JAK inhibitors in development and New indications

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CLINICAL REVIEW; JAK Inhibitors

Tofacitinib (Approved in US at 5 mg BID dose)

I. Under Development for RA:
1. Baricitinib
2. GLPG0634
3. VX-309

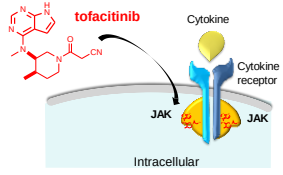
COI

1. I will be discussing products made by Lilly, Galapagos (Abbvie) and Vertex. I have consulted with all of these companies. I have performed research supported by Lilly and Abbvie.
2. I have conducted research and consulted with Pfizer.

Refs will be supplied during the presentation

II. Other JAKs in Development

Tofacitinib is a Novel Inhibitor of JAKs that Modulates Cytokines Important in Pathogenesis of RA



JAK=Janus kinase.
Shuai K, Liu B. *Nat Rev Immunol.* 2003;3(11):900-911; Flanagan ME et al, *J Med Chem* 2010; 53:8468-8484

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Baricitinib Phase 2

- Presented by Keystone et al, EULAR, 2012 and Genovese et al, ACR 2012

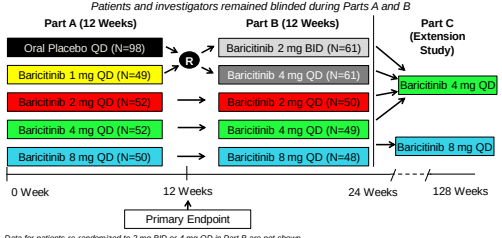
Baricitinib: Potent Selective JAK1/JAK2 Inhibitor

- **Nanomolar inhibitor of JAK1 and JAK2**
- **Minimal effect against JAK3 and non-JAK family kinases***
- **Potent inhibitor of IL-6 and IL-23 signaling, validated cytokine targets in inflammatory diseases**

	Assay	IC_{50} (nM)
Enzyme Potency (1 mM ATP)	JAK1	6
	JAK2	6
	JAK3	>400
	Tyk2	53
Cellular Potency	IL-6 stimulated monocytes	70
	IL-23 stimulated T-cells	20

*INCB28050 was evaluated against a panel of 28 non-JAK kinases and demonstrated no significant inhibition at a concentration > 100x its potency against JAK1/2

Figure 1. Study JADA Trial Design



Data for patients re-randomized to 2 mg BID or 4 mg QD in Part B are not shown.
BID: twice daily, QD: once daily, R: re-randomized.

NCT01185353

Entry Criteria

Major inclusion criteria

- ≥ 8 swollen and ≥ 8 tender joints based on the 66/68 joint count
- Stable use of MTX (10-25 mg/week) for at least 12 weeks
- Patients on corticosteriods were to be on a stable dose for 6 weeks (<10 mg of prednisone daily)
- CRP >1.2X ULN or ESR >28 mm/hr

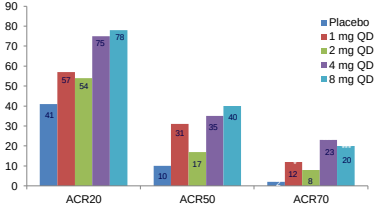
- Major exclusion criteria
  - Use of traditional DMARDs (other than MTX) within 8 - 12 weeks
  - Prior biologic DMARD therapy
  - ALT>3x ULN or total bili ≥1.5x ULN
  - eGFR <50 mL/min

Baseline Disease Activity

		Baricitinib				
Mean	**Placebo (N=98)**	**1 mg (N=49)**	**2 mg (N=52)**	**4 mg (N=52)**	**8 mg (N=50)**	**Combined (N=203)**
Tender joint count (68)	22.2	21.4	23.0	19.9	24.4	22.2
Swollen joint count (66)	15.8	15.2	17.0	14.8	16.1	15.8
DAS28-CRP	5.5	5.5	5.4	5.3	5.8	5.5
HAQ-DI	1.2	1.3	1.1	1.0	1.3	1.2
hsCRP * (mg/L)	14.0	11.2	12.0	11.4	14.3	12.2
ESR (mm/hr)	40	38	37	35	43	38

*hsCRP ULN = 3 mg/L

ACR Responses by Dose at 12 Weeks



Change in Hemoglobin over 12 Weeks

	Placebo (N=98)	1 mg (N=49)	2 mg (N=52)	4 mg (N=52)	8 mg (N=50)
Mean Change from Baseline to Week 12 (g/dL)					
	-0.14	0.09	-0.09	-0.15	-0.57
Maximum Decrease Post-baseline [g/dL; n (%)]					
Decrease ≥ 1.0 – < 1.5	16 (16%)	7 (15%)	10 (19%)	15 (29%)	15 (31%)
Decrease ≥ 1.5 – < 3.0	6 (6%)	1 (2%)	4 (8%)	4 (8%)	13 (26%)
Decreases ≥ 3 g/dL or values < 8.0 g/dL not observed.					
Shift from ≥LLN at baseline to <LLN at Week 12 [n (%)]					
	5 (7%)	3 (9%)	3 (7%)	2 (5%)	11 (27%)

Change in Renal Parameters over 12 Weeks

	Placebo (N=98)	1 mg (N=49)	2 mg (N=52)	4 mg (N=52)	8 mg (N=50)
Mean Change from Baseline to Week 12 (mg/dL)					
Creatinine	0.01	0.02	0.04	0.11	0.09
Cystatin C	0.01	-0.01	-0.02	-0.05	0.00
Maximum Increase in Creatinine Post-baseline [mg/dL; n (%)]					
≥ 0.11 – < 0.23	23 (23%)	12 (24%)	15 (29%)	12 (24%)	18 (36%)
≥ 0.23 – < 0.45	4 (4%)	3 (6%)	7 (13%)	7 (14%)	5 (10%)
≥ 0.45	1 (1%)	0	1 (2%)	2 (4%)	2 (4%)
Creatinine Shift from ≤ ULN* at baseline to > ULN at Week 12 [n (%)]	1 (1%)	2 (5%)	1 (2%)	2 (4%)	1 (2%)

* Creatinine ULN was 1.20 mg/dL for females and 1.30 mg/dL for males

Change in Cholesterol over 12 Weeks

	Placebo (N=98)	1 mg (N=49)	2 mg (N=52)	4 mg (N=52)	8 mg (N=50)
Mean Change from Baseline to Week 12 (mg/dL)					
HDL*	0.62	3.30	2.97	7.26	8.02
LDL	-4.36	3.42	7.95	9.52	11.95
HDL*/LDL Ratio	0.04	0.05	0.03	0.03	0.01
Shift from baseline to highest post-baseline LDL value [mg/dL; n/N]					
< 100 shift to ≥100	20/44	8/23	12/23	12/22	21/26
100 to <130 shift to ≥130	8/28	6/14	11/19	4/13	8/14
130 to <160 shift to ≥160	5/21	6/8	5/8	5/13	5/6

*DEXTRAN PRECIP

Baricitinib Effects on Serum Cholesterol and Circulating Lipid Particles in a Phase 2b Study in Patients With Rheumatoid Arthritis

