Το tofacitinib ως νέα θεραπευτική επιλογή στη Ρευματοειδή Αρθρίτιδα

Εαρινές Ημέρες Ρευματολογίας
Βόλος 2018

Δαούσης Δημήτρης
Επίκουρος καθηγητής
Παθολογίας/Ρευματολογίας
Ιατρική Σχολή Πανεπιστημίου Πατρών

Σύγκρουση συμφερόντων

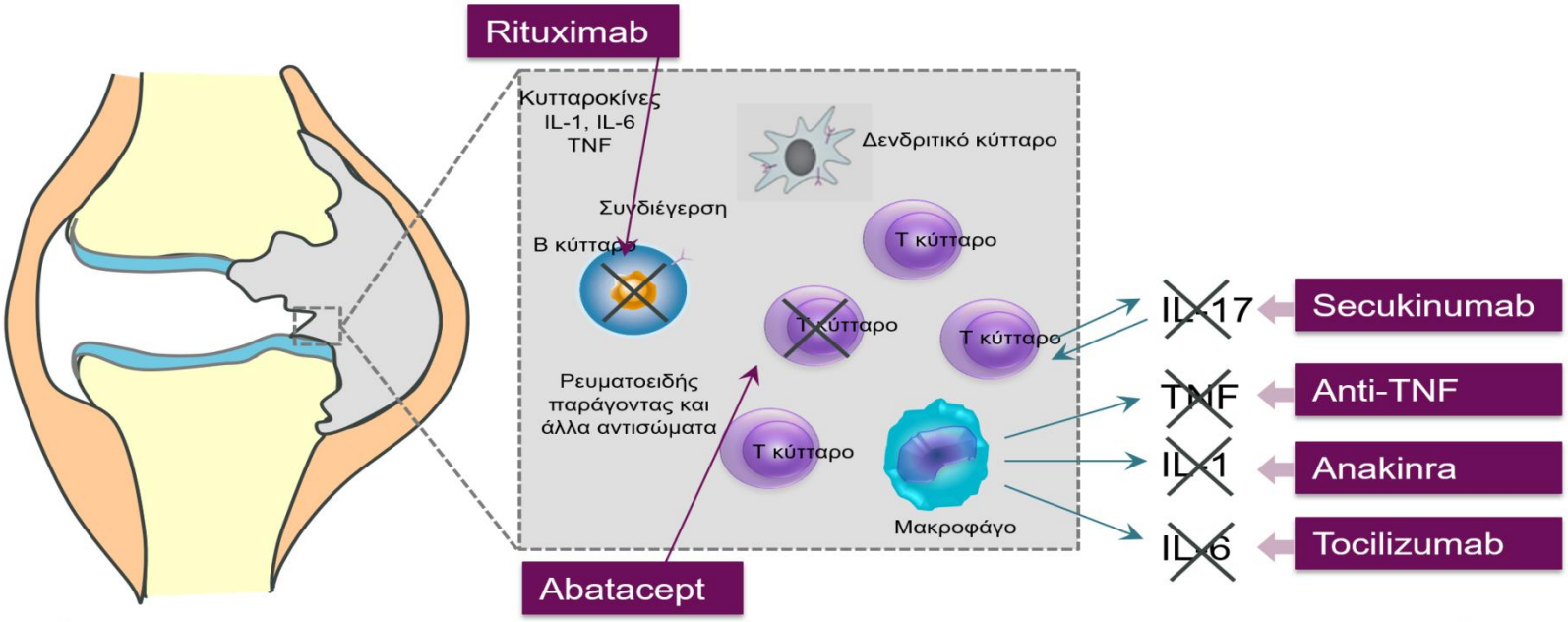
- Τιμητική αμοιβή για ομιλίες και συμμετοχή σε advisory boards από τις εταιρείες UCB, Pfizer, Novartis, BMS, MSD, Janssen, Abbvie

Οι απόψεις που εκφράζονται σε αυτή την παρουσίαση ανήκουν στον ομιλητή και δεν εκφράζουν απαραίτητα τις απόψεις της εταιρείας.

Για όλα τα φαρμακευτικά προϊόντα που αναφέρονται παρακαλείσθε να συμβουλεύεσθε τις εγκεκριμένες Περιλήψεις Χαρακτηριστικών των Προϊόντων

Νέοι θεραπευτικοί στόχοι στην ΡΑ.

Υπάρχουν αρκετοί εξωκυτταρικοί στόχοι

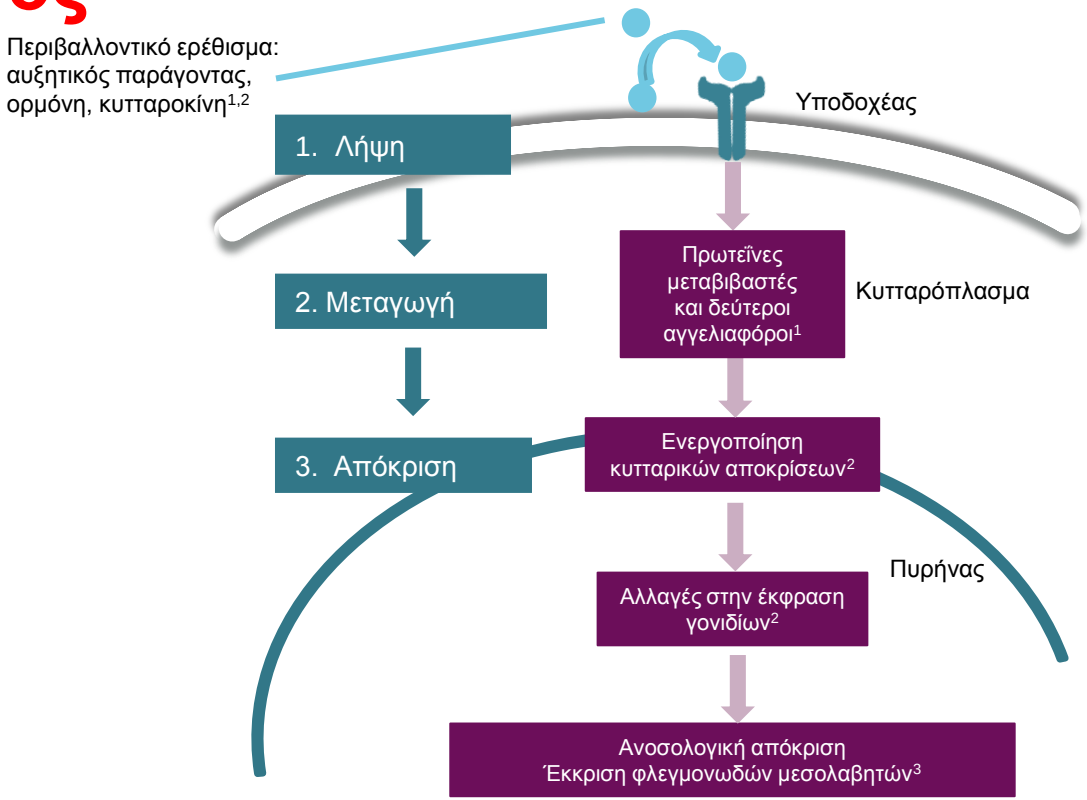


Οι βιολογικοί παράγοντες στοχεύουν τα εξωκυτταρικά συστατικά του καταρράκτη της φλεγμονής

IL: ιντερλευκίνη, TNF: παράγοντας νέκρωσης όγκου.

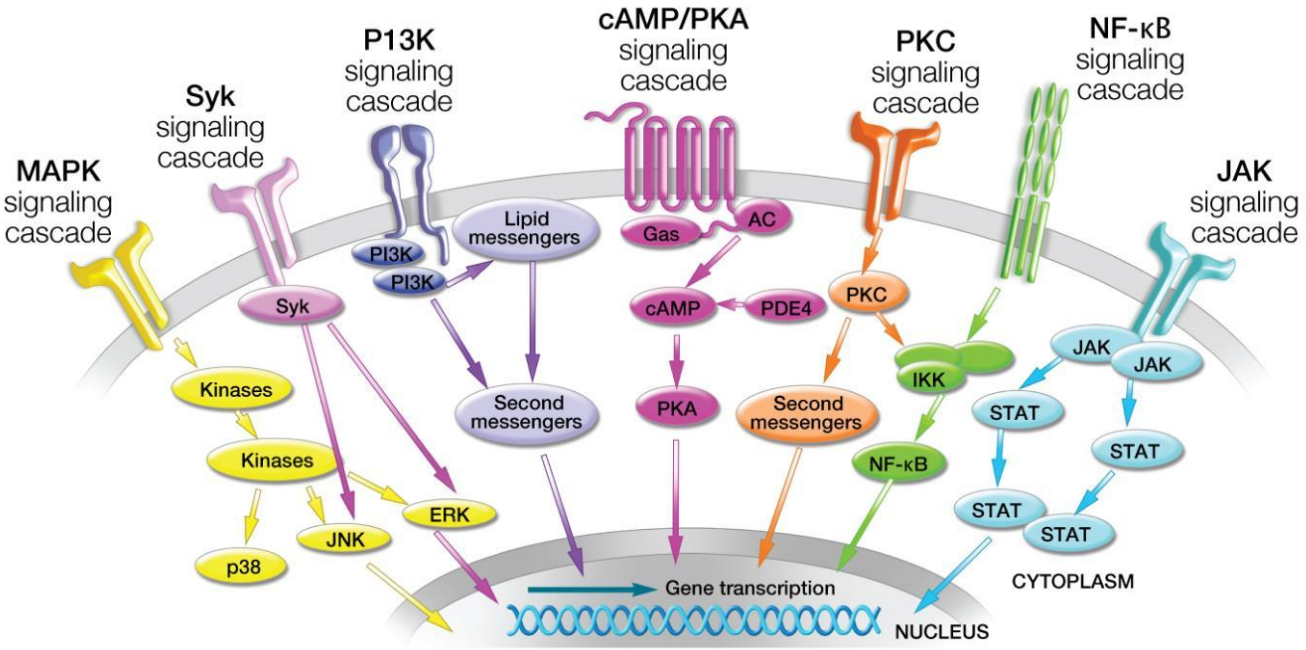
1. van Vollenhoven RF. *Nat Rev Rheumatol* 2009;5:531–541.

Από εξωκυττάρια σε ενδοκυττάρια: Μεταγωγή σήματος



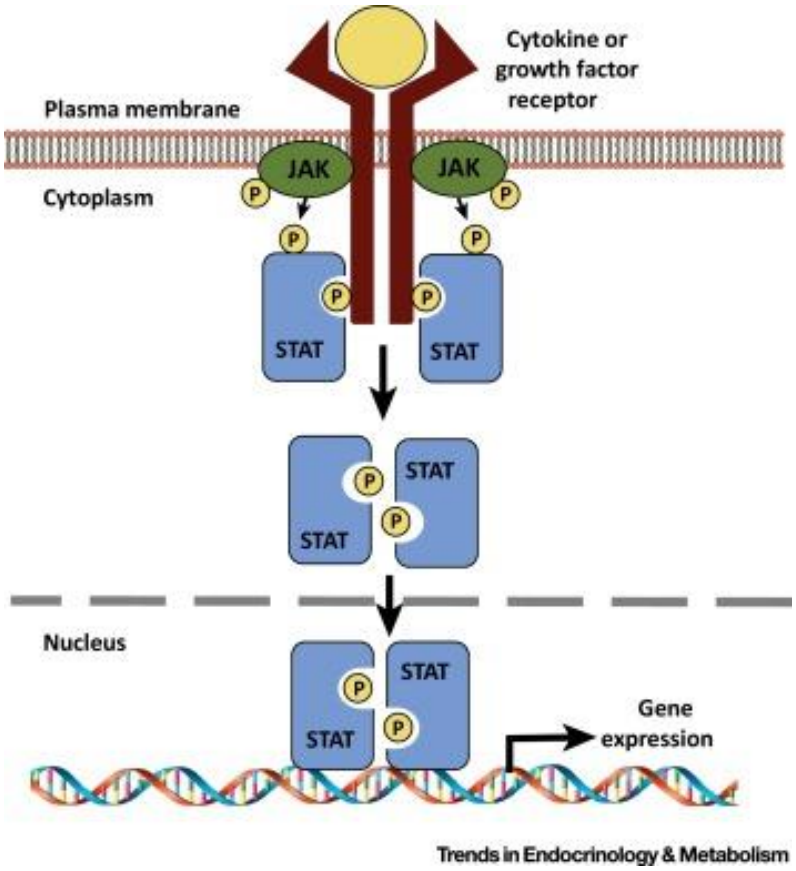
1. Scatizzi JC, et al. In: Firestein GS, et al. Kelley's Textbook of Rheumatology. 8th ed. Philadelphia: Saunders Elsevier; 2009.
2. Murphy K, et al. In: Janeway's Immunobiology. 7th ed. NY: Garland; 2008:1–38. 3. Mavers M, et al. *Curr Rheum Rep* 2009;11:378–385.

Υπάρχουν πολλά μονοπάτια σηματοδότησης των κυτταροκινών στη ρευματοειδή αρθρίτιδα[1]



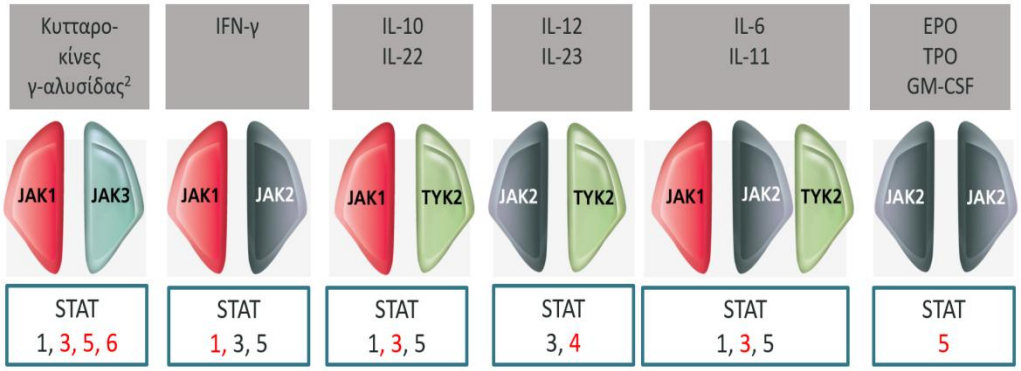
AC: αδενυλυλοκυκλάσης BTK: κινάση τυροσίνης Bruton, cAMP: κυκλική μονοφωσφορική αδενοσίνη? ERK: κινάσες ρυθμιζόμενες από εξωκυτταρικά σήματα, IKK: κΒ κινάσης, JAK: κινάση Janus, JNK: c-Jun NH2-τελική κινάση, MAPK: μονοπάτι της ενεργοποιούμενης από μιτογόνα πρωτεϊνικής κινάσης, NP-κΒ: πυρηνικός παράγοντας κάπα Β ελαφριάς αλυσίδας - ενισχυτή των ενεργοποιημένων Β κυττάρων PDE4: φωσφοδιεστεράση 4, PIK3: φωσφατιδυλινοσιτόλη-4,5-διφωσφορική 3-κινάση? PKC:κινάση πρωτεΐνης C, STAT, μεταγωγέας σήματος και ενεργοποιητής της μεταγραφής, Syk: κινάση της τυροσίνης Syk

1. Mavers M, et al. *Curr Rheum Rep* 2009;11:378–385. 2. Rommel C, et al. *Nat Rev Immunol* 2007;7:191–201. 3. Taskén K, et al. *Physiol Rev* 2004; 84:137–167. 4. Baier G, et al. *Curr Opin Cell Biol* 2009;21:262–267. 5. O'Sullivan LA, et al. *Molec Immunol* 2007; 44:2497–2506.



- Υπάρχουν τέσσερα μέλη της οικογένειας JAK: JAK1, JAK2, JAK3, και TYK2

Παράδειγμα κυτταροκινών που σηματοδοτούν μέσω συνδυασμών JAK/STAT[1–3]



Κόκκινο = επικρατέστερες STAT

Η μελλοντική έρευνα μπορεί να βοηθήσει στην πρόβλεψη επιδράσεων της αναστολής JAK σε διαφορετικούς ασθενείς και να επιτρέψει στους γιατρούς να λαμβάνουν τεκμηριωμένες αποφάσεις σχετικά με το ποιο ζεύγος JAK πρέπει να στοχεύουν σε κάθε ασθενή[4]

1. O'Sullivan LA et al. *Mol Immunol*. 2007;44(10):2497-2506; 2. Ghoreschi K et al. *Immunol Rev*. 2009;228(1):273-287; 3. Sanjabi S et al. *Curr Opin Pharmacol*. 2009;9(4):447-453; 4. Chizzolini C, et al. *Arthritis Res Ther* 2009;11:246.

