Κλινικά δεδομένα οκταετίας του Tofacitinib στη Ρευματοειδή Αρθρίτιδα

ΔΗΜΗΤΡΟΥΛΑΣ ΘΕΟΔΩΡΟΣ
ΕΠΙΚΟΥΡΟΣ ΚΑΘΗΓΗΤΗΣ ΡΕΥΜΑΤΟΛΟΓΙΑΣ ΑΠΘ
Δ' ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ
ΙΠΠΟΚΡΑΤΕΙΟ ΝΟΣΟΚΟΜΕΙΟ
ΘΕΣΣΑΛΟΝΙΚΗΣ

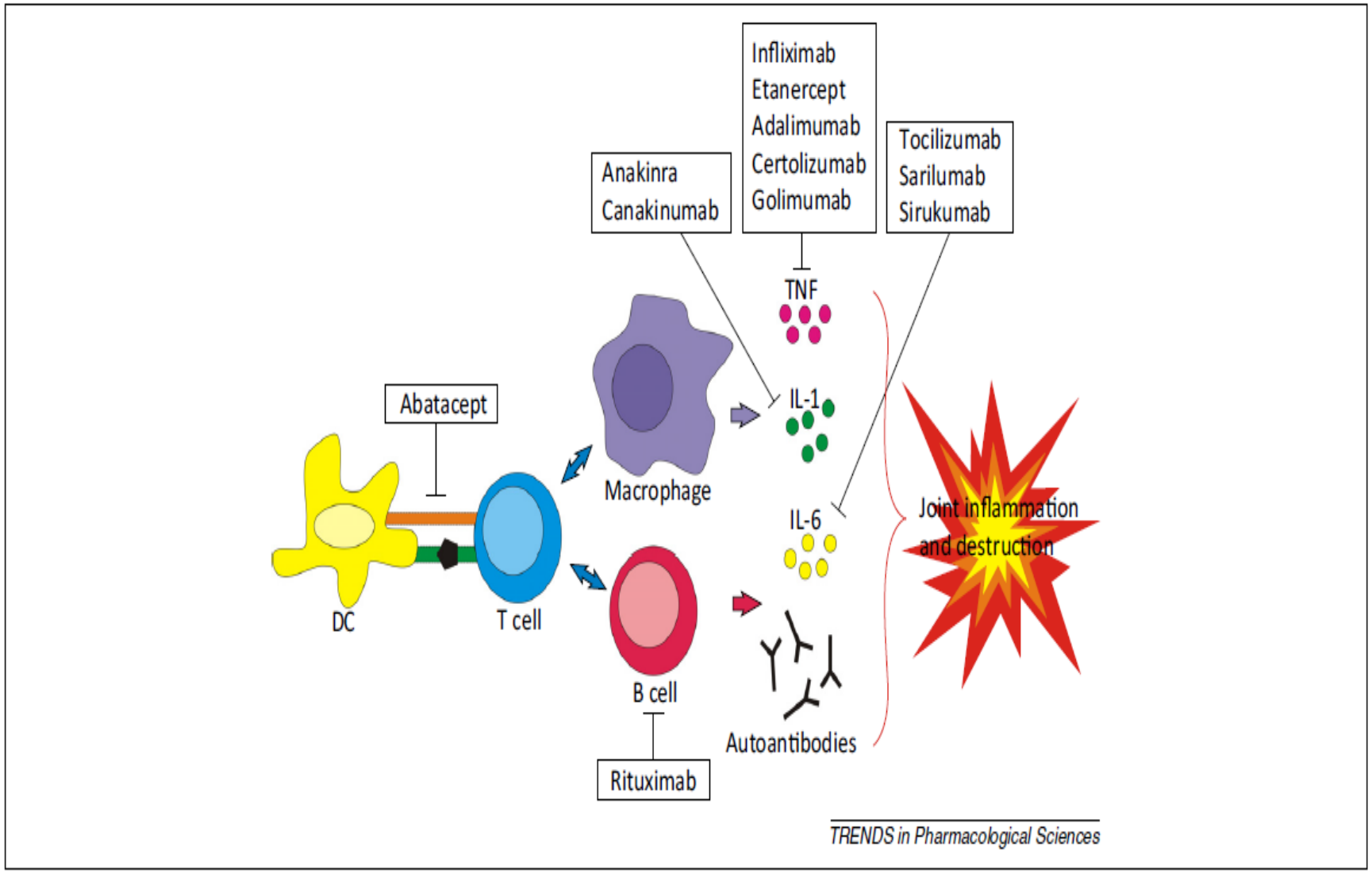
Σύγκρουση συμφερόντων

Παρούσα παρουσίαση: PRIZER

Honoraria for lectures and/or consultancy from Abbvie, Actelion, Enorasis, Elpen, BMS, Jansen, MSD, Genesis Pharma, Hospital Line, UCB, Novartis, Roche, Sandoz, Sanofi

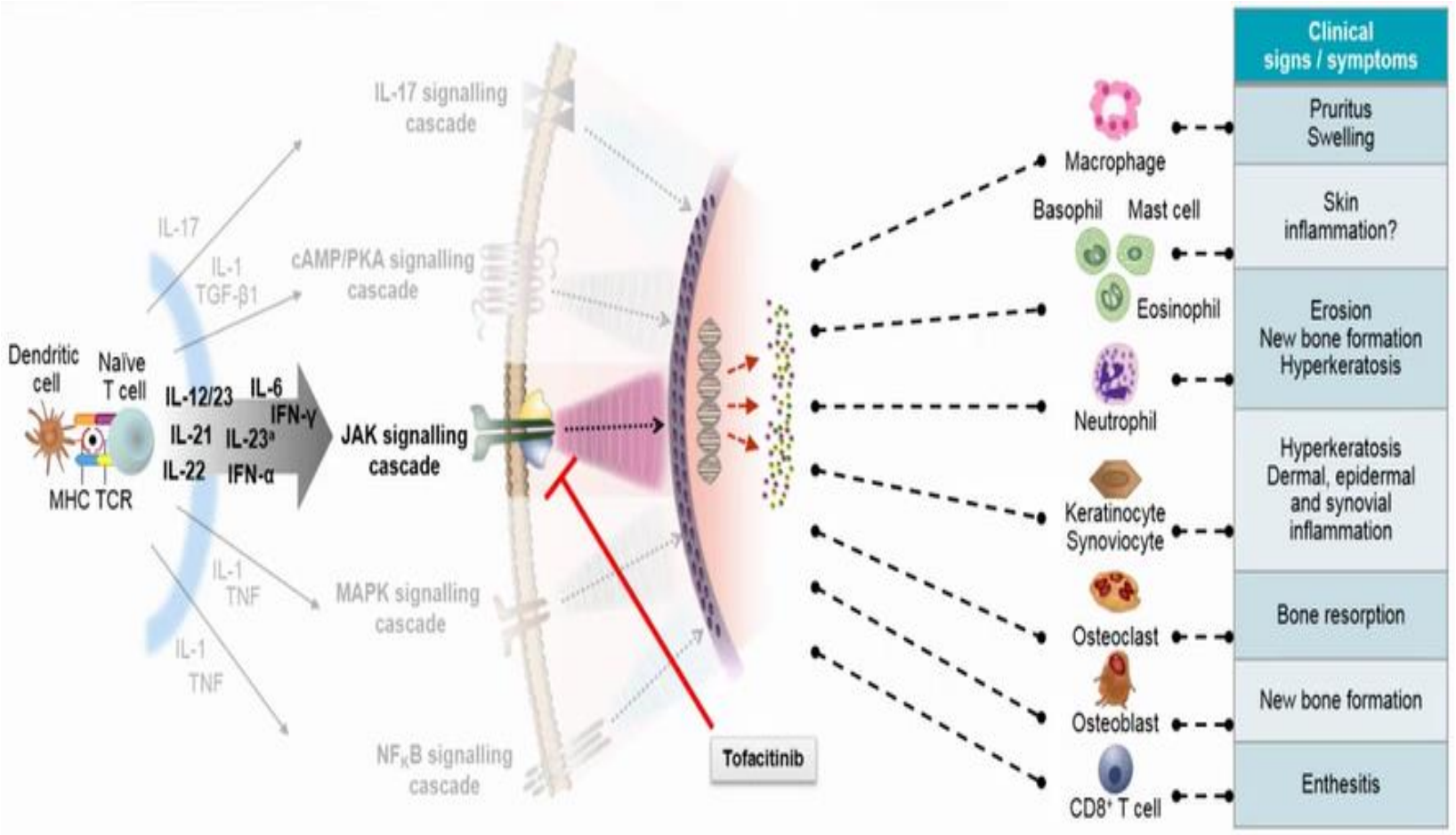
"Οι απόψεις που εκφράζονται σε αυτή την παρουσίαση ανήκουν στον ομιλητή και δεν εκφράζουν απαραίτητα τις απόψεις της εταιρείας.
Για όλα τα φαρμακευτικά προϊόντα που αναφέρονται παρακαλείσθε να συμβουλεύεστε τις εγκεκριμένες Περιλήψεις Χαρακτηριστικών των Προϊόντων"