Joel Kremer,[1] Mark C. Genovese,[2] Edward Keystone,[3] Peter Taylor,[4] Steven H. Zuckerman,[5] Douglas E. Schlichting,[5] Scott D. Beattie,[5] William L. Macias[5]

[1]Albany Medical College, Albany, NY, USA; [2]Stanford University Medical Center, Palo Alto, CA, USA; [3]University of Toronto, Toronto, ON;

Methods

- Patients with moderate to severe RA were randomized to once daily (QD) dosing with placebo or 1, 2, 4, or 8 mg of baricitinib.
- Serum lipids were determined using conventional chemistry methods at screening and at Weeks 0, 2, 4, 8, 12, 14, 16, 20, and 24.
  - Fasting lipids were measured at baseline, Week 12, and Week 24
- Particle size and number were determined by NMR spectroscopy at Weeks 0, 12, and 24.[6]
  - Particle concentrations of lipoproteins of different sizes were calculated from the measured amplitudes of their spectroscopically distinct lipid methyl group NMR signals.
  - Weighted-average very-low density lipoprotein (VLDL), LDL, and HDL particle sizes were derived from the sum of the diameter of each subclass multiplied by its relative mass percentage based on the amplitude of its methyl NMR signal.

Table 2. Changes in LDL, HDL, Total Cholesterol, and Triglycerides

	LDL (mg/dL)			HDL (mg/dL)			Total Cholesterol (mg/dL)		
mean ± SD	Baseline	Week 12	Week 24	Baseline	Week 12	Week 24	Baseline	Week 12	Week 24
Placebo (n=98)	108 ± 34	105 ± 31	--	57 ± 15	58 ± 16	--	193 ± 40	190 ± 34	--
1 mg QD (n=47)	102 ± 35	108 ± 35	--	57 ± 19	59 ± 19	--	192 ± 44	202 ± 42*	--
2 mg QD (n=52)	107 ± 31	115 ± 40*	119 ± 37	56 ± 16	58 ± 19	61 ± 18	192 ± 38	206 ± 49**	211 ± 45
4 mg QD (n=52)	109 ± 33	120 ± 33*	119 ± 32	54 ± 14	62 ± 19*	60 ± 17	**191 ± 39**	**213 ± 39****	**208 ± 39**
8 mg QD (n=50)	107 ± 30	117 ± 31**	125 ± 33	54 ± 17	62 ± 18*	64 ± 19	**189 ± 37**	**212 ± 39****	**219 ± 37**
	Triglycerides (mg/dL)								
Placebo (n=98)	131 ± 73	119 ± 72	--						
1 mg QD (n=47)	143 ± 86	155 ± 93	--						
2 mg QD (n=52)	121 ± 65	138 ± 87*	137 ± 69						
4 mg QD (n=52)	130 ± 65	141 ± 71	134 ± 55						
8 mg QD (n=50)	120 ± 58	136 ± 84*	124 ± 76						

Data for patients re-randomized to 2 mg BID or 4 mg QD in Part B are not shown

HDL: high-density lipoprotein, LDL: low-density lipoprotein

Change from baseline analysis:
**p<0.05 vs. placebo*
***p<0.001 vs. placebo*

Table 3. LDL Cholesterol Increases With Baricitinib are Not Observed in Patients on Concomitant Statins

	Mean LDL Cholesterol (mg/dL)			Mean Change from Baseline (mg/dL)			
	Baseline	Week 12	Week 24	Week 12	p-value Within Treatment	Week 24	p-value Within Treatment
With Statin Use							
Placebo (n=19)	122 ± 30	105 ± 28	--	−19 ± 31	0.021	--	--
1 mg QD (n=6)	113 ± 43	126 ± 46	--	13 ± 40	0.453	--	--
2 mg QD (n=3)	97 ± 56	98 ± 66	81 ± 49	2 ± 35	0.946	−10 ± 28	0.705
4 mg QD (n=11)	**108 ± 37**	**110 ± 33**	**123 ± 33**	−4 ± 24	0.584	8 ± 32	0.436
8 mg QD (n=11)	**131 ± 28**	**135 ± 35**	**124 ± 34**	8 ± 32	0.429	−9 ± 40	0.510
Without Statin Use							
Placebo (n=79)	104 ± 35	105 ± 32	--	−1 ± 22	0.788	--	--
1 mg QD (n=41)	101 ± 34	105 ± 32	--	2 ± 21	0.617	--	--
2 mg QD (n=49)	108 ± 30	116 ± 39	121 ± 36	8 ± 24	0.021	12 ± 22	<0.001
4 mg QD (n=41)	109 ± 33	123 ± 33	118 ± 32	13 ± 31	0.012	9 ± 33	0.107
8 mg QD (n=39)	100 ± 28	113 ± 29	125 ± 34	13 ± 21	<0.001	21 ± 25	<0.001

Data are mean ± SD unless noted otherwise.
Approximately 17% of the patients enrolled were on statins at the time of entry.
n: number of patients with baseline data

Table 4. No Increase in Total LDL Particle Number With Baricitinib Across Treatment Groups

	Mean Total LDL Particles (nmol/L)			Mean Change in Total LDL Particles from Baseline (nmol/L)			
	Baseline	Week 12	Week 24	Week 12	p-value Within Treatment	Week 24	p-value Within Treatment
Placebo (n=94)	1251 ± 386	1191 ± 374	--	−80 ± 280	0.013	--	--
1 mg QD (n=49)	1269 ± 474	1243 ± 441	--	−55 ± 307	0.245	--	--
2 mg QD (n=52)	1324 ± 504	1275 ± 512	1309 ± 474	−56 ± 294	0.177	−18 ± 344	.707
4 mg QD (n=52)	**1319 ± 374**	**1306 ± 404**	**1233 ± 422**	**−4 ± 288**	**0.924**	**−69 ± 301**	**.124**
8 mg QD (n=50)	**1285 ± 398**	**1248 ± 414**	**1270 ± 429**	**−35 ± 303**	**0.428**	**−67 ± 366**	**.232**

Data are mean ± SD unless noted otherwise.
LDL: low-density lipoprotein, n: number of patients with baseline data, QD: once daily, SD: standard deviation.

Table 5. Increases in LDL Cholesterol With Baricitinib are Associated With an Increase in the Number of Large LDL Particles

	Mean Large LDL Particle Number (nmol/L)			Mean Change in Large LDL Particle Number from Baseline (nmol/L)			
	Baseline	Week 12	Week 24	Week 12	p-value Within Treatment	Week 24	p-value Within Treatment
Placebo (n=94)	521 ± 293	507 ± 226	--	−29 ± 200	0.197	--	--
1 mg QD (n=49)	463 ± 283	494 ± 293	--	45 ± 193	0.129	--	--
2 mg QD (n=52)	476 ± 207	536 ± 265	569 ± 302	61 ± 168	0.012	88 ± 212	0.005
4 mg QD (n=52)	**512 ± 242**	**564 ± 271**	**544 ± 263**	**56 ± 163**	**0.018**	**42 ± 220**	**0.195**
8 mg QD (n=50)	**490 ± 234**	**555 ± 284**	**581 ± 251**	**61 ± 250**	**0.092**	**69 ± 229**	**0.053**

Data are mean ± SD unless noted otherwise.
n: number of patients with baseline data