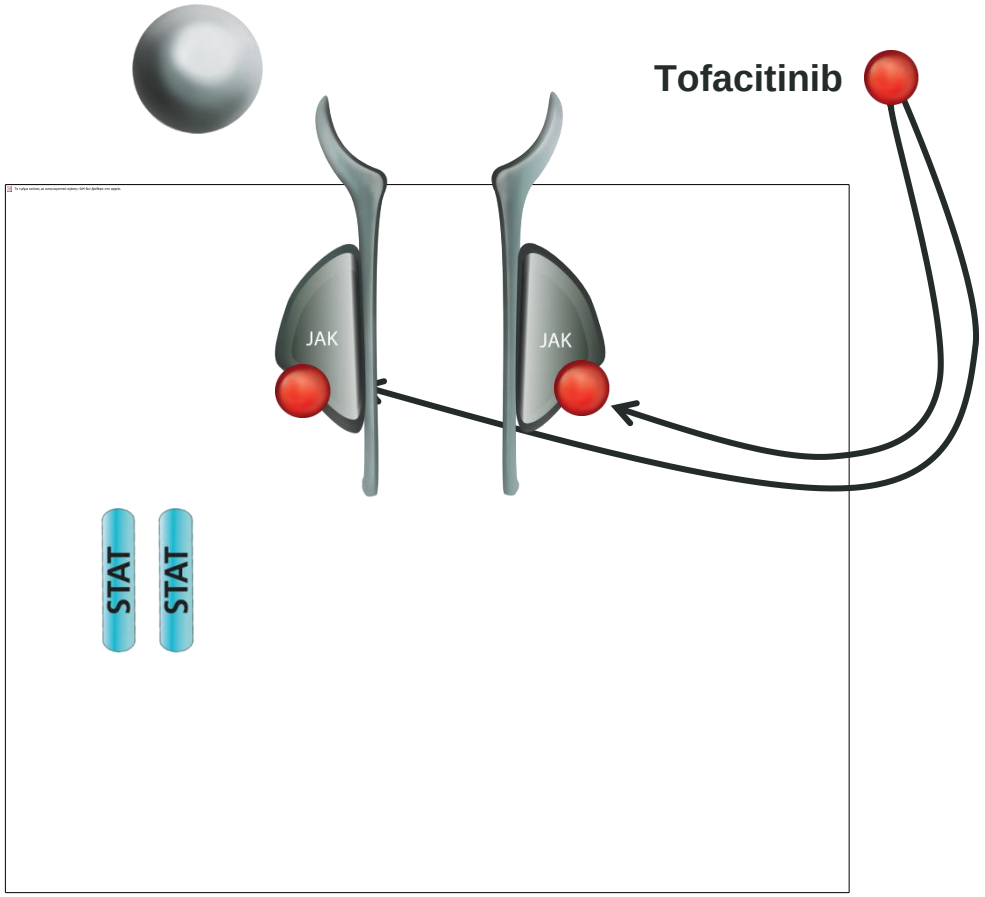
Tofacitinib targets JAK intracellular signalling pathways

1 Tofacitinib enters the cell and binds to the JAK phosphorylation site

2 Cytokine binding to its cell surface receptor leads to receptor polymerisation[1]

3 Tofacitinib inhibits the autophosphorylation and activation of JAK.[2] JAKs cannot phosphorylate the receptors, which therefore cannot dock STATs

4 JAKs cannot phosphorylate STATs, which cannot dimerise and move to the nucleus to activate new gene transcription of inflammatory mediators

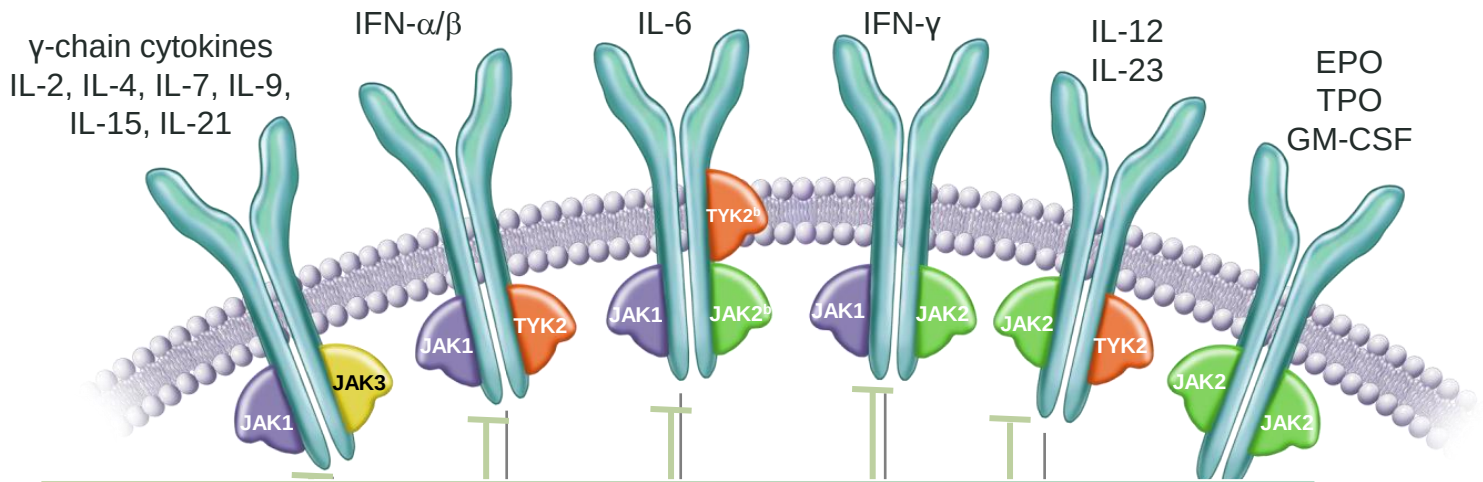


Tofacitinib blocks the JAK signalling pathway at the point of JAK phosphorylation

1. Shuai K et al. *Nat Rev Immunol* 2003;3:900–911,
2. Jiang JK et al. *J Med Chem* 2008;51:8012–8018.

JAK, Janus kinase;
STAT, signal transducer and activator of transcription.

Current JAK inhibitors target different receptors based on their selectivity[1-4]



	IC_{50}, nM[5]			
Inhibitor	JAK1	JAK2	JAK3	TYK2
Tofacitinib	15	77	55	489
Baricitinib	4	7	787	61

tofacitinib
JAK 1,3,2
baricitinib
Jak 1,2

FUNCTION[1, 4]

JAK1 / JAK3	**JAK1 / TYK2**	**JAK1 / JAK2 / TYK2**	**JAK1 / JAK2**	**JAK2 / TYK2**	**JAK2 / JAK2**
• Growth / maturation lymphoid cells • Differentiation / homeostasis T cells, NK cells • B-cell class switching • Inflammation	• Antiviral • Inflammation • Antitumor	• Naïve T-cell differentiation • T-cell homeostasis • Inflammation	• Antiviral • Inflammation	• Innate immunity • Differentiation/ proliferation of Th17 cells • Inflammation	• Erythropoiesis • Myelopoiesis • Megakaryocyte / platelet production • Growth • Mammary development

1. O'Sullivan LA et al. *Mol Immunol*. 2007;44(10):2497-2506; 2. Ghoreschi K et al. *Immunol Rev*. 2009;228(1):273-287; 3. Sanjabi S et al. *Curr Opin Pharmacol*. 2009;9(4):447-453; 4. Vijayakrishnan L et al. *Trends Pharmacol Sci*. 2011;32(1):25-34; 5.Gadina M. et al. *Arthritis Rheumatol*. 2016 January; 68(1): 31–34. doi:10.1002/art.39463.

EPO, erythropoietin; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; JAK, janus kinase;TYK, tyrosine kinase; TPO, thrombopoietin.

Therapeutic indication and dosing

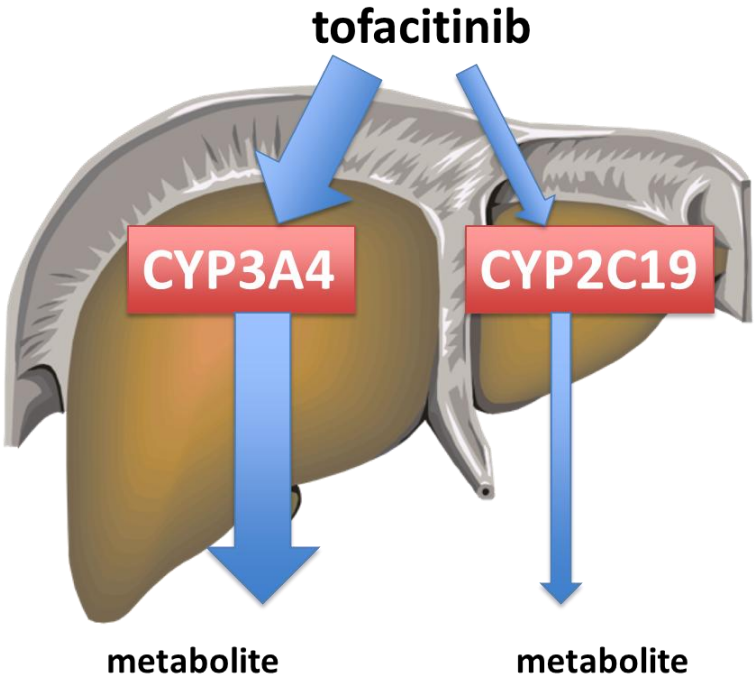
Tofacitinib in combination with MTX is indicated for the treatment of moderate to severe RA in adult patients who have responded inadequately to, or who are intolerant to ≥1 DMARDs.

Tofacitinib can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate

The recommended dose is 5 mg twice daily

Tofacitinib absorption and elimination

- Rapid absorption (peak plasma concentrations reached within 0.5-1 hour) and rapid elimination (half-life of ~3 hours)
- Tofacitinib clearance is 70% by hepatic metabolism (30% renal)[1]
- Primarily mediated by CYP3A4 (~53%) with a minor contribution from CYP2C19 (~17%)[2]



1. Xeljanz SmPC Dec 2017.
2. FDA Advisory Committee Meeting, 9 May 2012 (NDA 203214). Briefing book.

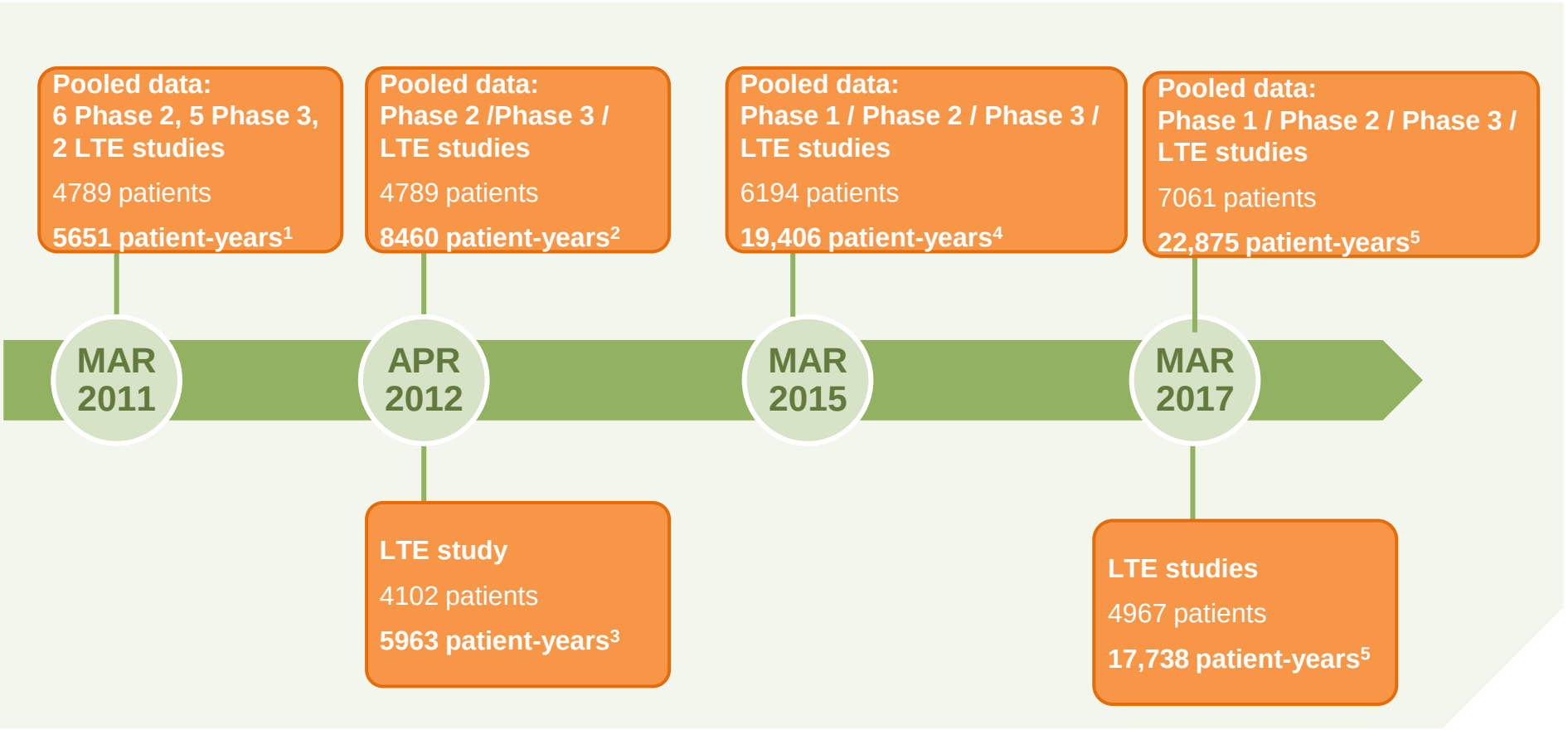
Tofacitinib Pharmacology(2)

- No dose adjustment on the basis of **gender** is required
- Effective irrespectively of **Race**
- Modest effect of **body weight**, no need for dose adjustment even in low body weight
- Dosing not influenced by **food** (including a high-fat meal)
- Low potential for tofacitinib to affect co-administered drugs that are metabolised by CYP450 or by UGT enzymes

Xeljanz SmPC, Dec 2017
Xeljanz EPAR , 26 January 2017

Tofacitinib Phase 3/4 Programme Overview

Experience with tofacitinib in clinical trials



1. Winthrop KL et al. *Arthritis Rheumatol*. 2014;66(10):2675-2684.
2. Cohen S et al. *Arthritis Rheumatol*. 2014;66(11):2924-2937.
3. Wollenhaupt J et al. *J Rheumatol*. 2014;41(5):837-852.
4. Cohen S et al. *Ann Rheum Dis*. 2017 Jan 31. pii: annrheumdis-2016-210457.
5. Data on file. Pfizer Inc, New York, NY.
N and PY as of March 2017

LTE, long-term extension.

A broad range of patient types were studied in the tofacitinib Phase 3/4 studies

	DMARD-IR		MTX-IR			TNFi-IR
Study	**ORAL Solo[1]**	**ORAL Sync[2]**	**ORAL Scan[3]**	**ORAL Standard[4]**	**ORAL Strategy[5]**	**ORAL Step[6]**
Duration	6 months	12 months	24 months	12 months	12 months	6 months
Background treatment	**None**	Nonbiologic DMARDs	MTX	MTX	MTX / none	MTX
Feature	Monotherapy	Background DMARDs	X-ray	Active control (adalimumab)	Tofa+MTX vs ADA+MTX Tofa vs Tofa+MTX Tofa vs ADA+MTX	TNFi failure
Patients randomised	611	795	797	717	1152	399

DA, adalimumab; DMARD, disease-modifying antirheumatic drug; IR, inadequate responder; mTSS, modified total Sharp score; MTX, methotrexate; TNFi, tumour necrosis factor inhibitor; Tofa, tofacitinib; ADA, adalimumab

1. Fleischmann R et al. *N Engl J Med* 2012;367:495–507.
2. Kremer J et al. *Ann Intern Med* 2013;159:253–61.
3. van der Heijde D et al. *Arth Rheum* 2013;65(3):559–70
4. van Vollenhoven R et al. *NEJM* 2012;367:508–19.
5. Fleischmann R et al. *Lancet* 2017; S0140-6736(17)31618-5.
6. Burmester G et al. *Lancet* 2013;381:451–60.

