JAK Inhibition in RA

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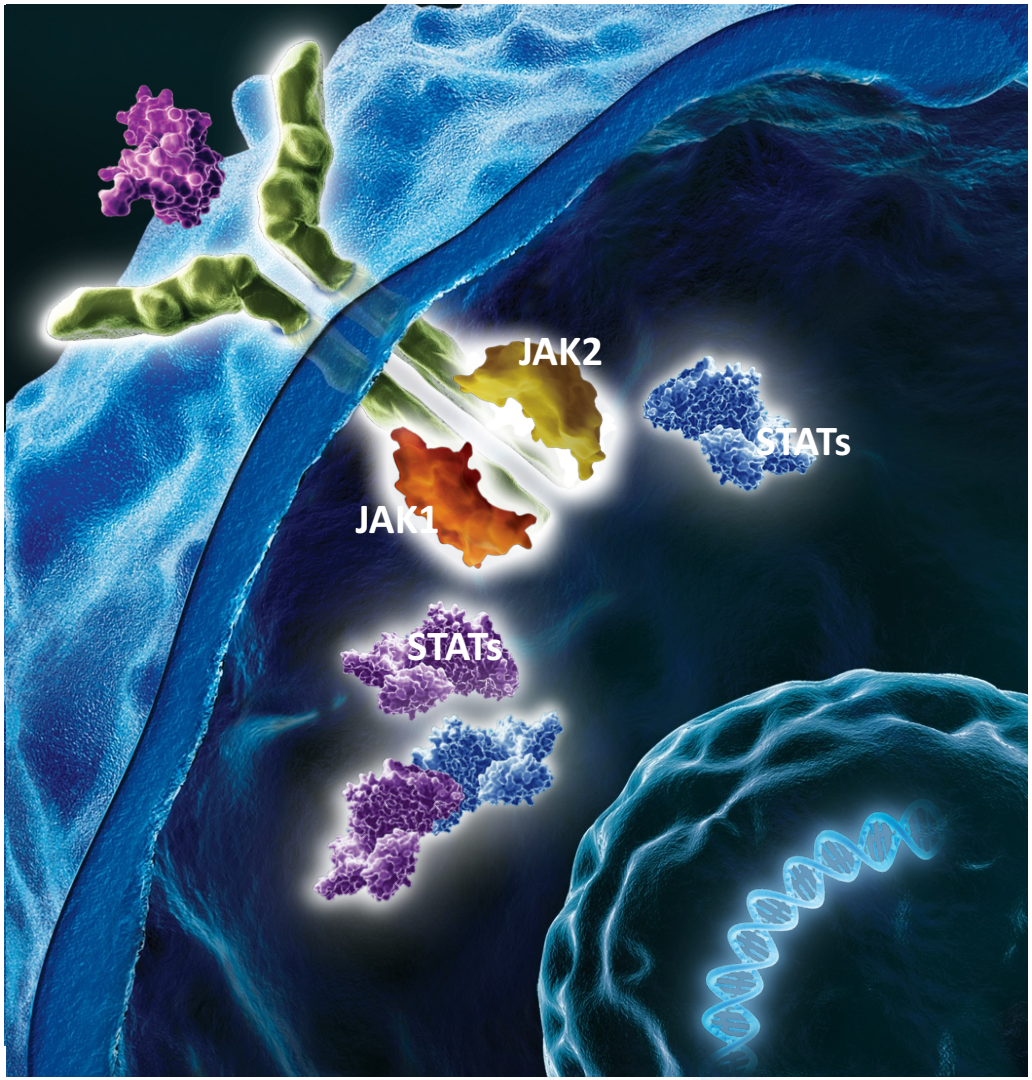
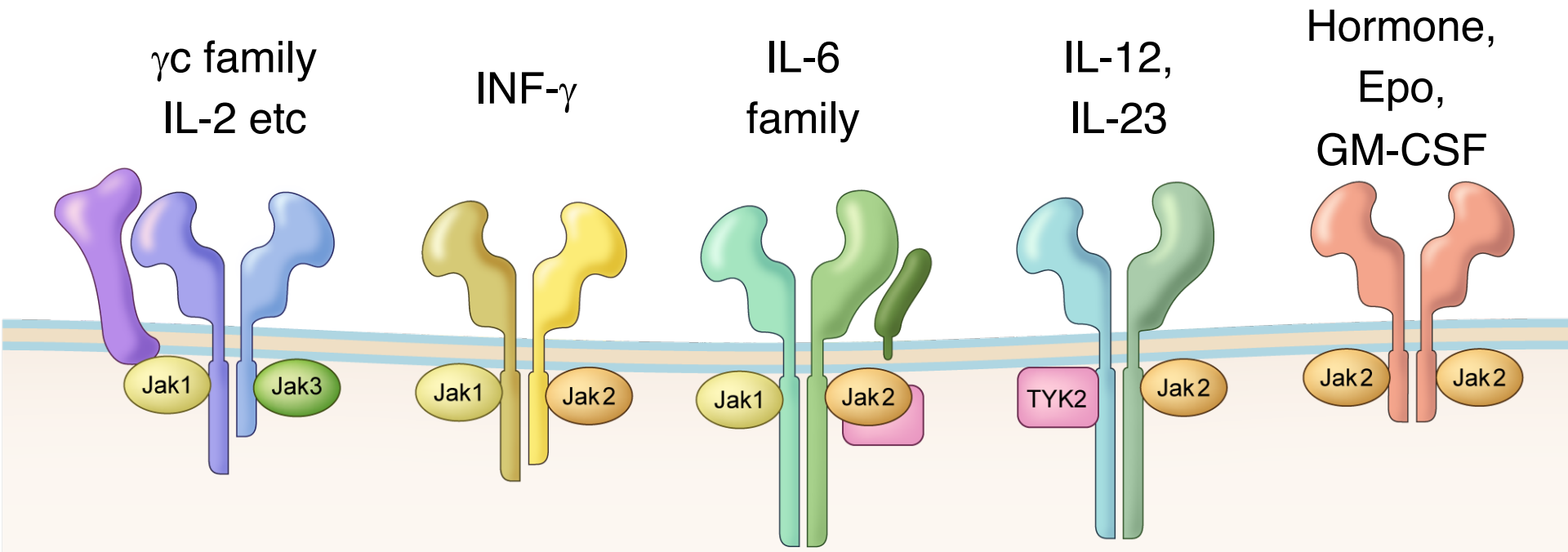
Targeting JAKs For the Treatment of Rheumatoid Arthritis

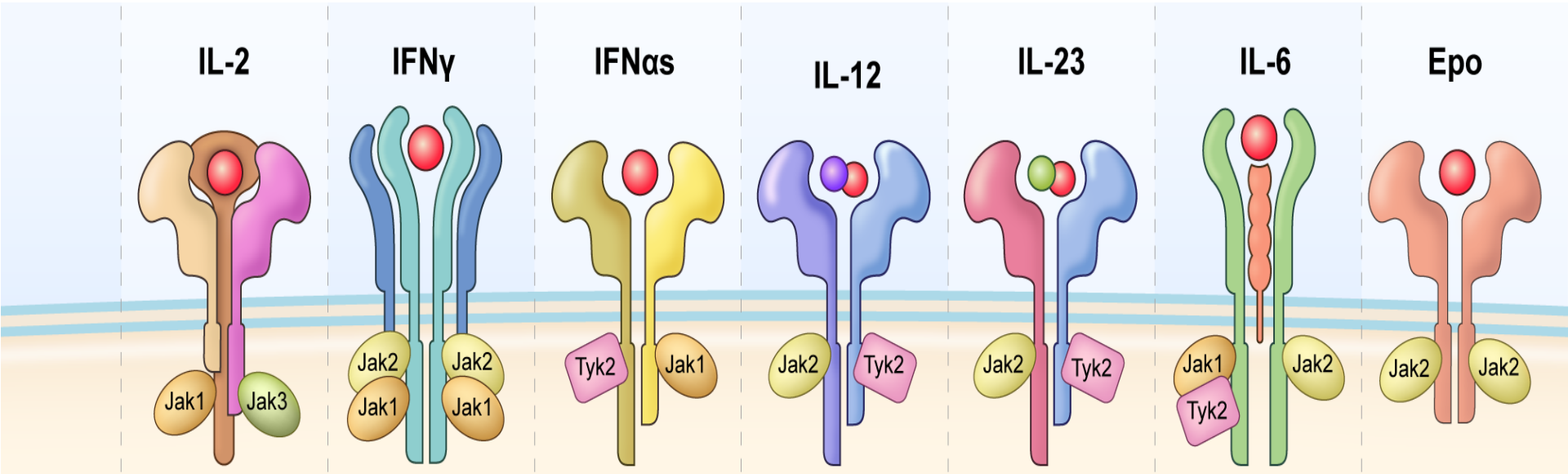
- **Four members of JAK tyrosine kinase family**
  - JAK1, JAK2, JAK3 and Tyk2
- **Non-receptor tyrosine kinases required for signaling of cytokines and growth factors**
- **Typically 2 different JAKs associate with the cytokine receptors to initiate signaling**
  - **JAK2 is an exception**
- **JAK1 and JAK2 mediate the signals of cytokine targets in inflammatory diseases**
- **JAK3 is primarily involved in T-cell-mediated immune function**



Jaks and Signaling by Type I/II Cytokine Receptors

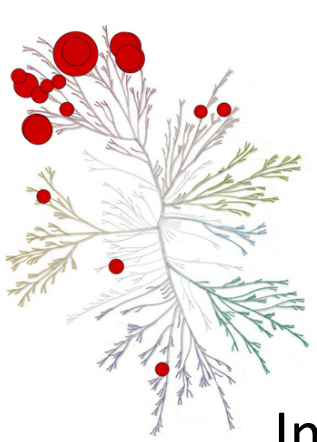


- Four Jaks: Jak1, Jak2, Jak3, Tyk2
- work in pairs, except homodimeric hormone receptors



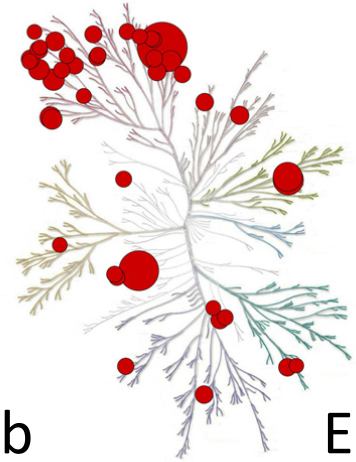
Inhibitor	IL-2	IFNγ	IFNαs	IL-12	IL-23	IL-6	Epo
Jak1	+	+	+	−	−	+	−
Jak2	−	+	+	+	+	+	+
Jak3	+	−	−	−	−	−	−
Tyk2	−	−	+	+	+	−	−

Tyrosine Kinase Inhibitors: far from selective



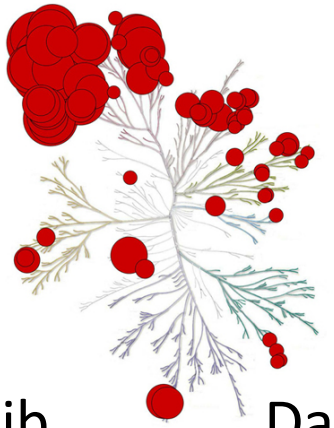
Imatinib

(Bcr-abl)