Table 6. Baricitinib Appears to Decrease the Number of Very Small LDL Particles

	Mean Very Small LDL Particle Number (nmol/L)			Mean Change in Very Small LDL Particle Number from Baseline (nmol/L)			
	Baseline	Week 12	Week 24	Week 12	p-value Within Treatment	Week 24	p-value Within Treatment
Placebo (n=94)	547 ± 339	512 ± 333	--	−39 ± 208	0.097	--	--
1 mg QD (n=49)	607 ± 439	559 ± 423	--	−79 ± 250	0.043	--	--
2 mg QD (n=52)	638 ± 403	547 ± 418	551 ± 396	−97 ± 218	0.002	−86 ± 317	0.062
4 mg QD (n=52)	**613 ± 314**	**555 ± 413**	**509 ± 409**	**−52 ± 244**	**0.137**	**−96 ± 275**	**0.021**
8 mg QD (n=50)	**597 ± 360**	**511 ± 392**	**512 ± 399**	**−81 ± 330**	**0.094**	**−106 ± 348**	**0.049**

Data are mean ± SD unless noted otherwise.
n: number of patients with baseline data

Table 7. Increases in HDL Cholesterol With Baricitinib are Associated With an Increase in Total HDL Particle Number

	Mean Total HDL Particles (µmol/L)			Mean Change in Total HDL Particles from Baseline (µmol/L)			
	Baseline	Week 12	Week 24	Week 12	p-value Within Treatment	Week 24	p-value Within Treatment
Placebo (n=94)	32 ± 6	32 ± 7	--	1 ± 6	0.448	--	--
1 mg QD (n=49)	33 ± 7	34 ± 7	--	2 ± 7	0.065	--	--
2 mg QD (n=52)	32 ± 8	33 ± 8	35 ± 8	1 ± 6	0.331	2 ± 6	0.009
4 mg QD (n=52)	**34 ± 7**	**38 ± 8**	**37 ± 8**	**4 ± 6**	**<0.001**	**3 ± 5**	**<0.001**
8 mg QD (n=50)	**31 ± 8**	**36 ± 9**	**37 ± 7**	**4 ± 6**	**<0.001**	**5 ± 6**	**<0.001**

Data are mean ± SD unless noted otherwise.
n: number of patients with baseline data

Table 8. Increases in Total HDL Particle Number are Consistent With an Increase in Medium-Sized HDL Particles

	Mean Medium HDL Particle Number (µmol/L)			Mean Change in Medium HDL Particle Number from Baseline (µmol/L)			
	Baseline	Week 12	Week 24	Week 12	p-value Within Treatment	Week 24	p-value Within Treatment
Placebo (n=94)	4 ± 4	3 ± 3	--	−1 ± 3	0.067	--	--
1 mg QD (n=49)	4 ± 5	4 ± 3	--	−1 ± 4	0.226	--	--
2 mg QD (n=52)	4 ± 4	5 ± 7	5 ± 5	1 ± 5	0.084	1 ± 3	0.007
4 mg QD (n=52)	**3 ± 3**	**4 ± 5**	**4 ± 4**	**2 ± 5**	**0.030**	**1 ± 3**	**0.033**
8 mg QD (n=50)	**4 ± 5**	**5 ± 7**	**6 ± 6**	**1 ± 4**	**0.132**	**1 ± 5**	**0.068**

Data are mean ± SD unless noted otherwise.
n: number of patients with baseline data

Lipid changes, summary and conc.

- Increases in LDL cholesterol with baricitinib treatment are associated with increases in number of **large** LDL particles. Treatment with baricitinib is not associated with an increase in number of very small LDL particles (considered more atherogenic).
- The total number of LDL particles did not increase, suggesting that the increase in the proportion of large LDL particles may be related to particle remodeling (i.e. a shift from small to large particle size).

Baricitinib, an Oral Janus Kinase Inhibitor, in the Treatment of Rheumatoid Arthritis: 52-Week Safety and Efficacy in an Open-Label, Long-Term Extension Study

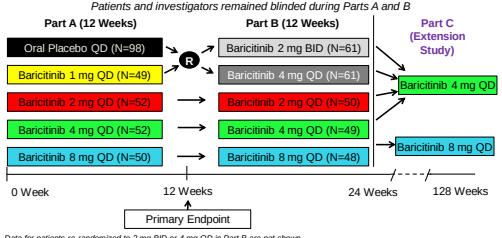
Peter Taylor, MA, PhD, FRCP

Study was funded by Eli Lilly & Company and Incyte Corporation

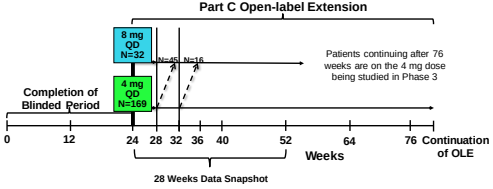
Peter Taylor[1], Mark C. Genovese[2], Edward Keystone[3], Douglas Schlichting[4], Scott D. Beattie[4], William L. Macias[4]

[1]University of Oxford, United Kingdom; [2]Stanford University Medical Center, Palo Alto, CA, USA; [3]University of Toronto, Toronto, ON, Canada; [4]Eli Lilly & Company, Indianapolis, IN, USA

Figure 1. Study JADA Trial Design



JADA Study Design (Part C)



Dashed arrow represents optional dose escalation at Weeks 28 and 32.
Patients with ≥6 tender and ≥6 swollen joints were eligible for escalation.

Demographics and Disease Activity

Mean ± SD	All Treatment Groups Combined: All Patients Entering Part A at Week 0 N=301	All Patients Entering Part C at Week 24 N=201
Gender, female, %	83	83
Age, years	51 ± 12	52 ± 12
Duration of RA, years	6 ± 4	6 ± 5
ACPA+ (>5 U/mL), %	69	67
RF+ (>14 IU/mL), %	71	70
Weekly dose of MTX, mg	16.3 ± 6.8	15.6 ± 4.1
Concomitant prednisone, %	49	50
Tender joint count (28)	14.3 ± 6.2	4.9 ± 5.3
Swollen joint count (28)	11.7 ± 5.1	4.2 ± 4.6
CRP, mg/L	12.8 ± 19.4	6.1 ± 11.9
ESR, mm/hr	38.8 ± 18.4	27.4 ± 19.3

100 patients did not continue to Part C: 42 patients who discontinued during treatment in Part A or B and 58 patients who completed Part B (47 patients from sites not participating in Part C and 11 patients who elected not to participate).