ΒΙΟΛΟΓΙΚΟΙ ΠΑΡΑΓΟΝΤΕΣ ΚΑΙ ΡΑ



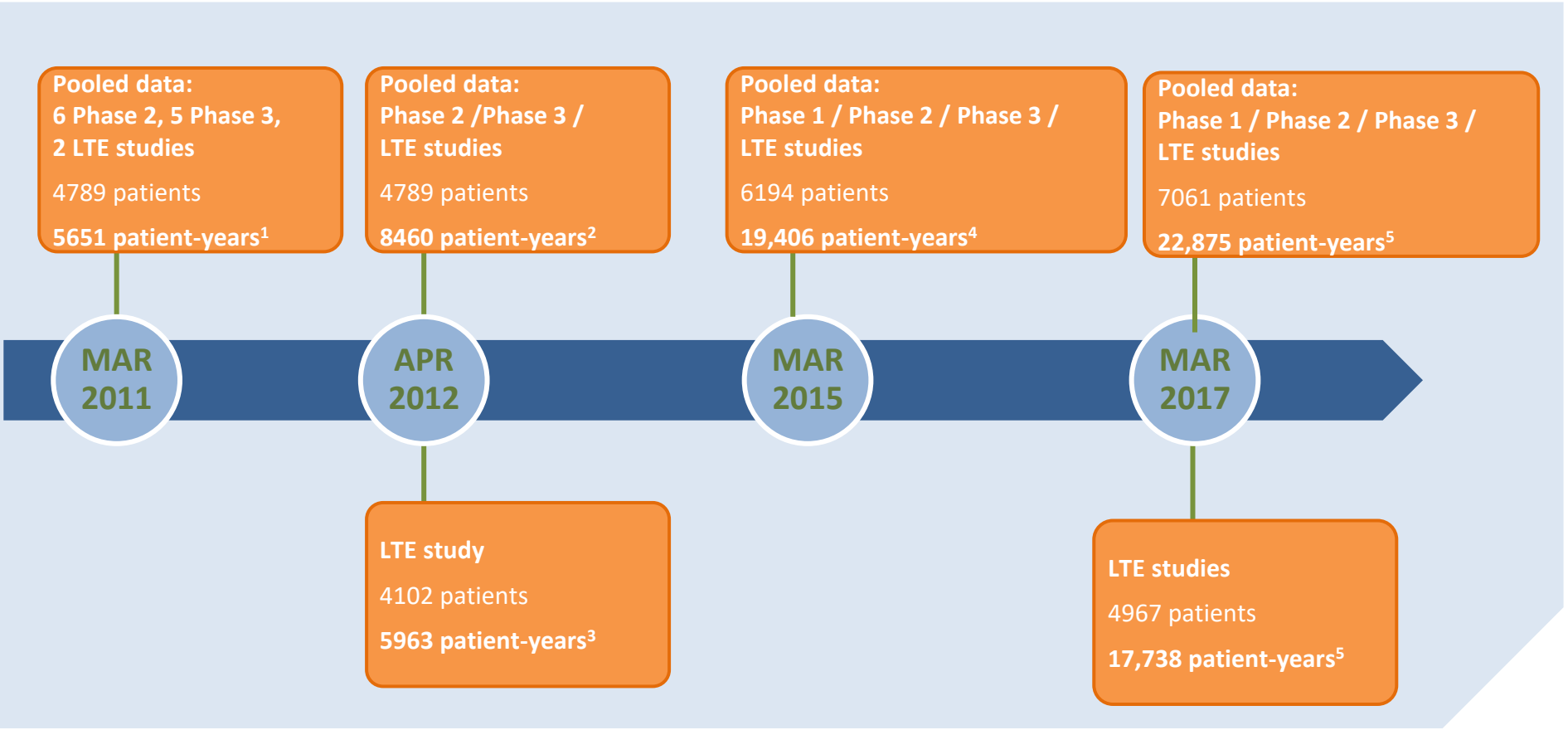
Koenders et al, Trends Pharm Sci 2015

Ενδοκυττάρια σηματοδοτικά μονοπάτια



Adapted from Coates et al, Semin Arthr Rheum 2016

Experience with tofacitinib in clinical trials

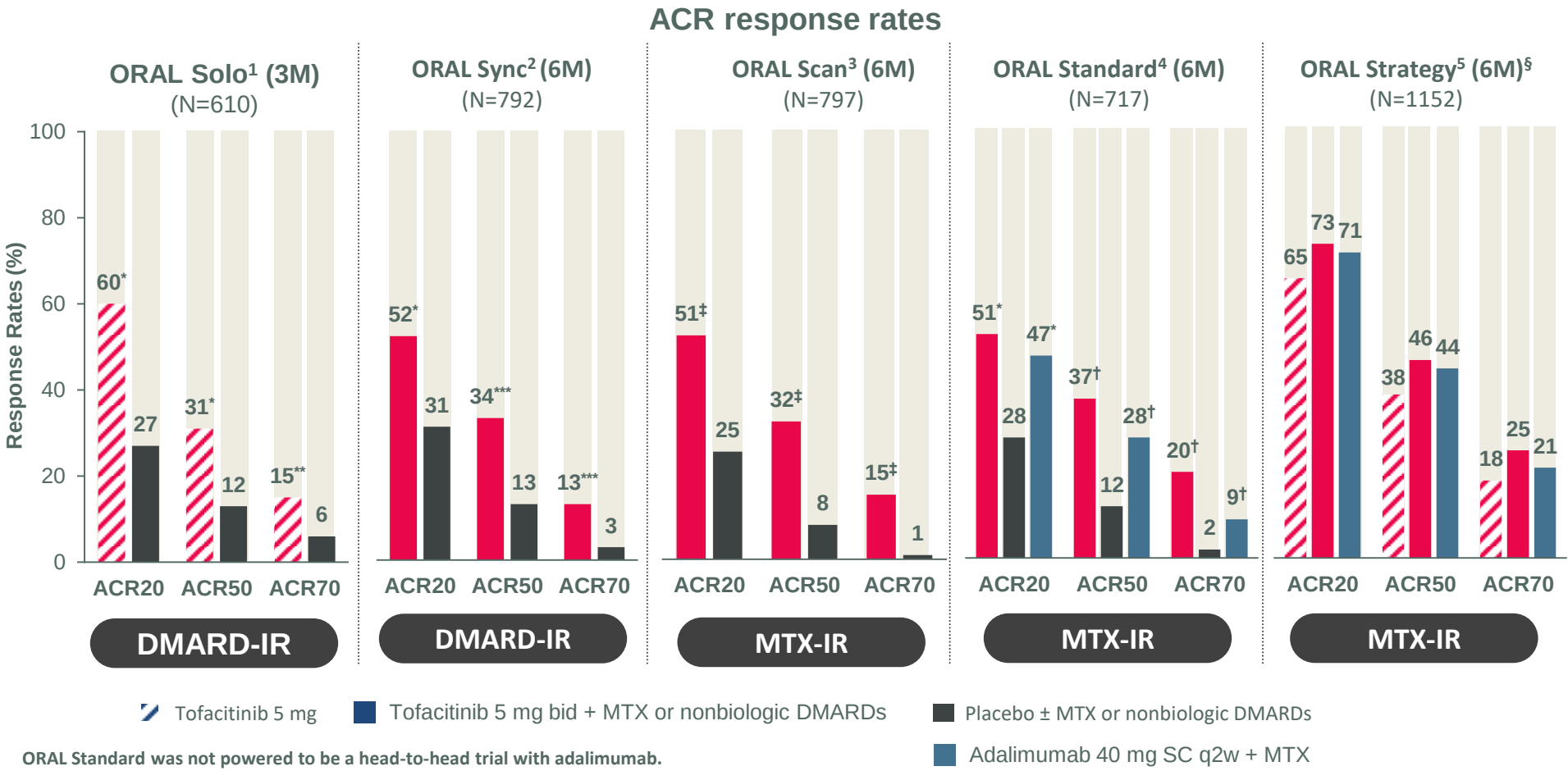


1. Winthrop KL et al. *Arthritis Rheumatol*. 2014;66(10):2675-2684.
2. Cohen S et al. *Arthritis Rheumatol*. 2014;66(11):2924-2937.
3. Wollenhaupt J et al. *J Rheumatol*. 2014;41(5):837-852.
4. Cohen S et al. *Ann Rheum Dis*. 2017 Jan 31. pii: annrheumdis-2016-210457.
5. Data on file. Pfizer Inc, New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

LTE, long-term extension.

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.

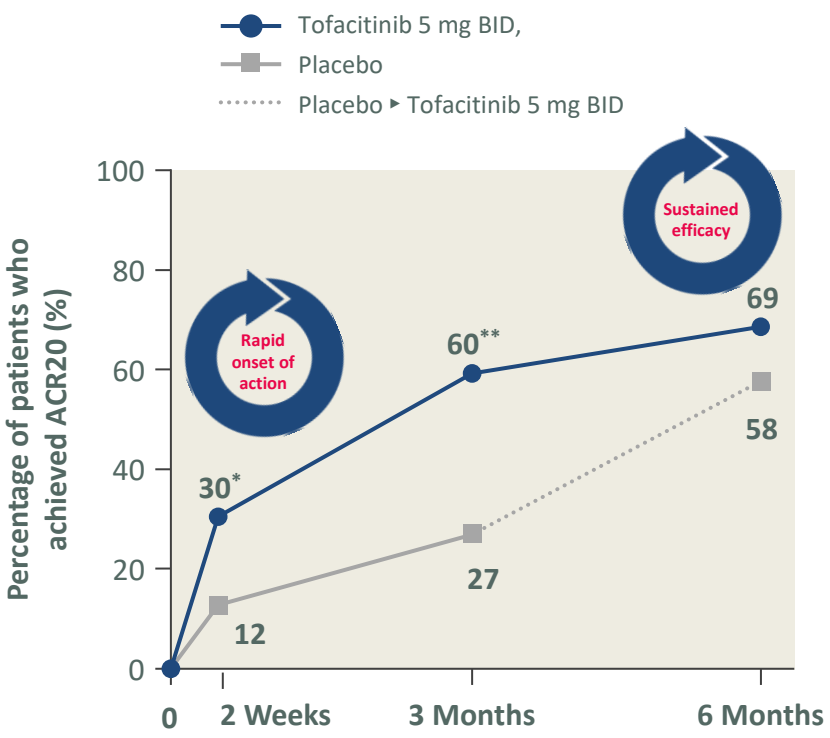
1. Fleischmann et al. *N Engl J Med* 2012;367:495–507.
2. Kremer et al. *Ann Intern Med* 2013;159:253–61.
3. van der Heijde et al. *Arth Rheum* 2013;65:559–70.
4. van Vollenhoven et al. *N Engl J Med* 2012;367:508–19.
5. Fleischmann R et al. *Lancet* 2017; S0140-6736(17)31618-5.

*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

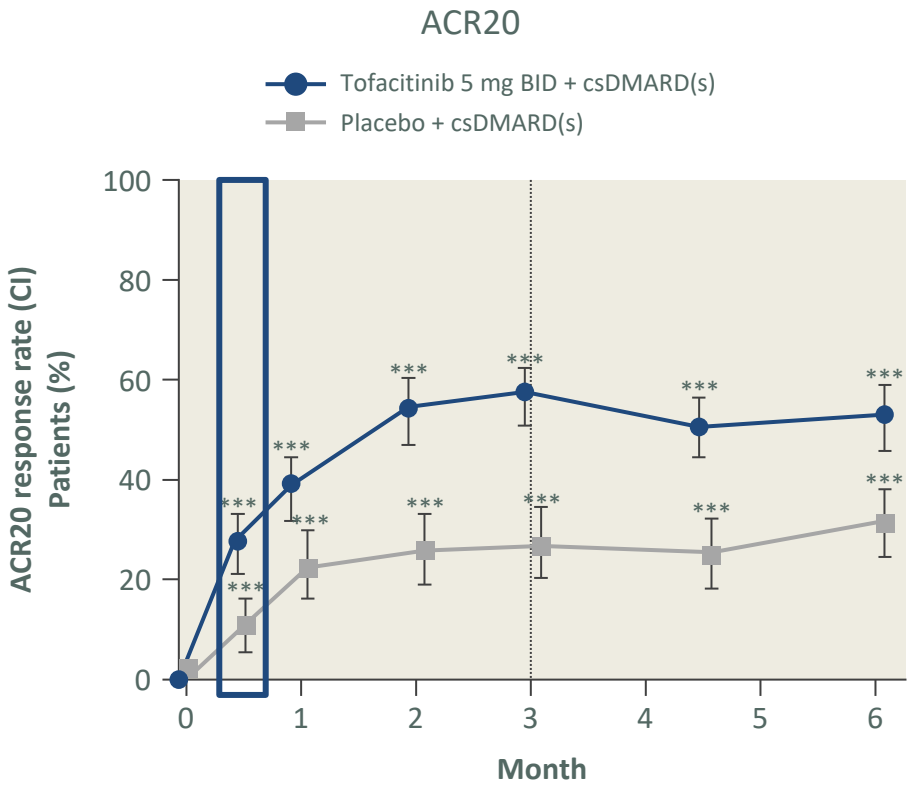
ACR20 at month 6 was a primary endpoint in ORAL Sync, ORAL Standard, and ORAL Scan. ACR20 was a primary endpoint at month 3 and a secondary endpoint at month 6 in ORAL Step.

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

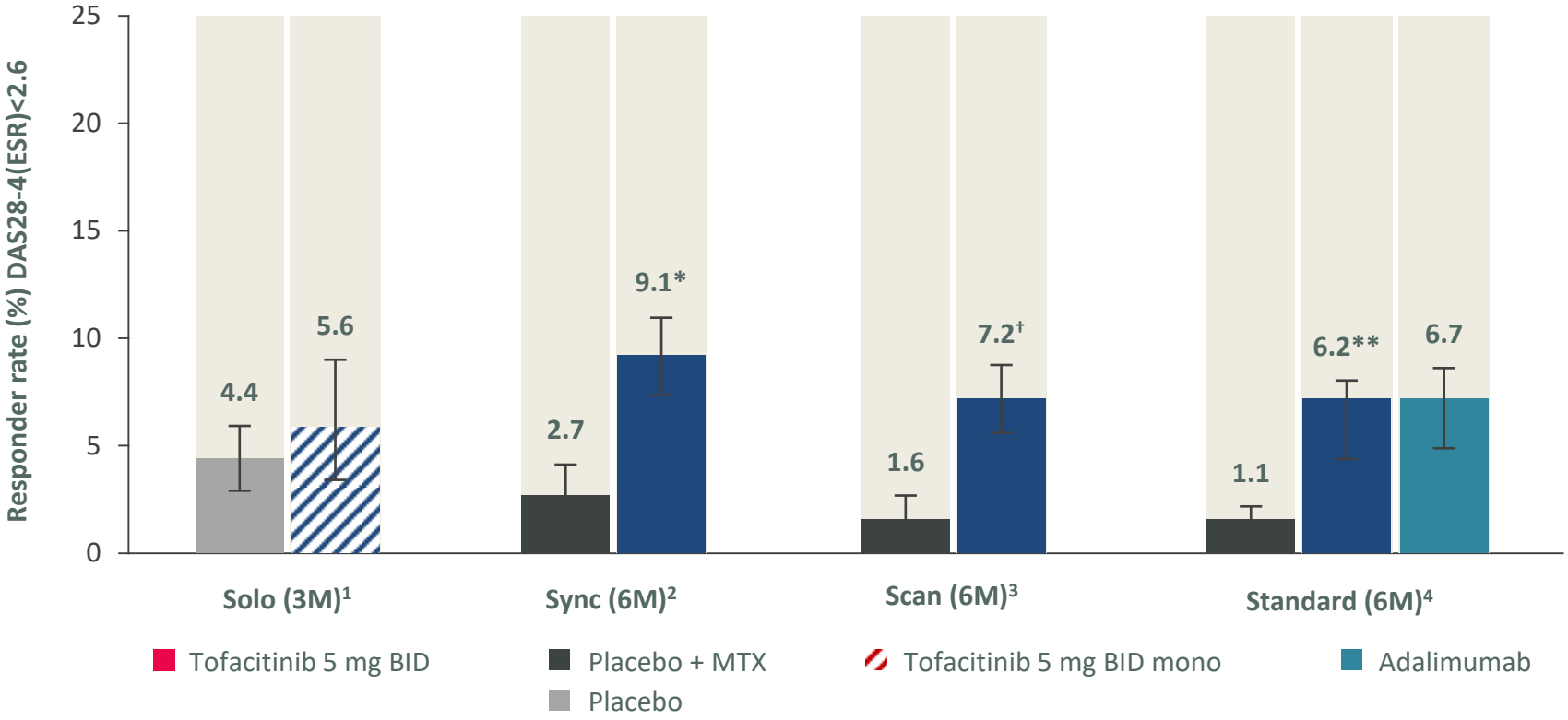
*p<0.0001; **p<0.001; ***p≤0.001 vs. baseline.