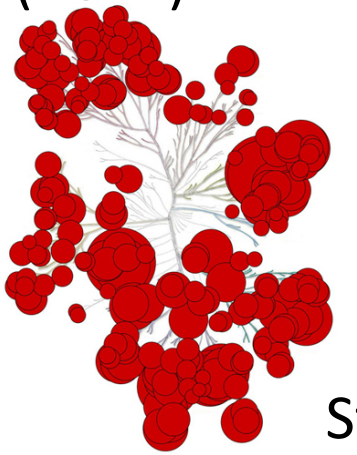
Erlotinib

(EGFR)



Dasatinib

Sunitinib



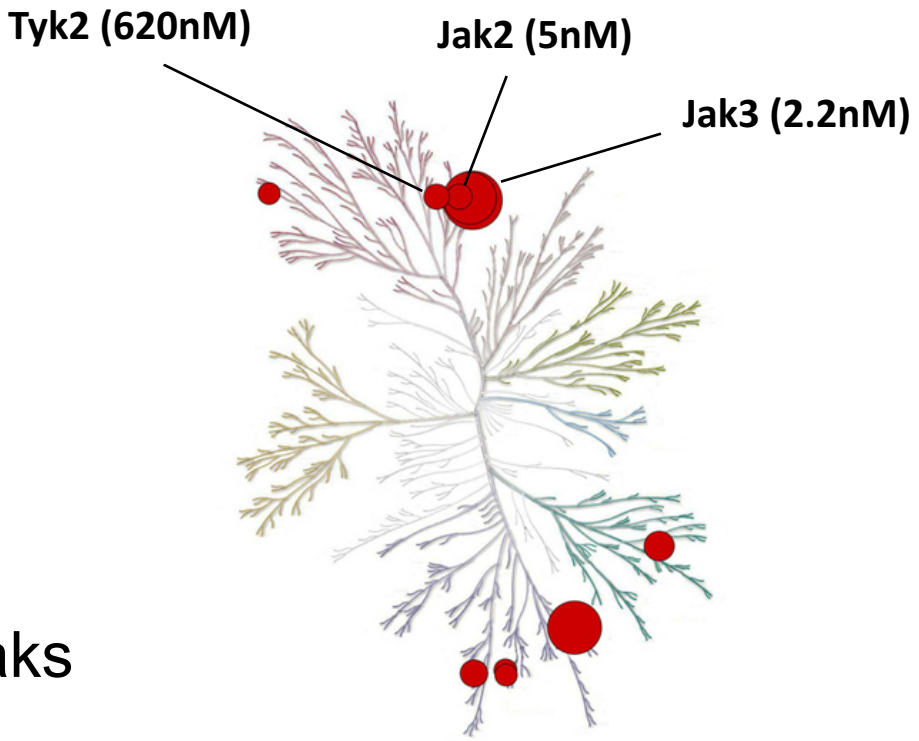
Staurosporine

Karaman et al *Nature Biotechnology*, 2005

Comparison of JAK inhibitors in Clinical Development (Enzyme Assays)

JAK inhibitor	Selectivity	JAK1 (IC50, nM)	JAK2 (IC50, nM)	JAK3 (IC50, nM)	TYK2 (IC50, nM)
Tofacitinib	JAK1, 2, and 3	23	41	16	340
baricitinib	JAK1 and 2	5.9	5.7	>400	53
VX-509	JAK3	Unknown	Unknown	Unknown	Unknown
filgotinib	JAK1	10	28	810	116

Selectivity of Tofacitinib



- Reasonably selective for Jaks
- Selectivity amongst Jaks?
  - Limitations of assay
- Cellular selectivity for Jaks: Jak3, Jak1 > Jak2 >> Tyk2
- Relevance to efficacy? Blocks innate and adaptive responses

Safety and Efficacy After 24-Week Dosing of the Oral JAK Inhibitor CP-690,550 as Monotherapy in Patients with Active Rheumatoid Arthritis

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KS Kannik[3] GV Wallenstein,[3] B Wilkinson,[3] SH Zwillich[3]

[1]Metroplex Clinical Research Center, Dallas, TX; [2]Stanford University, Stanford, CA; [3]Pfizer Inc., New London, CT

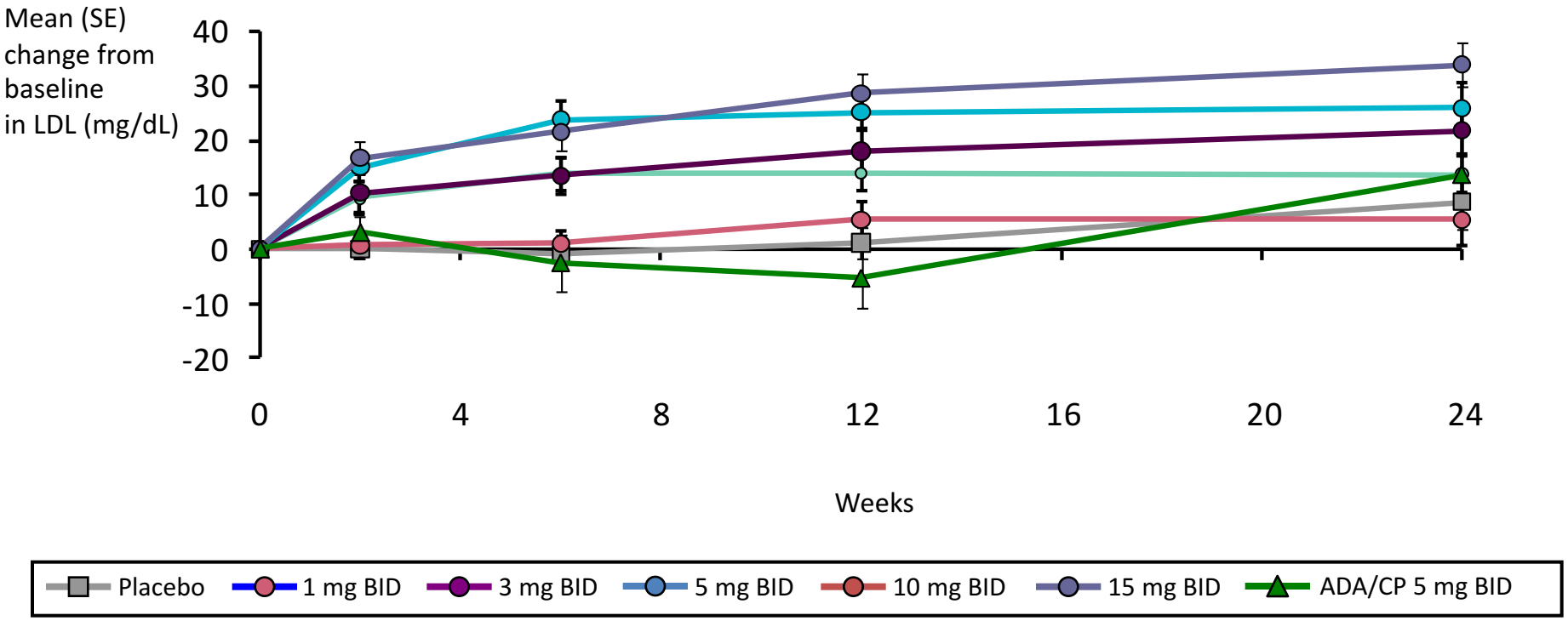
Incidence of Transaminase Single and Sustained Elevations Over 24 Weeks

Dose	ALT, n (%)					AST, n (%)				
	Normal baseline (n)	>1x ULN	>2x ULN	>3x ULN	>1x ULN sustained until end of study	Normal baseline (n)	>1x ULN	>2x ULN	>3x ULN	>1x ULN sustained until end of study
Placebo	54	12 (22)	0	0	1 (4)[a]	54	7 (13)	0	0	1 (4)[a]
1 mg BID	50	4 (8)	0	0	1 (3)	48	4 (8)	0	0	0
3 mg BID	48	9 (19)	2 (4)	0	1 (3)	49	9 (18)	1 (2)	1 (2)	1 (3)
5 mg BID	48	6 (13)	1 (2)	0	2 (4)	48	9 (19)	1 (2)	1 (2)	3 (6)
10 mg BID	61	8 (13)	1 (2)	0	1 (2)	59	13 (22)	1 (2)	0	2 (3)
15 mg BID	55	13 (24)	2 (4)	2 (4)	3 (5)	56	12 (21)	2 (4)	2 (4)	4 (7)
40 mg ADA QOW / CP 5 mg BID	50	10 (20)	3 (6)	2 (4)	4 (8)[b]	51	10 (20)	3 (6)	0	4 (8)[b]

- No patient who experienced AST or ALT > 3x ULN also experienced an increase in total bilirubin >2x ULN or 2mg/dL

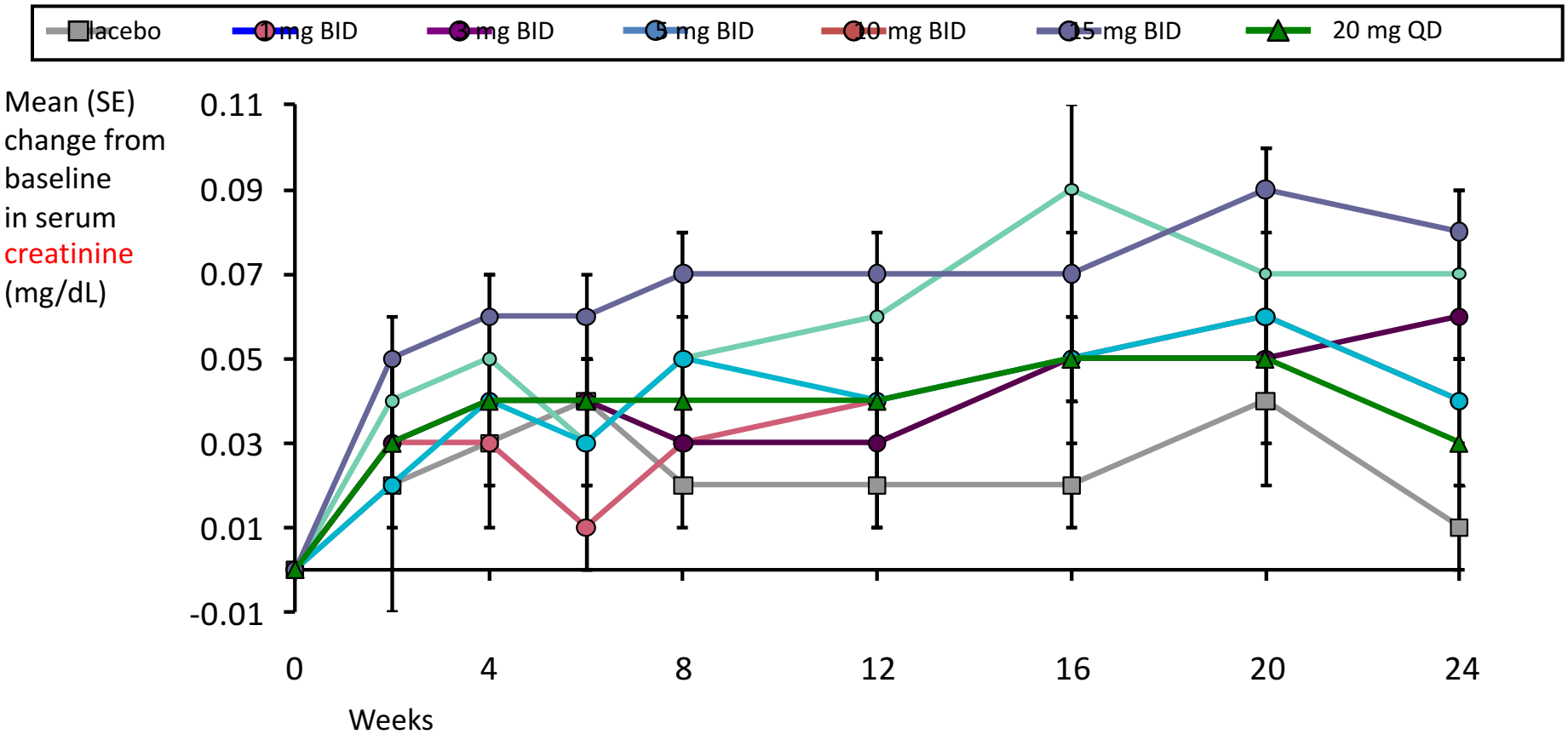
[a]Occurrence in 1 patient post-reassignment; [b]occurrence in 1 (ALT)/ 2 (AST) patients post-reassignment. Patients allowed to enroll with AST/ALT ≤2x ULN. Only patients with normal baseline values are included; ALT, alanine aminotransferase; AST, aspartate aminotransferase