Percent of Patients Escalating to 8 mg

	Part A dose → Part B dose → Part C starting dose: PBO/1 mg → 2 mg BID → 4 mg (N=46)	PBO/1 mg → 4 mg → 4 mg (N=46)	2 mg → 2 mg → 4 mg (N=37)	4 mg → 4 mg → 4 mg (N=40)	8 mg → 8 mg → 8 mg (N=32)
Patients escalating dose in Part C (%)	15 (33%)	22 (48%)	16 (43%)	8 (20%)	NA

Observed data

- Investigators and patients remained unaware of original (first 24 weeks) treatment assignments for all dose groups except 8 mg dose group
- Patients with ≥6 tender and ≥6 swollen joints were eligible for escalation at investigator discretion
- The dose-escalation option was utilized more often in treatment groups where patients had not received 6 months of stable treatment at 4 mg

Clinical Outcomes for Patients Randomized to 4 mg or 8 mg QD in Part A

	Part A dose → Part B dose → Part C starting dose			
	4 mg → 4 mg → 4 mg		8 mg → 8 mg → 8 mg	
n (%)	Week 24	Week 52 (NRI)	Week 24	Week 52 (NRI)
ACR20	31/40 (78%)	31/39 (79%)	24/32 (75%)	21/32 (66%)
ACR50	22/40 (55%)	22/39 (56%)	18/32 (56%)	16/32 (50%)
ACR70	13/40 (33%)	15/39 (38%)	9/32 (28%)	9/32 (28%)
CDAI Remission ≤2.8	12/40 (30%)	13/39 (33%)	9/31 (29%)	7/31 (23%)
DAS-ESR ≤3.2	15/40 (38%)	21/39 (54%)	12/31 (39%)	13/31 (42%)
DAS-ESR <2.6	12/40 (30%)	14/39 (36%)	7/31 (23%)	7/31 (23%)

Observed data at Week 24, NRI data at Week 52

- Response is durable across most parameters among patients receiving at least 4 mg for 6 months prior to entering Part C

Shift from Baseline to Week 52: Hemoglobin

	Always on 4 mg (n=32)		
	Baseline		
Week 52	No Grade	Grade 1	Grade 2
No Grade	24 (80%)	3 (10%)	0
Grade 1 (< LLN and ≥ 10.0 g/dL)	1 (3%)	2 (7%)	0
Grade 2 (< 10.0 g/dL and ≥ 8.0 g/dL)	0	0	0

	Always on 8 mg (n=32)		
	Baseline		
Week 52	No Grade	Grade 1	Grade 2
No Grade	14 (52%)	2 (7%)	0
Grade 1 (< LLN and ≥ 10.0 g/dL)	4 (15%)	4 (15%)	2 (7%)
Grade 2 (< 10.0 g/dL and ≥ 8.0 g/dL)	1 (4%)	0	0

One patient each in 4 mg > 8 mg group and PBO > 2 mg BID> 4 mg group had Grade 3 through 52 weeks; AE assessments not completed at time of data snapshot

Incidence of Selected Adverse Events

	Weeks 0-24[1]		Weeks 24-52	
	4 mg (N=52)	8 mg (N=50)	Remained on 4 mg (N=108)	On 8 mg or Escalated to 8 mg (N=93)
Patients with ≥1 TEAE, n (%)	32 (62%)	36 (72%)	57 (53%)	59 (63%)
Blood/lymphatic disorders	4 (8%)	5 (10%)	1 (1%)	5 (5%)
Anemia	2	2	1	4
Neutropenia	0	1	0	1
GI disorders	5 (10%)	9 (18%)	7 (6%)	13 (14%)
Nausea	1	2	2	0
Colitis	0	0	0	3
Infections & Infestations	13 (25%)	14 (28%)	34 (31%)	37 (40%)
Bronchitis	2	1	9	5
Gastroenteritis	0	1	1	5
Herpes zoster	0	0	4	3
Influenza	0	0	3	3
Pharyngitis	3	0	1	4
Sinusitis	0	0	3	0
URI	2	3	7	5
UTI	3	4	10	7

1. Data for placebo, 1-mg and 2-mg dose groups not shown

Incidences of Serious Adverse Events

	Weeks 0-24[1]		Weeks 24-52	
	4 mg (N=52)	8 mg (N=50)	Remained on 4 mg (N=108)	On 8 mg or Escalated to 8 mg (N=93)
SAEs, n (%)	0	4 (8%)	11 (10%)	7 (8%)
ALT increased	0	0	1	0
Anemia	0	1	0	1
Angioedema	0	0	1	0
Blood CK increased	0	0	1	0
Cataract	0	0	2	0
Colitis	0	0	0	2
Dehydration	0	0	1	1
Gastroenteritis	0	0	1	2
Herpes simplex	0	0	0	1
Herpes zoster	0	0	3	0
Myocardial infarction	0	0	0	1
Pancytopenia	0	1	0	0
Pneumonia bacterial	0	1	0	0
Presyncope	0	0	0	1
Renal failure	0	1	0	0
Trauma	0	0	3	0

n = number of patients reporting an SAE 1. Data for placebo, 1-mg and 2-mg dose groups not shown.

Safety Summary

	Weeks 0-24[1]		Weeks 24-52	
n (%)	4 mg (N=52)	8 mg (N=50)	Remained on 4 mg (N=108)	On 8 mg or Escalated to 8 mg (N=93)
SAEs	0	4 (8%)	11 (10%)	8 (9%)
TEAEs	32 (62%)	36 (72%)	57 (53%)	59 (63%)

- No opportunistic infections, cases of tuberculosis, or lymphomas
- 1 death attributed to presumed myocardial infarction (8 mg group)

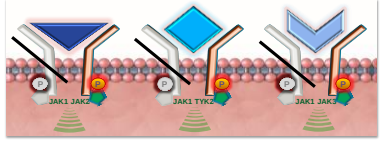
1 subject discontinued due to laboratory abnormality (increased ALT)

1. Data for placebo, 1-mg and 2-mg dose groups not shown

GLGP0634

Inhibition of JAK Signaling

1. **JAK signaling requires activation of both JAKs bound to a receptor. The common JAK pairs are shown below**[1–3]
2. **Inhibition of one member of the pair effectively blocks downstream signal transduction**[2]



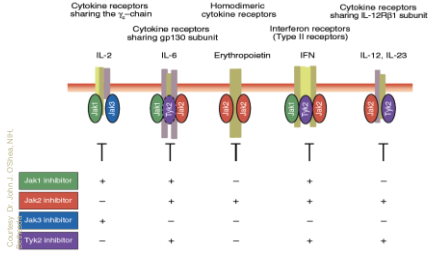
1. Wu W, Sun XH. *Acta Biochem Biophys Sin (Shanghai).* 2012;44:187-196; 2. Gómez-Valadés AG et al. *Mol Ther Nucleic Acids.* 2012;1:e42; 3. O'Shea JJ et al. *N Engl J Med.* 2013;368:161-170.

However…..

Inhibition of activation of 1 of the 2 JAK heterodimer pairs is not all or nothing

- "**Recent findings suggest that JAK1 dominates JAK1/JAK3/γ signalling, suggesting that JAK1 inhibition might be largely responsible for the in vivo efficacy of JAK inhibitors in immune-inflammatory diseases.**"
- Van Rompaey et al J Immunol, Published online 4 Sept, 2013
- Haan C, et al. Jak1 has a dominant role over Jak3 in signal transduction through γc-containing cytokine receptors. Chem Biol 2011;18:314-323.
- Other JAK3 selective inhibitors have been abandoned.

JAKs signal for cytokines and growth factors



Courtesy Dr. John J. O'Shea, NIH.

JAK selectivity in biochemical assay

IC_{50} (nM) potency data of compounds in **biochemical** assays

Compound	JAK1	JAK2	JAK3	TYK2
GLPG0634	10	28	810	116
baricitinib	5.9	5.7	>400	53
tofacitinib	1.3	1.9	0.2	23
VX-509	11	13	2.5	11
ASP015K	3.9	5.0	0.7	4.8

* Ki values by radiometric assay; NA: not available

- Discrepancy in JAK selectivity among biochemical and cellular assays
  - May be associated with incomplete JAK constructs in biochemical systems

Van Rompaey, JI, published online Sept 4, 2013, cont'd

GLPG0634 Biochemical assays show marked inhibition of both JAK 1 and 2, and very low activity for JAK3.