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

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

DAS28-4(ESR) response rates across tofacitinib Phase 3 studies

DAS28-4 (ESR)<2.6

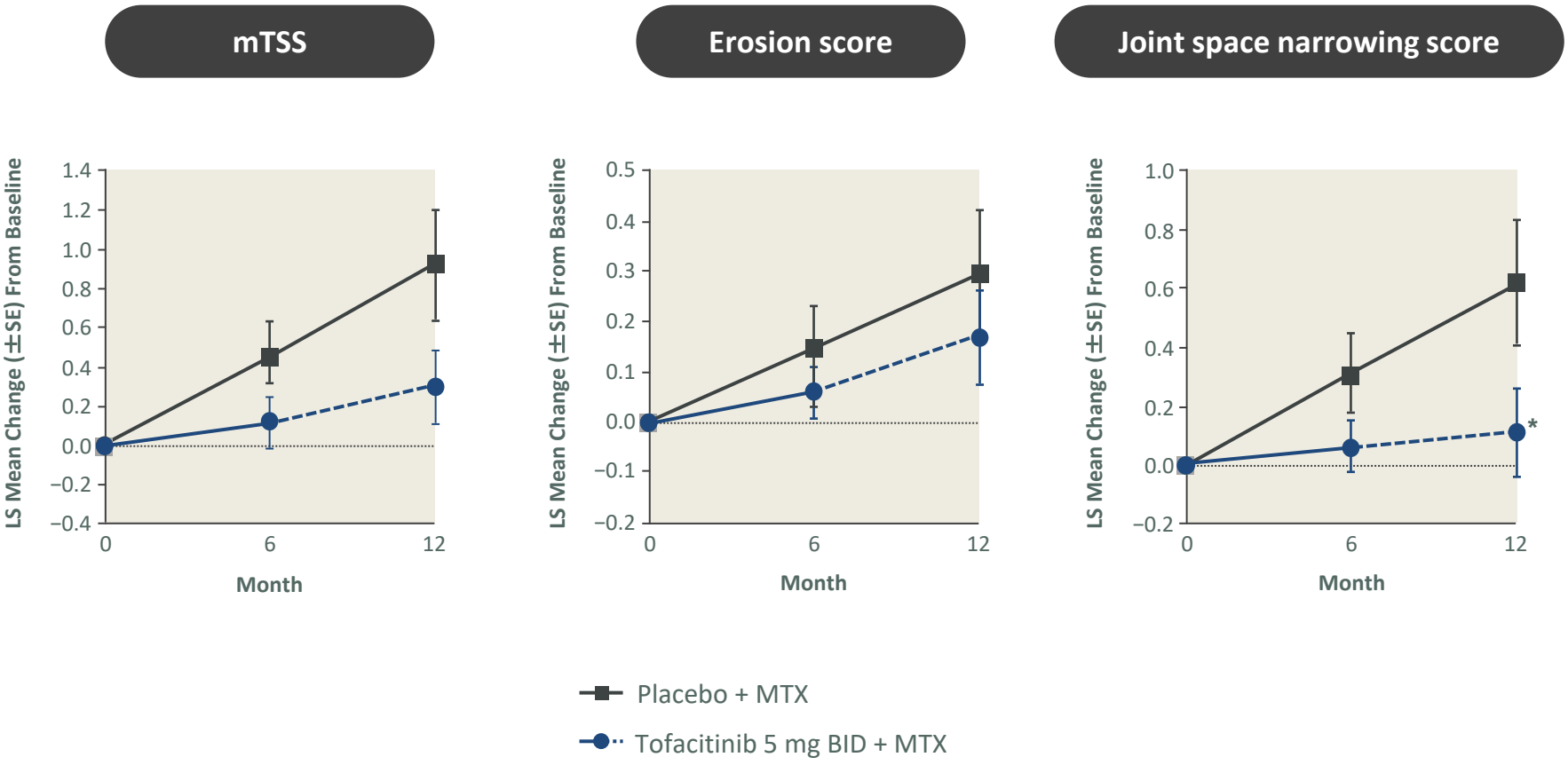


Significant reductions in mean DAS28-4 (ESR) scores vs placebo at Month 6

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.

**p=0.0038; **p<0.05 †Statistical significance could not be declared in the ORAL Scan study due to the step-down procedure
BID, twice daily; DAS, Disease Activity Score;
ESR, erythrocyte sedimentation rate; MTX, methotrexate

Secondary radiographic endpoints for patients on tofacitinib



Tofacitinib resulted in numerically less progression from baseline in both components of mTSS (erosion score and JSN score) versus placebo at Months 6 and 12

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

* p≤0.05
12-month data was imputed using linear extrapolation.

JSN, joint space narrowing; mTSS modified Total Sharp Score; MTX, methotrexate

ORIGINAL ARTICLE

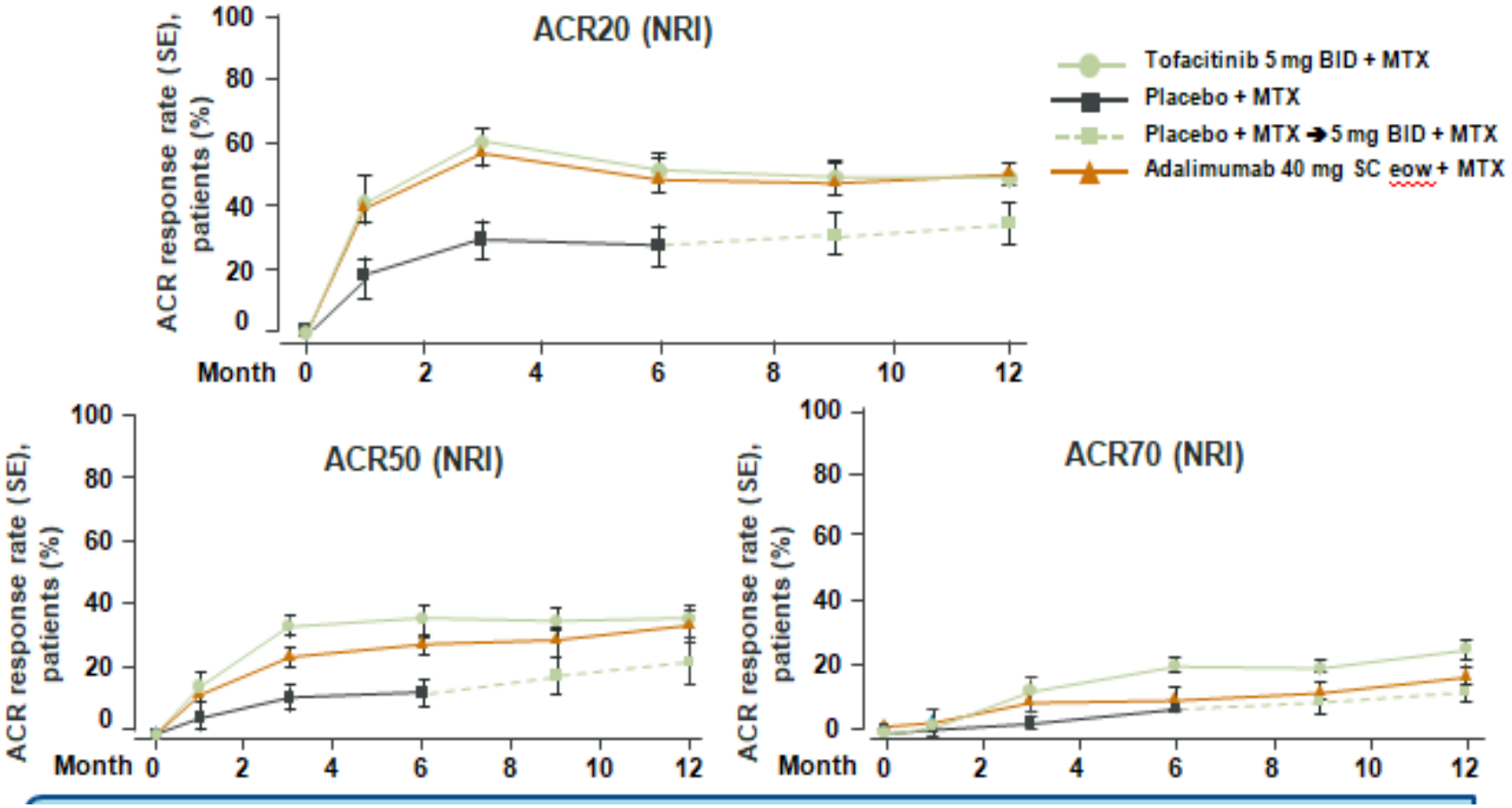
The NEW ENGLAND JOURNAL of MEDICINE

Tofacitinib or Adalimumab versus Placebo in Rheumatoid Arthritis

Ronald F. van Vollenhoven, M.D., Roy Fleischmann, M.D., Stanley Cohen, M.D., Eun Bong Lee, M.D., Ph.D., Juan A. García Meijide, M.D., Sylke Wagner, M.D., Sarka Forejtova, M.D., Samuel H. Zwillich, M.D., David Gruben, Ph.D., Tamas Koncz, M.D., Gene V. Wallenstein, Ph.D., Sriram Krishnaswami, Ph.D., John D. Bradley, M.D., and Bethanie Wilkinson, Ph.D., for the ORAL Standard Investigators*

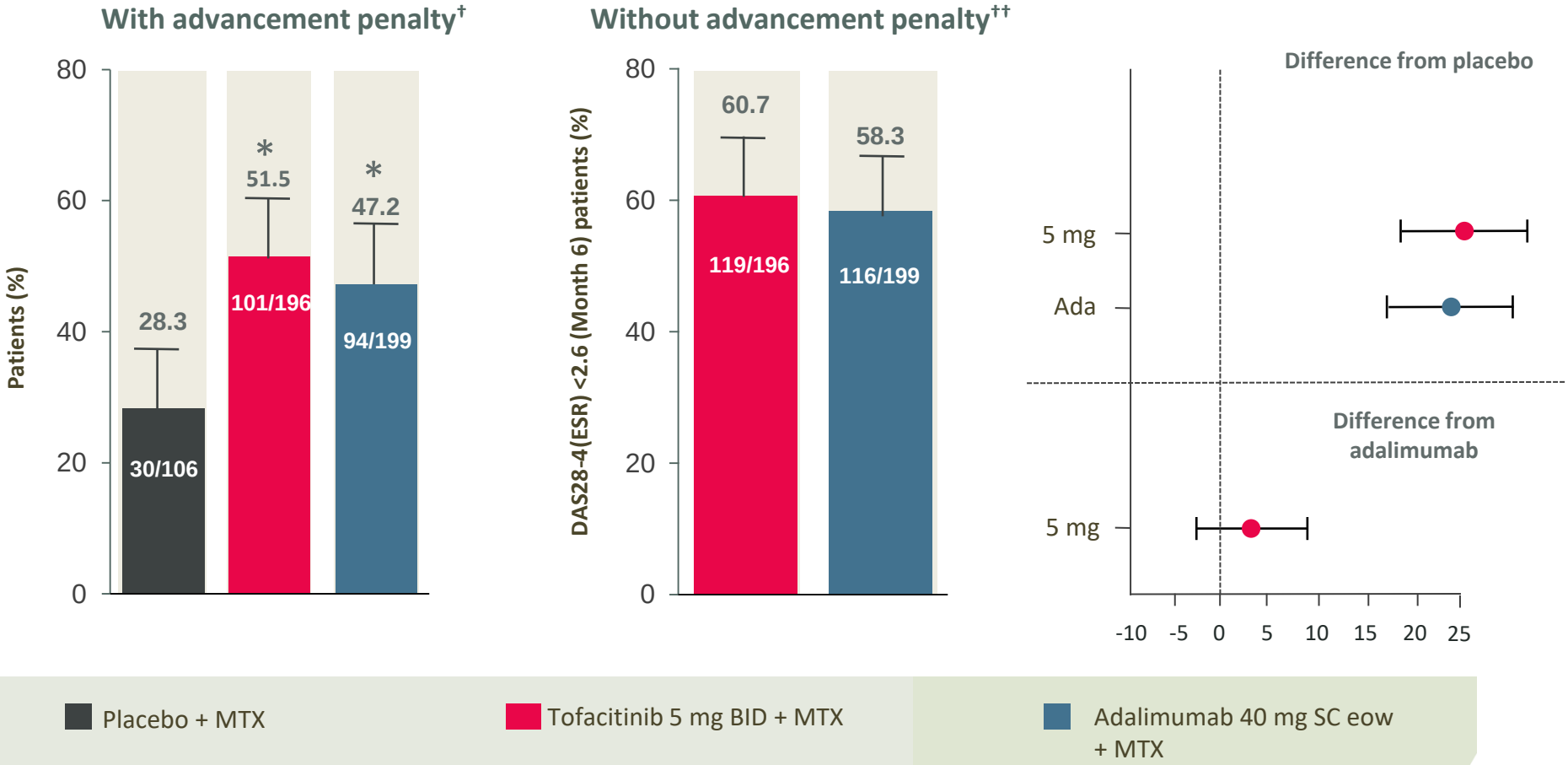
N Engl J Med. 2012 Aug 9;367(6):508-19. doi: 10.1056/NEJMoa1112072.