Change from Baseline in LDL Over 24 Weeks (No Imputation; Observed Values)



- The number of CP-690,550 patients with an LDL <130 mg/dL at baseline that increased to >130 mg/dL during the study were: 5 mg: 14 (29%); 10 mg: 22 (36%); 15 mg: 21 (37%)

Placebo, 1 mg BID, and 3 mg BID dose groups do not include patients reassigned to CP-690,550 5 mg BID at Week 12
LDL, low-density lipoprotein



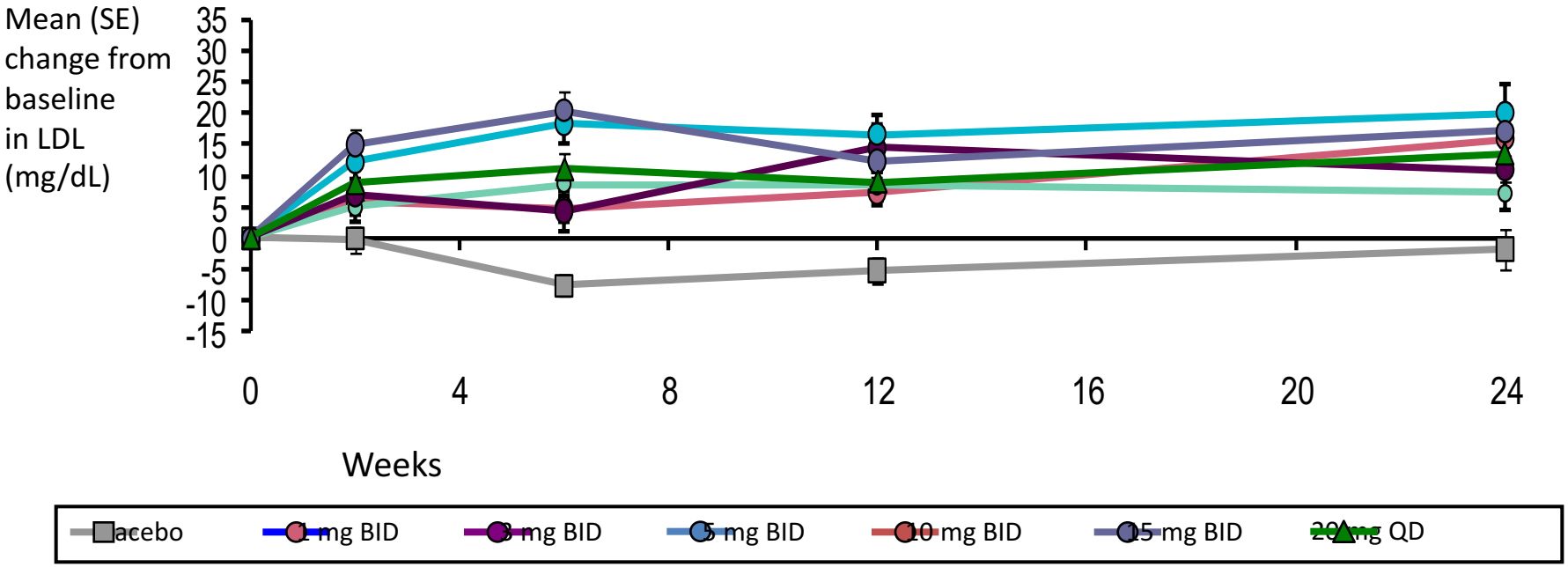
- Five patients receiving CP-690,550 and 1 patient receiving placebo had confirmed[a] 50% increase in serum creatinine levels from baseline; none discontinued

[a]Confirmed = occurrence at 2 consecutive visits
Placebo, 1 mg BID, and 3 mg BID dose groups do not include patients reassigned to CP-690,550 5 mg BID at Week 12;

Key Laboratory Safety Data

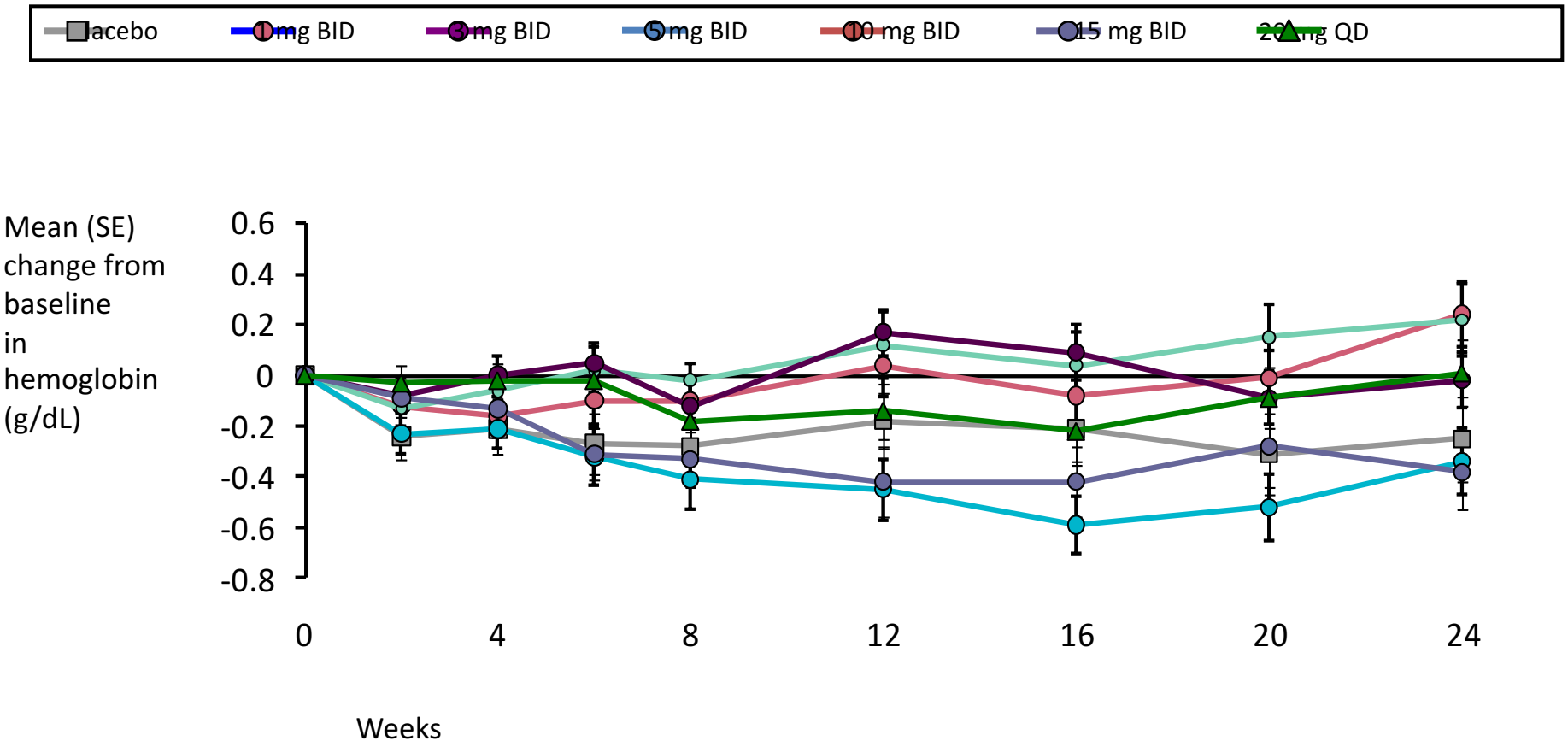
- Six (2.2%) patients on CP-690,550 experienced confirmed[a] severe anemia (OMERACT[b] criteria)
- No patients experienced confirmed[a] severe neutropenia (OMERACT[b] criteria)
- Six patients experienced a confirmed[a] >50% increase in serum creatinine levels from a single baseline measurement: four in the CP-690,550 treatment group and two in the ADA treatment group
  - All resolved either on or post-therapy
  - Of the ADA patients, the increase occurred prior to reassignment to CP-690,550 in one patient; after reassignment in another patient
- Sixteen patients experienced a confirmed[a] >30% and >0.2 mg/dL increase in serum creatinine levels from a single baseline measurement.

[a]Confirmed = occurrence at two consecutive visits; [b]OMERACT, Outcome Measures in Rheumatology. Severe neutropenia: absolute neutrophil counts 500 – 1000/µl; Severe anemia: ≥2 - ≤3g/dL decrease from baseline or hemoglobin 7 – 8 g/dL