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Previous biologic experience: Solo (16.2%), Sync (6.6%), Scan (15.9%), Standard (7.5%)

Baseline characteristics overview across tofacitinib Phase 3/4 studies

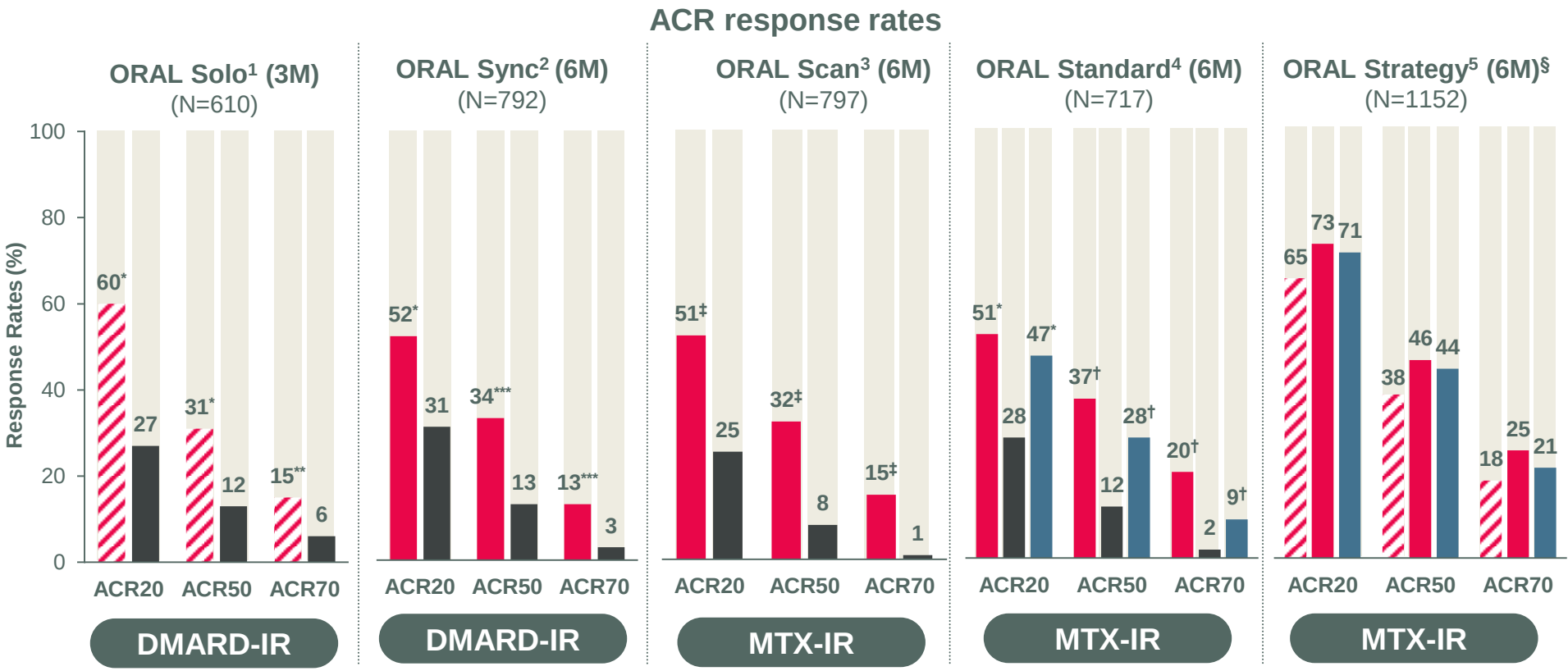
	Solo (5 mg)[1] N=610	Sync (5 mg)[2] N=792	Scan (5 mg)[3] N=797	Standard (5 mg)[4] N=717	Strategy (5 mg)[5] Monotherapy N=384	Strategy (5 mg)[5] + MTX N=376	Step (5 mg)[6] N=399
Female (%)	85.2	83.8	83.8	85.3	83	83	85
Age, mean (years)	52.2	52.7	53.7	53	49.7	50.0	55.4
Duration of RA (years)	8.0	8.1	8.9	7.6	6.1	5.4	13
RF positive (%)	76.8*	73.9	75.2	66.8	412.9 (601.0)**	439.3 (896.5)**	60.6
Anti-CCP positive (%)	76.8*	69.6	85.9	71.3	76	75	68.5
TJC (68)	29.4	25.0	24.1	28.5	15.4†	15.6†	28.4
SJC (66)	16.3	14.5	14.1	16.7	11.2†	11.8†	16.2
CRP, mg/L, mean	22.9	17.7	15.5	14.9	16.6	18.7	19.3
HAQ-DI (0–3), mean	1.53	1.44	1.41	1.5	1.6	1.6	1.6
DAS28-4(ESR), mean	6.71	6.27	6.34	6.6	6.5	6.6	6.5

1. Fleischmann et al. *N Engl J Med* 2012;367:495–507.
2. Kremer et al. *Ann Intern Med* 2013;159:253–61.
3. van der Heijde et al. *Arth Rheum* 2013;65:559–70.
4. van Vollenhoven et al. *N Engl J Med* 2012;367:508–19.
5. Fleischmann R et al. *Lancet* 2017; S0140-6736(17)31618-5.
6. Burmester et al. *Lancet* 2013;381:451–60.

*Positive for rheumatoid factor, anti–cyclic citrullinated peptide antibodies, or both
**In patients assessed (IU/mL)
†Out of 28
CCP, Cyclic Citrullinated Peptide; CRP, C-reactive protein;
DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate;
HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count.

Tofacitinib in DMARD & MTX IR patient populations

Tofacitinib monotherapy and combination therapy demonstrated significant and consistent improvements in disease signs and symptoms



ORAL Standard was not powered to be a head-to-head trial with adalimumab.

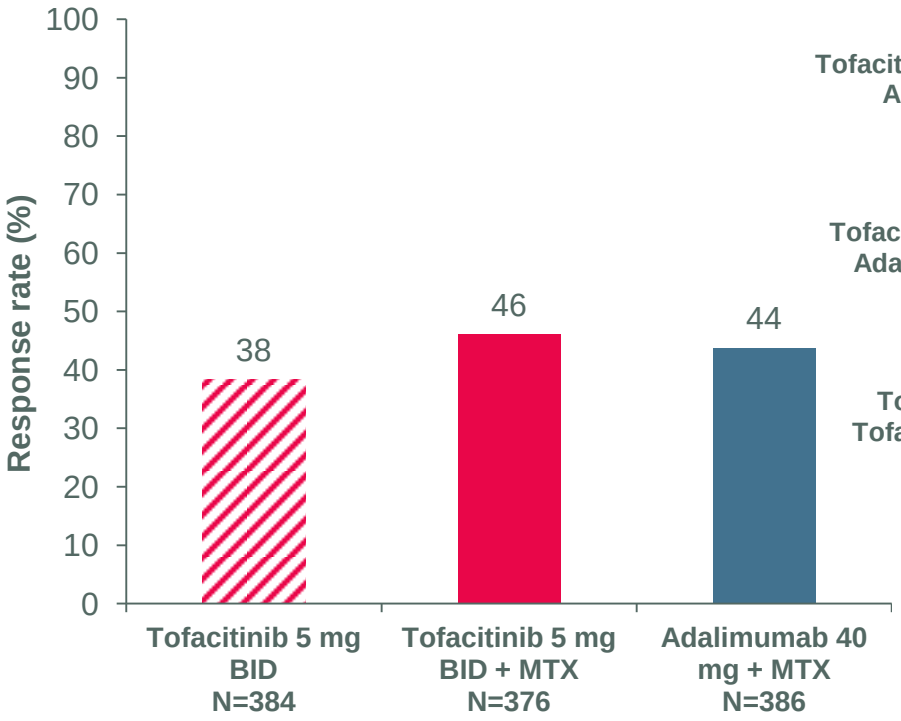
Tofacitinib demonstrated disease-modifying efficacy in DMARD & MTX-IR patients

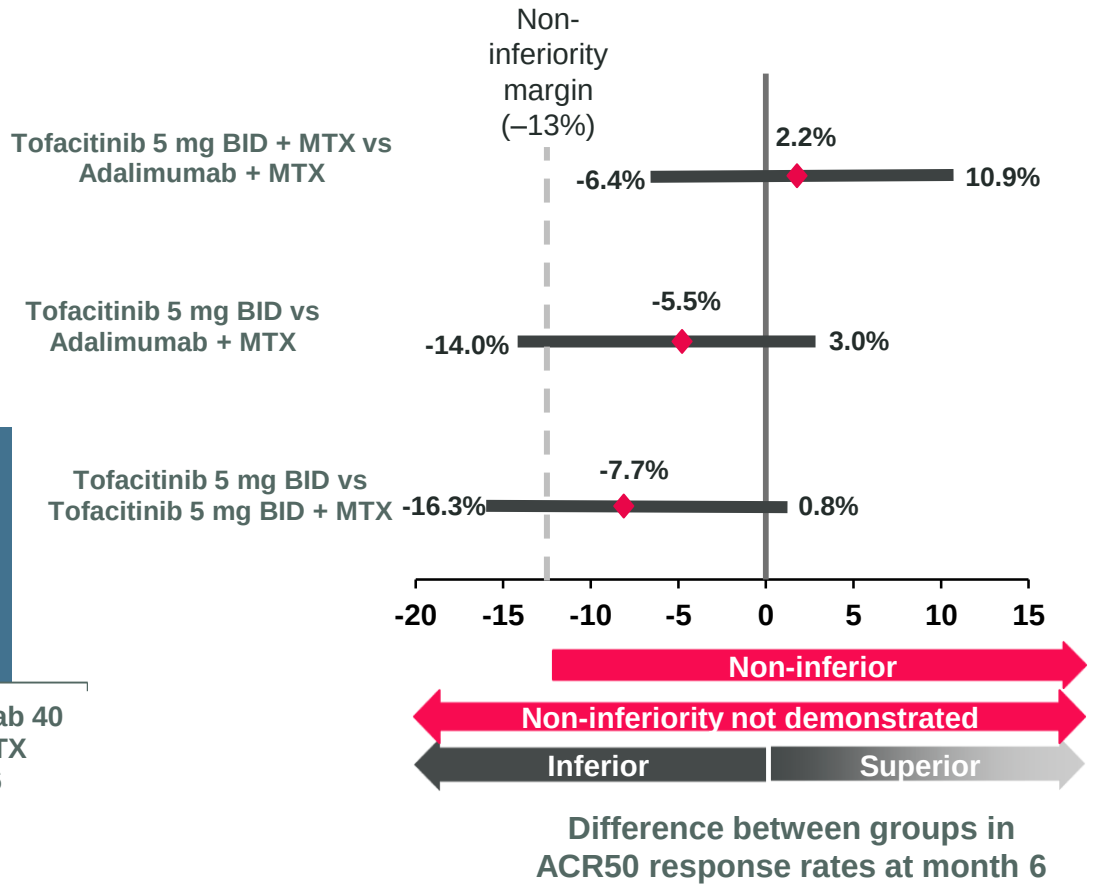
1. Fleischmann et al. *N Engl J Med* 2012;367:495–507.
2. Kremer et al. *Ann Intern Med* 2013;159:253–61.
3. van der Heijde et al. *Arth Rheum* 2013;65:559–70.
4. van Vollenhoven et al. *N Engl J Med* 2012;367:508–19.
5. Fleischmann R et al. *Lancet* 2017; S0140-6736(17)31618-5.

*P<0.001 **P=0.003 ***P≤0.001 vs baseline †P≤0.05 ‡P<0.0001 §All patients receiving active treatment, no advancement penalty applied

ACR20 at month 6 was a primary endpoint in ORAL Sync, ORAL Standard, and ORAL Scan. ACR20 was a primary endpoint at month 3 and a secondary endpoint at month 6 in ORAL Step.

ORAL Strategy primary endpoint: ACR50 at Month 6



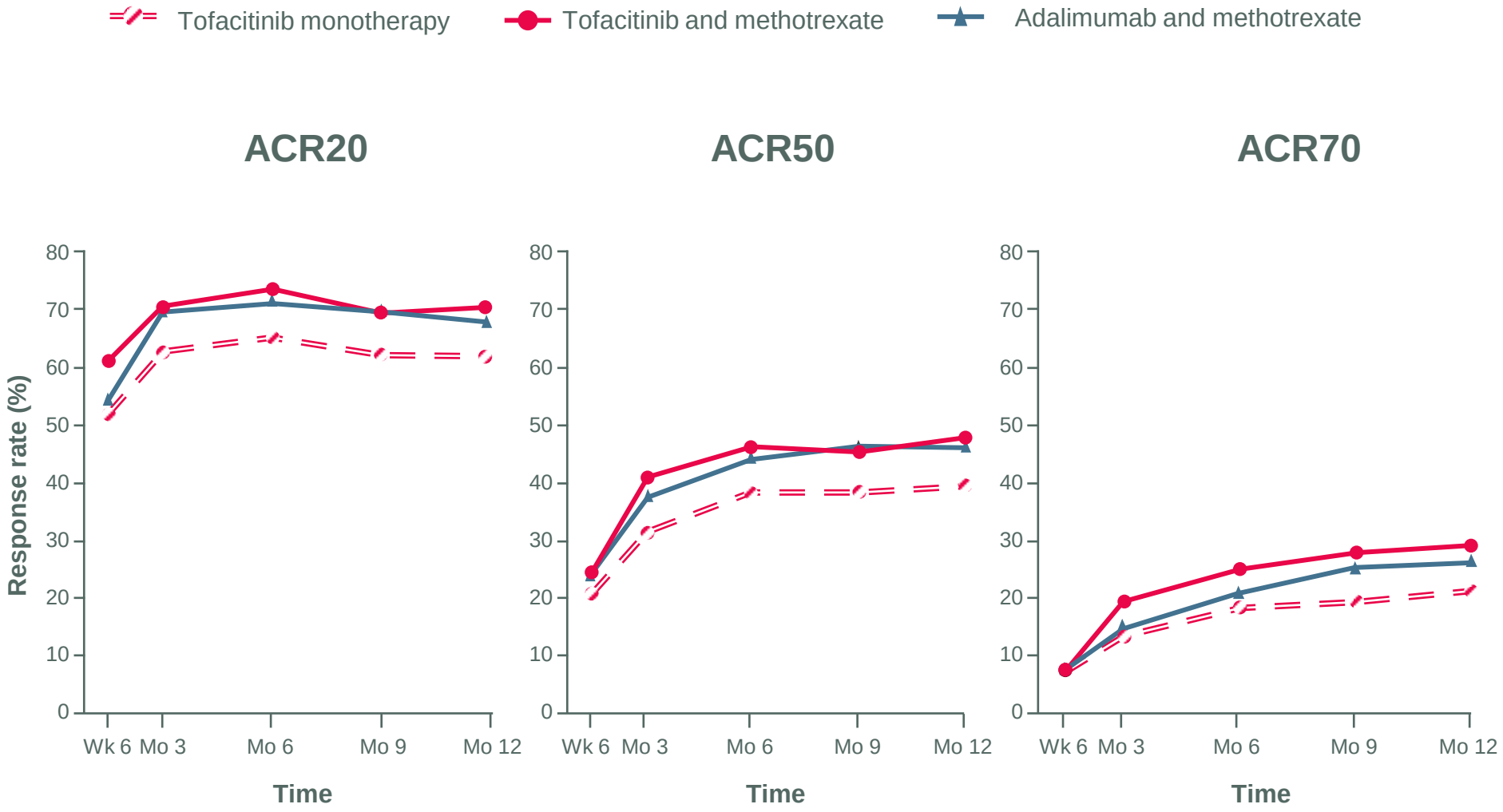


Tofacitinib plus MTX demonstrated similar efficacy and safety compared to adalimumab plus MTX

ACR50, 50% improvement in American College of Rheumatology response criteria; BID, twice daily; MTX, methotrexate.

Fleischmann R et al. *Lancet* 2017; S0140-6736(17)31618–5.

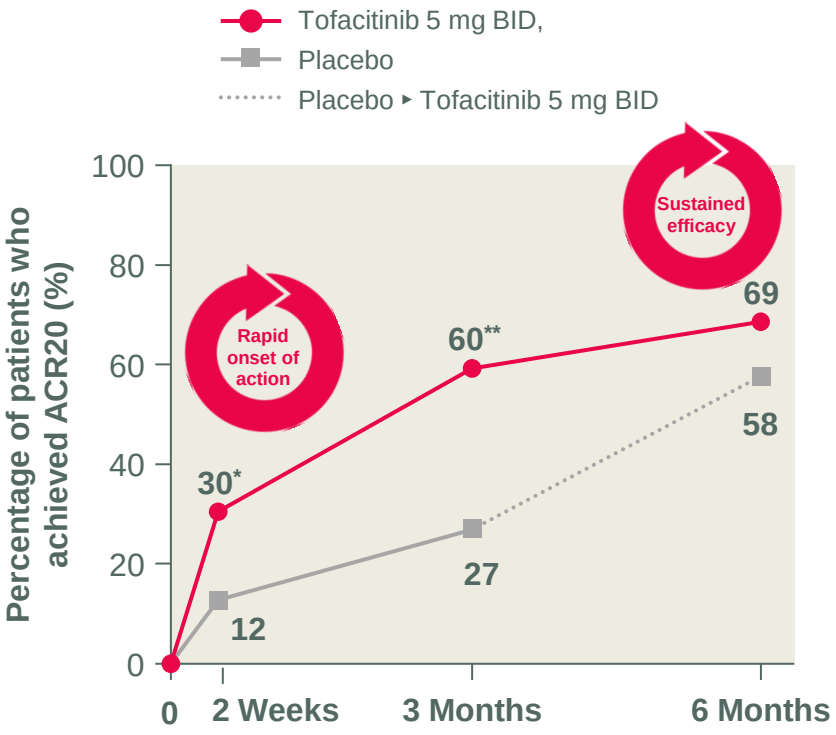
ACR20, ACR50 and ACR70 response rates in ORAL Strategy



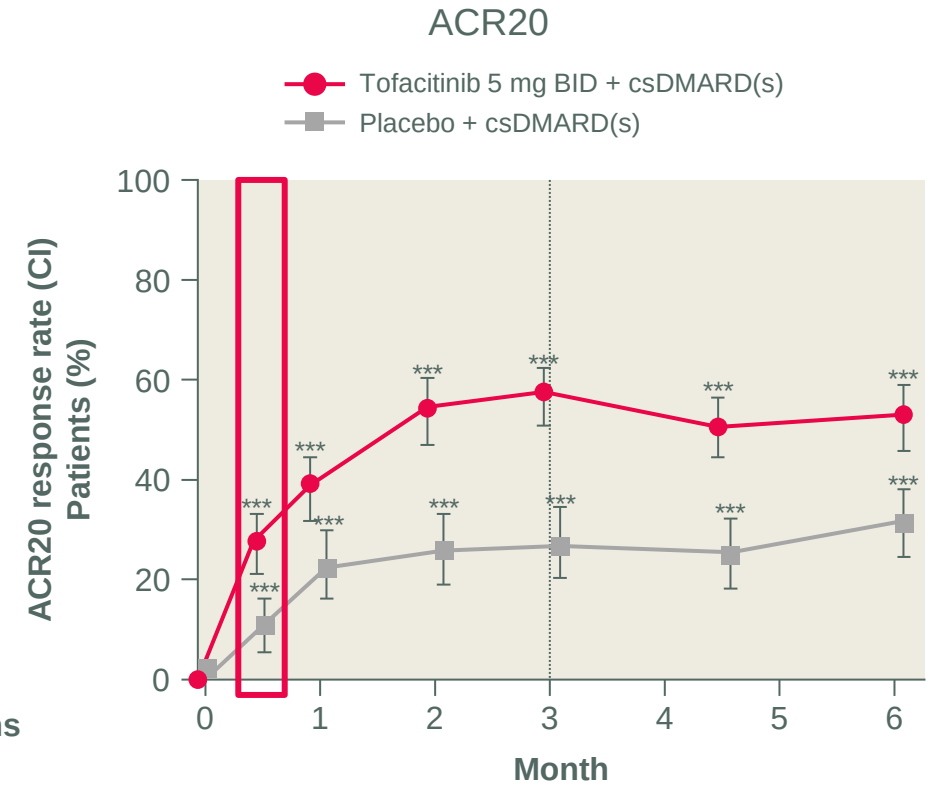
Fleischmann et al. *Lancet* 2017; S0140-6736(17)31618–5.