Phase 3 study 717 patients who were receiving stable doses of methotrexate were randomly assigned to 5 mg of tofacitinib twice daily, 10 mg of tofacitinib twice daily, 40 mg of adalimumab once every 2 weeks, or placebo



Impact of NRI with advancement penalty on ACR 20 response rates

ORAL Standard ACR20 (NRI) at month 6



*p≤0.001 vs placebo.
†Primary analysis: NRI (with advancement penalty)
†† Actual response rates at Month 6 for active treatment groups, not penalised for lack of efficacy at Month 3.

van Vollenhoven RF, et al. *N Engl J Med*. 2012;367:508-519, Supplm.

ACR, American College of Rheumatology; BID, twice-daily; DAS28-4(ESR), Disease Activity Score for 28 joints, erythrocyte sedimentation rate; eow, every 2 weeks; MTX, methotrexate; NRI, non-responder imputation; SC, subcutaneous.

This study was not designed for non-inferiority/superiority comparisons between tofacitinib and adalimumab

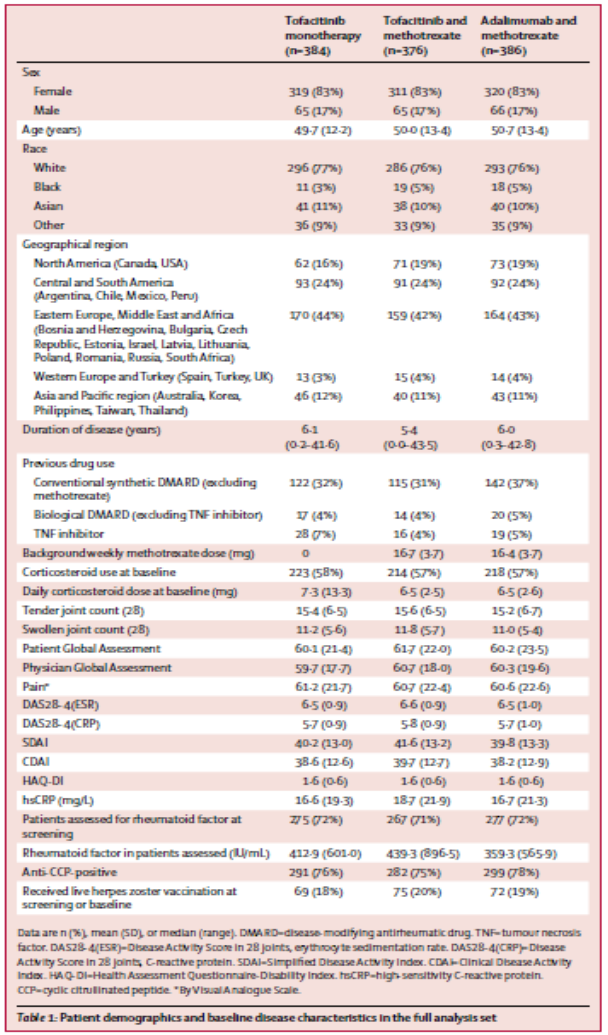
Lancet. 2017 Jul 29;390(10093):457-468. doi: 10.1016/S0140-6736(17)31618-5. Epub 2017 Jun 16.

Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial.

Fleischmann R[1], Mysler E[2], Hall S[3], Kivitz AJ[4], Moots RJ[5], Luo Z[6], DeMasi R[7], Soma K[8], Zhang R[9], Takiya L[7], Tatulych S[8], Mojcik C[9], Krishnaswami S[8], Menon S[8], Smolen JS[10]; ORAL Strategy investigators.

1152 RA patients from 194 centers in 25 countries, moderate to severe RA, unresponsive to csDMARS and bDMARSD

	TOFA monotherapy n=384	TOFA + MTX n=376	ADA+MTX n=386
DAS28 (ESR)	6.5 (0.9)	6.6(0.8)	6.6(0.9)
Anti-CCP	291 (76%)	282 (75%)	299 (78%)
MTX (mg/week)	0	16,2	16,4
Corticosteroid (5-10mg/day)	223 (58%)	214 (57%)	218 (57%)
Cs DMARD (excluding MTX)	122 (32%)	115 (31%)	142 (37%)
TNF inhibitor	28 (7%)	16 (4%)	19 (5%)
Other bDMARDS	17 (4%)	14 (4%)	20 (5%)
Herpes zoster vaccination	69 (18%)	75 (20%)	72 (19%)

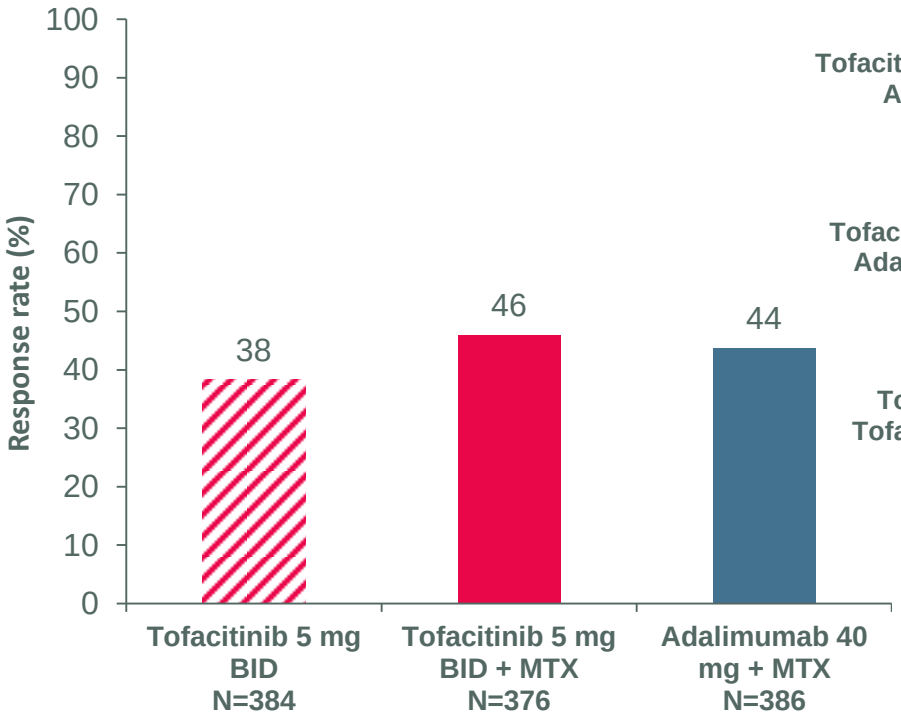


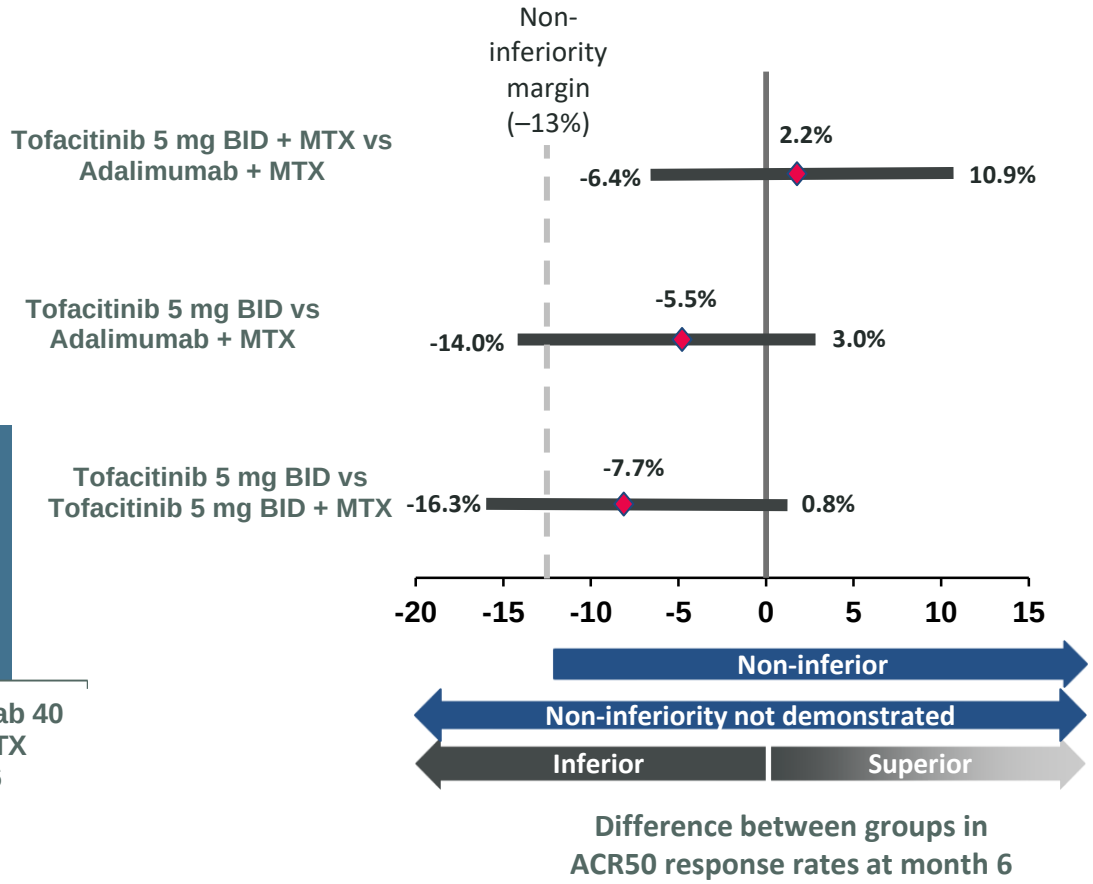
	Tofacitinib monotherapy (n=384)	Tofacitinib and methotrexate (n=376)	Adalimumab and methotrexate (n=386)
Sex			
Female	319 (83%)	311 (83%)	320 (83%)
Male	65 (17%)	65 (17%)	66 (17%)
Age (years)	49·7 (12·2)	50·0 (13·4)	50·7 (13·4)
Race			
White	296 (77%)	286 (76%)	293 (76%)
Black	11 (3%)	19 (5%)	18 (5%)
Asian	41 (11%)	38 (10%)	40 (10%)
Other	36 (9%)	33 (9%)	35 (9%)
Geographical region			
North America (Canada, USA)	62 (16%)	71 (19%)	73 (19%)
Central and South America (Argentina, Chile, Mexico, Peru)	93 (24%)	91 (24%)	92 (24%)
Eastern Europe, Middle East and Africa (Bosnia and Herzegovina, Bulgaria, Czech Republic, Estonia, Israel, Latvia, Lithuania, Poland, Romania, Russia, South Africa)	170 (44%)	159 (42%)	164 (43%)
Western Europe and Turkey (Spain, Turkey, UK)	13 (3%)	15 (4%)	14 (4%)
Asia and Pacific region (Australia, Korea, Philippines, Taiwan, Thailand)	46 (12%)	40 (11%)	43 (11%)
Duration of disease (years)	6·1 (0·2–41·6)	5·4 (0·0–43·5)	6·0 (0·3–42·8)
Previous drug use			
Conventional synthetic DMARD (excluding methotrexate)	122 (32%)	115 (31%)	142 (37%)
Biological DMARD (excluding TNF inhibitor)	17 (4%)	14 (4%)	20 (5%)
TNF inhibitor	28 (7%)	16 (4%)	19 (5%)
Background weekly methotrexate dose (mg)	0	16·7 (3·7)	16·4 (3·7)
Corticosteroid use at baseline	223 (58%)	214 (57%)	218 (57%)
Daily corticosteroid dose at baseline (mg)	7·3 (13·3)	6·5 (2·5)	6·5 (2·6)
Tender joint count (28)	15·4 (6·5)	15·6 (6·5)	15·2 (6·7)
Swollen joint count (28)	11·2 (5·6)	11·8 (5·7)	11·0 (5·4)
Patient Global Assessment	60·1 (21·4)	61·7 (22·0)	60·2 (23·5)
Physician Global Assessment	59·7 (17·7)	60·7 (18·0)	60·3 (19·6)
Pain*	61·2 (21·7)	60·7 (22·4)	60·6 (22·6)
DAS28-4(ESR)	6·5 (0·9)	6·6 (0·9)	6·5 (1·0)
DAS28-4(CRP)	5·7 (0·9)	5·8 (0·9)	5·7 (1·0)
SDAI	40·2 (13·0)	41·6 (13·2)	39·8 (13·3)
CDAI	38·6 (12·6)	39·7 (12·7)	38·2 (12·9)
HAQ-DI	1·6 (0·6)	1·6 (0·6)	1·6 (0·6)
hsCRP (mg/L)	16·6 (19·3)	18·7 (21·9)	16·7 (21·3)
Patients assessed for rheumatoid factor at screening	275 (72%)	267 (71%)	277 (72%)
Rheumatoid factor in patients assessed (IU/mL)	412·9 (601·0)	439·3 (896·5)	359·3 (565·9)
Anti-CCP-positive	291 (76%)	282 (75%)	299 (78%)
Received live herpes zoster vaccination at screening or baseline	69 (18%)	75 (20%)	72 (19%)

Data are n (%), mean (SD), or median (range). DMARD=disease-modifying antirheumatic drug. TNF=tumour necrosis factor. DAS28-4(ESR)=Disease Activity Score in 28 joints, erythrocyte sedimentation rate. DAS28-4(CRP)=Disease Activity Score in 28 joints, C-reactive protein. SDAI=Simplified Disease Activity Index. CDAI=Clinical Disease Activity Index. HAQ-DI=Health Assessment Questionnaire-Disability Index. hsCRP=high-sensitivity C-reactive protein. CCP=cyclic citrullinated peptide. *By Visual Analogue Scale.