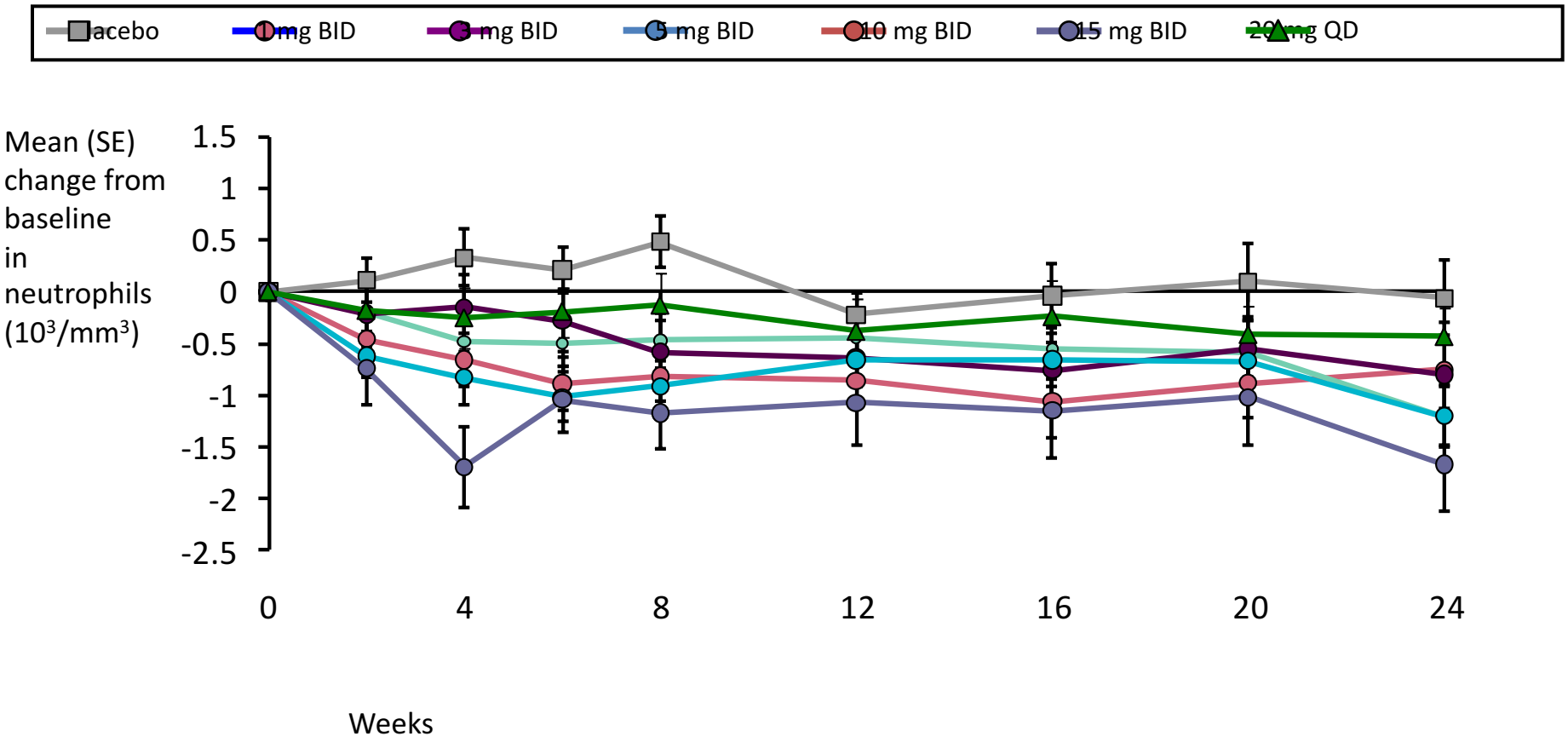
- The proportion of CP-690,550 patients with a LDL <130 mg/dL at baseline that increased to >130 mg/dL at any time during the study ranged from 32% to 42% for the highest doses
- The increase in LDL and HDL peaked at Week 6, and did not continue to increase for the duration of the study

Placebo, 1 mg BID, and 3 mg BID dose groups do not include patients reassigned to CP-690,550 5 mg BID at Week 12



- Thirteen patients on CP-690,550 and 1 patient receiving placebo had confirmed[a] severe anemia (OMERACT criteria[b]); none discontinued

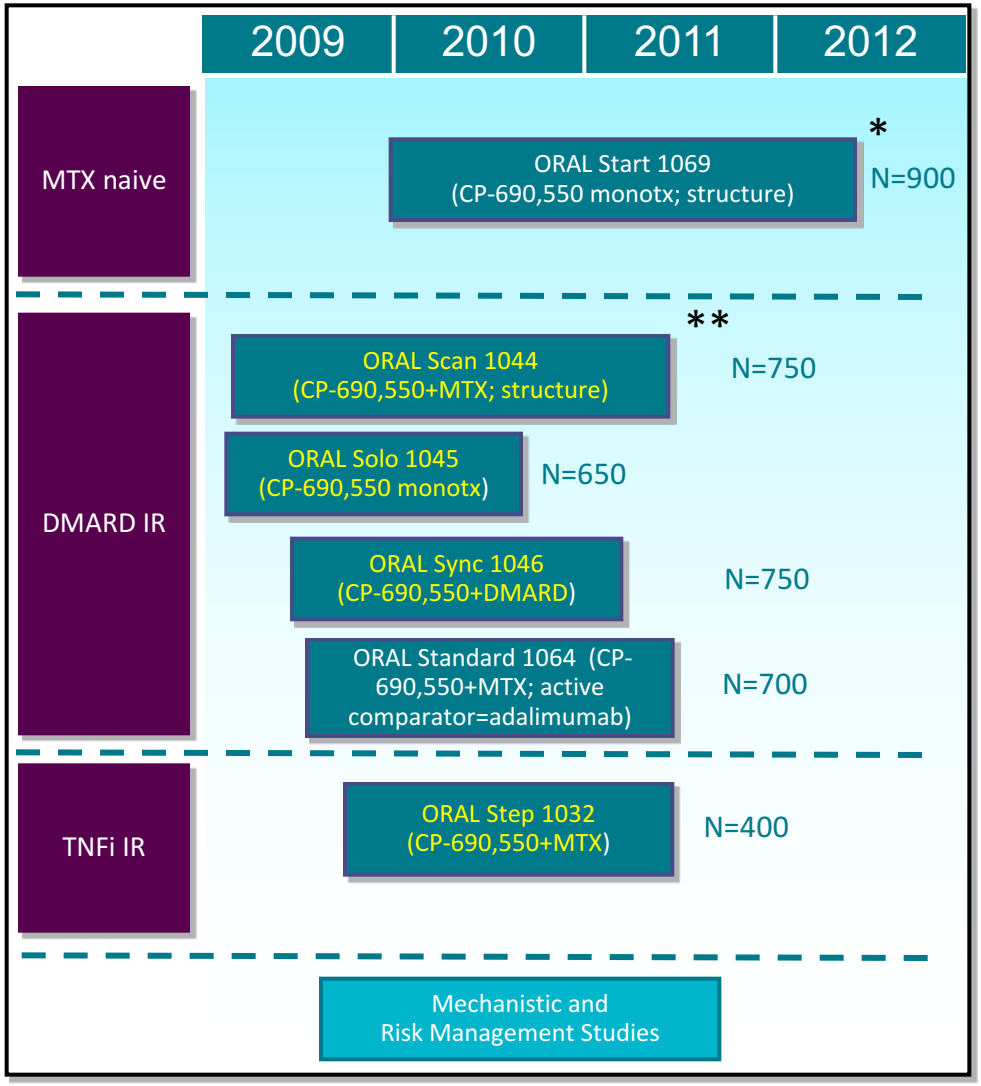
[a]Confirmed = occurrence at 2 consecutive visits; [b]OMERACT, Outcome Measures in Rheumatology.
Placebo, 1 mg BID, and 3 mg BID dose groups do not include patients reassigned to CP-690,550 5 mg BID at Week 12



- No patients had confirmed severe neutropenia (OMERACT criteria); none discontinued

[a]Confirmed = occurrence at 2 consecutive visits; [b]OMERACT, Outcome Measures in Rheumatology.
Placebo, 1 mg BID, and 3 mg BID dose groups do not include patients reassigned to CP-690,550 5 mg BID at Week 12

CP-690,550 RA Phase 3 Development Program



*Interim analysis, study end 2013
**Interim analysis, study end 2012

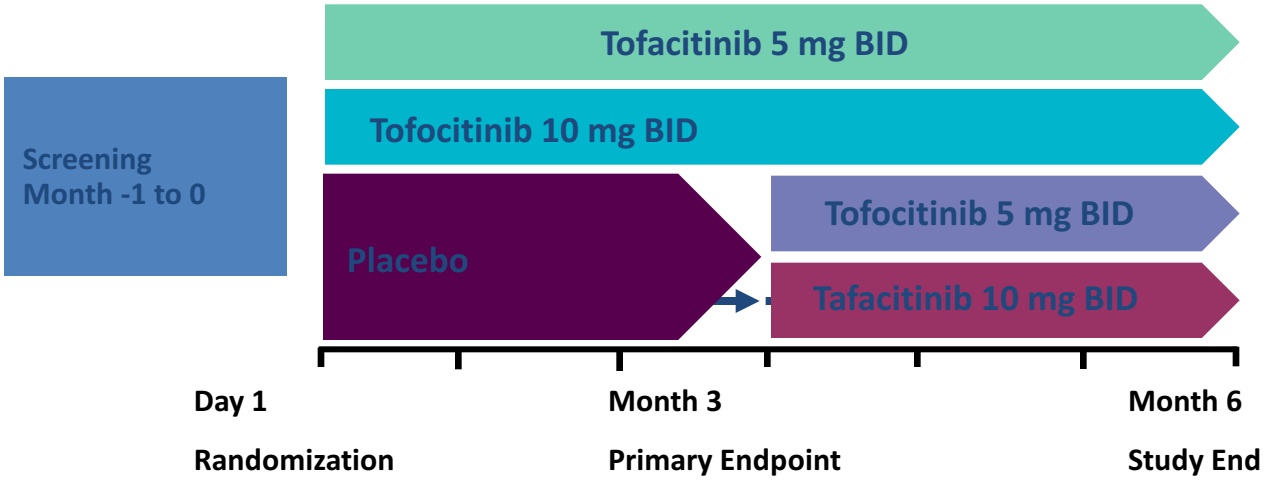
Phase 3 Study of Oral JAK Inhibitor Tofacitinib (CP-690,550) Monotherapy in Patients with Active Rheumatoid Arthritis

Roy Fleischmann
American College of Rheumatology
Atlanta, Georgia, November 6-11, 2010

R Fleischmann,[1] J Kremer,[2] J Cush,[3] H Schulze-Koops,[4] CA Connell,[5] J Bradley,[5] D Gruben,[5] G Wallenstein,[5] SH Zwillich,[5] KS Kanik[5]

[1]Metroplex Clinical Research Center, Dallas, TX; [2]Center for Rheumatology, Albany Medical College, Albany, NY; [3]Baylor Research Institute, Dallas, TX; [4]Division of Rheumatology, University of Munich, Munich, Germany; [5]Pfizer Inc., New London, CT, USA