However, the biochemical observation did not translate in WB assays for effects on INFa (JAK1-tyk1,JAK2) and IL-2(JAK1-3),as both p'ways are inhibited.

GLPG0634

Potency in cellular assays

GLPG0634 in cellular assays		
JAKs	Assay	IC_{50} (nM)
JAK1/JAK3	IL-4/pSTAT6 (THP1 cells)	180
JAK1/TYK2	IFNα/pSTAT1 (U2OS cells)	460
JAK1/JAK2	OSM/STAT1 (HeLa reporter)	1,040
JAK2	EPO/pSTAT5 (UT-7 cells)	>10,000

GLPG0634 in human whole blood		
JAKs	Assay	IC_{50} (nM)
JAK1	IL-6/pSTAT1	620
JAK1/JAK3	IL-2/pSTAT5	1,700
JAK1/TYK2	IFNα/pSTAT1	1,120
JAK2	GM-CSF/pSTAT5	17,500

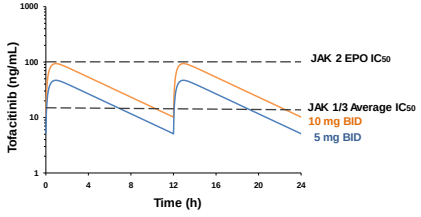
Van Rompaey JI, 2013, cont'd

Conclusion

"No univocal explanation for the discrepancy between the biochemical and cellular/whole blood assay results. But:

1. Biochemical assays rely on truncated purified protein vs wild-type protein in the cellular/whole blood assay.
2. JAKs part of a large cellular complex, including cytoplasmic receptor tails, STATs, and other proteins.
3. Endogenous JAKs susceptible to posttranslational modification such as phosphorylation which gives rise to different IC50 values.
4. The potential exists for differential positive feedback mechanisms for JAK1 vs JAK2 signaling by means of phosphatases which can impact the amplitude and kinetics of JAK enzyme activity and output."

Partial and Reversible Inhibition of JAK with 5 and 10 mg BID Tofacitinib



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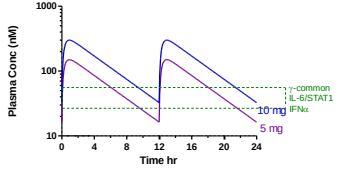
Tofacitinib Partially And Reversibly Inhibits Multiple JAK Dependent Cytokine Signaling Pathways



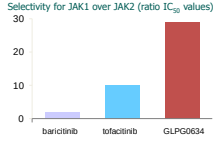
IL=interleukin; STAT=signal transducer and activator of transcription; IFN=interferon alpha

N5

JAK1 selectivity over JAK2

Baricitinib, tofacitinib and GLPG0634 in human whole blood

- JAK1 assay: IL-6 induced pSTAT1 in CD4+ cells
- JAK2 assay: GM-CSF induced pSTAT5 in CD33+ cells



GLPG0634 in moderate to severe RA

Design PoC and Phase 2a studies

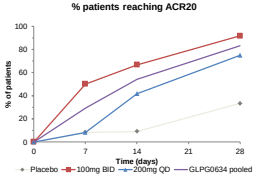
	PoC	Phase 2a
# patients on stable MTX	36	91
doses	Placebo *vs* 200 mg daily (100 mg BID, 200 mg QD)	Placebo *vs* 30, 75, 150, 300 mg QD
duration	28 days	28 days
study centers	1	19
countries	Moldova	Hungary, Moldova Russia, Ukraine

PoC: designed to give rapid evaluation
Phase 2a: extended version of PoC

GLPG0634 PoC study

ACR response

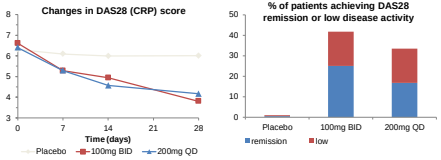
- Achieved primary endpoint
- ACR20 scores at Day 28: 42-58% improvement over placebo



rapid onset of action

GLPG0634 PoC study

DAS28 response



- GLPG0634 rapidly improves disease activity score

GLPG0634

Clinical safety summary

- "Favorable safety profile was observed"
- No SAEs on GLPG0634 treatment
- Few patients reported treatment-emergent side-effects
- No effects on cardiovascular safety (incl. blood pressure)
- No overall change to LDL-cholesterol or ALT
- Slight hemoglobin increase
- No significant changes in lymphocyte counts and lymphocyte differentials
- Modest decrease in neutrophils – no dose trend

GLPG0634

- Phase IIA, 4 week trial of 91 pts
- Mean DAS improvements of -1.7, -1.8,-2.3 in 75, 150 and 300 mg groups respectively.
- Improvements in 300 mg "similar to those with 200 mg in prior PoC";(45%ACR 50)
- "no anemia, no SAEs, no impact on lymphs, limited decrease in neutrophils"
- Abstract 2381, Tuesday poster session

GLPG0634

Ongoing Phase 2b program in moderate to severe RA

Patients with inadequate response to MTX

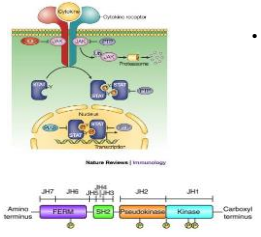
Darwin1 — Add-on to MTX 24 weeks
- Daily doses GLPG0634 : 50 mg, 100mg and 200mg
- QD and BID dosing regimens

Darwin2 — Monotherapy 24 weeks
- Daily doses GLPG0634 : 50 mg, 100mg and 200mg
- QD dosing regimen

Darwin3 — Long term extension

VX-509

JAK-STAT Network and Implications for Drug Selectivity



- JAK family kinases have high sequence homology – which required significant innovation when designing a JAK3 selective inhibitor (VX-509)

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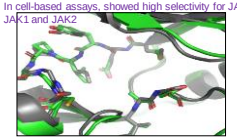
Discovery of VX-509: A Selective JAK3 Inhibitor

The Goal:	Target JAK3 specifically to prevent broad effects of JAK1/2 inhibition and create molecules with benefits in safety, efficacy and dosing
The Challenge:	The high degree of similarity in structure of the ATP binding pocket between JAK2 and JAK3 posed a significant challenge in the design of molecules selective for JAK3
Vertex Solution:	Identification of these co-complex structures of the different JAKs and our compounds led to creation of compounds that are highly selective for JAK3
In Vitro Evidence:	In cell-based assays, showed high selectivity for JAK3 compared to JAK1 and JAK2



JAK3 and JAK2 structures superimposed at hinge

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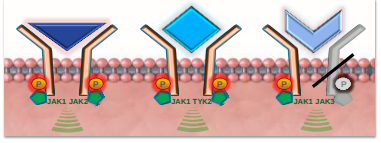
Inhibition of JAK3 Blocks Only JAK1/3 Pair Signaling

3 **Selective inhibition of JAK3 blocks downstream signal transduction for JAK1/3 pair without impacting the other JAK pairs[1,2]**



1. Hoock T et al. Presented at ACR; November 5–9, 2011; Chicago, IL, USA. Abstract 1136;
2. Fleischmann R et al. Presented at ACR; November 5–9, 2011; Chicago, IL. Poster L9.