Rapid onset of action of tofacitinib

ORAL Solo in MTX-IR patients[1]



ORAL Sync in DMARD-IR patients[2]



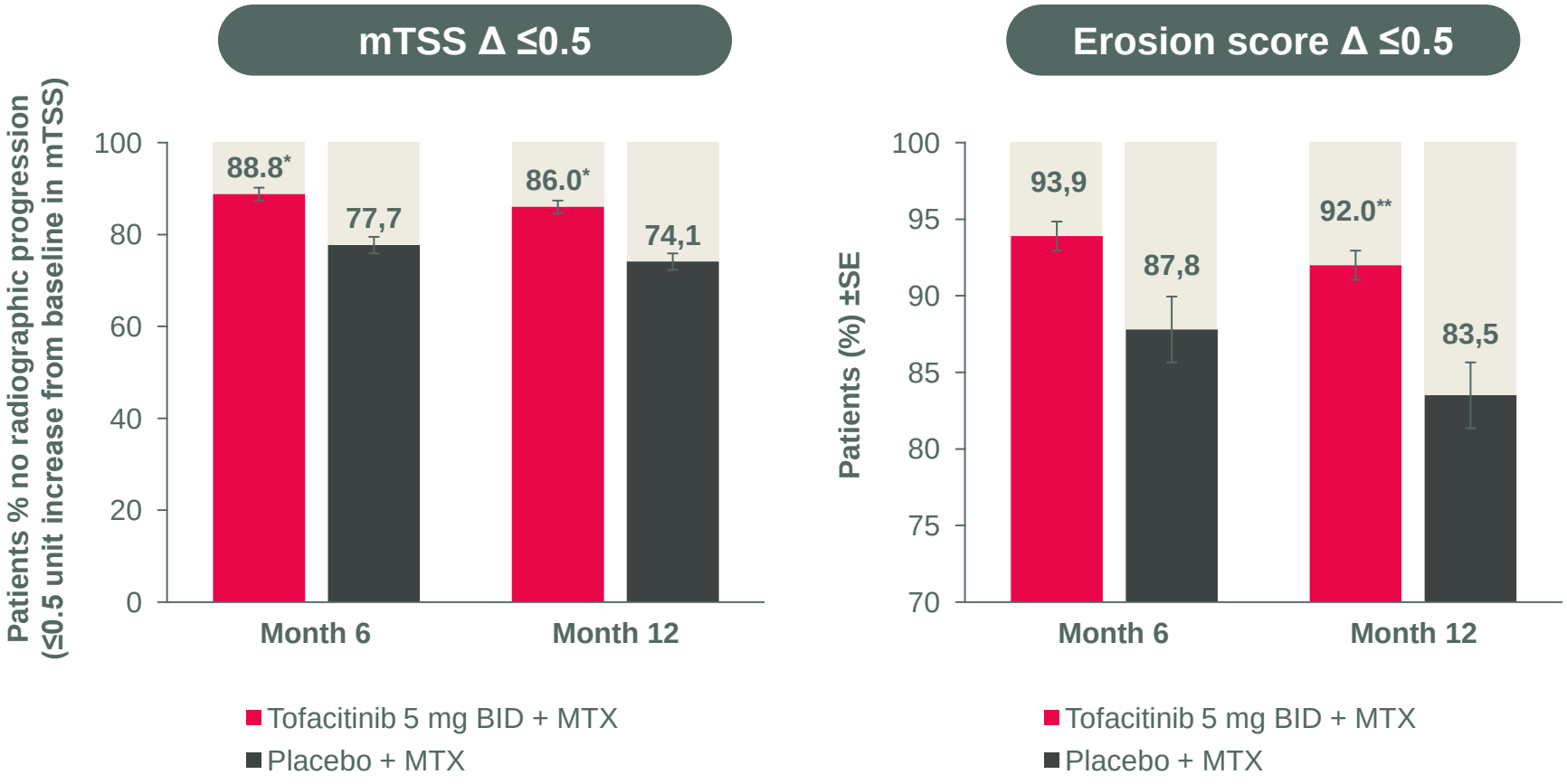
Significant improvements with both in monotherapy and combination therapy
ACR20 response rates vs placebo, as early as week 2

*p<0.0001; **p<0.001; ***p≤0.001 vs. baseline.

1. Fleischmann et al. *N Engl J Med*. 2012;367(6):495–507;
2. Kremer et al. *Ann Intern Med* 2013;159:253–61:Suppl

ACR American college rheumatology; BID, twice daily; DMARD, disease modifying anti-rheumatic drug; IR, inadequate response; MTX, methotrexate

Patients on tofacitinib with no radiographic progression



Significantly greater proportion of patients on tofacitinib had no radiographic progression (mTSS increase from baseline) compared with placebo

van der Heijde et al. *Arthritis Rheum*. 2013;65(3):559–70.

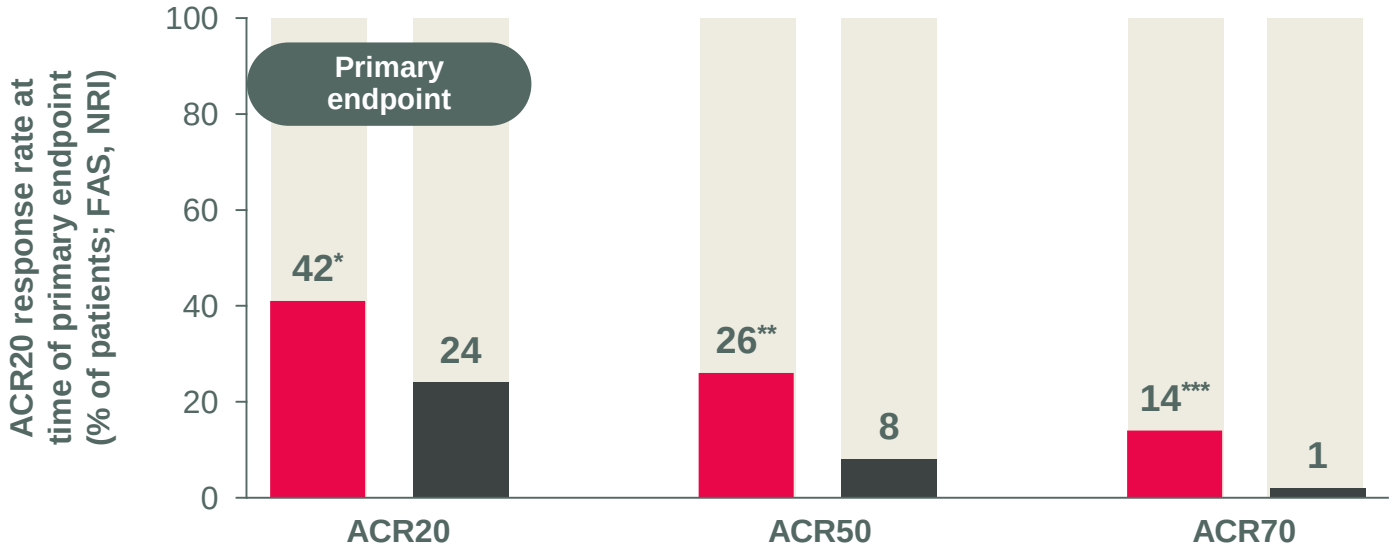
*p<0.01 vs placebo. **p≤0.05 vs placebo.

12-month data was imputed by linear extrapolation.

mTSS modified Total Sharp Score; MTX, methotrexate; SE, standard error

Tofacitinib in bDMARD-IR patient populations

ACR response rates in TNF-IR patients on tofacitinib



	Step (N=399)
Patient type	**TNFi-IR**
Tofacitinib regimen (5 mg BID)	**+ MTX**
Time of primary endpoint (mo)	**3**

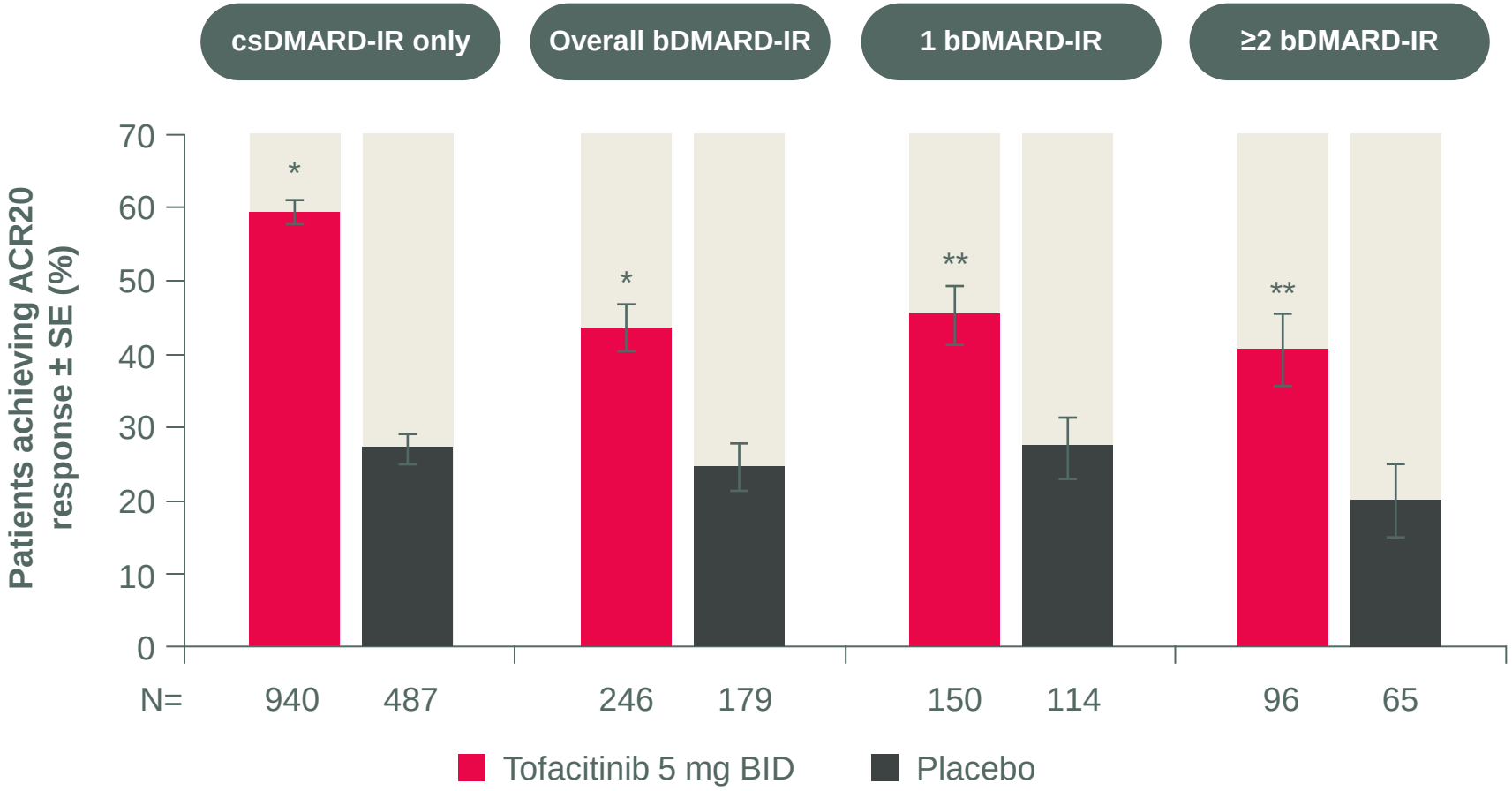
Tofacitinib 5 mg BID + MTX or nonbiologic DMARDs (N=132) Placebo + MTX or nonbiologic DMARDs (N=131)

Tofacitinib produced significantly superior ACR response rates compared with placebo

Burmester et al. *Lancet* 2013;381(9865):451–60.

*p=0.0024; **p<0.0001; ***p<0.001 vs placebo + MTX
ACR, American college rheumatology; DMARD, disease modifying anti-rheumatic drug; FAS, full analysis set; MTX, methotrexate; NRI, nonresponder imputation; TNF-IR, tumor necrosis factor inadequate responders;

Influence of previous DMARD use on tofacitinib ACR20 response rates



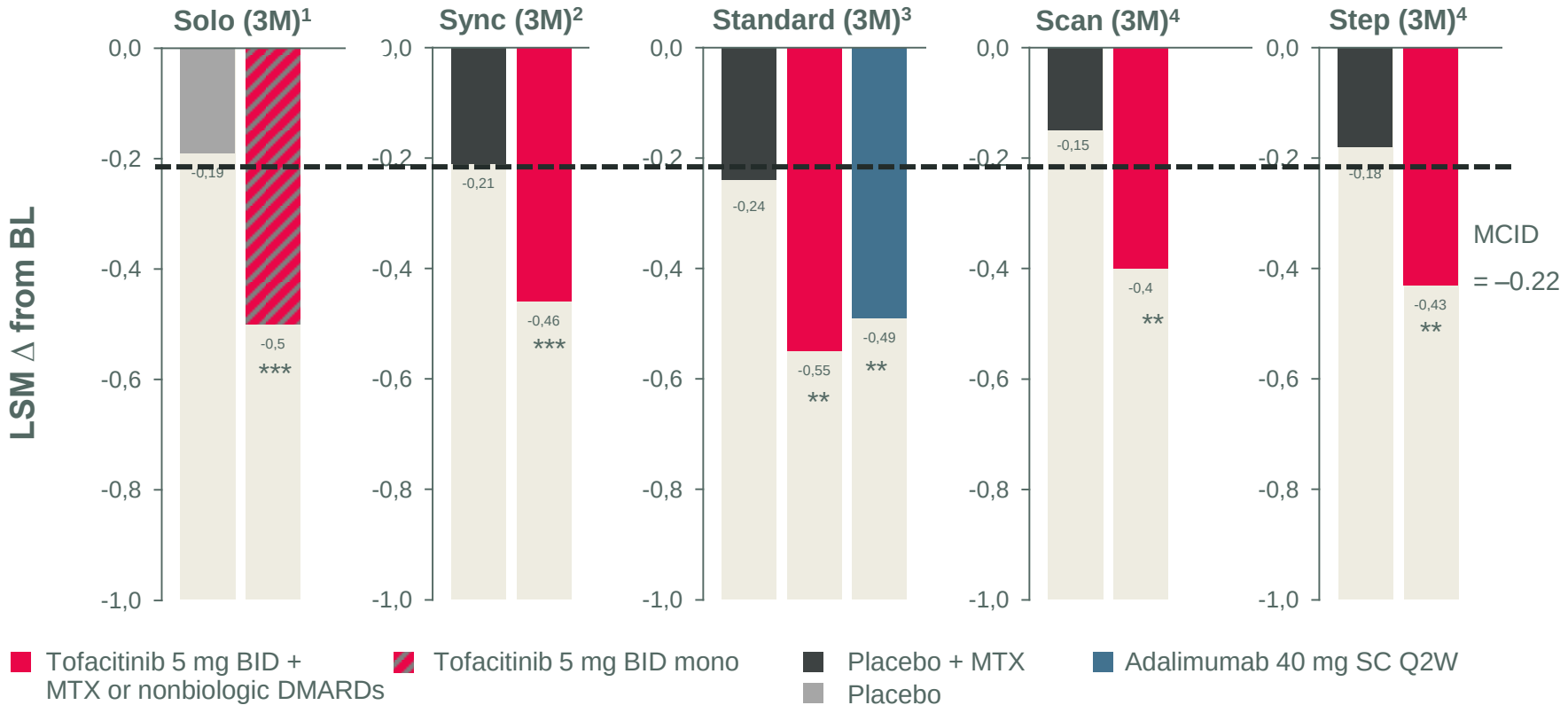
Irrespective of a prior IR to csDMARD or bDMARD, significantly greater efficacy was observed for patients receiving tofacitinib compared with placebo

Adapted from Charles-Schoeman et al. Presentation THU0185. EULAR 2017

*p<0.0001; **p<0.05 vs placebo
ACR, American College of Rheumatology; BID, twice daily; bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; IR, inadequate responders; SE, standard error.