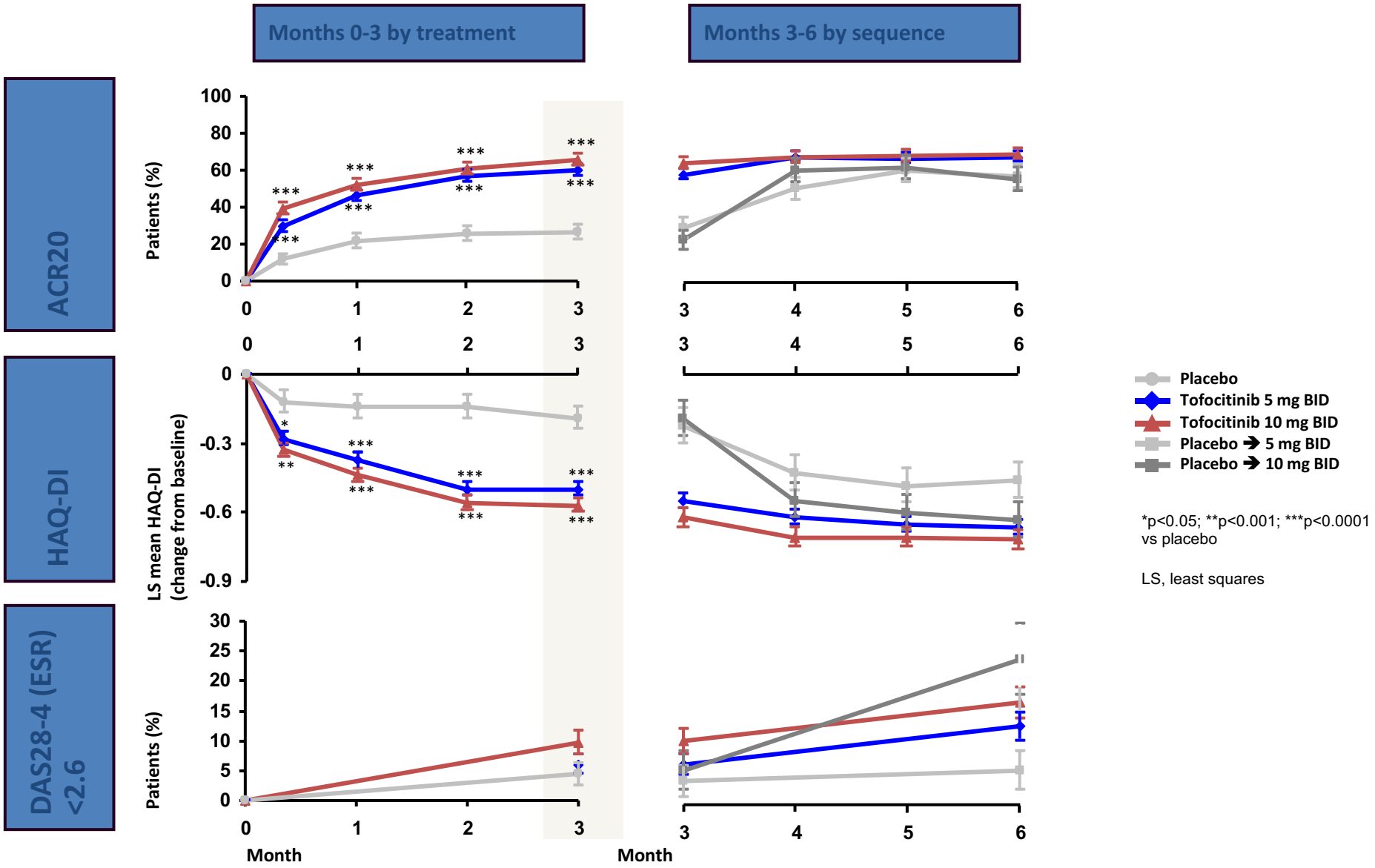
Study Design



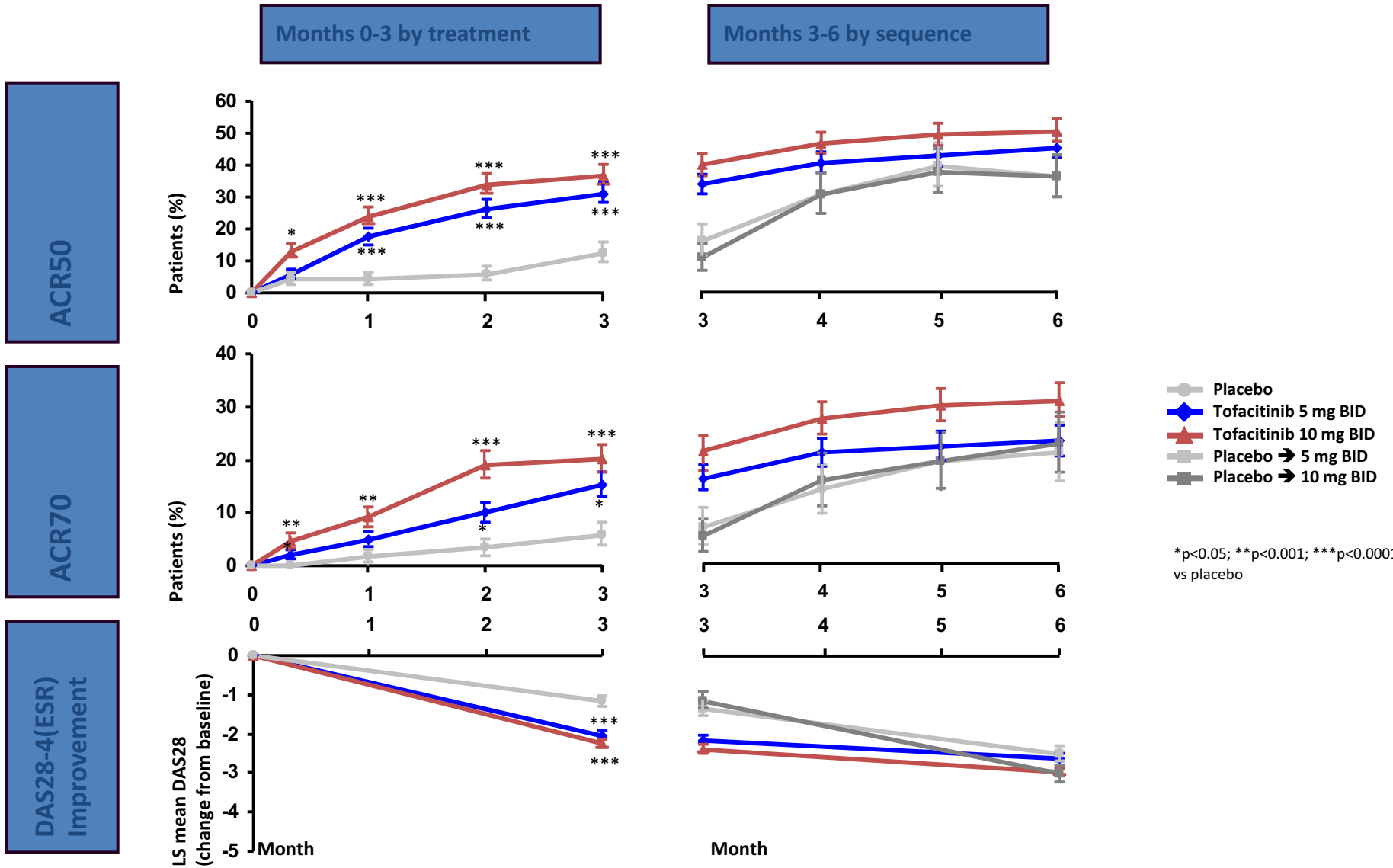
- Patients with active RA were randomized 2:2:1 to tasocitinib 5 or 10 mg BID or placebo
- At Month 3, all placebo patients were blindly advanced to tofacitinib 5 or 10 mg BID
- Primary efficacy endpoint
  - ACR20 responder rate vs placebo at Month 3
  - Change from baseline in the Health Assessment Questionnaire – Disability Index (HAQ-DI) at Month 3
  - Rate of patients achieving a DAS28-4(ESR) <2.6 vs placebo at Month 3
- Key secondary efficacy endpoints
  - ACR 20/50/70 at all visits
  - DAS28-4(ESR) improvement over time

DAS, disease activity score; ESR, erythrocyte sedimentation rate

Primary Efficacy Endpoints



Key Secondary Efficacy Endpoints



Safety: Laboratory Tests

	Month 3			Month 6			
	PBO N=122	5 mg BID N=243	10 mg BID N=245	PBO→5 N=61	PBO→10 N=61	5 mg BID N=243	10 mg BID N=245
LS mean (standard error) change from baseline							
Neutrophil count, $10^3/mm^3$	-0.06 (0.17)	-0.83 (0.11)†	-1.35 (0.12)‡	-0.90 (0.24)	-1.18 (0.26)	-0.78 (0.12)	-1.15 (0.12)
Hemoglobin, g/dL	-0.12 (0.76)	0.28 (0.88)	0.03 (0.97)	0.21 (0.97)	-0.22 (1.05)	0.25 (0.96)	0.15 (0.94)
% LDL, mg/dL	3.5 (2.3)	13.6 (1.6)†	19.1 (1.6)‡	16.9 (3.3)	16.8 (3.4)	12.8 (1.6)	19.1 (1.7)
% HDL, mg/dL	-0.8 (1.9)	12.2 (1.3)‡	15.0 (1.3)‡	11.3 (2.8)	11.0 (2.9)	10.4 (1.4)	16.6 (1.4)
Serum creatinine, mg/dL	0 (0.02)	0.04 (0.01)	0.05 (0.01)	0.06 (0.03)	0.08 (0.03)	0.06 (0.01)	0.08 (0.01)
Incidence, n (%)[a]	**N=103**	**N=223**	**N=216**	**N=53**	**N=50**	**N=224**	**N=210**
Neutropenia	1 (<1.0)	10 (4.5)	10 (4.6)	3 (5.7)	0	6 (2.7)	10 (4.8)
Decreased hemoglobin	15 (14.6)	13 (5.8)	31 (14.4)	5 (9.4)	6 (12.0)	18 (8.0)	22 (10.5)
Incidence of > ULN, n (%)[a]	**N=122**	**N=243**	**N=245**	**N=57**	**N=52**	**N=239**	**N=232**
AST>1x ULN	7 (5.8)	23 (9.5)	29 (11.8)	6 (10.5)	6 (11.5)	28 (11.7)	28 (12.1)
AST>3x ULN	1 (0.8)	4 (1.7)	0	1 (1.8)	0	2 (0.8)	0
ALT>1x ULN	11 (9.1)	23 (9.5)	28 (11.4)	12 (21.1)	7 (13.5)	31 (13.0)	24 (10.3)
ALT>3x ULN	1 (0.8)	1 (0.4)	0	1 (1.75)	0	2 (0.84)	2 (0.86)

[a]Incidence during Months 0-3 and 3-6; †p<0.001; ‡p<0.0001 vs PBO

HDL, high-density lipoprotein; LDL, low-density lipoprotein; ULN, upper limit of normal

Tofacitinib (CP-690,550) an Oral JAK Inhibitor, in Combination with Traditional DMARDs: Phase 3 Study in Patients with Active Rheumatoid Arthritis with Inadequate Response to DMARDs

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Albany Medical College,

Director of Research,

The Center for Rheumatology

ORAL Sync: Safety – Adverse Events

	Months 0-3				Months 3-6				Post Month 6			
	5 mg BID n=315	10 mg BID n=318	PBO n=159	PBO n=81	5 mg BID n=315	10 mg BID n=318	PBO →5 n=38	PBO →10 n=40	5 mg BID n=315	10 mg BID n=318	PBO →5 n=79	PBO →10 n=80
AE, n (%)	166 (52.7)	173 (54.4)	97 (61.0)	21 (25.9)	121 (38.4)	124 (39.0)	16 (42.1)	18 (45.0)	104 (33.0)	135 (42.5)	34 (43.0)	29 (36.3)
Serious AE n (%)	9 (2.9)	8 (2.5)	6 (3.8)	0	5 (1.6)	7 (2.2)	0	0	7 (2.2)	9 (2.8)	2 (2.5)	0
Severe AE n (%)	10 (3.2)	11 (3.5)	6 (3.8)	1 (1.2)	7 (2.2)	6 (1.9)	0	0	8 (2.5)	7 (2.2)	1 (1.3)	0
Serious IE n (%)	2 (0.6)	4 (1.2)	0	0	0	0	1 (0.3)	1 (0.3)	3 (1.0)	8 (2.5)	0	0
D/Cs due to AEs n (%)	13 (4.1)	13 (4.1)	2 (1.3)	1 (1.2)	6 (1.9)	8 (2.5)	0	1 (2.5)	1 (0.3)	9 (2.8)	0	1 (1.3)