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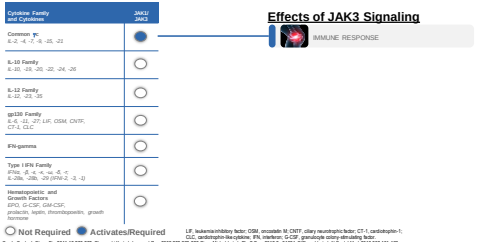
Signaling Controlled by JAK3 Is Restricted to Common γc



LIF, leukemia inhibitory factor; OSM, oncostatin M; CNTF, ciliary neurotrophic factor; CT-1, cardiotrophin-1; CLC, cardiotrophin-like cytokine; IFN, interferon; G-CSF, granulocyte colony-stimulating factor.

Cao L, Costa J. Chem Bio. 2011;18:277-278; Ghoreschi K et al. Immunol Rev. 2009;228:273-287;Giron-Michel J et al. PLoS One. 2012;7:e31624; O'Shea JJ et al. N Engl J Med. 2013;368:161-170; O'Sullivan LA et al. Mater Immunol. 2007;44:2497-2506; Pesu M et al. Immunol Rev. 2008;223:132-142; Brusk K, Liu B. Nature Rev. 2003;3:800-811.

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VX-509 shows >25-fold selectivity for JAK3 compared to Jak1, Jak2 & Jak1/Tyk2, in JAK dependent cell assays

Cell Assay	JAK Involved	VX-509 IC_{50} (nM)
HT-2/IL-2/P-STAT5	JAK3	99 ± 40
TF-1/GMCSF/P-STAT5	JAK2	2600 ± 1600
Mouse 2-Way MLR	JAK3	170 ± 100
1° Human IL-2 T-cell Blast	JAK3	140, 400
Human CFU-E 3 U/ml EPO	JAK2	7700 ± 6100
Human CFU-E 0.3 U/ml EPO	JAK2	5300 ± 3600
HeLa IFN-α STAT2	JAK1/TYK2	11900 ± 3650
Ratio CFU-E to MLR IC50 3 U/ml EPO		45.3
Ratio CFU-E to MLR IC50 0.3 U/ml EPO		31.3

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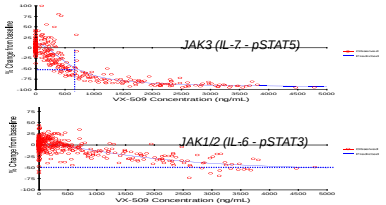
VX-509 JAK3 Selectivity Confirmed with Ph1 Biomarkers



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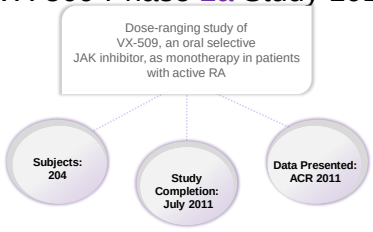
VX-509 Phase 2a Study 101



Vertex, data on file.

61

Study Endpoints

Primary Endpoints

- Proportion of subjects who achieve an ACR20 response at Week 12
- Change from baseline in DAS28-CRP at Week 12

Secondary Endpoints

- ACR 50/70, DAS28-CRP, EULAR responses, HAQ-DI
- PK
- QoL: SF-36
- Safety and tolerability: adverse events, laboratory results, ECG

CRP, C-reactive protein; QoL, quality of life; SF-36, Short-Form 36 Health Survey; ECG, electrocardiogram.
Vertex, data on file.

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Patient Population

- Active RA
  - ≥6 swollen AND ≥6 tender joints (28 joint counts)
  - CRP ≥1.5×ULN
- Failure of ≥1 nonbiologic DMARD for any reason
- Previous use of ≤1 biologic other than rituximab allowed if failure for reasons other than inadequate response
- No concurrent DMARD allowed
- Stable doses of oral corticosteroids (≤10 mg/day prednisone equivalent) and 1 NSAID permitted

ULN, upper limit of normal; NSAID, nonsteroidal anti-inflammatory drug.
Vertex, data on file.

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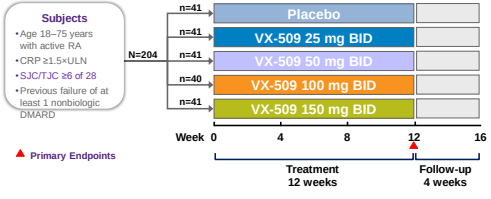
Study Design



SJC, swollen joint count; TJC, tender joint count.
Fleischmann R et al. Presented at ACR; November 5–9, 2011; Chicago, IL. Poster L9; Vertex, data on file.

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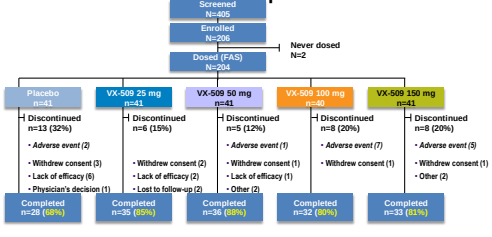
Patient Disposition



Vertex, data on file.

65

Baseline Characteristics and Patient Demographics

		VX-509 BID				
	Placebo (n=41)	25 mg (n=41)	50 mg (n=41)	100 mg (n=40)	150 mg (n=41)	Overall (N=204)
Female, %	78	78	83	85	83	81
Race, Caucasian, %	98	95	98	95	95	96
Age, mean (range), years	54.9 (31–74)	56.8 (31–74)	55.6 (22–75)	56.5 (24–75)	57.0 (35–73)	56.1 (22–75)
RA duration, mean, years	10.0	8.5	6.3	6.7	7.1	7.7

RF+, rheumatoid factor (RF) positive; CCP+, anti-cyclic citrullinated peptide (CCP) positive.
Fleischmann R et al. Presented at ACR; November 5–9, 2011; Chicago, IL. Poster L9..

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Baseline Disease Activity

		VX-509 BID				
	Placebo (n=41)	25 mg (n=41)	50 mg (n=41)	100 mg (n=40)	150 mg (n=41)	Overall (N=204)
TJC (28 joints), mean	15.6	17.0	17.4	15.6	16.5	16.4
SJC (28 joints), mean	13.5	13.3	13.3	11.6	12.9	12.9
CRP, mean, mg/L†	22.8	19.1	22.8	29.1	24.9	23.7
ESR, mean, mm/h	44.0	53.1	47.5	52.5	56.8	50.7
HAQ-DI, mean	1.61	1.70	1.58	1.64	1.70	1.65
DAS28-CRP, mean	6.0	6.2	6.2	6.0	6.1	6.1

†ULN for CRP was 5 mg/L.
Fleischmann R et al. Presented at ACR; November 5–9, 2011; Chicago, IL. Poster L9; Vertex, data on file.

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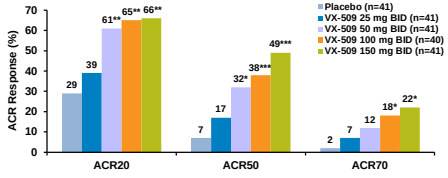
ACR Responses at Week 12†



*P<0.05; **P<0.01; ***P≤0.001; *P* values vs placebo.