PRO data for tofacitinib

Mean change in HAQ-DI from baseline in patients on tofacitinib



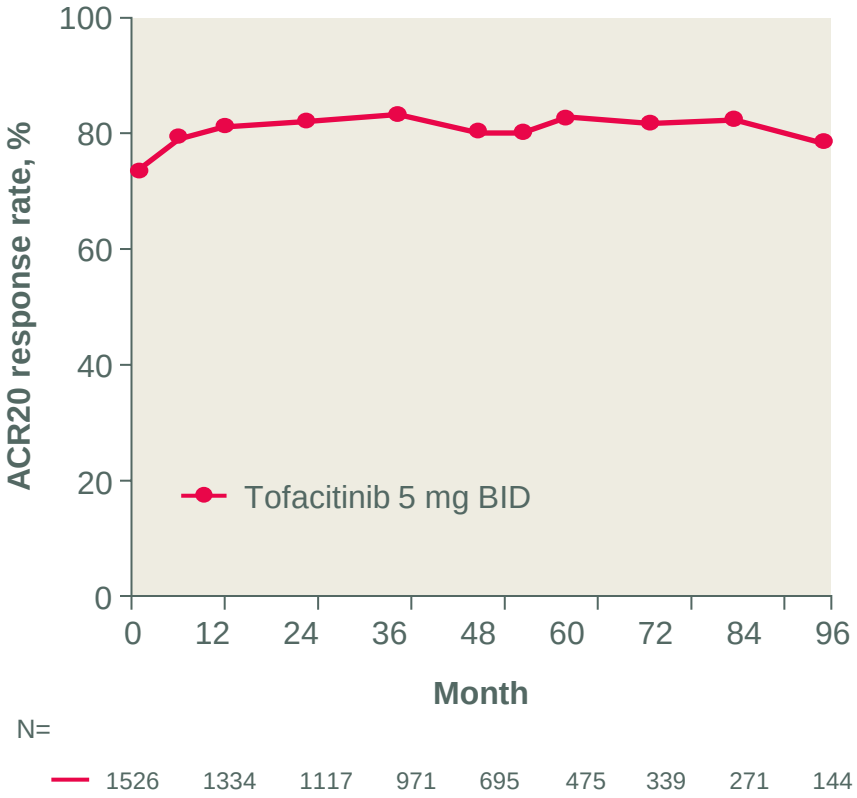
Tofacitinib produced significant decreases in HAQ-DI scores compared with placebo and methotrexate

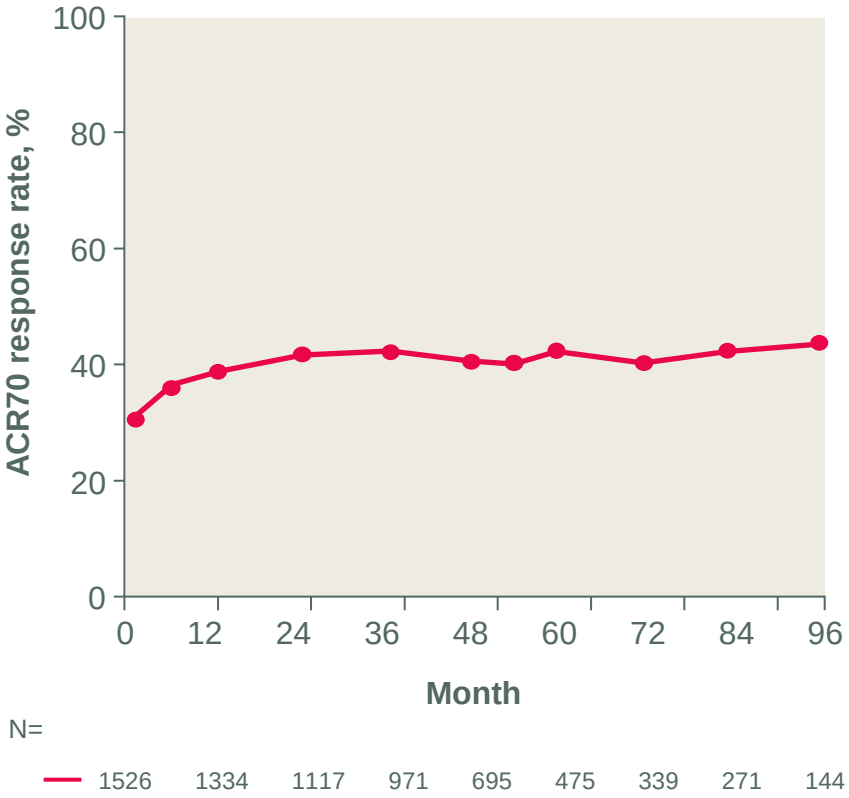
1. Strand V et al. *Arth Res Ther* 2015;17:307.
2. Strand V et al. *Arthritis Rheum* 2011;63 Suppl 10:2627.
3. van Vollenhoven RF et al. *N Engl J Med* 2012;367:508–19.
4. Burmester GR et al. *Arthritis Rheum* 2012;64 Suppl 10:1283.

**p<0.001, ***p<0.0001 vs placebo vs methotrexate
FAS, Longitudinal model, BID, twice daily; BL, baseline; FAS, full analysis set FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-Disability Index; LSM, least squares mean; MTX, methotrexate; SC, subcutaneous; Q2W, every two week

Tofacitinib LTE Programme

Sustained efficacy in the LTE studies of tofacitinib





Tofacitinib provided sustained improvement in signs and symptoms of RA up to 96 months

Wollenhaupt et al. Poster 522 presented at ACR 2017

ACR, American college rheumatology; BID, twice daily; csDMARD, conventional synthetic disease-modifying antirheumatic drug; LTE, long-term extension

Summary

- Tofacitinib has been studied in an extensive clinical programme consisting of six Phase 3 trials, one Phase 3/4 trial and two long-term extension studies[1–7]
- Tofacitinib demonstrated powerful reduction of RA signs and symptoms across five Phase 3 studies and one Phase 3/4 study[1–6]
- Tofacitinib demonstrated a rapid onset of action [1,2]
- Tofacitinib showed sustained rates of response as monotherapy and in combination with csDMARDs[1–6]
- Tofacitinib and methotrexate was deemed non-inferior to adalimumab and methotrexate[6]
- Tofacitinib showed a significant difference from placebo in a variety of PRO measures[1–5]
- Long-term extension study data shows sustained efficacy response up to 96 months[7]

1. Fleischmann et al. *N Engl J Med* 2012;367:495–507
2. Kremer et al. *Ann Intern Med* 2013;159:253–61.
3. van der Heijde et al. *Arth Rheum* 2013;65(3):559–70
4. van Vollenhoven et al. *NEJM* 2012;367:508–19.
5. Burmester et al. *Lancet* 2013;381:451–60.
6. Fleischmann et al. *Lancet* 2017; S0140-6736(17)31618-5.
7. Wollenhaupt et al. Poster 522 presented at ACR 2017

Tofacitinib RA Safety Narrative

Tofacitinib leads the JAK class with a well-characterized safety profile, in the largest RA clinical programs to date

~7000 patients studied[1]

>22,000 pt-yrs of exposure[1]

PHASE 1
PHASE 2
PHASE 3

19 clinical studies[3,4]

>9 yrs of observation in clinical trials[2]

As of March 2017, no new safety risks identified in LTE database compared with previous reports of RCT and LTE data[1]

Real-world experience

>55,000 **Patients**[5] (as of May 2015)

consistent with findings from the clinical trial program

- M**ost commonly reported Adverse Reactions** during the first 3 months:
  headache, upper respiratory tract infections, nasopharyngitis, diarrhea, nausea, and hypertension
- M**ost common Serious Infections** reported:
  pneumonia, cellulitis, HZ, urinary tract infection, diverticulitis, and appendicitis
- 3.8% of patients d**iscontinued** due to adverse reactions during first 3 months:
  The most common infections resulting in discontinuation of therapy were HZ and pneumonia

Tofacinitib SmPC, Accessed 10MAY17 at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004214/WC500224911.pdf

Cohen SB et al. *Ann Rheum Dis*. 2017;76(7):1253-1262; Supplement to: Cohen SB et al. *Ann Rheum Dis*. 2017;76(7):1253-1262.; Curtis JR et al. *Clin Rheumatol.* 2017;36(3):683-688; Strand V et al. *Arthritis Res Ther.* 2015;17:362; Vieira MC et al. *Clin Ther*. 2016;38(12):2628-2641; Yamaoka K. *Drug Saf*. 2016;39(9):823-840; Curtis JR et al. *Ann Rheum Dis.* 2016;75(10):1843-1847; Weinblatt ME et al. *J Rheumatol.* 2013;40(6):787-797; Keystone EC et al. *J Rheumatol*. 2013;40(9):1487-1497; Bykerk VP et al. *Ann Rheum Dis.* 2015;74(1):96-103; Burmester GR et al. *Ann Rheum Dis.* 2013;72(4):517-524; Kay J et al. *J Rheumatol.* 2016;43(12):2120-2130; Schiff MH et al. *Arthritis Res Ther.* 2011;13(5):R141; Gomez-Reino JJ et al. Presented at: EULAR Annual Congress of Rheumatology; June 14-17, 2017; Madrid, Spain. Poster THU0196; Maneiro JR et al. *Semin Arthritis Rheum*. 2017. In press. http://www.semarthritisrheumatism.com/article/S0049-0172(16)30306-7/fulltext. Accessed May 17, 2017; Gottlieb AB et al. *J Drugs Dermatol.* 2011;10(3):289-300; Centocor. Remicade® (Infliximab). Presentation to the Food and Drug Administration Arthritis Advisory Committee. URL: http://www.fda.gov/ohrms/dockets/ac/03/slides/3930s1.htm. Accessed October 10, 2014; Charles-Schoeman C et al. *Semin Arthritis Rheum.* 2016;46(3):261-271; Alten R et al. *Arthritis Rheumatol.* 2014;66(8):1987-1997; van Vollenhoven RF et al. *J Rheumatol.* 2015;42(10):1761-1766; Kavanaugh A et al. Presented at: ACR/ARHP Annual Meeting; November 11-16, 2016; Washington, DC. Poster 2595; Wolfe F et al. *Arthritis Rheum*. 2004;50(2):372-379; Brassard P et al. *Clin Infect Dis*. 2006;43(6):717-722; Askling J et al. *Arthritis Rheum*. 2005;52(7):1986-1992; Dixon WG et al. *Arthritis Rheum*. 2006;54(8):2368-2376; Seong SS et al. *J Rheumatol.* 2007;34(4):706-711; Jung SM et al. Int J Rheum Dis. 2015;18(3):323-330; Ke WM et al. *Int J Tuberc Lung Dis*. 2013;17(12):1590-1595; Chiu YM et al. *Int J Rheum Dis*. 2014;17(suppl 3):9-19; Winthrop KL et al. Arthritis Rheumatol. 2017. DOI: 10.1002/art.40189

Tofacitinib is not indicated in MTX-naïve patients. The approved dose of tofacitinib is 5 mg twice daily

Incidence rate for AEs of special interest with tofacitinib are comparable to bDMARDs, except for HZ

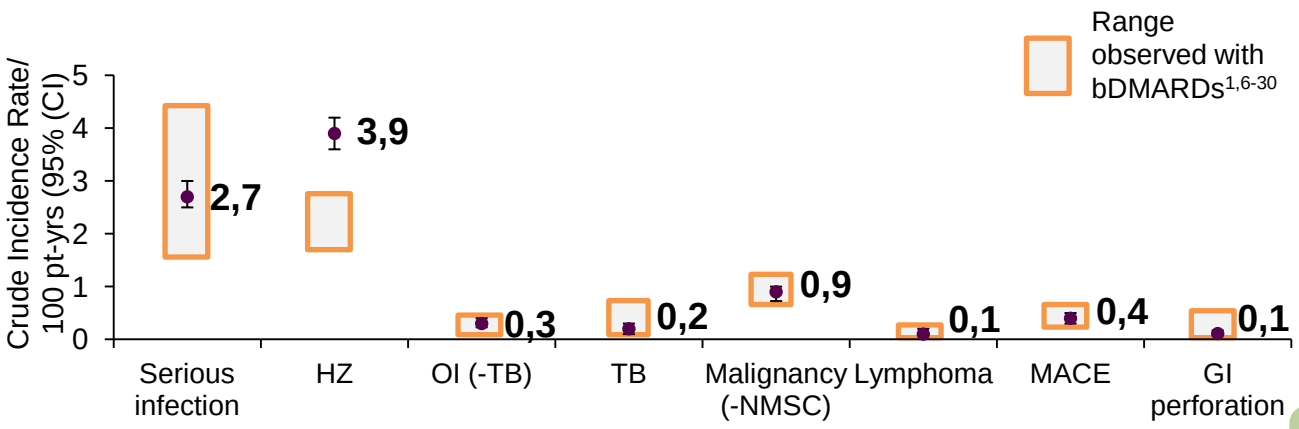
Incidence rate Is **stable over time**[1–4]

HZ events were **medically manageable**[5]

Incidence rate is **similar to bDMARDs** except for HZ[1,6–30]

AEs of special interest

(Overall tofacitinib population—phase 123 LTE)[1,2]



AE, adverse event; bDMARD, biologic disease-modifying antirheumatic drug; CI, confidence intervals; GI, gastrointestinal; HZ, herpes zoster; LTE, long-term extension; MACE, major adverse cardiac event; NMSC, non-melanoma skin cancer; OI, opportunistic infections; RA, rheumatoid arthritis; RCT, randomized controlled trial; TB, tuberculosis.

Vaccination recommendation[31,32]

Administer live zoster vaccine prior to treatment with tofacitinib, preferably 4 weeks before start

The approved dose of tofacitinib is 5 mg twice daily

Cohen SB et al. *Ann Rheum Dis*. 2017;76(7):1253-1262. Supplement to: Cohen SB et al. *Ann Rheum Dis*. 2017;76(7):1253-1262. Winthrop KL et al. *Ann Rheum Dis*. 2016;75(6):1133-1138. Mariette X et al. *Arthritis Care Res (Hoboken).* 2017 Sep 21. doi: 10.1002/acr.23421. [Epub ahead of print]. Winthrop KL et al. *Arthritis Rheumatol.* 2017. DOI: 10.1002/art.40189 Strand V et al. *Arthritis Res Ther.* 2015;17:362. Vieira MC et al. *Clin Ther*. 2016;38(12):2628-2641. Yamaoka K. *Drug Saf*. 2016;39(9):823-840. Curtis JR et al. *Ann Rheum Dis.* 2016;75(10):1843-1847. Weinblatt ME et al. *J Rheumatol.* 2013;40(6):787-797. Keystone EC et al. *J Rheumatol*. 2013;40(9):1487-1497. Bykerk VP et al. *Ann Rheum Dis.* 2015;74(1):96-103. Burmester GR et al. *Ann Rheum Dis.* 2013;72(4):517-524. Kay J et al. *J Rheumatol.* 2016;43(12):2120-2130. Schiff MH et al. *Arthritis Res Ther.* 2011;13(5):R141. Gomez-Reino JJ et al. Presented at: EULAR Annual Congress of Rheumatology; June 14-17, 2017; Madrid, Spain. Poster THU0196. Maneiro JR et al. *Semin Arthritis Rheum*. 2017. In press. http://www.semarthritisrheumatism.com/article/S0049-0172(16)30306-7/fulltext. Accessed May 17, 2017. Gottlieb AB et al. *J Drugs Dermatol.* 2011;10(3):289-300. Centocor. Remicade® (Infliximab). Presentation to the Food and Drug Administration Arthritis Advisory Committee. URL: http://www.fda.gov/ohrms/dockets/ac/03/slides/3930s1.htm. Accessed October 10, 2014. Charles-Schoeman C et al. *Semin Arthritis Rheum.* 2016;46(3):261-271. Alten R et al. *Arthritis Rheumatol.* 2014;66(8):1987-1997. van Vollenhoven RF et al. *J Rheumatol.* 2015;42(10):1761-1766. Wolfe F et al. *Arthritis Rheum*. 2004;50(2):372-379. Brassard P et al. *Clin Infect Dis*. 2006;43(6):717-722. Askling J et al. *Arthritis Rheum*. 2005;52(7):1986-1992. Dixon WG et al. *Arthritis Rheum*. 2006;54(8):2368-2376. Seong SS et al. *J Rheumatol*. 2007;34(4):706-711. Jung SM et al. Int J Rheum Dis. 2015;18(3):323-330. Ke WM et al. *Int J Tuberc Lung Dis*. 2013;17(12):1590-1595. Chiu YM et al. Int J Rheum Dis. 2014;17(suppl 3):9-19 Singh JA et al. *Arthritis Care Res (Hoboken)*. 2016;68(1):1-25. Singh JA et al. *Arthritis Care Res (Hoboken)*. 2016;68(1):1-252 Harpaz R et al. *MMWR Morb Mortal Wkly Rep.* 2008;57(RR-5). 1-30; quiz CE2-4.