Table 1: **Patient demographics and baseline disease characteristics in the full analysis set**

ORAL Strategy primary endpoint: ACR50 at Month 6

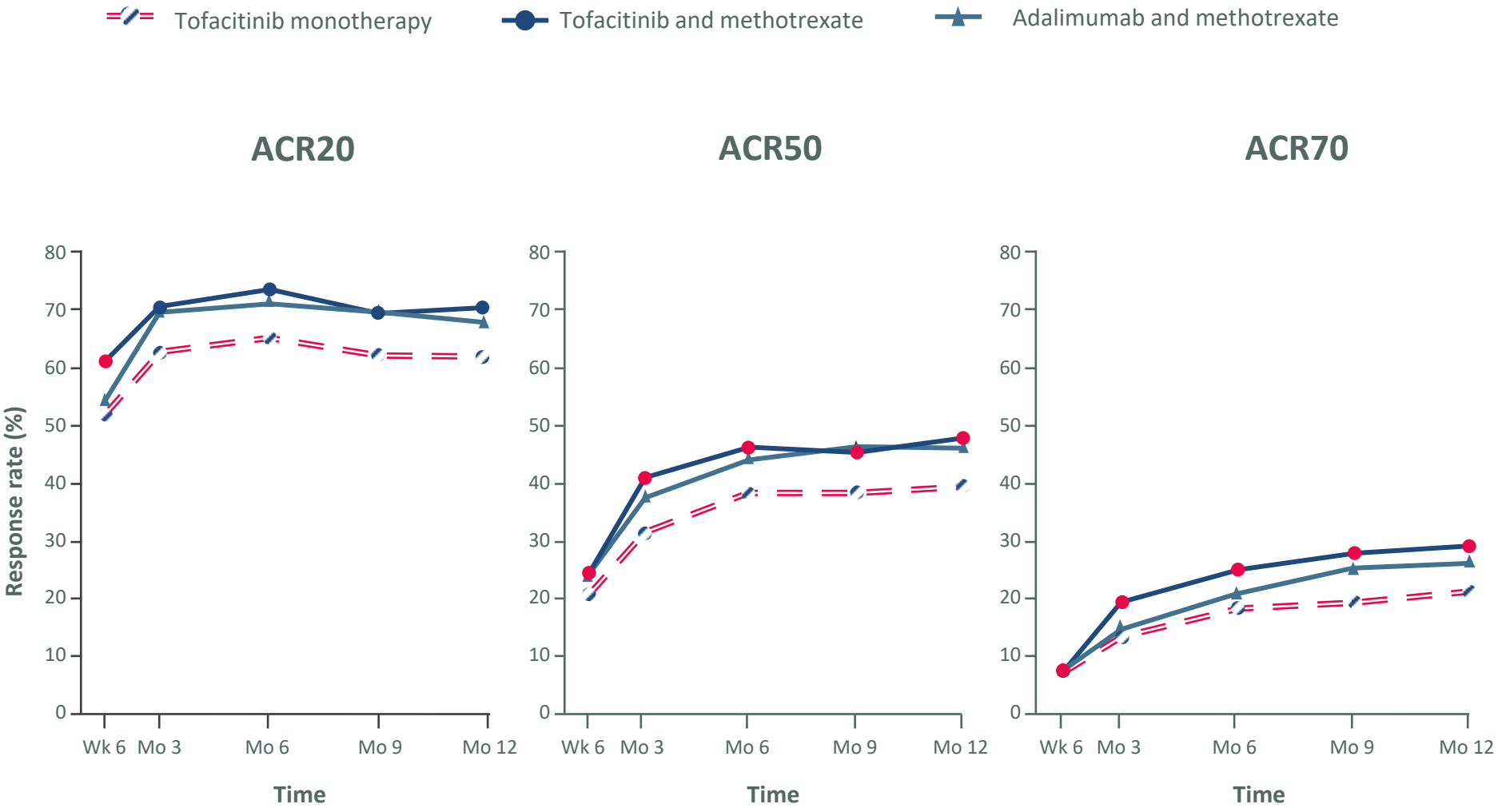




ACR50, 50% improvement in American College of Rheumatology response criteria; BID, twice daily; MTX, methotrexate.

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.

ORAL STARATEGY: SAFETY ISSUES

Δεν εμφανίστηκαν μη αναμενόμενες ανεπιθύμητες ενέργειες

	Tofacitinib monotherapy (n=384)	Tofacitinib and methotrexate (n=376)	Adalimumab and methotrexate (n=386)
Total number of adverse events*	598	652	620
Patients with adverse events	226 (59%)	231 (61%)	253 (66%)
Patients with treatment-related adverse events	101 (26%)	111 (30%)	133 (35%)
Patients with serious adverse events	35 (9%)	27 (7%)	24 (6%)
Patients discontinuing due to adverse events	23 (6%)	26 (7%)	37 (10%)
Patients with severe adverse events (defined by the investigator)	24 (6%)	17 (5%)	23 (6%)
Deaths†	2 (1%)	0	0
Adverse events of special interest			
Serious infections	6 (2%)	10 (3%)	6 (2%)
Herpes zoster (serious and non-serious)	4 (1%)	8 (2%)	6 (2%)
Herpes zoster (serious and non-serious) in patients who were vaccinated	1/69 (1%)	2/75 (3%)	0/72 (0%)
Opportunistic infections (excluding tuberculosis)	2 (1%)	1 (<1%)	2 (1%)
Tuberculosis	0	2 (1%)	0
MACE (non-fatal)	0	0	2 (1%)
Malignancy (excluding non-melanoma skin cancer)	1 (<1%)	0	0
Non-melanoma skin cancer	2 (1%)	0	1 (<1%)

Data are n, n (%), or n/N (%). MACE=major adverse cardiovascular event (includes non-fatal myocardial infarction, fatal cardiovascular event, and non-fatal cerebrovascular accident). *Patients could have had more than one adverse event. †One patient died of urosepsis; one patient died of atypical pneumonia and respiratory distress syndrome associated with influenza A.

Table 3: Summary of adverse events, serious adverse events, and discontinuations in the safety analysis set

ORAL STRATEGY: CONCLUSIONS

Ασθενείς με μετρίου σοβαρού βαθμού PA με ανεπαρκή ανταπόκριση στη MTX η προσθήκη tofacitinib είναι εξίσου αποτελεσματική με την προσθήκη adalimumab προκειμένου να επιτευχθούν οι θεραπευτικοί στόχοι σε ότι αφορά τη μείωση της ενεργότητας της νόσου και τη λειτουργική κατάσταση των ασθενών

Ασθενείς με μετρίου σοβαρού βαθμού PA με ανεπαρκή ανταπόκριση στη MTX η αλλαγή σε μονοθεραπεία με tofacitinib δε φαίνεται να οδηγεί στα επιθυμητά θεραπευτικά αποτελέσματα

Η χορήγηση tofacitinib ως μονοθεραπεία δε μπορεί να αποκλειστεί σε ασθενείς που δε μπορούν να λάβουν μεθοτρεξάτη

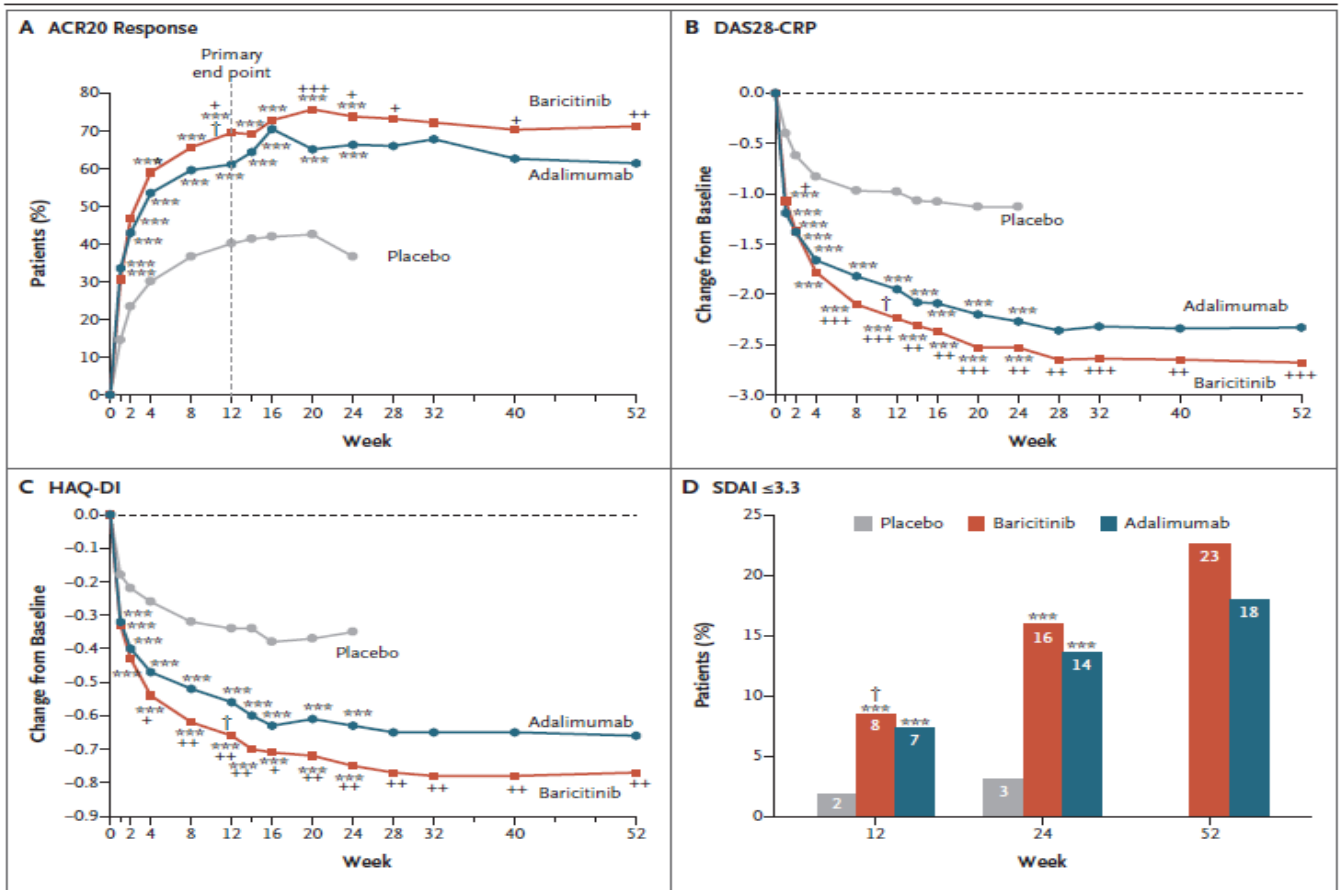
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis

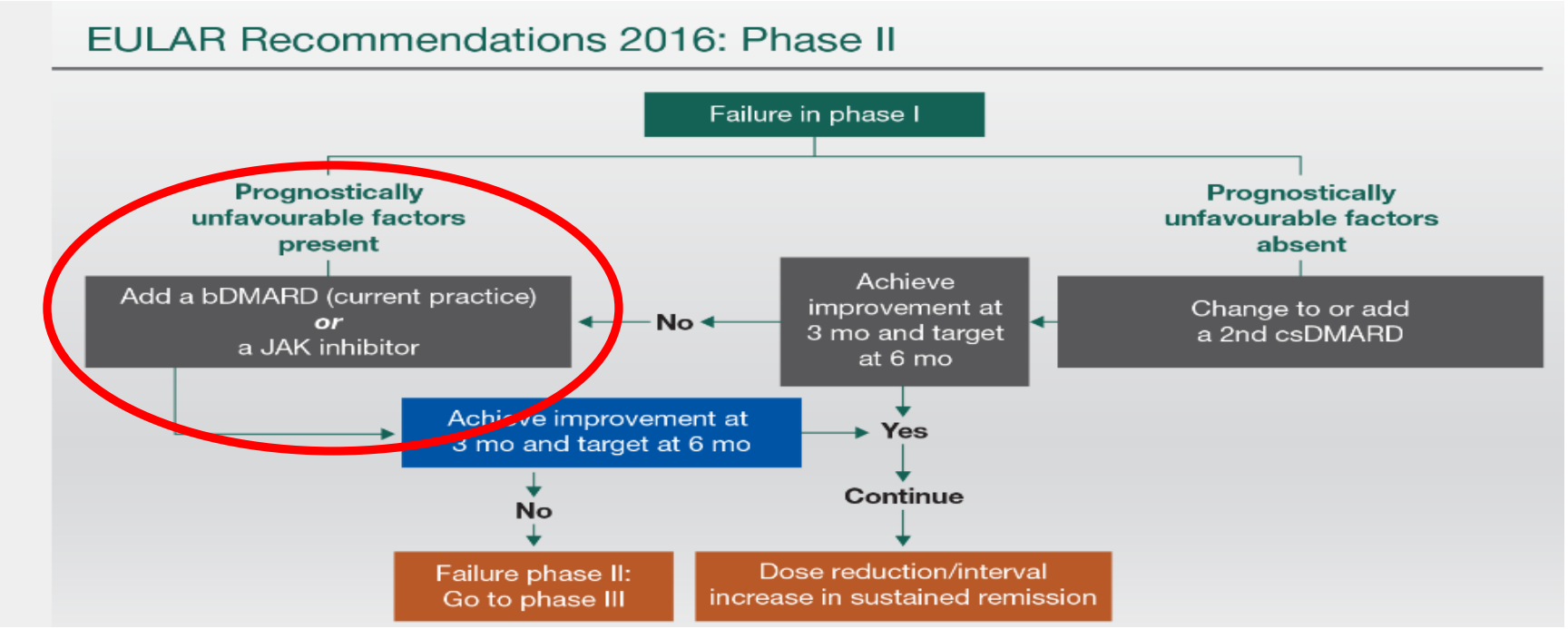
Peter C. Taylor, M.D., Ph.D., Edward C. Keystone, M.D., Désirée van der Heijde, M.D., Ph.D., Michael E. Weinblatt, M.D., Liliana del Carmen Morales, M.D., Jaime Reyes Gonzaga, M.D., Sergey Yakushin, M.D., Taeko Ishii, M.D., Kahaku Emoto, M.D., Scott Beattie, Ph.D., Vipin Arora, Ph.D., Carol Gaich, Pharm.D., Terence Rooney, M.D., Douglas Schlichting, R.N., Ph.D., William L. Macias, M.D., Ph.D., Stephanie de Bono, M.D., Ph.D., and Yoshiya Tanaka, M.D., Ph.D.