†Nonresponder imputation.
Fleischmann R et al. Presented at ACR; November 5–9, 2011; Chicago, IL. Poster L9.

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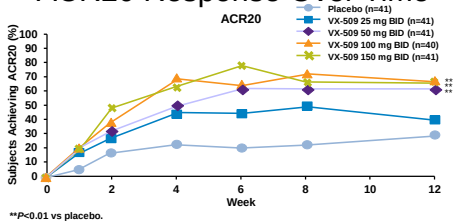
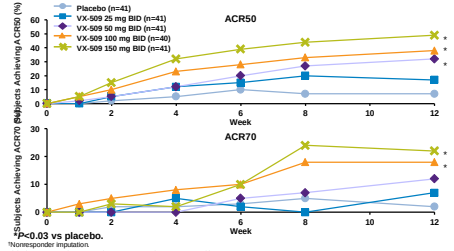
ACR20 Response Over Time†



**P<0.01 vs placebo.

†Nonresponder imputation.
Fleischmann R et al. Presented at ACR; November 5–9, 2011; Chicago, IL. Poster L9.

ACR50 and ACR70 Over Time†

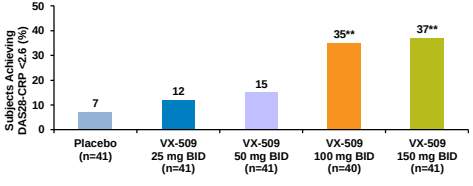


*P<0.03 vs placebo.

†Nonresponder imputation.
Fleischmann R et al. Presented at ACR; November 5–9, 2011; Chicago, IL. Poster L9.

70

DAS28-CRP <2.6 at Week 12†



**P<0.01 vs placebo.

†Nonresponder imputation.
Fleischmann R et al. Presented at ACR; November 5–9, 2011; Chicago, IL. Poster L9.

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Treatment-Emergent Adverse Events (TEAEs) Summary†

		VX-509 BID				
Event, n (%)	Placebo (n=41)	25 mg (n=41)	50 mg (n=41)	100 mg (n=40)	150 mg (n=41)	All VX-509 (n=163)
Any TEAE	19 (46.3)	12 (29.3)	18 (43.9)	25 (62.5)	22 (53.7)	77 (47.2)
Discontinuation due to adverse event	2 (4.9)	0	1 (2.4)	7 (17.5)	5 (12.2)	13 (7.9)
Serious adverse event	1 (2.4)	0	1 (2.4)	5 (12.5)	2 (4.9)	8 (4.9)
Any infection	7 (17.0)	5 (12.2)	5 (12.2)	10 (25.0)	8 (19.5)	28 (17.2)
Serious infection	0	0	0	3 (7.5)	2 (4.9)	5 (3.1)
Death	0	0	0	2 (5.0)	0	2 (1.2)

†69% of placebo/84% of VX-509 subjects completed 12 weeks of dosing.
Fleischmann R et al. Presented at ACR; November 5–9, 2011; Chicago, IL. Poster L9.

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Most Common TEAEs†

Adverse Event, n (%)	Placebo (n=41)	VX-509 BID 25 mg (n=41)	50 mg (n=41)	100 mg (n=40)	150 mg (n=41)	All VX-509 (n=163)
Nausea	0	0	5 (12)	1 (2.5)	4 (9.8)	10 (6.1)
ALT increased	2 (4.9)	0	0	4 (10)	3 (7.3)	7 (4.3)
Headache	2 (4.9)	1 (2.4)	2 (4.9)	2 (5.0)	2 (4.9)	7 (4.3)
Hypercholesterolemia	0	0	0	4 (10.0)	2 (4.9)	6 (3.7)
AST increased	0	0	0	2 (5.0)	3 (7.3)	5 (3.1)
Bronchitis	1 (2.4)	0	0	1 (2.5)	4 (9.8)	5 (3.1)
Diarrhea	1 (2.4)	0	2 (4.9)	1 (2.5)	2 (4.9)	5 (3.1)
Constipation	0	1 (2.4)	1 (2.4)	2 (5.0)	0	4 (2.5)
Peripheral edema	0	1 (2.4)	0	3 (7.5)	0	4 (2.5)
Urinary tract infection	2 (4.9)	0	2 (4.9)	2 (5.0)	0	4 (2.5)

†Occurring in ≥2% of all patients treated with VX-509

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl.
Fleischmann R et al. Presented at ACR; November 5–9, 2011; Chicago, IL. Poster L9.

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VX-509 phase 2b trial

- N=358; 100 mg QD, 150 mg QD, 200 mg QD and 100 mg BID
- Efficacious
- Higher rate of serious infection (2.8% vs 1.4%) and "elevations in transaminase levels and decreases in median neutrophil and lymphocyte counts were observed."
- Genovese, abstract L3, Tuesday oral late breaker, 3PM

JAK Inhibition in RA, Summary

1. There are multiple possible approaches which affect different JAK targets.
2. Tofacitinib has the most clinical data, by far!
3. The 'real world' effects of different degrees of JAK selective targeting may be somewhat difficult to predict from in-vitro assays alone. (eg., it is possible that the biochemical complexities and stoichiometry of **partial target inhibition** of 1 of the 2 JAK heterodimers confers a variable degree of clinical inhibition [that is, not an "all or nothing phenomenom".])
4. **The actual effects in humans is what bears watching**!

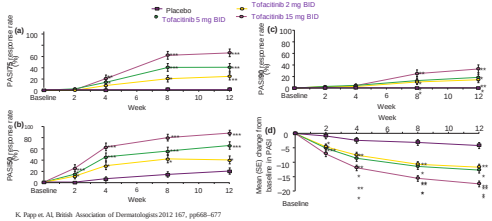
The "ideal" JAK target for the best Efficacy/Toxicity profile has not yet been determined.

Other Indications

JAKs

Tofacitinib Oral Psoriasis Program: Phase 2b

Oral Psoriasis Phase 2b, 12 week dose-ranging study in 196 subjects characterizing the exposure–response, efficacy and safety of tofacitinib vs.placebo in patients with moderate-to-severe chronic plaque psoriasis.



K. Papp et. Al, British Association of Dermatologists 2012 167, pp668–677

Tofacitinib Oral Psoriasis Program: Phase 3

OPT Compare, a 12-week, non-inferiority study comparing the efficacy and safety of tofacitinib 5 and 10 mg twice-daily (BID) to high-dose etanercept 50 mg twice-weekly (BIW), and placebo for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis.

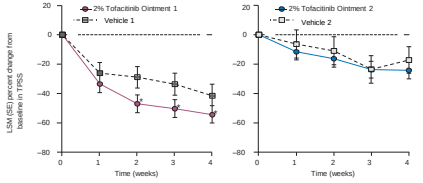
- Tofacitinib met the primary endpoint of non-inferiority to high-dose ENBREL at the 10 mg BID dose.
- Tofacitinib did not meet the non-inferiority criteria to high-dose ENBREL at the 5 mg BID dose. Additionally, rates of important safety events were similar across the active treatment arms.

OPT Retreatment , a 56-week study compared the efficacy and safety of withdrawal and retreatment with tofacitinib 5 and 10 mg BID to placebo for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis.