HZ Events Are Medically Manageable, and Patients Receiving Concomitant Therapies Are at Increased Risk of Experiencing HZ

Severity of HZ Events[1,6,a]

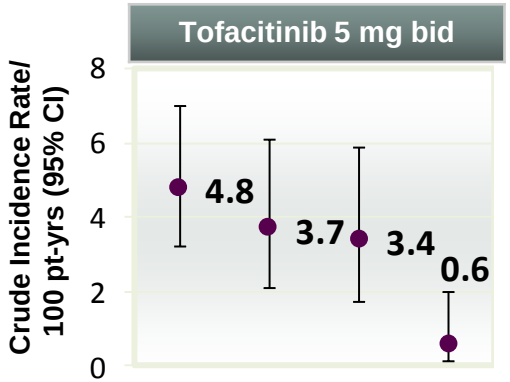
- Events were medically manageable:
  - Patients recorded as treated with antivirals in 90% of cases
  - Most cases of HZ resolved regardless of severity or number of dermatomes involved

~95%	Events were **mild to moderate** in severity
4%-7%	Events were serious (0,3/100PY)
~95%	Events were **single dermatome**
0	**No visceral dissemination**; although 2 had skin dissemination
~7%	Rates of **postherpetic neuralgia** (PHN); **comparable to rates in general population**[2]

HZ Risk Factors[5,6]

- Tofacitinib combination therapy, geographic region (Japan and Korea) and GC use are associated with a higher incidence of HZ[5]
- The incidence rate of HZ infections were numerically lower in patients receiving tofacitinib monotherapy -GC use compared with those receiving tofacitinib combination +GC use[6]

Incidence Rate of HZ (Nonserious and Serious) With Tofacitinib Monotherapy or Combination ± GCs, in the 6 Phase 3 Studies[5,6]



Pts	579	394	320	296
Pt-yrs	603	412	367	361
Pts w/ events	28	15	12	2

1. Cohen SB et al. Ann Rheum Dis. 2017 Jul;76(7):1253-1262
2. Sampathkumar P et al. *Mayo Clin Proc.* 2009;84(3):274-280.
3. Singh JA et al. *Arthritis Care Res (Hoboken)*. 2016;68(1):1-25.
4. Harpaz R et al. *MMWR Morb Mortal Wkly Rep.* 2008;57(RR-5). 1-30; quiz CE2-4.
5. Winthrop K IV et al. [abstract]. *Arthritis Rheumatol.* 2015;67(suppl 10). http://acrabstracts.org/abstract/herpes-zoster-and-tofacitinib-the-risk-of-concomitant-nonbiologic-therapy/. Accessed March 28, 2017.
6. Winthrop KL et al. Arthritis Rheumatol 2017. DOI: 10.1002/art.40189

CI=confidence interval; csDMARD=conventional synthetic disease-modifying antirheumatic drug; GC=glucocorticoid; HZ=herpes zoster; IR=incidence rate; nbDMARD=nonbiologic disease-modifying antirheumatic drug; pt-yrs=patient-years.

[a]Data as of April 2014.

Incidence rates for serious adverse events, serious infections and malignancies[a]

	All tofacitinib N=4967	Tofacitinib 5 mg BID N=1535	All tofacitinib + csDMARDs N=3215	All tofacitinib monotherapy N=1752
Total exposure, pt-yr	17,738	5891	11,482	6256
IR (patients with events/100 pt-yr [95% CI])[b]				
SAEs	9.1 (8.7, 9.6)	8.7 (7.9, 9.5)	9.5 (8.9, 10.1)	8.5 (7.8, 9.3)
Serious infections[c]	2.5 (2.2, 2.7)	2.2 (1.8, 2.6)	2.5 (2.3, 2.8)	2.3 (2.0, 2.7)
Herpes zoster (non-serious + serious)	3.7 (3.4, 4.0)	3.6 (3.1, 4.1)	3.9 (3.5, 4.3)	3.4 (3.0, 3.9)
Opportunistic infections (excluding tuberculosis)	0.4 (0.3, 0.5)	0.2 (0.1, 0.4)	0.4 (0.3, 0.6)	0.4 (0.3, 0.6)
Tuberculosis	0.1 (0.1, 0.2)	0.1 (0.0, 0.2)	0.1 (0.1, 0.2)	0.1 (0.1, 0.3)
Malignancies (excluding NMSC)	0.8 (0.7, 1.0)	0.9 (0.6, 1.1)	0.8 (0.7, 1.0)	0.9 (0.7, 1.1)
NMSC	0.7 (0.5, 0.8)	0.5 (0.3, 0.7)	0.7 (0.6, 0.9)	0.5 (0.3, 0.7)
MACE (adjudicated)[d]	0.4 (0.3, 0.5)	0.4 (0.3, 0.7)	0.4 (0.3, 0.6)	0.3 (0.2, 0.5)

[a]The safety population included all patients who received at least one dose of study medication; [b]exposure-adjusted IRs were based on patient-years (pt-yr) of exposure censored at the time of event; [c] requiring hospitalisation and/or administration of parenteral antibiotics; [d]total exposure per group is less than for other AEs of interest, since MACE adjudication applies only to data collected after Feb 25, 2009: 14,399, 4792 9607, 9221 and 5178 pt-yr, respectively

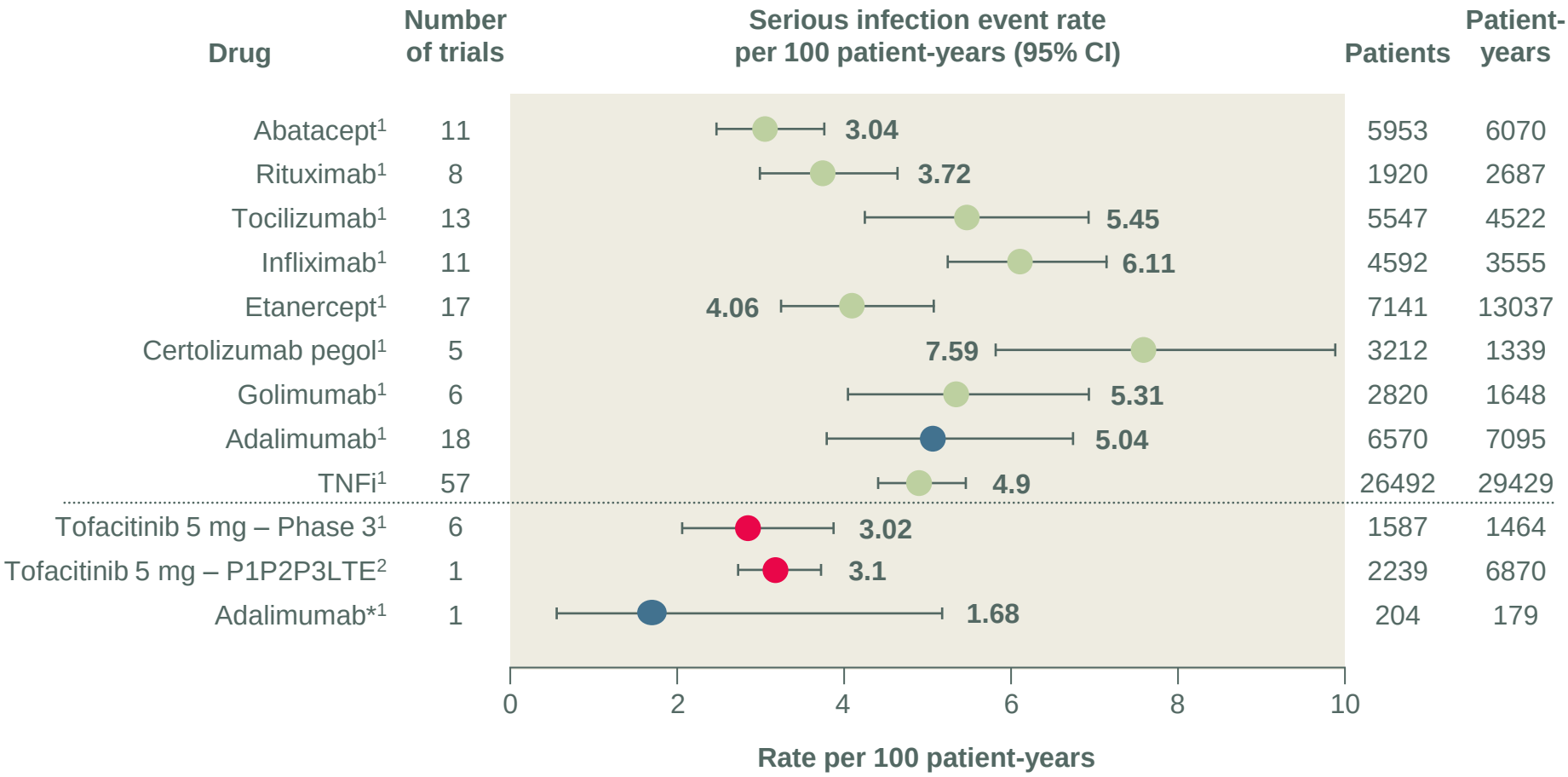
Wollenhaupt J, et al. Poster 522 presented at ACR 2017

BID, twice daily; CI, confidence interval;
csDMARDS, conventional synthetic disease-modifying anti-rheumatic drugs;
IR, incidence rates; MACE, major adverse cardiac events;
N, number of patients exposed; NMSC, non-melanoma skin cancer;
SAEs, serious adverse events

The approved dose of tofacitinib is 5 mg twice daily

Incidence rates for serious infections with biological DMARDs and tofacitinib across RCTs and LTE studies

Post-hoc analysis
April 2013 data cut



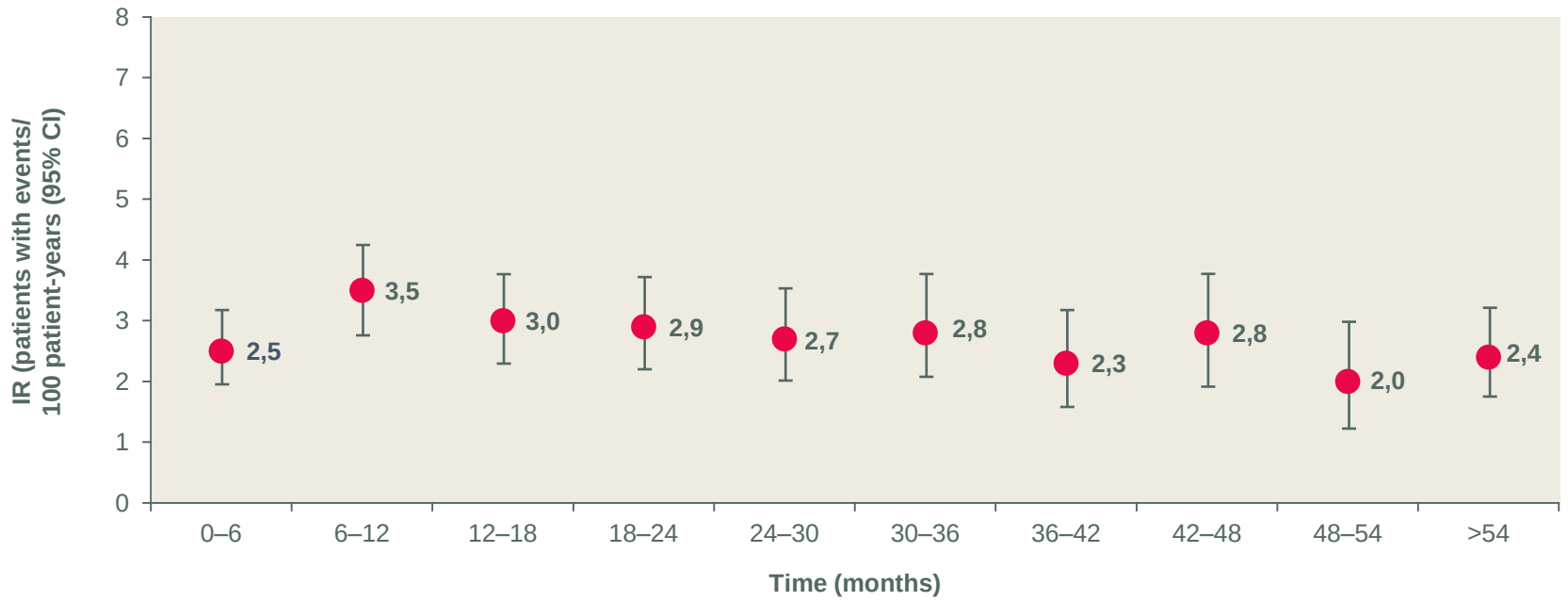
Tofacitinib data as of April , 2013.
*Adalimumab was evaluated in a RCT with tofacitinib (A3921064; ORAL Standard)

1. Strand V et al. *Arthritis Res Ther*. 2015 Dec 15;17:362. doi: 10.1186/s13075-015-0880-2. 2. Cohen S, et al. *Ann Rheum Dis* 2017;0:1–10

CI, confidence interval; LTE, long-term extension; RCT, randomised controlled trial; TNFi, tumour necrosis factor inhibitor.

Incidence rates for serious infection events over time

ISS 2015 data cut



Patients with SIE (n)	71	86	67	61	51	49	36	38	22	46
Total pt exposure (N)	6,194	5,293	4,823	4,420	4,106	3,645	3,372	2,996	2,605	1,979

- The most common serious infection events were: pneumonia, HZ, urinary tract infection and cellulitis

Serious infection rates are stable over time

Cohen S, et al. *Ann Rheum Dis*. 2017;0:1–10.

CI, confidence interval; HZ, herpes zoster; SIE, serious infection events. Bars indicate 95% confidence limits; incidence rate of patients per 100 patient-years; Phase 2, Phase 3 and LTE data as of 31 March 2015

The approved dose of tofacitinib is 5 mg twice daily

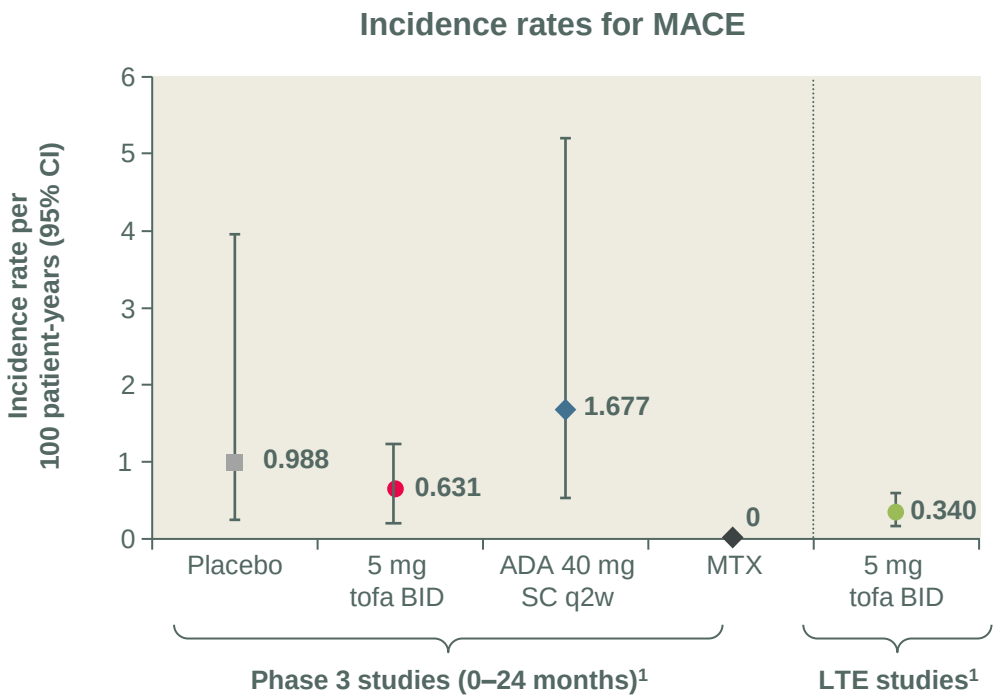
GI perforations

- 22 patients experienced GI perforations throughout the tofacitinib programme (P1P2P3LTE). IRs were 0.14 (0,08 to 0.22) for average 5 mg twice daily and 0.00 (0.00 to 0.10) for constant 5 mg twice daily
- Perforations occurred in large bowel, excluding anus and rectum (n=13), gastroduodenal area (n=3), small bowel (n=1), anus and rectum (n=2) and undetermined locations (n=3)
- All received concomitant therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids
- 10 patients received NSAIDs and corticosteroids; 9 NSAIDs alone and 3 chronic corticosteroid therapy alone
- 13 patients had a history of diverticulitis or diverticulosis and 2 additional patients had a history of gastric ulcers

1. Cohen SB et al. Ann Rheum Dis. 2017;76(7):1253-1262.

Incidence rate for major adverse cardiovascular events in patients on tofacitinib

Post-hoc analysis data cut



Patients with events	2	11	3	0	12
Exposure, pt years	203	1744	179	268	3538

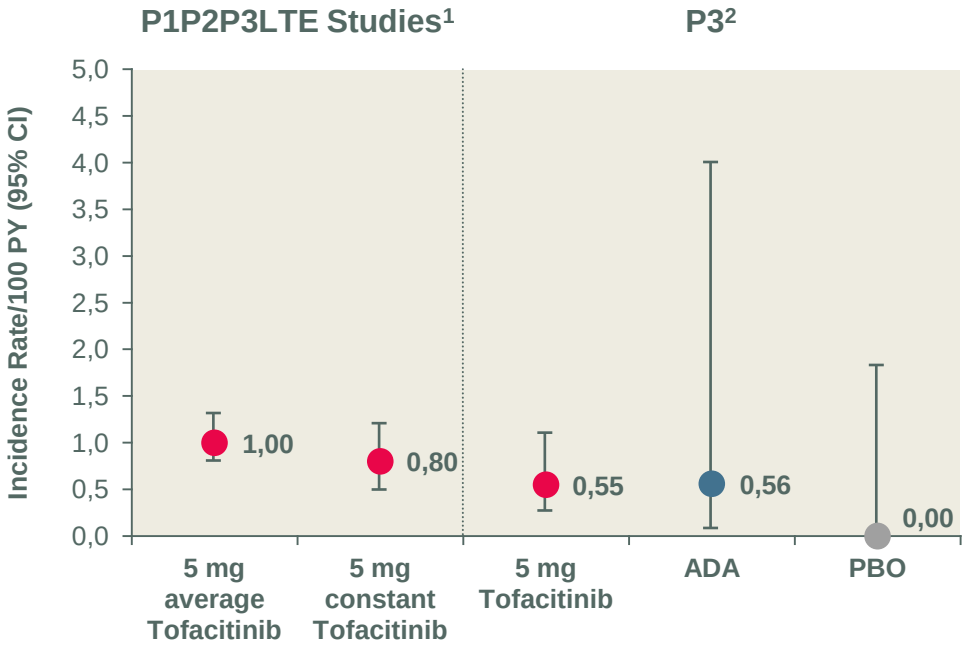
The incidence rate for MACE with tofacitinib in Phase 3 was comparable to the placebo group

1. Charles-Schoeman C, et al. *Seminars in Arthritis and Rheumatism* 2016;46:261–271.

Bars indicate 95% confidence limits; incidence of patients per 100 patient-years.
Data as of 29 September 2011: US FDA 4-month safety update.
ADA, adalimumab; BID, twice daily; CI, confidence interval; LTE, long-term extension; MACE, major adjudicated cardiovascular events; MTX, methotrexate.