N Engl J Med 2017;376:652-62.



EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update

Josef S Smolen,[1,2] Robert Landewé,[3,4] Johannes Bijlsma,[5] Gerd Burmester,[6] Katerina Chatzidionysiou,[7] Maxime Dougados,[8] Jackie Nam,[9] Sofia Ramiro,[10] Marieke Voshaar,[11] Ronald van Vollenhoven,[3,4] Daniel Aletaha,[1] Martin Aringer,[12] Maarten Boers,[13] Chris D Buckley,[14] Frank Buttgereit,[6] Vivian Bykerk,[15,16] Mario Cardiel,[17] Bernard Combe,[18] Maurizio Cutolo,[19] Yvonne van Eijk-Hustings,[20] Paul Emery,[10] Axel Finckh,[21] Cem Gabay,[21] Juan Gomez-Reino,[22] Laure Gossec,[23] Jacques-Eric Gottenberg,[24] Johanna M W Hazes,[25] Tom Huizinga,[11] Meghna Jani,[26] Dmitry Karateev,[27] Marios Kouloumas,[28,29] Tore Kvien,[30] Zhanguo Li,[31] Xavier Mariette,[32] Iain McInnes,[33] Eduardo Mysler,[34] Peter Nash,[35] Karel Pavelka,[36] Gyula Poór,[37] Christophe Richez,[38] Piet van Riel,[39] Andrea Rubbert-Roth,[40] Kenneth Saag,[41] Jose da Silva,[42] Tanja Stamm,[43] Tsutomu Takeuchi,[44] René Westhovens,[45,46] Maarten de Wit,[47] Désirée van der Heijde[10]



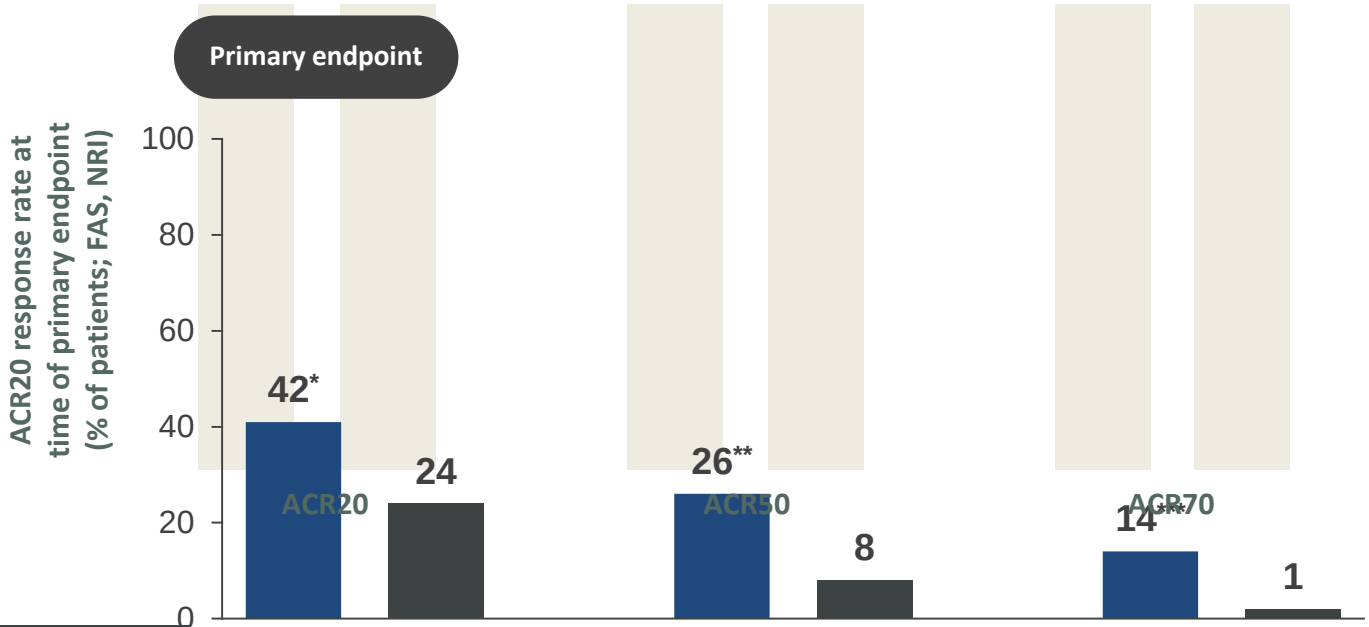
Tofacitinib in bDMARD-IR patient populations

Lancet. 2013 Feb 9;381(9865):451-60. doi: 10.1016/S0140-6736(12)61424-X. Epub 2013 Jan 5.

Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial.

Burmester GR[1], Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, Gruben D, Wallenstein G, Krishnaswami S, Zwillich SH, Koncz T, Soma K, Bradley J, Mebus C; ORAL Step investigators.

399 patients with inadequate response to tumour necrosis factor inhibitors (TNFi) (1/3 of patients treated with 2 or more TNFi)



	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)

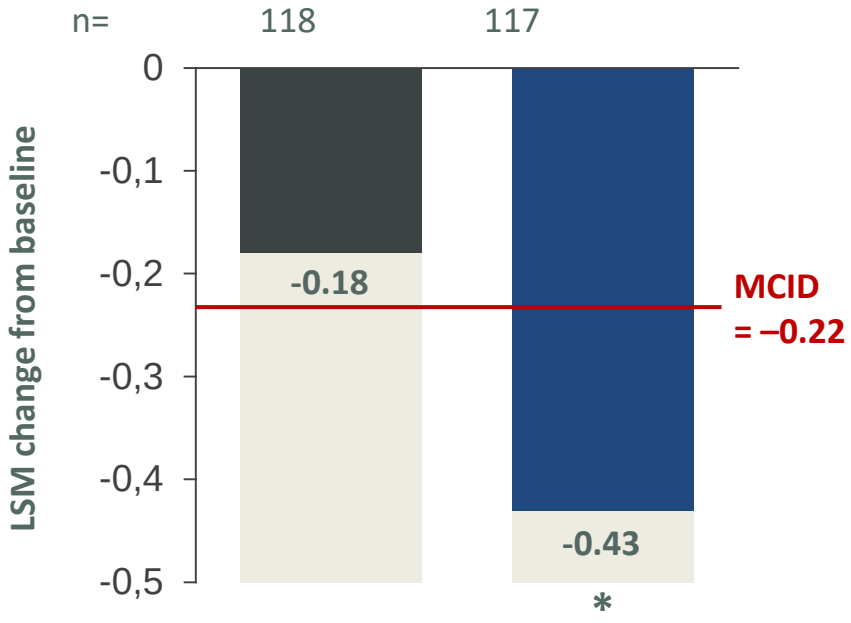
Placebo + MTX or nonbiologic DMARDs (N=131)

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

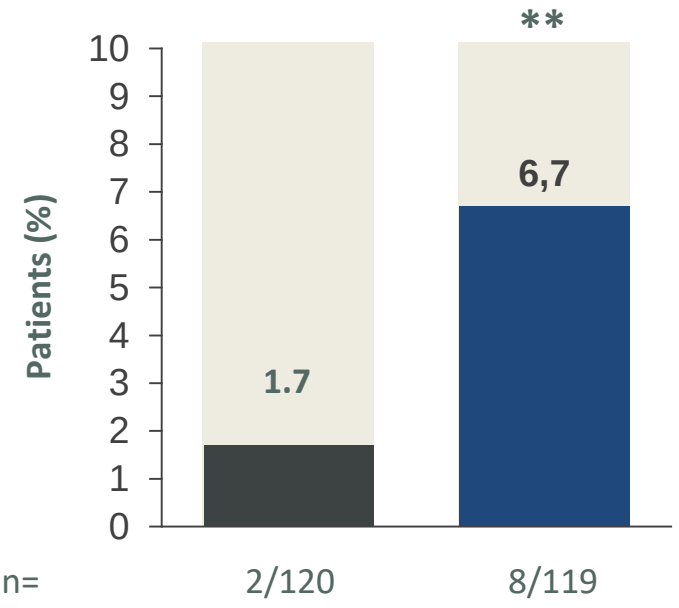
p=0.0024; **p<0.0001; ***p<0.001 vs placebo + MTX
ACR, American college rheumatology; DMARD, disease modifying anti-rheumatic drug; FAS, full analysis set; MTX, methotrexate; NRI, nonresponder imputation;
TNF-IR, tumor necrosis factor inadequate responders;

HAQ-DI and DAS28-4(ESR)<2.6 in TNF-IR patients on tofacitinib

HAQ-DI improvement at Month 3 (FAS, longitudinal model)



DAS28-4(ESR)<2.6 At Month 3



Tofacitinib 5 mg BID + MTX Placebo + MTX

*p<0.0001; **p≤0.05 vs placebo at month 3 (unadjusted).
BID, twice daily; DAS, Disease Activity Score; DMARD, disease modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-Disability Index; LSM, least squares mean; MCID, minimum clinically important difference; TNF-IR, tumor necrosis factor inadequate responders

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

Poster Presentations

Rheumatoid arthritis - non biologic treatment

THU0185 Comparison of tofacitinib safety and efficacy in rheumatoid arthritis patients with inadequate response to conventional synthetic dmards, or to one or more biological dmards

C Charles-Schoeman[1], J Kremer[2], S Krishnaswami[3], K Soma[4], J Geier[4], R Zhang[4], S Strengholt[4], G Burmester[5]

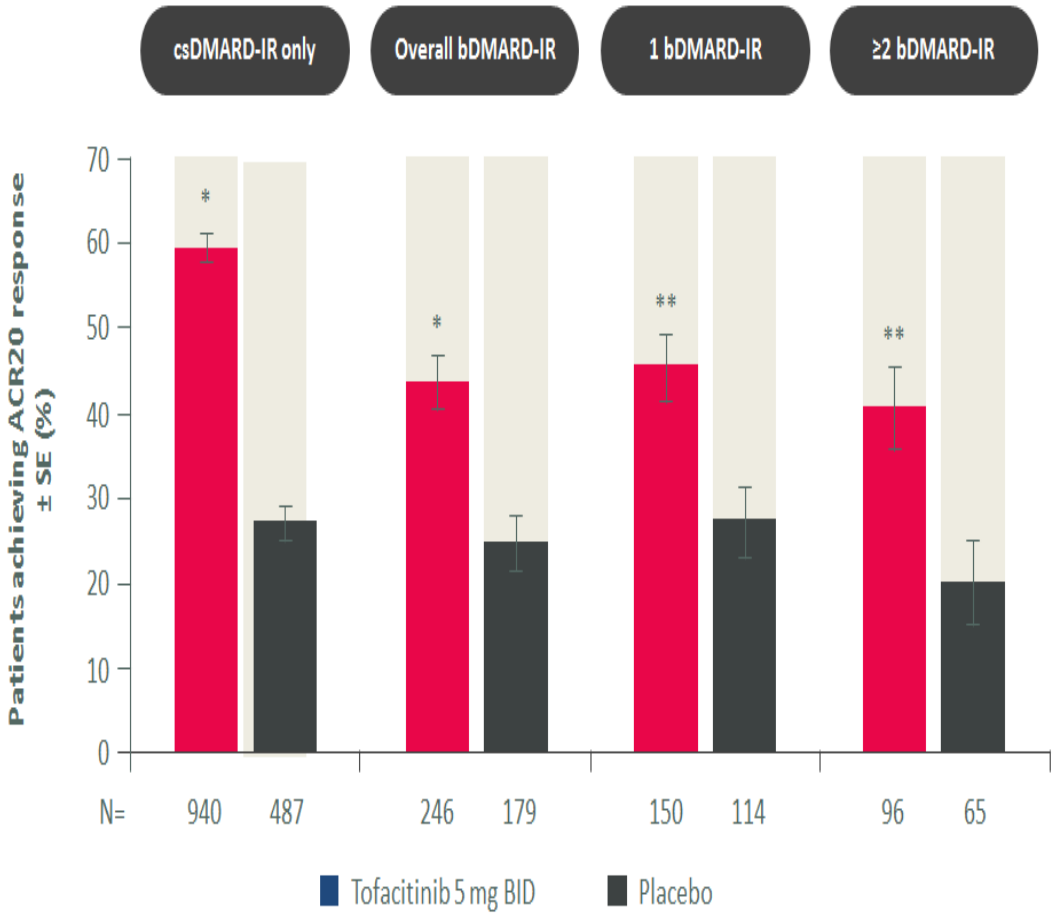
Table. Selected safety and efficacy outcomes by prior failed treatment.

