PYE	308	140	298	438		
n (rate/100 PY)	1 (0.3)	2 (1.4)	7 (2.4)	9 (2.1)	1.6 (0.1, 3.1)*	1.4 (-2, 4.8)
0-52 weeks						
PYE		336	904	1318		
n (rate/100 PY)		5 (1.5)	10 (1.1)	16 (1.2)		-0.4 (-2.1, 1.2)
>52 weeks						
PYE		155	653	1215		
n (rate/100 PY)		1 (0.4)	14 (1.2)	21 (0.9)		1.7 (0.3, 3.1)*

0-16 weeks: Studies JADA, JADC, JADN, JADV, JADW, and JADX
0-52 and >52 weeks: JADA/Y, JADC, JADN, JADV/Y, JADX/Y, JADW/Y
IRD=incidence rate difference; CI=confidence interval; BARI=baricitinib; N=number of subjects; PYE=patient year exposure; n=number of patients with event; PY=patient year

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4 mg dose was NOT approved by FDA

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Meanwhile, another JAK2 (fedratinib) showed Wernicke's encephalopathy

- Fedratinib = JAK2
- High profile program at Sanofi
  - had completed a Ph 3 in MF and had ongoing PV trials when it was put on hold
- Reason for **FDA clinical hold** = Wernicke's encephalopathy
  - acute neurological condition which features drowsiness, cognitive defects, confusion, ataxia etc
- 8 cases in an estimated 877 pts exposed.
- In addition, 4/8 cases happened in JAKARTA-1 (Ph 3 in myelofibrosis)

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Next, we saw an interesting preclinical disclosure on a JAK1, filgotinib:

- Galapagos SEC filing:
  - *In connection with the DARWIN clinical program, we agreed with the FDA to exclude the 200 mg filgotinib daily dose for male subjects; males will receive a maximum daily dose of 100 mg in the U.S. sites in these trials.*
  - ***We agreed to this limitation because in both rat and dog toxicology studies, filgotinib induced adverse effects on the male reproductive system and the FDA determined there was not a sufficient safety margin between the filgotinib exposure at the no-observed-adverse-effect-level, or NOAEL, observed in these studies and the anticipated human exposure at the 200 mg daily filgotinib dose.***

- BTW, I do find it interesting that GILD's characterization was less intense:
  - *We believe our margin is adequate **above and beyond** the minor histological abnormalities that we're seeing in the pre-clinical models and we'll evaluate the data as it comes in.*
  - *in animal models we saw a testicular finding, histological finding, and it's about an interpretation of the margins compared to what level of exposure we're seeing indication for the disease.*

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In response to this filgotinib finding, FDA has required a dedicated testicular safety trial

	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
- GILD is in discussions with FDA on filing strategy

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And also, PFE decided not to take its Tyk2/JAK1 forward in alopecia despite v good efficacy

- PF-06700841 = oral Tyk2/JAK1

Safety

Adverse Events Leading to Discontinuation From Treatment	PF-06651600 N=48 n (%)	PF-06700841 N=47 n (%)	Placebo N=47 n (%)
Angioedema	1 (2)		
Blood creatine phosphokinase increased	1 (2)	1 (2)	
Deafness neurosensory			1 (2)
Nephrolithiasis			1 (2)
Neutropenia		1 (2)	
Rhabdomyolysis		2 (4)	
Serum ferritin decreased		1 (2)	

- We've seen cases of rhabdomyolysis on other JAKs too:

Tofacitinib for Rheumatoid Arthritis

One SAE of rhabdomyolysis (highest CPK level was 2942) occurred in the context of a critically ill patient (1046-10091004) with severe pulmonary hypertension, congestive heart failure, and respiratory failure who died. The cause of death was adjudicated as non-cardiovascular event of infection by the CV adjudication committee. No SAE of rhabdomyolysis were reported in the LTE studies.

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So let's open up the discussion:

Data observation	Implication	My take	
Xeljanz 10 mg and baricitinib 4 mg wasn't approved in RA	High doses of JAK inhibitors have higher safety baggage at no incremental efficacy	If this was true, then Xeljanz 10 mg would not have been approved in UC	**But that still leaves bari 4 mg and DVT risk unresolved**
Filgotinib testicular tox concern	JAKs cause reproductive tox	No effect of filgotinib on male hormones in human trials	
Rhabdomyolysis on Pfizer Tyk2/JAK1	JAKs cause severe muscle injury	No clear explanation	

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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

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Let's put all the key JAK safety observations in one place:

Drug	Key safety observation	JAK affinity
Xeljanz	Clots at 10 mg dose?	Pan-JAK
Baricitinib	Clot risk	JAK2
Fedratinib	Wernicke's encephalopathy	JAK2
Filgotinib	Preclinical testicular tox signal	JAK1
PF-06700841	Rhabdo causing tx d/c	Tyk2/JAK1

Given GILD's characterization of filgotinib safety in human males, and limited # of rhabdo events on Tyk2/JAK1, our focus really turns to **JAK2**

Hold this thought on JAK2 for a second

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How JAK-STAT signaling works:

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

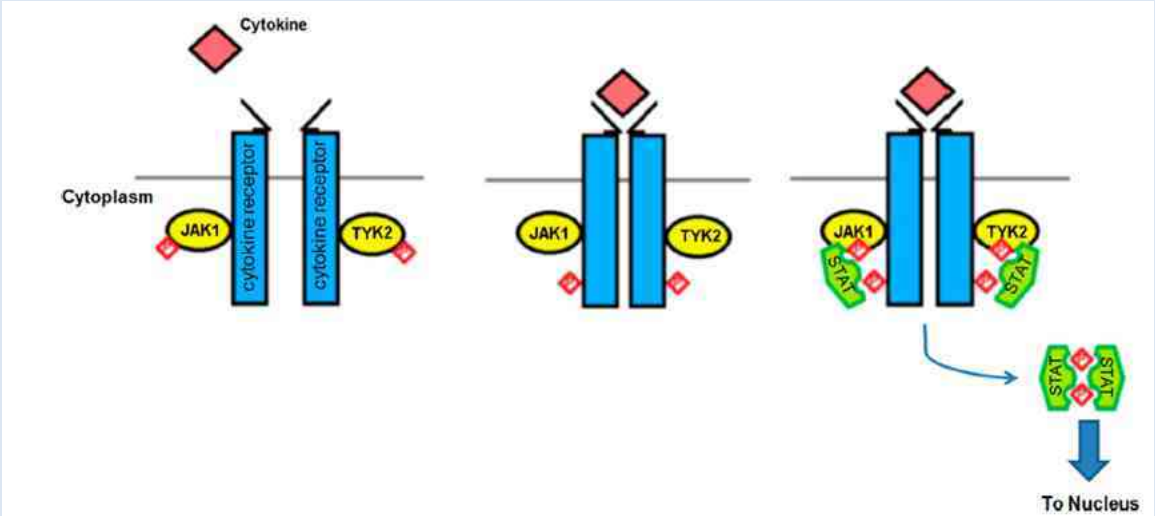

Figure 2. Basic mechanism of JAK/STAT mediated cytokine signaling.