Incidence rate for all malignancies (excluding NMSC) in patients on tofacitinib

ISS 2015 data cut



	5 mg average Tofacitinib	5 mg constant Tofacitinib	5 mg Tofacitinib	ADA	PBO
Patients with event (n)	*	*	8	1	0
Exposure, pt years	6, 870	3,623	1,464	179	203

*173 cases reported for all doses of tofacitinib

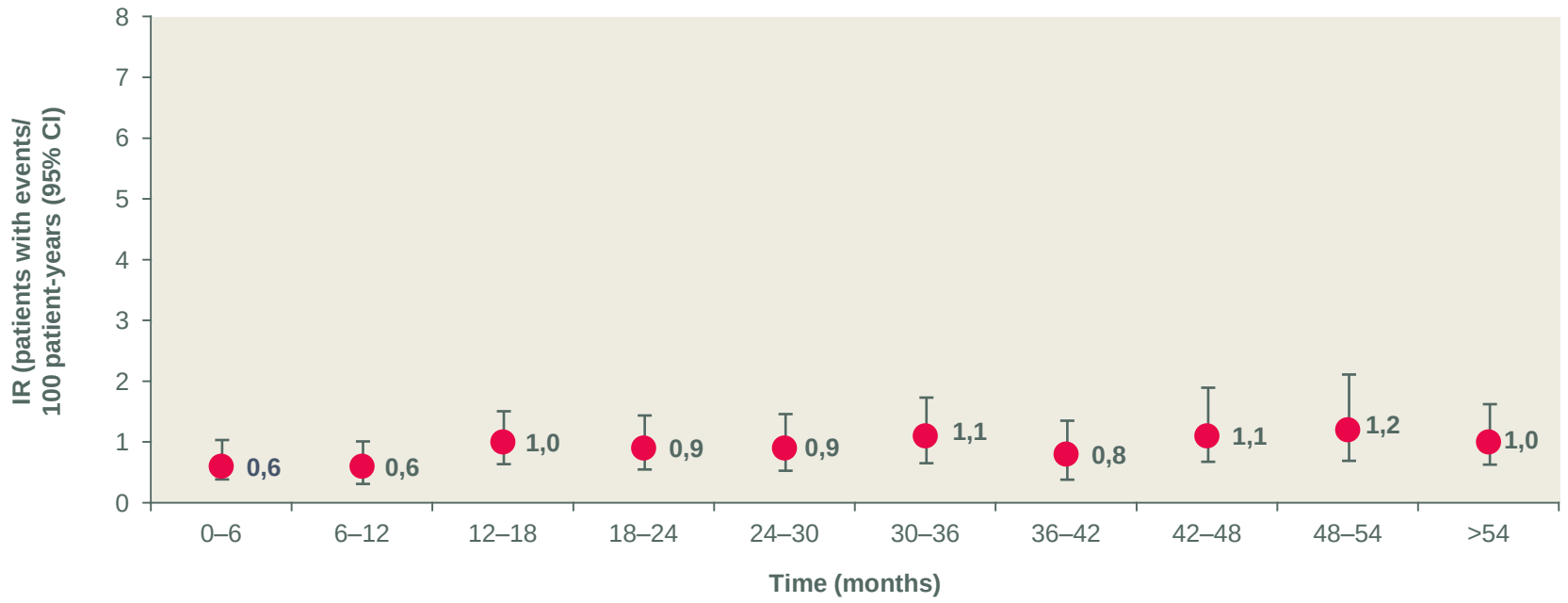
The malignancies that occurred are consistent with the type and distribution of malignancies expected for patients with moderately to severely active RA

1. Cohen S, et al. *Ann Rheum Dis.* 2017;0:1–10.
2. Curtis JR, et al. *Ann Rheum Dis*. 2016;75:831–41.

ADA, adalimumab; CI, confidence interval; DMARD, disease-modifying anti-rheumatic disease; LTE; long-term extension;
N, total number of patients; n, number of patients with an event; NMSC, non-melanoma skin cancer; PBO, placebo; pyo, patient years of observation.

Incidence rates for malignancies (excluding NMSC) over time

ISS 2015 data cut



	0–6	6–12	12–18	18–24	24–30	30–36	36–42	42–48	48–54	>54
Patient with malignancies (N)	18	15	23	19	17	19	12	16	14	20
Total pt exposure (N)	6,194	5,306	4,852	4,450	4,143	3,681	3,407	3,030	2,640	1,999

Malignancy rates in tofacitinib-treated patients remain stable over time

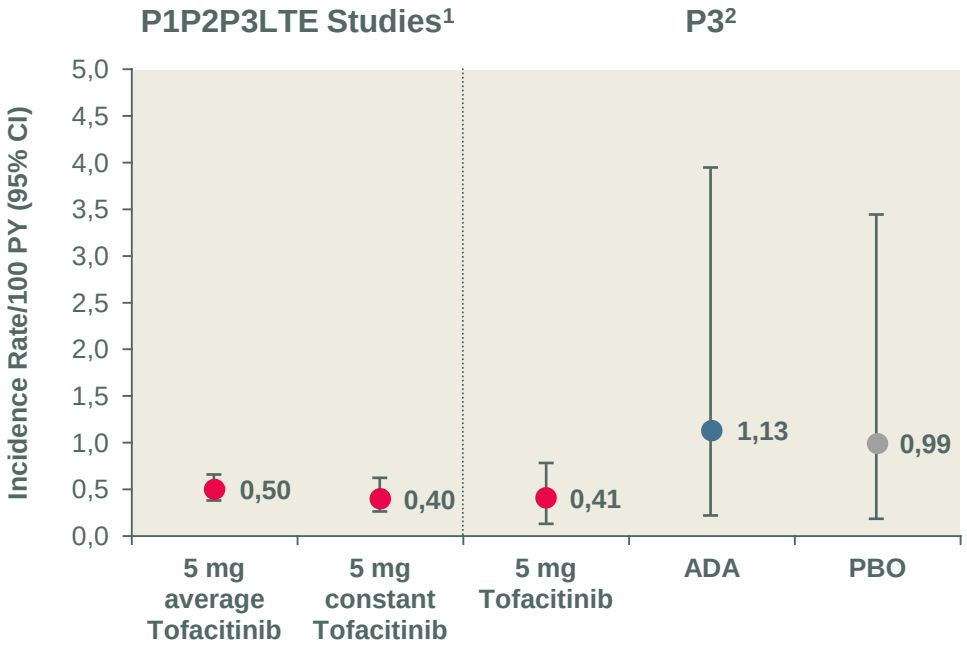
Cohen S, et al. *Ann Rheum Dis* 2017;0:1–10.

CI, confidence interval; IR, inadequate responders; LTE, long-term extension; NMSC, non-melanoma skin cancer

The approved dose of tofacitinib is 5 mg twice daily

Incidence rate for NMSC in patients on tofacitinib

ISS 2015 data cut



Patients with event (n)	*	*	6	2	2
Exposure, pt years	6,870	3,623	1,464	179	203

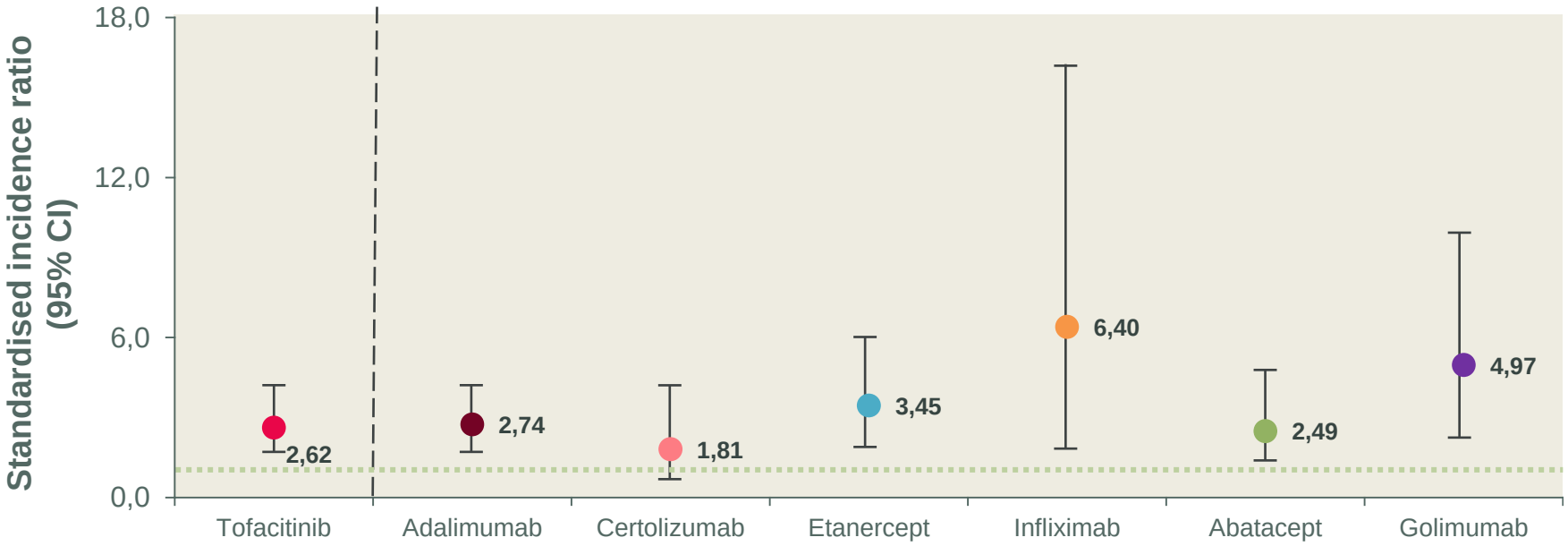
*118 cases reported for all doses of tofacitinib

IRs for NMSC are similar for the Phase 3 5mg tofacitinib group and the P1P2P3LTE 5mg constant tofacitinib group

1. Cohen S, et al. *Ann Rheum Dis.* 2017;0:1–10.
2. Curtis JR, et al. Ann Rheum Dis 2016;75:831–841

ADA, adalimumab; CI, confidence interval; DMARD, disease-modifying anti-rheumatic disease; IR, inadequate responders; LTE; long-term extension; N, total number of patients; n, number of patients with an event; NMSC, non-melanoma skin cancer; PBO, placebo; pyo, patient years of observation.

Incidence ratio for lymphoma for tofacitinib and bDMARDs



Data source	*This analysis*	*Burmester et al, 2013*	*Bykerk et al, 2015*	*Gottlieb et al, 2011*	*FDA advisory committee, 2003*	*Weinblatt et al, 2013*	*Kay et al, 2016*
Total exposure PY	19,404	23,943	9277	11,765	2458	12,132	5604

Lymphoma IR in the tofacitinib RA program was similar to rates observed in long-term clinical studies of patients with RA treated with bDMARDs

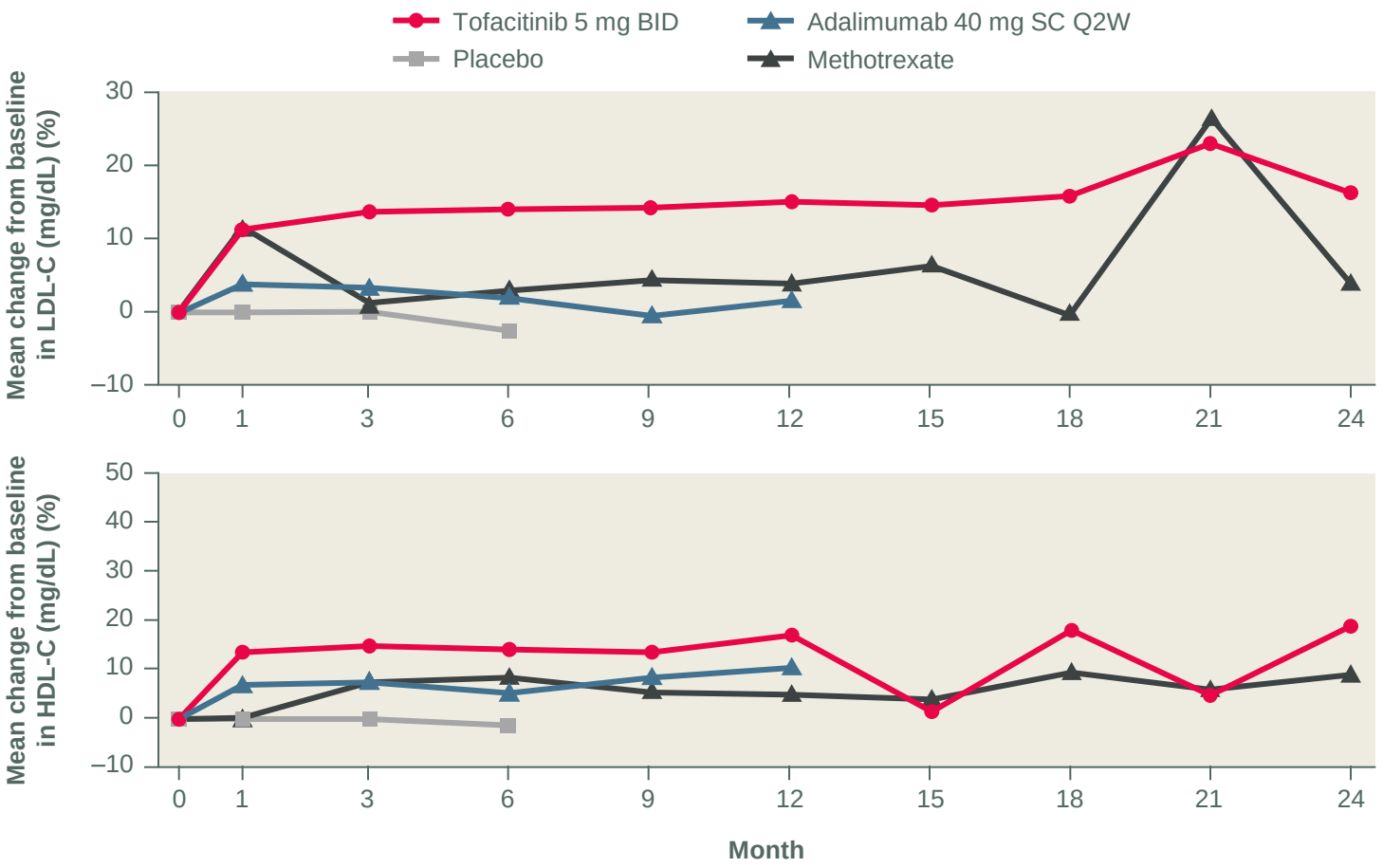
1. Mariette X et al. *Arthritis Care Res (Hoboken).* 2017 Sep 21. doi: 10.1002/acr.23421. [Epub ahead of print].

Clinical trial data for tofacitinib, adalimumab, certolizumab, etanercept, infliximab, abatacept, and golimumab is standardised against the SEER database. For golimumab combined data for 50 mg and 100 mg dose groups are presented. Data for tofacitinib are adjusted for age and gender. The dashed horizontal line represents SIR = 1.0 i.e., no difference in lymphoma rate vs the US general population. bDMARD, biologic disease-modifying antirheumatic drug; CI, confidence interval; FDA, Food and Drug Administration PY, patient-years.