		csDMARD-IR-only	Overall bDMARD-IR	1 bDMARD-IR	≥2 bDMARD-IRs
P2/P3 RCT population (0–24 months);[a] incidence rate (pts with event/100 pt-years) (95% CI)					
SAEs	Tofacitinib 5 mg BID	12.4 (10.3, 14.8)	12.6 (7.8, 19.3)	12.7 (6.8, 21.7)	12.6 (5.4, 24.7)
	Tofacitinib 10 mg BID	9.7 (7.9, 11.8)	12.5 (7.6, 19.3)	12.1 (6.3, 21.1)	13.1 (5.6, 25.7)
	Placebo	11.5 (7.6, 16.8)	20.5 (9.8, 37.7)	19.8 (7.3, 43.1)	21.6 (5.9, 55.4)
SIs	Tofacitinib 5 mg BID	3.4 (2.4, 4.7)	1.7 (0.4, 5.0)	0.9 (0.0, 5.2)	2.9 (0.4, 10.6)
	Tofacitinib 10 mg BID	3.4 (2.4, 4.7)	3.0 (1.0, 7.1)	3.0 (0.6, 8.7)	3.2 (0.4, 11.4)
	Placebo	1.7 (0.5, 4.3)	4.1 (0.5, 14.7)	3.3 (0.1, 18.3)	5.4 (0.1, 30.1)
HZ	Tofacitinib 5 mg BID	3.9 (2.8, 5.3)	5.3 (2.4, 10.0)	2.8 (0.6, 8.3)	9.1 (3.4, 19.9)
	Tofacitinib 10 mg BID	4.8 (3.5, 6.3)	6.3 (3.0, 11.6)	6.2 (2.3, 13.4)	6.6 (1.8, 16.8)
	Placebo	2.6 (0.9, 5.5)	0.0 (0.0, 7.5)	0.0 (0.0, 12.1)	0.0 (0.0, 19.8)
All RA population (up to 96 months); incidence rate (pts with event/100 pt-years) (95% CI)					
SAEs	Tofacitinib 5 mg BID	9.7 (8.9, 10.6)	14.8 (11.4, 18.9)	15.9 (11.5, 21.3)	12.8 (7.7, 20.0)
	Tofacitinib 10 mg BID	9.7 (9.0, 10.4)	11.6 (10.0, 13.3)	11.8 (9.8, 14.0)	11.3 (8.8, 14.3)
	All tofacitinib doses	9.7 (9.2, 10.2)	12.2 (10.8, 13.8)	12.6 (10.8, 14.7)	11.6 (9.3, 14.3)
SIs	Tofacitinib 5 mg BID	2.9 (2.5, 3.4)	4.5 (2.8, 6.8)	4.7 (2.7, 7.8)	4.1 (1.6, 8.4)
	Tofacitinib 10 mg BID	2.7 (2.3, 3.1)	3.5 (2.7, 4.4)	4.0 (2.9, 5.3)	2.6 (1.5, 4.1)
	All tofacitinib doses	2.8 (2.5, 3.1)	3.7 (2.9, 4.5)	4.1 (3.2, 5.3)	2.9 (1.9, 4.2)
HZ	Tofacitinib 5 mg BID	3.7 (3.2, 4.3)	4.8 (3.0, 7.2)	3.6 (1.8, 6.4)	7.1 (3.5, 12.7)
	Tofacitinib 10 mg BID	4.2 (3.8, 4.7)	4.4 (3.5, 5.5)	4.1 (3.0, 5.5)	4.9 (3.3, 7.0)
	All tofacitinib doses	4.0 (3.7, 4.4)	4.5 (3.6, 5.5)	4.0 (3.0, 5.2)	5.4 (3.9, 7.2)
Efficacy endpoints in the P3 RCT population at Month 3; % of pts					
ACR20	Tofacitinib 5 mg BID	59.4***	43.5***	45.3*	40.6*
	Tofacitinib 10 mg BID	65.4***	50.6***	50.6***	50.6***
	Placebo	27.1	24.6	27.2	20.0
DAS28-4(ESR) ≤3.2	Tofacitinib 5 mg BID	15.9***	12.7*	11.9	14.0*
	Tofacitinib 10 mg BID	21.1***	15.8**	15.7*	16.5*
	Placebo	3.9	4.9	5.8	3.4

*p<0.05; **p<0.001; ***p<0.0001 vs placebo

[a]Placebo data up to 6 months only

Δ, change from baseline; BID, twice daily; bDMARD, biological disease-modifying antirheumatic drug; CI, confidence interval; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-4(ESR), Disease Activity Score in 28 joints with erythrocyte sedimentation rate; HZ, herpes zoster; IR, inadequate response; P, Phase; pts, patients; pt-years, patient-years; RA, rheumatoid arthritis; RCT, randomised controlled trial; SAE, serious adverse event; SI, serious infection



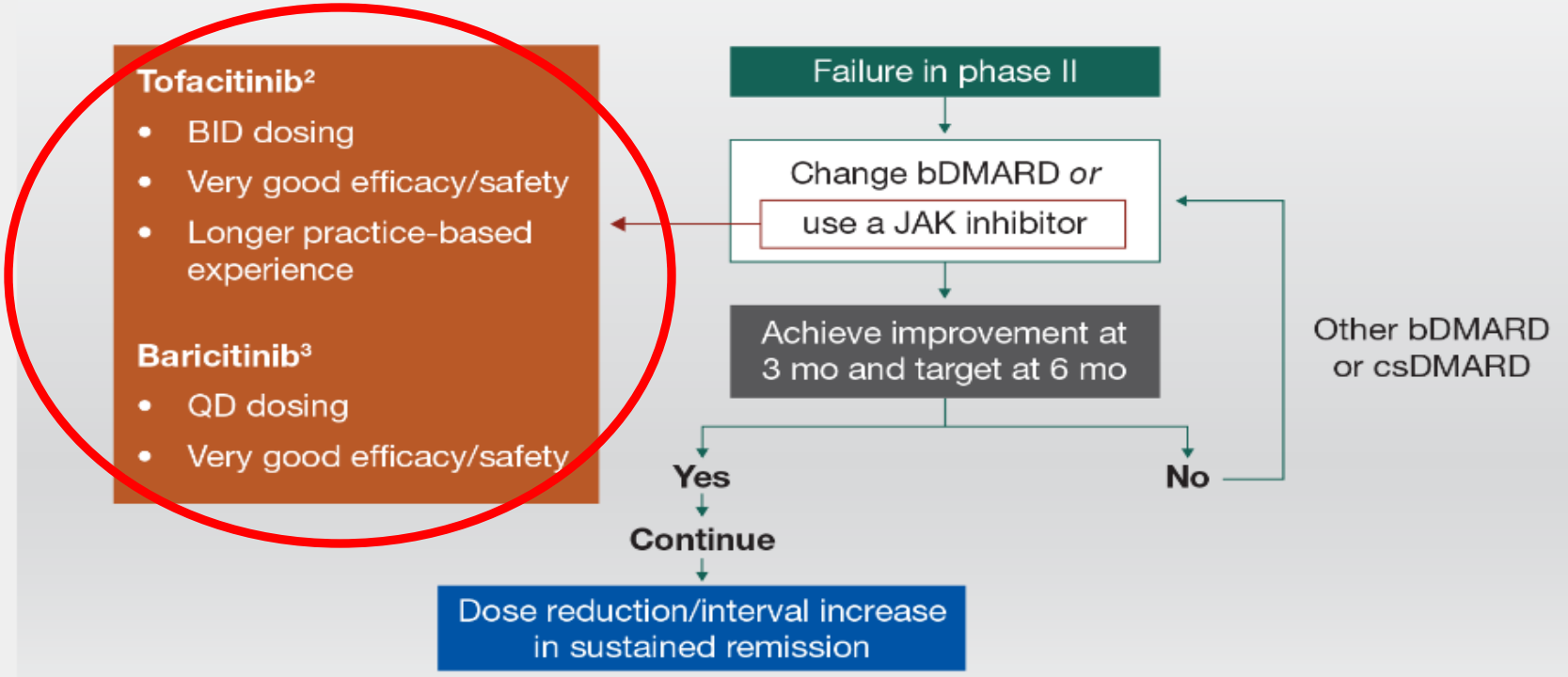
The approved dose of tofacitinib is 5 mg twice daily

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

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update

Josef S Smolen,[1,2] Robert Landewé,[3,4] Johannes Bijlsma,[5] Gerd Burmester,[6] Katerina Chatzidionysiou,[7] Maxime Dougados,[8] Jackie Nam,[9] Sofia Ramiro,[10] Marieke Voshaar,[11] Ronald van Vollenhoven,[3,4] Daniel Aletaha,[1] Martin Aringer,[12] Maarten Boers,[13] Chris D Buckley,[14] Frank Buttgereit,[6] Vivian Bykerk,[15,16] Mario Cardiel,[17] Bernard Combe,[18] Maurizio Cutolo,[19] Yvonne van Eijk-Hustings,[20] Paul Emery,[10] Axel Finckh,[21] Cem Gabay,[21] Juan Gomez-Reino,[22] Laure Gossec,[23] Jacques-Eric Gottenberg,[24] Johanna M W Hazes,[25] Tom Huizinga,[11] Meghna Jani,[26] Dmitry Karateev,[27] Marios Kouloumas,[28,29] Tore Kvien,[30] Zhanguo Li,[31] Xavier Mariette,[32] Iain McInnes,[33] Eduardo Mysler,[34] Peter Nash,[35] Karel Pavelka,[36] Gyula Poór,[37] Christophe Richez,[38] Piet van Riel,[39] Andrea Rubbert-Roth,[40] Kenneth Saag,[41] Jose da Silva,[42] Tanja Stamm,[43] Tsutomu Takeuchi,[44] René Westhovens,[45,46] Maarten de Wit,[47] Désirée van der Heijde[10]

EULAR Recommendations 2016: Phase III[1]



PRO data for tofacitinib

Significant differences from placebo at Month 3

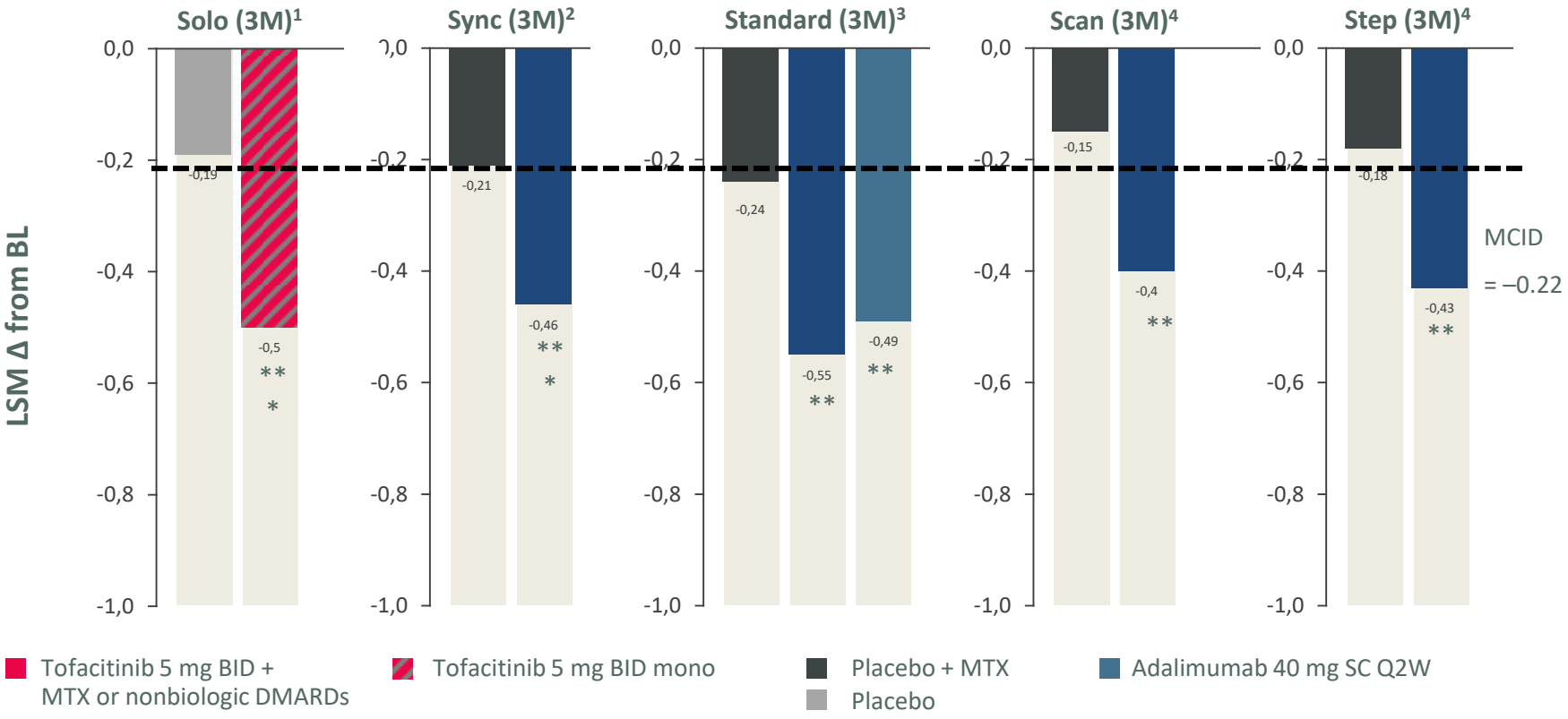
	Solo 1045 [1,2] 5 mg	Sync 1046[3] 5 mg	Standard 1064[4,5] 5 mg	Scan 1044[6,7] 5mg	Step 1032[6,8] 5 mg
Patient pain	✓	✓	✓	✓	✓
Patient global	✓	✓	✓	✓	✓
HAQ-DI	✓	✓	✓	NS*	✓
SF-36 - PCS	✓	✓	✓	✓	✓
SF-36 - MCS	✓	✓	NS	✓	✓
FACIT-fatigue	✓	✓	✓	✓	✓
MOS Sleep	NS	✓	✓	✓	NS