- The OPT Retreatment study met its primary efficacy endpoints at the 5 and 10 mg BID doses by demonstrating that a greater proportion of patients continuing tofacitinib treatment maintained their response during the treatment withdrawal phase compared to patients who switched to placebo.

Top-line results for the OPT Pivotal 1 and OPT Pivotal 2 trials (A3921078 and A3921079) are anticipated in the second quarter of 2014.

Tofacitinib Topical Psoriasis Program: Phase 2a



W. Peris et al. British Journal of Dermatology (2013) 169, pp137–145

Tofacitinib: Other Psoriasis Studies in Progress

Tofacitinib Ointment For Plaque Psoriasis (PhasII)
Estimated Enrollment: 480

Study Start Date: May 2013
Estimated Study Completion Date: July 2014
Estimated Primary Completion Date: July 2014 (Final data collection date for primary outcome measure)

Tofacitinib In Psoriatic Arthritis Subjects With Inadequate Response to TNF Inhibitors (OPAL BEYOND)

Estimated Enrollment:	390
Study Start Date:	July 2013
Estimated Study Completion Date:	August 2015
Estimated Primary Completion Date:	April 2015 (Final data collection date for primary outcome measure)

Efficacy And Safety Of Tofacitinib In Psoriatic Arthritis: Comparator Study (OPAL BROADEN)

Estimated Enrollment:	400
Study Start Date:	September 2013
Estimated Study Completion Date:	January 2016
Estimated Primary Completion Date:	March 2015 (Final data collection date for primary outcome measure)

Tofacitinib in Ulcerative Colitis

Completed Phase 2b Study in UC

194 adults with moderately to severely active ulcerative colitis.

Patients were randomly assigned to receive tofacitinib at a dose of 0.5 mg, 3 mg, 10 mg, or 15 mg or placebo twice daily for 8 weeks

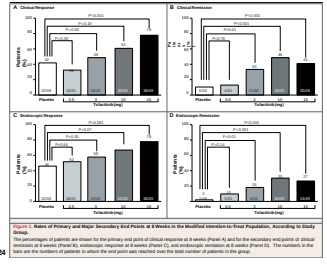


Figure 1. Rates of Primary and Major Secondary End Points at 8 Weeks in the Modified Intention-to-Treat Population, According to Study Group.
The percentages of patients are shown for the primary end point of clinical response at 8 weeks (Panel A) and for the secondary end points of clinical remission at 8 weeks (Panel B), endoscopic response at 8 weeks (Panel C), and endoscopic remission at 8 weeks (Panel D). The numbers in the bars are the numbers of patients in whom the end point was reached over the total number of patients in the group.

Sandborn et al., N Engl JMed 2012;367:616-24

Tofacitinib: Other IBD Studies in Progress

A Study Of Oral CP-690550 As A Maintenance Therapy For UC (OCTAVE)

Estimated Enrollment:	654
Study Start Date:	July 2012
Estimated Study Completion Date:	January 2016
Estimated Primary Completion Date:	December 2015 (Final data collection date for primary outcome measure)

A Study Evaluating The Efficacy And Safety Of CP-690,550 In Patients With Moderate To Severe Ulcerative Colitis (OCTAVE)

Estimated Enrollment:	545
Study Start Date:	April 2012
Estimated Study Completion Date:	January 2015
Estimated Primary Completion Date:	December 2014 (Final data collection date for primary outcome measure)

Tofacitinib: Other Arthropathy Studies in Progress

Pharmacokinetics Of CP-690,550 In Pediatric Patients With Juvenile Idiopathic Arthritis (JIA)

Estimated Enrollment:	24
Study Start Date:	December 2012
Estimated Study Completion Date:	December 2014
Estimated Primary Completion Date:	December 2014 (Final data collection date for primary outcome measure)

Long-Term Safety Study Of CP-690,550 In Patients With JIA

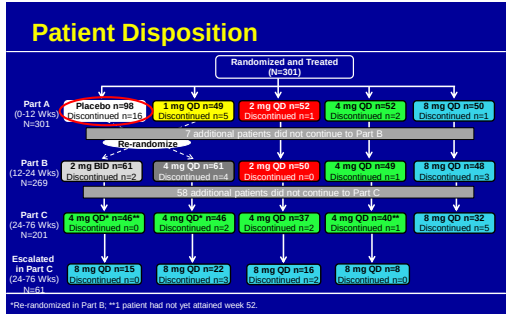
Estimated Enrollment:	290
Study Start Date:	March 2013
Estimated Study Completion Date:	September 2020
Estimated Primary Completion Date:	September 2020 (Final data collection date for primary outcome measure)

Dose-Ranging Study Of Tofacitinib In Adults With Active Ank Spond

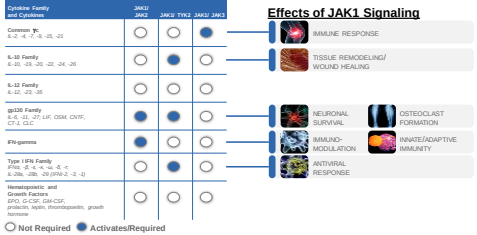
Estimated Enrollment:	200
Study Start Date:	April 2013
Estimated Study Completion Date:	September 2014
Estimated Primary Completion Date:	August 2014 (Final data collection date for primary outcome measure)

Drug	Target	Status	Diseases
Ruxolitinib	Jak1, Jak2	FDA approved Phase II	Polycythemia, Myelofibrosis, Various cancers
Tofacitinib	Jak1, Jak3	FDA approved Phase III Phase II	RA Psoriasis, Ulcerative colitis spondyloarthropathy juvenile arthritis
Baracitinib	Jak1, Jak2	Phase II	RA, Psoriasis, Diabetic nephropathy
INCB047986	check	Not open yet	Malignancy
GLPG0778 GSK2586184	Jak1	Phase II	SLE, Psoriasis
GLPG0634	Jak1 (check)	Phase II	RA, Crohn's
CYT387	Jak1, Jak2	Phase II	Myelofibrosis
ASP015K(Astellas/Janssen; NCT01711814 clinical trials.gov)	JAK1,3	Phase II	Psoriasis, RA
R256			Asthma
R333			Discoid lupus
ABT-494 (Abbott)	**Jak1**	**Phase I**	
PF-04965842	Jak1	Phase I	-
GLG0778	Jak1	Phase II	SLE
VX-509 Lestaurtinib	Jak3	Phase II	RA

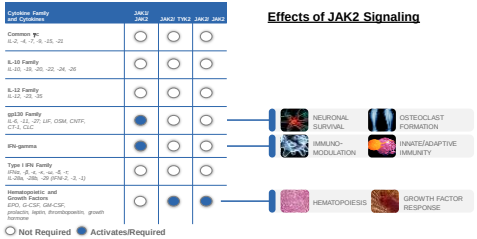
Thank you!



Signaling Controlled by JAK1 Effects Multiple Cytokine Families

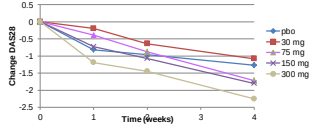


Signaling Controlled by JAK2 Includes Hematopoietic and Growth Factors



GLPG0634

DAS28 scores



GLPG0634 rapidly improves disease activity score

Apparent dose response – 30 mg less active