The approved dose of tofacitinib is 5 mg twice daily

Mean percentage change (mg/dL) in LDL and HDL cholesterol in patients on tofacitinib

Phase 3



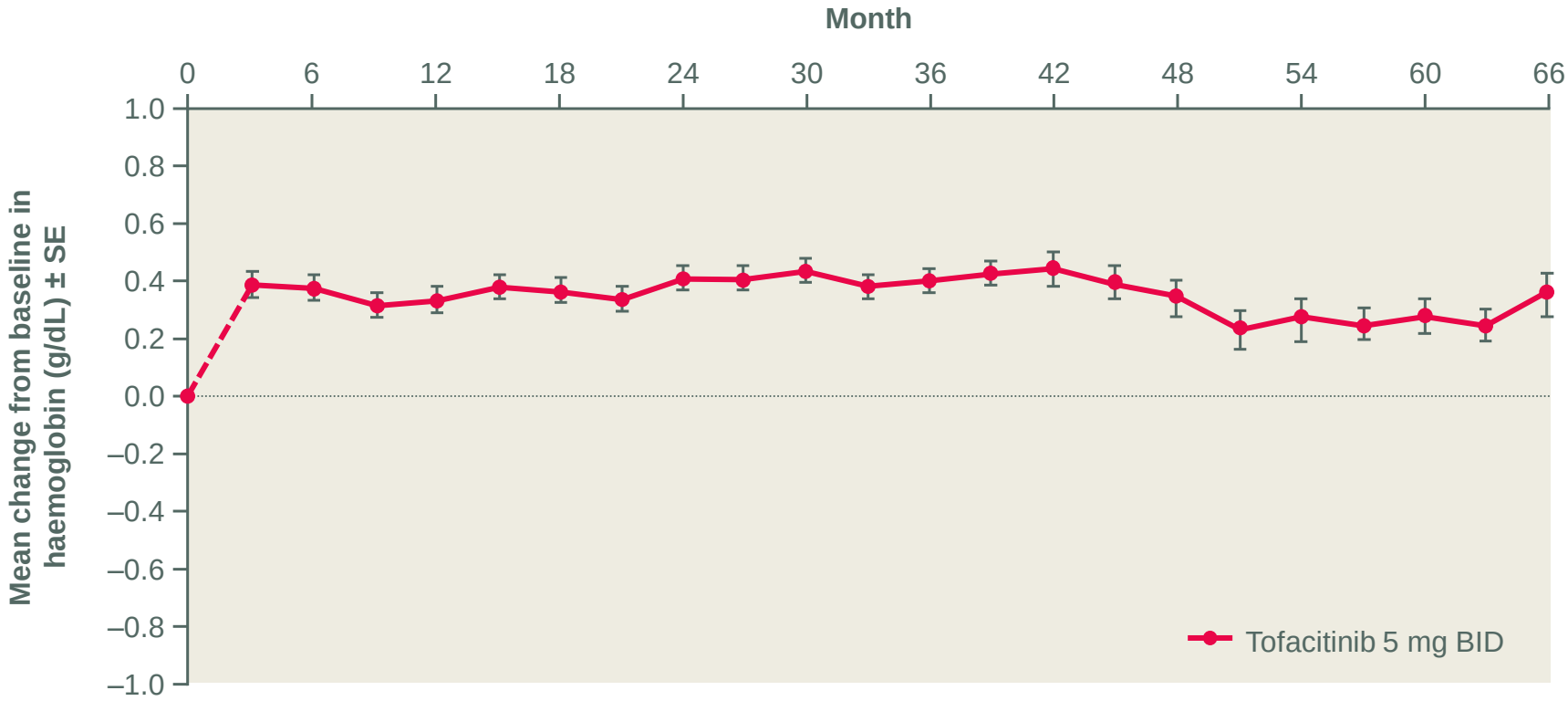
Tofacitinib induces a reversible increase in lipids that peaks at Week 6 and then stabilises

Charles-Schoeman C, et al. *Sem Arthri Rheum* 2016;46:261–71

BID, twice daily; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; Q2W, every two weeks; SC, subcutaneous.

Changes in haemoglobin over time in patients on tofacitinib

April 2014 data cut



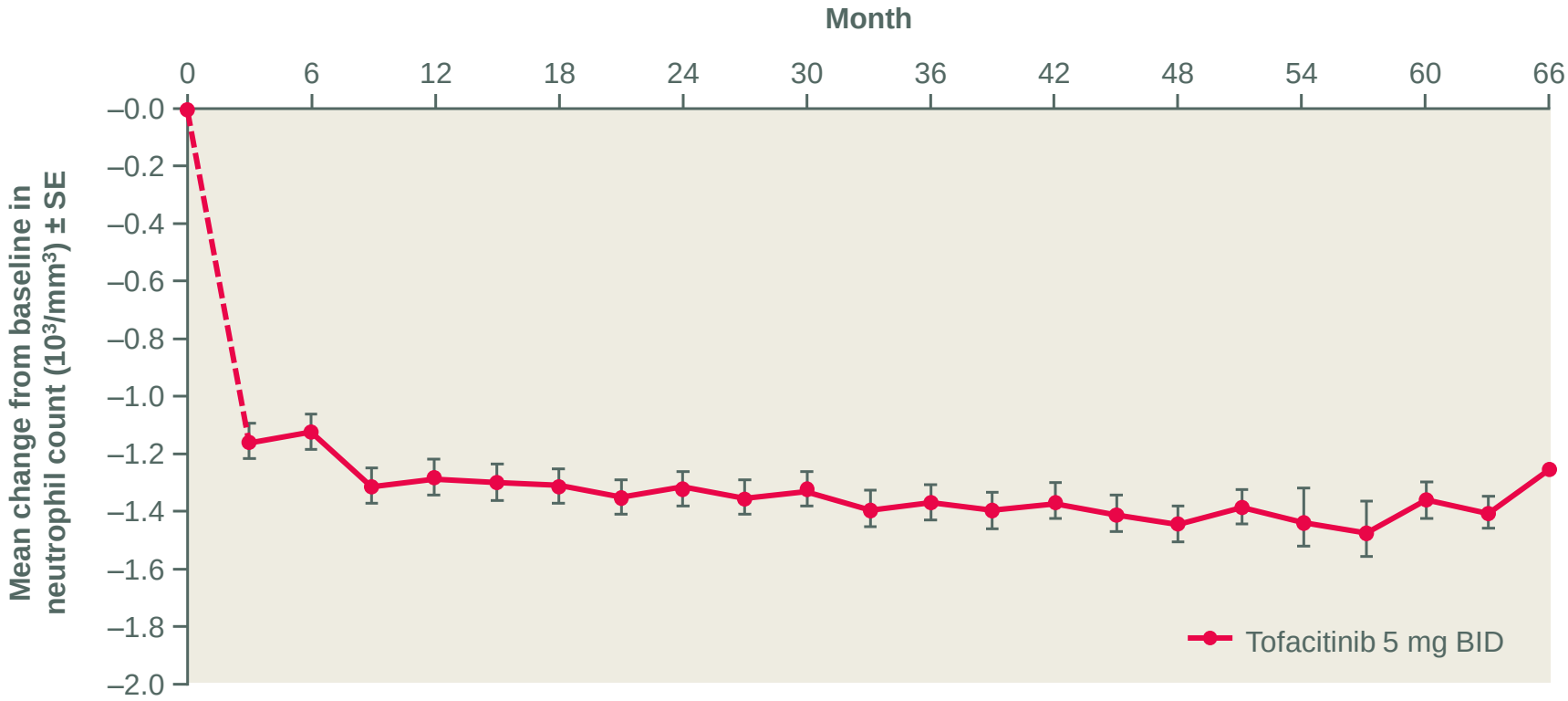
Changes in haemoglobin were observed that generally stabilised over time with longer treatment duration

Schulze-Koops H, et al. *Rheumatology (Oxford).* 2017 Jan;56:46–57.

BID, twice daily; SE, standard error.

Changes in neutrophil counts over time in patients on tofacitinib

April 2014 data cut



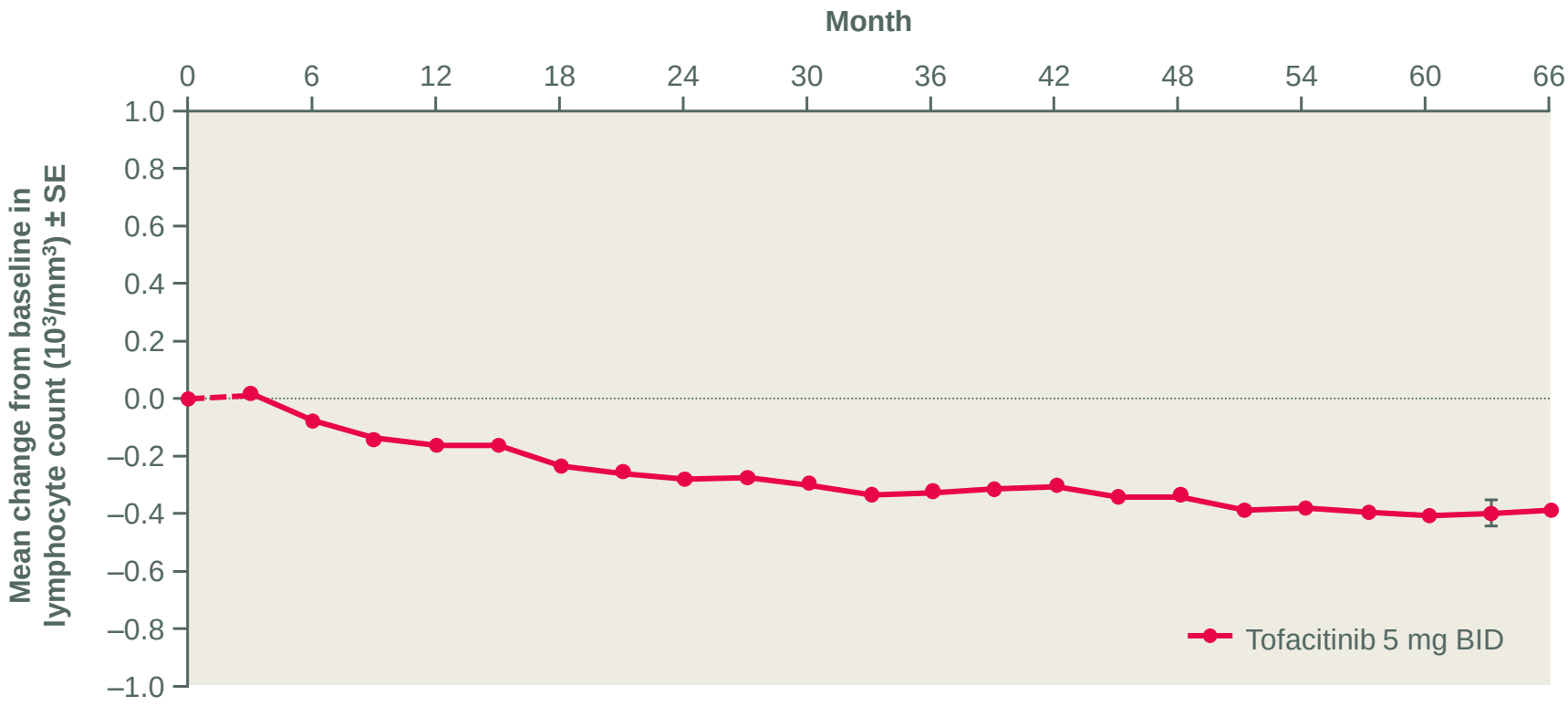
Decreases in neutrophil counts were observed that generally stabilised over time with longer treatment duration

Schulze-Koops H, et al. *Rheumatology (Oxford).* 2017 Jan;56(1):46–57.

BID, twice daily; SE, standard error.

Changes in lymphocyte counts over time in patients on tofacitinib

April 2014 data cut



Baseline was that of the phase 2 or phase 3 index study for patients who enrolled within 7 (Study A3921041) or 14 (Study A3921024) days of index study finalization; for the other patients, baseline values were derived from the final pre-drug visit on entry into the long-term extension studies

Decreases in lymphocyte counts were observed that generally stabilised beyond month 48

Schulze-Koops H, et al. *Rheumatology (Oxford).* 2017 Jan;56(1):46–57.

BID, twice daily; DMARD, disease-modifying antirheaumatic drug; SE, standard error.

Monitoring

Laboratory monitoring recommendations for patients considering or receiving XELJANZ

	Laboratory Monitoring Recommendations		
	At baseline	4–8 weeks	Every 3 months
Lymphocytes	✓		✓
Neutrophils	✓	✓	✓
Haemoglobin	✓	✓	✓
Lipids		✓[a]	
Liver enzymes[b]	Routine monitoring of liver tests is recommended		

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[a]Assessment of lipid parameters should be performed after 8 weeks following initiation of XELJANZ therapy. Patients should be managed according to clinical guidelines for the management of hyperlipidaemia.
[b]Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ.

Laboratory monitoring: Dose recommendations

	Laboratory value	Dose recommendations
Lymphocytes	≥750 cells/mm^3	Maintain dose
	500–750 cells/mm^3	For persistent (2 sequential values in this range on routine testing) decrease in this range, dosing should be interrupted until ALC is greater than 750 When ALC is greater than 750, resume 5 mg twice daily
	<500 cells/mm^3 (confirmed by repeat testing)	If lab value confirmed by repeat testing within 7 days, dosing should be discontinued
Neutrophils	ANC >1000 cells/mm^3	Maintain dose
	ANC 500–1000 cells/mm^3 (confirmed by repeat testing)	For persistent decreases (2 sequential values on routine testing) in this range, interrupt dosing until ANC is greater than 1000cells/mm^3 When ANC is greater than 1000, resume tofacitinib 5 mg twice daily
	ANC <500 cells/mm^3 (confirmed by repeat testing)	If lab value confirmed by repeat testing within 7 days, dosing should be discontinued
Haemoglobin	≤2 g/dL decrease from baseline and ≥9.0 g/dL	Maintain dose
	>2 g/dL decrease from baseline, or <8.0 g/dL (confirmed by repeat testing)	Interrupt the administration of tofacitinib until haemoglobin values have normalised

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ALC, absolute lymphocyte count; ANC, absolute neutrophil count.

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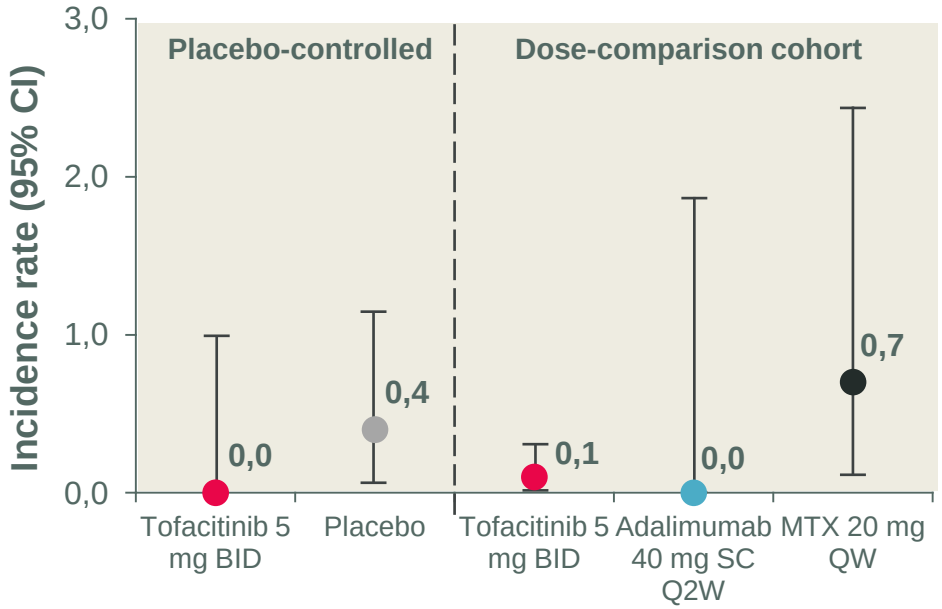
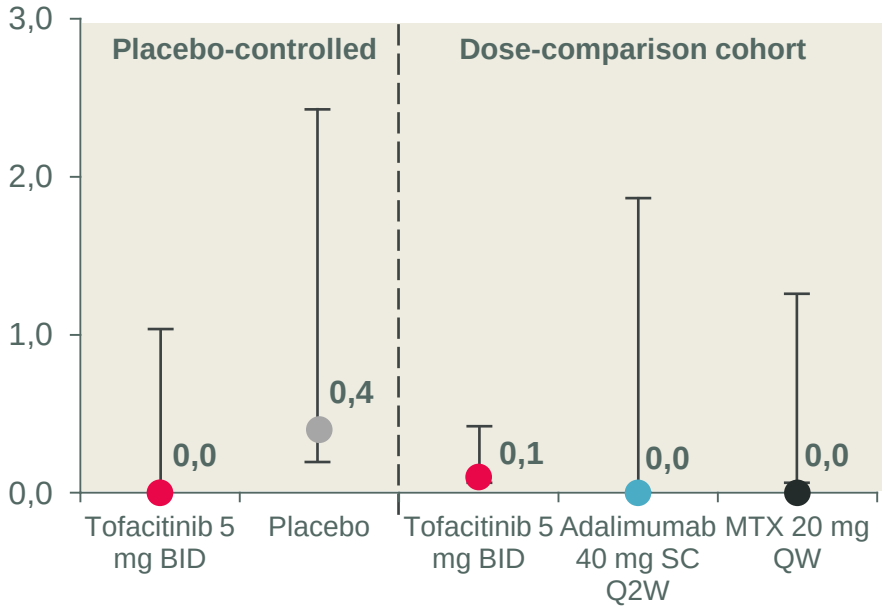
Incidence rate for thromboembolic events in patients with RA on tofacitinib

Incidence rates for DVT



Pts with event	0	1	1	0	2
Pts in tx group	1849	1079	1849	257	223
Drug exposure (PY)	426	228	1818	190	292

Incidence rates for PE



0	1	21	0	0
1849	1079	1849	257	223
426	228	1818	190	293

There was no imbalance of DVT or PE events with tofacitinib compared with placebo or adalimumab

1. Mease et al. Poster 16L presented at ACR 2017.

Placebo-controlled cohort: patients randomised to tofacitinib BID or placebo up to Month 3 (before any placebo-treated patients advanced to tofacitinib). Dose-comparison cohort: patients randomised to tofacitinib BID, adalimumab 40 mg SC q2w (active control), or MTX 20 mg QW (active control) up to Month 24. Incidence rate = patients with events per 100 PY of exposure. BID, twice daily; CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; PY, patient years; QW, once weekly; Q2W, once every 2 weeks; SC, subcutaneous.