	5 mg BID	10 mg BID	PBO→5 mg BID	PBO→10 mg BID
Deaths, n (%)	2 (0.6)	2 (0.6)	0	0

ORAL Sync: Safety – Lab Tests

Patients	Month 3			Months 3-6					Post Month 6			
	PBO n=159	5 mg BID n=315	10 mg BID n=313	5 mg BID n=292	10 mg BID n=297	PBO n=71	PBO →5 n=38	PBO →10 n=40	5 mg BID n=272	10 mg BID n=270	PBO →5 n= 72	PBO →10 n=69
AST>1x ULN, n (%)	22 (13.8)	74 (23.5)	92 (29.4)	52 (17.8)	63 (21.2)	9 (12.7)	4 (10.5)	9 (22.5)	52 (19.1%)	72 (26.7%)	14 (19.4%)	17 (24.6%)
AST>3x ULN, n (%)	1 (<1.0)	3 (<1.0)	1 (<1.0)	1 (<1.0)	0	0	0	0	3 (1.1%)	1 (<1.0)	0	1 (1.4%)
ALT>1x ULN, n (%)	28 (17.6)	88 (27.9)	107 (34.2)	57 (19.5)	70 (23.6)	13 (18.3)	5 (13.2)	4 (10.0)	51 (18.8%)	74 (27.4%)	16 (22.2%)	16 (23.2%)
ALT>3x ULN, n (%)	1 (<1.0)	6 (1.9)	3 (<1.0)	3 (1.0)	3 (1.0)	1 (1.4)	0	1 (2.5)	7 (2.6%)	5 (1.9%)	0	1 (1.4%)

Tofacitinib (CP-690,550), an Oral Janus Kinase Inhibitor, in Combination with Methotrexate Reduced the Progression of Structural Damage in Patients with Rheumatoid Arthritis: a 24-month Phase 3 Study

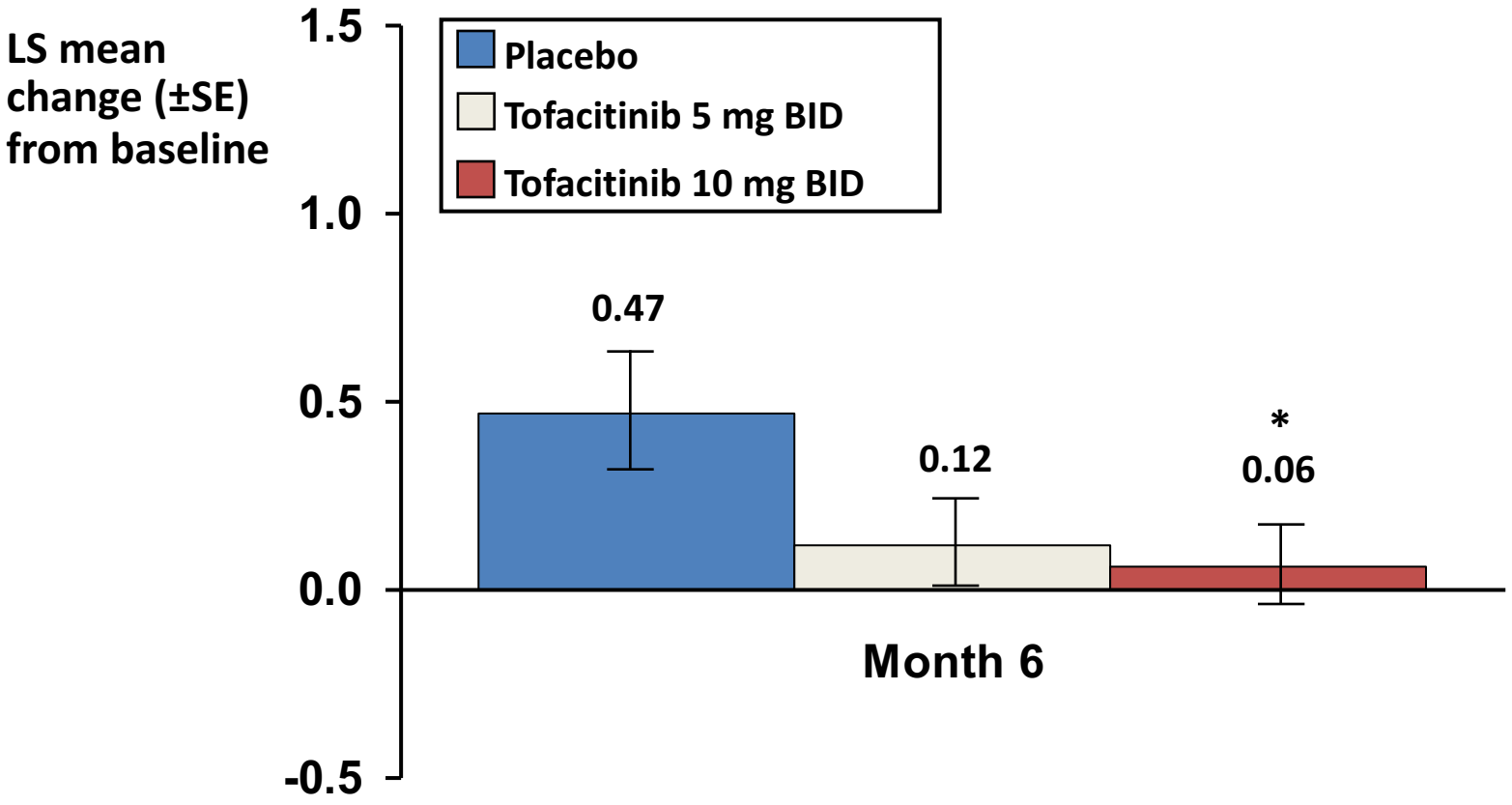
Désirée van der Heijde

Presentation Number: 2592

D van der Heijde,[1] Y Tanaka,[2] R Fleischmann,[3] E Keystone,[4] J Kremer,[5] C Zerbini,[6] M Cardiel,[7] S Cohen,[3] P Nash,[8] Y Song,[9] D Tegzova,[10] B Wyman,[11] D Gruben,[11] B Benda,[12] S Krishnaswami,[11] G Wallenstein,[11] SH Zwillich,[11] J Bradley,[11] C Connell[11]

[1]Leiden University Medical Center, Leiden, The Netherlands; [2]University of Occupational and Environmental Health, Kitakyushu, Japan; [3]Metroplex Clinical Research Center, Dallas, TX, USA; [4]University of Toronto, Toronto, Canada; [5]Albany Medical College, Albany, NY, USA; [6]Centro Paulista de Investigação Clinica, São Paulo, Brazil; [7]Centro de Investigacion Clinica de Morelia, Morelia, Mexico; [8]Nambour Hospital, Sunshine Coast; and University of Queensland, Queensland, Australia; [9]Seoul National University Hospital, Seoul, Korea; [10]Institute of Rheumatology, Prague, Czech Republic; [11]Pfizer Inc., Groton, CT, USA; [12]Pfizer Inc., Collegeville, PA, USA

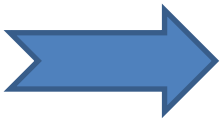
ORAL Scan: mTSS (Primary Endpoint)



*p≤0.05 vs placebo; LS, least squares

Tofacitinib, Phase III

- **Consistent efficacy** in all trials at 5 and 10 mg BID
- **Radiographic Inhibition**
- **Consistent side effect profile**:

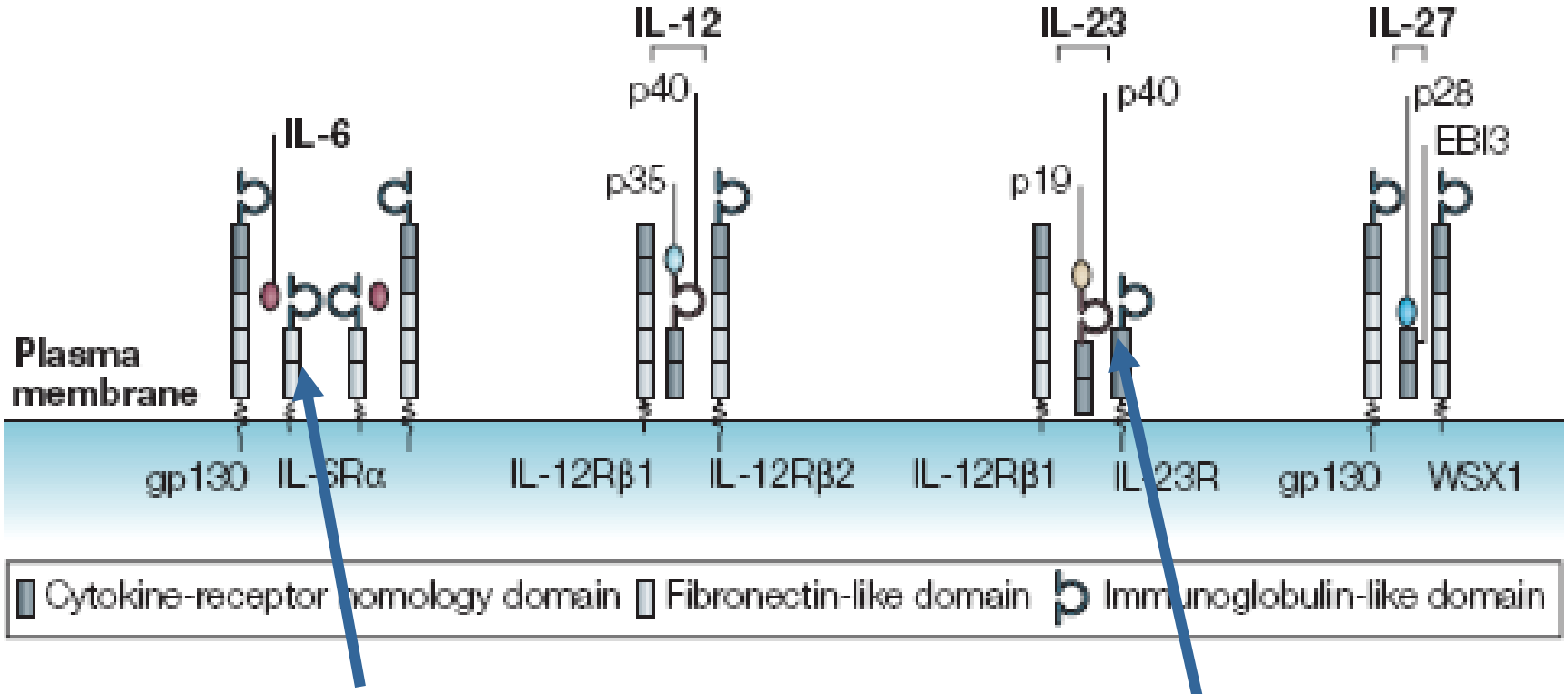


Infections, rare opportunistic infections,

anemia, transaminitis, lipid effects,

occasional neutropenia & increased Cr

Cytokine Targets in Inflammation Which Signal Through JAK1 and JAK2



Tocilizumab
Rheumatoid Arthritis

Ustekinumab
Psoriasis

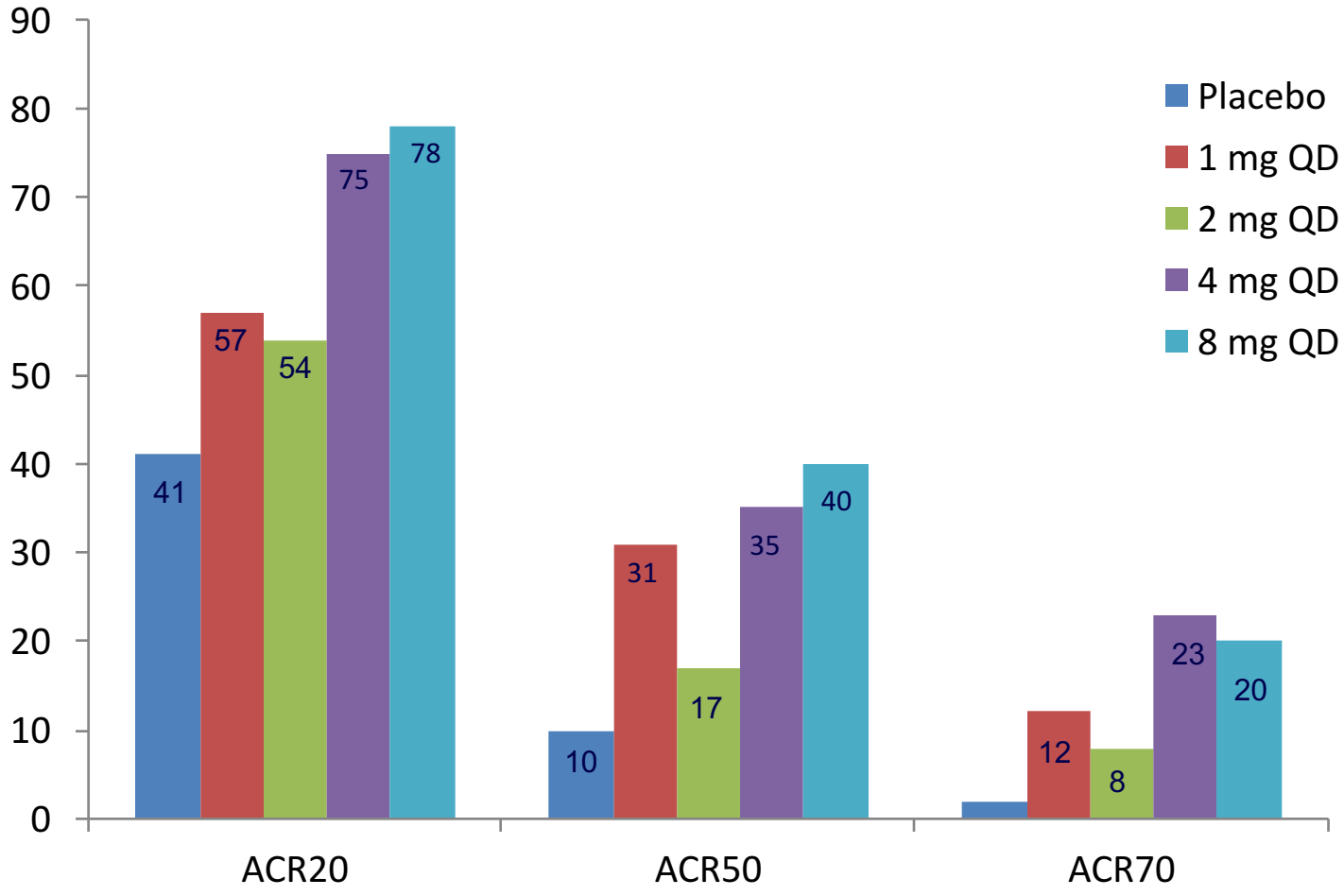
Baricitinib: Potent Selective JAK1/JAK2 Inhibitor

- **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**

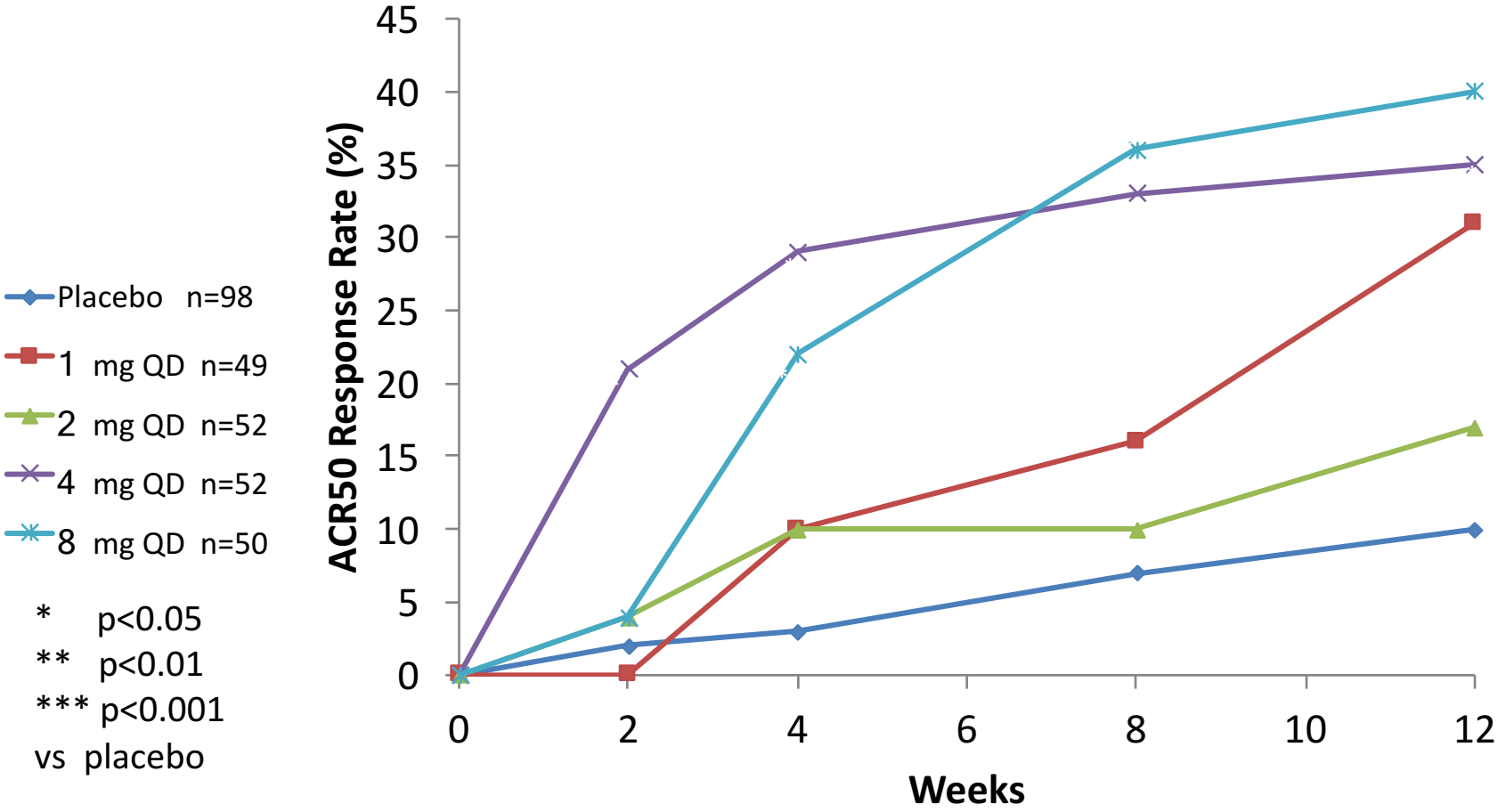
	Assay	IC_{50} (nM)
Enzyme Potency (1 mM ATP)	JAK1	6
	JAK2	6
	JAK3	>400
	Tyk2	53
Cellular Potency	IL-6 stimulated monocytes	70
	IL-23 stimulated T-cells	20

*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

Baricitinib ACR Responses by Dose at 12 Weeks



ACR50 Response Rate Over Time (NRI)



NRI = Non-responder Imputation

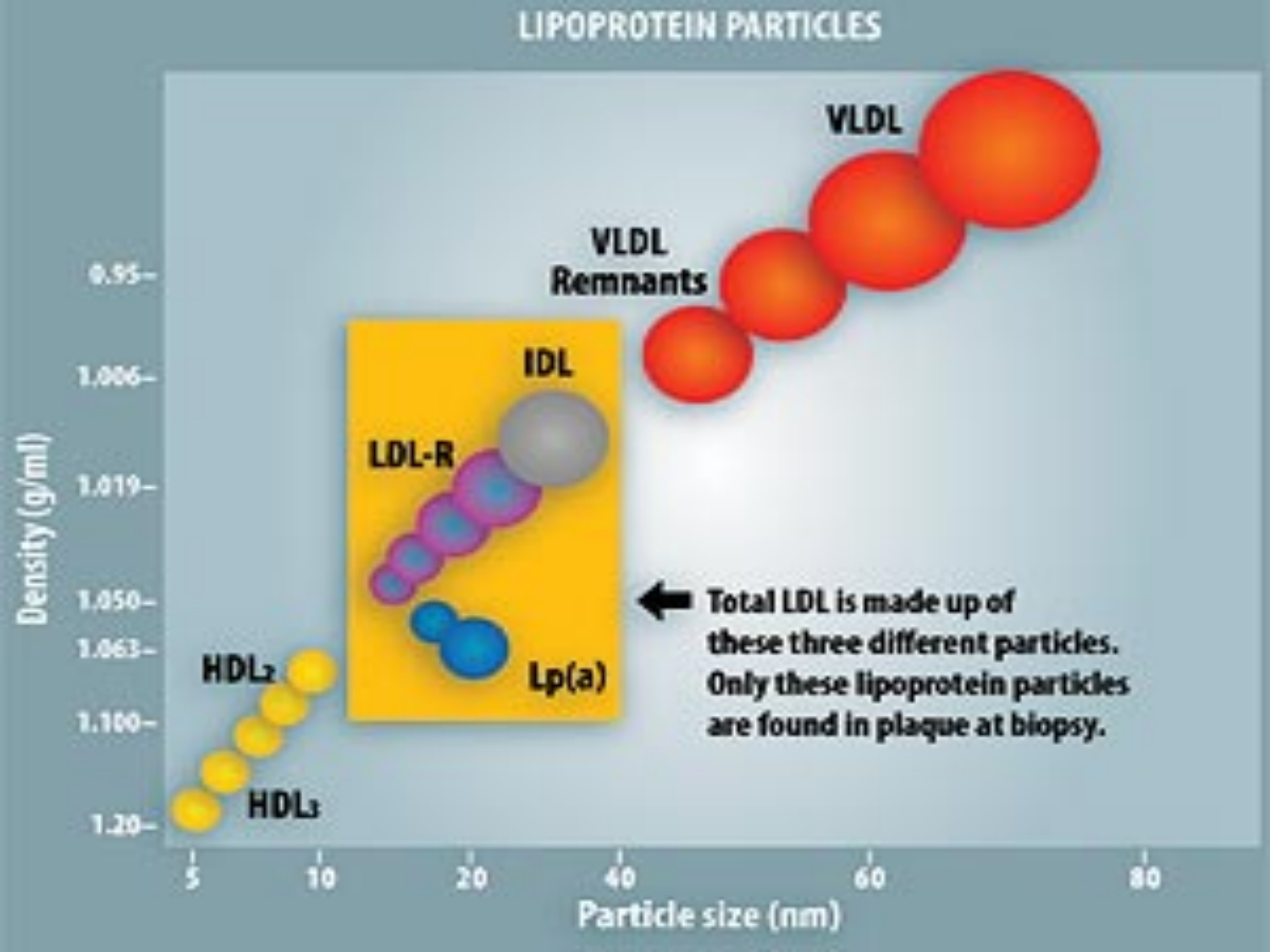
Change in Hemoglobin over 12 Weeks

	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%)

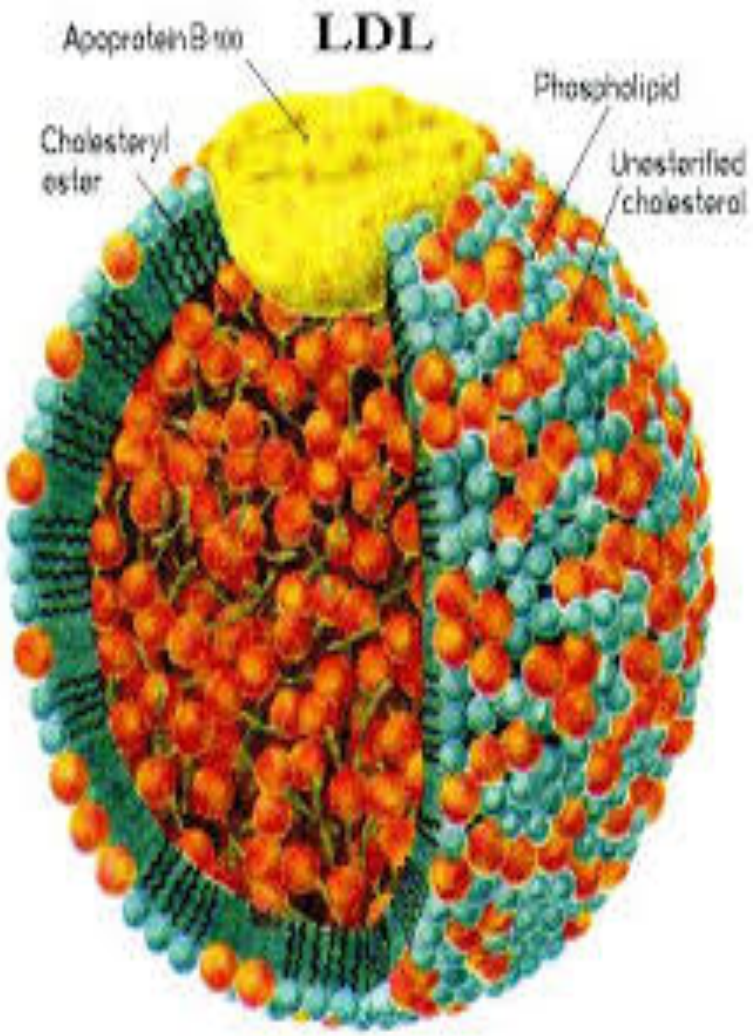
Change in Renal Parameters over 12 Weeks

	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%)

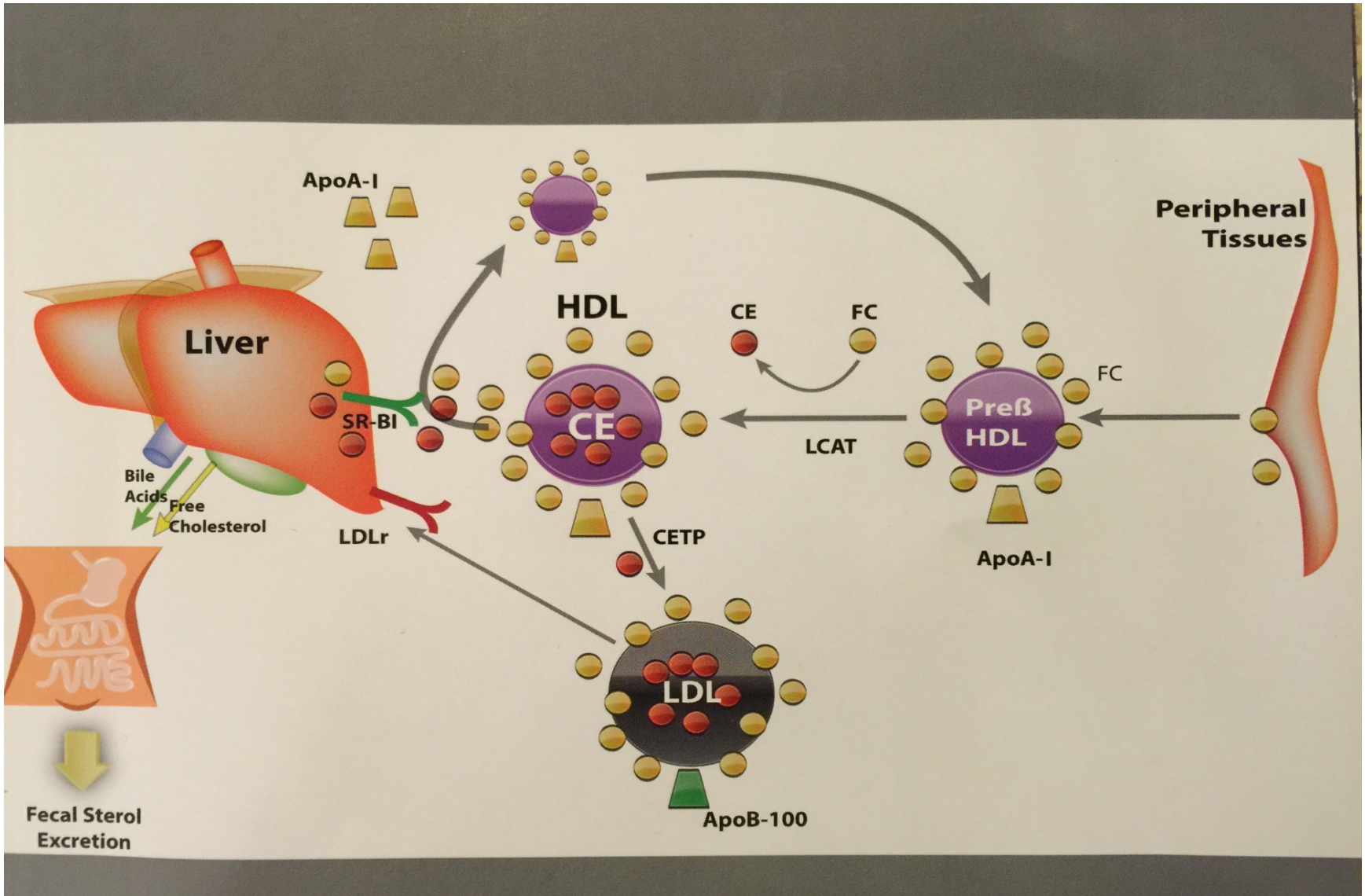
* Creatinine ULN was 1.20 mg/dL for females and 1.30 mg/dL for males


LIPOPROTEIN PARTICLES
VLDL
VLDL Remnants
IDL
LDL-R
Lp(a)
HDL2
HDL3
Total LDL is made up of these three different particles. Only these lipoprotein particles are found in plaque at biopsy.
Density (g/ml)
0.95
1.006
1.019
1.050
1.063
1.100
1.20
5
10
20
40
60
80
Particle size (nm)

LDL


LDL
Apoprotein B-100
Phospholipid
Cholesteryl ester
Unesterified cholesterol

Charles-Schoeman C,2015 A&R;67:616-625



Increases in Serum Cholesterol with Baricitinib Treatment are Associated with Favorable Changes in Apolipoprotein Content and with Improvement in DAS28-CRP 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], Eric Nantz[5], Scott D. Beattie[5], William L. Macias[5]

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Apolipoprotein Changes with Baricitinib

	Placebo (N=96)	4 mg QD (N=52)	8 mg QD (N=50)
Apolipoprotein B (mg/dL)			
Baseline	105 ± 3.0	110.5 ± 6.5	100 ± 6.5
Percent change from baseline at Week 4	-4.5 ± 2.6†	3.6 ± 2.4*	0.85 ± 3.0*
Percent change from baseline at Week 12	-4.5 ± 0.9†	6.8 ± 3.6*	7.1 ± 3.8*
Apolipoprotein A-I (mg/dL)			
Baseline	184.0 ± 5.5	188.0 ± 10.0	178.5 ± 8.5
Percent change from baseline at Week 4	-1.9 ± 3.0	5.1 ± 4.1†,*	11.6 ± 3.9††,**
Percent change from baseline at Week 12	1.1 ± 2.5	9.5 ± 3.8†,*	12.2 ± 3.0††,*
Apolipoprotein B/Apolipoprotein A-I Ratio (mg/dL)			
Baseline	0.6 ± 0.03	0.6 ± 0.03	0.6 ±0.03
Percent change from baseline at Week 4	-3.4 ± 2.5†	-2.7 ± 3.0	-9.8 ± 5.3*
Percent change from baseline at Week 12	-6.6 ± 2.7†	-5.3 ± 2.7	-4.9 ± 6.2
Apolipoprotein CIII (mg/dL)			
Baseline	8.3 ± 0.4	7.6 ± 0.6	7.4 ± 0.6
Percent change from baseline at Week 4	-4.2 ± 4.3	17.0 ± 13.0	22.3 ± 10.5††,*
Percent change from baseline at Week 12	-8.9 ± 4.3	23.0 ± 6.9†,*	19.7 ± 3.8††,**
LDL Associated Apolipoprotein CIII (mg/dL)			
Baseline	1.1 ± 0.1	1.2 ± 0.2	1.2 ± 0.1
Percent change from baseline at Week 4	-20.8 ± 14.8	-4.7 ± 18.7	-1.3 ± 18.1
Percent change from baseline at Week 12	0 ± 8.3	-4.5 ± 10.8	-9.0 ± 18.9

HDL and Lipoprotein(a)

	Placebo (N=96)	Baricitinib 4 mg QD (N=52)	Baricitinib 8 mg QD (N=50)
HDL Associated Serum Amyloid A (mg/L)			
Baseline	5.7 ± 0.6	6.4 ± 0.9	11.1 ± 3.5
Percent change from baseline at Week 4	12.0 ± 14.3	-51.3 ± 5.3††,**	-50.2 ± 7.5†,**
Percent change from baseline at Week 12	11.3 ± 6.5	-36.0 ± 3.5†,*	-32.0 ± 16.1†,*
Lipoprotein (a) (mg/dL)			
Baseline	8.4 ± 1.5	10.7 ± 3.0	11.1 ± 2.3
Percent change from baseline at Week 4	0.7 ± 5.4	2.5 ± 7.4	-8.1 ± 6.5†,*
Percent change from baseline at Week 12	-2.4 ± 3.9	-4.6 ± 4.5	-16.6 ± 2.6†

Data are median ± SE due to skewed distribution.
*†p<0.05 (within treatment), ††p<0.001 (within treatment), *p<0.05 vs. placebo, **p<0.001 vs. placebo*
Abbreviations: HDL=high density lipoprotein; LDL=low density lipoprotein; SE=standard error

JAK Inhibition in RA, Summary

There are multiple possible approaches which affect different JAK targets.

All Jakinhibs have some associated toxicity. I don't worry about Lipids, Or Transaminases (adjust dose).

Must watch for zoster (higher in Jaks) and other infections, *just as in all of the biologics.*