1. Fleischmann R et al. *N Engl J Med* 2012;367:495–507.
2. Strand V et al. *Ann Rheum Dis* 2011;70(Suppl3):88.
3. Strand V et al. *Arthritis Rheum* 2011;63 Suppl 10:2627.
4. van Vollenhoven RF et al. *N Engl J Med* 2012;367:508–19.
5. Strand V et al. *Rheumatology* (Oxford). 2016;55:1031-41.
6. Burmester GR et al. *Arthritis Rheum* 2012;64 Suppl 10:1283.
7. Clinical Trials https://clinicaltrials.gov/ct2/show/NCT00847613. Accessed 2nd February 2018
8. Strand V et al. *Arthritis Care Res* (Hoboken). 2015;67:475-83.

Significant differences between tofacitinib (5 and 10 mg BID) versus placebo/MTX at Month 3 at P <0.05. (FAS, longitudinal model). *For ORAL Scan nominal significance only due to failed primary endpoint. Grey columns indicate where the primary endpoint was not reached.

BID, twice daily; FAS, full analysis set; FACIT, functional assessment of chronic illness therapy; HAQ-DI, health assessment questionnaire disability index; MTX, methotrexate; NS, not significant; SF-36, Short Form Health Survey 36.

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

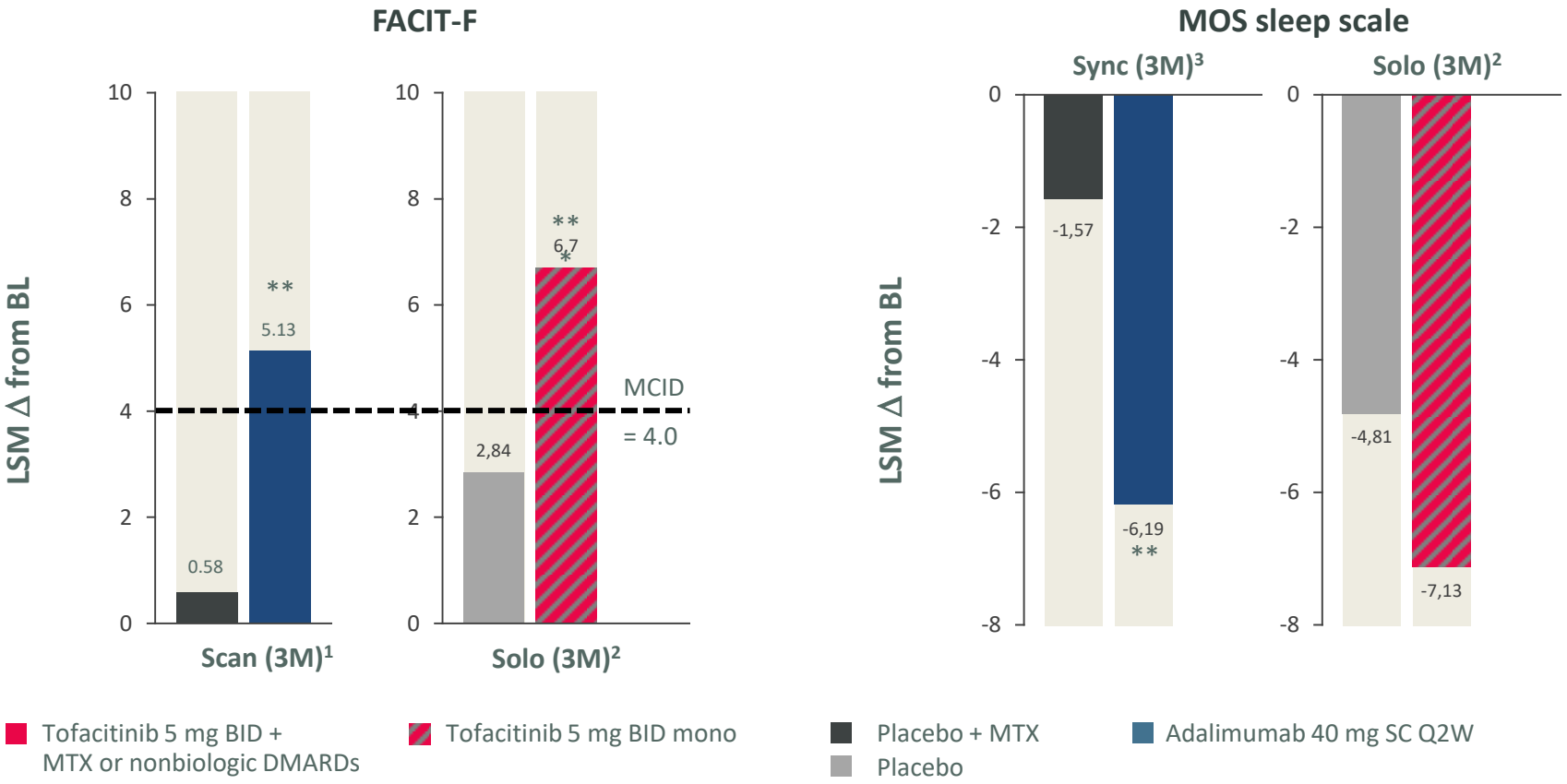


Tofacitinib produced significant decreases
in HAQ-DI scores compared with placebo and methotrexate

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

Mean change in FACIT-F and MOS sleep scale (overall sleep) from baseline in patients on tofacitinib



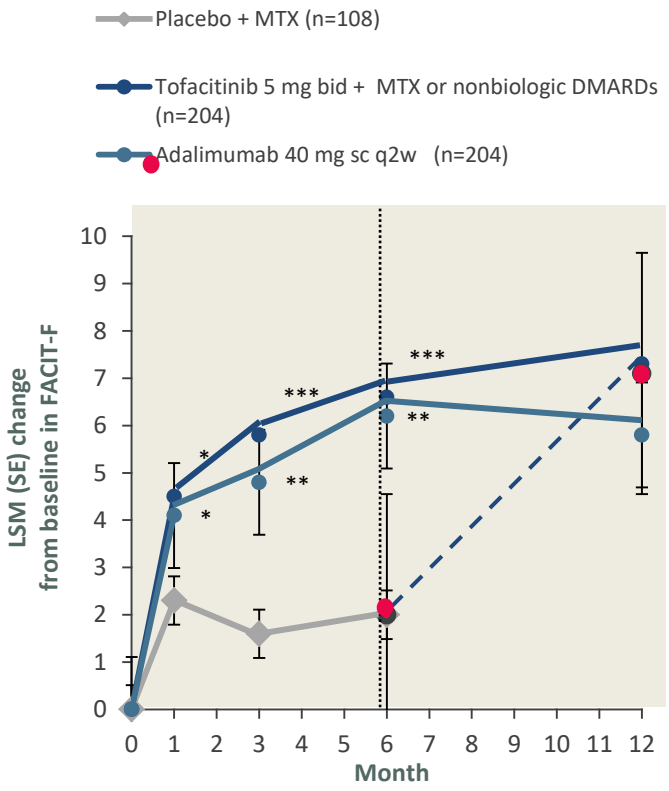
Tofacitinib produced greater improvements in fatigue and sleep compared with placebo

1. Burmester GR et al. *Arthritis Rheum* 2012;64 Suppl 10:1283;
2. Strand V et al. *Arth Res Ther* 2015;17:307;
3. Strand V et al. *Arthritis Rheum* 2011;63 Suppl 10:2627

**p<0.001; ***p<0.0001 vs placebo
BID, twice daily; BL, baseline; DMARDs, disease-modifying anti-rheumatic drugs;
FAS, Longitudinal model; FACIT-F, Functional Assessment of Chronic Illness Therapy - Fatigue; LSM, least squares mean; MCID, minimal clinically important difference; MTX, methotrexate; MOS, medical outcomes survey; Q2W, every two week; SC subcutaneous;

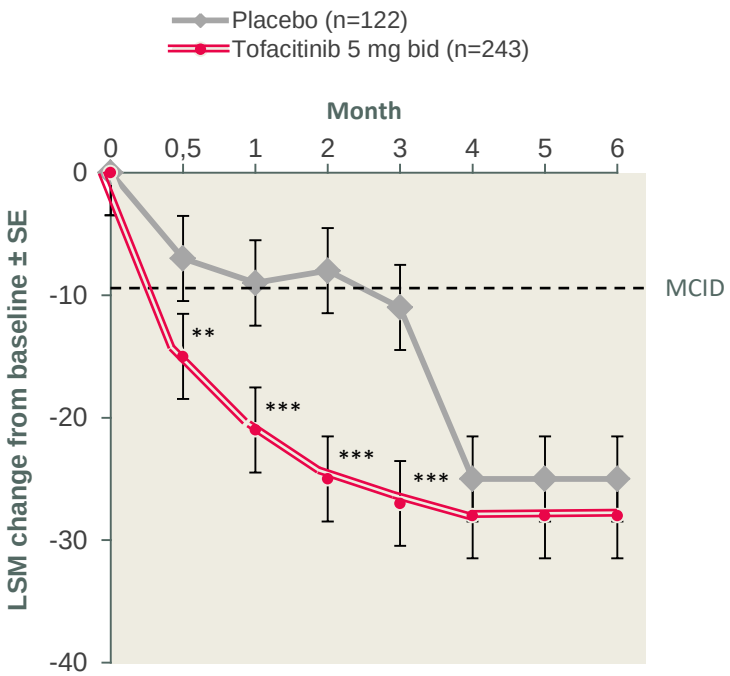
Improvement in fatigue and pain with tofacitinib treatment at month 3 compared with placebo

Fatigue



Tofacitinib combination therapy in MTX-IR patients[1,2]

Pain



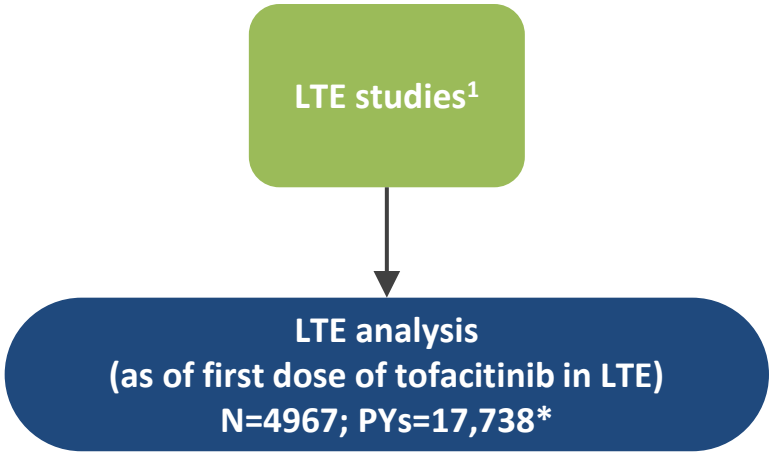
Tofacitinib monotherapy in DMARD-IR patients[3]

*P<0.05. **P<0.01. ***P<0.0001.
BID, twice daily; DMARD, disease modifying anti rheumatic drug; FACIT, functional assessment of chronic illness therapy-fatigue; IR, inadequate responder; LSM, least squares mean; MTX, methotrexate; SE, standard error

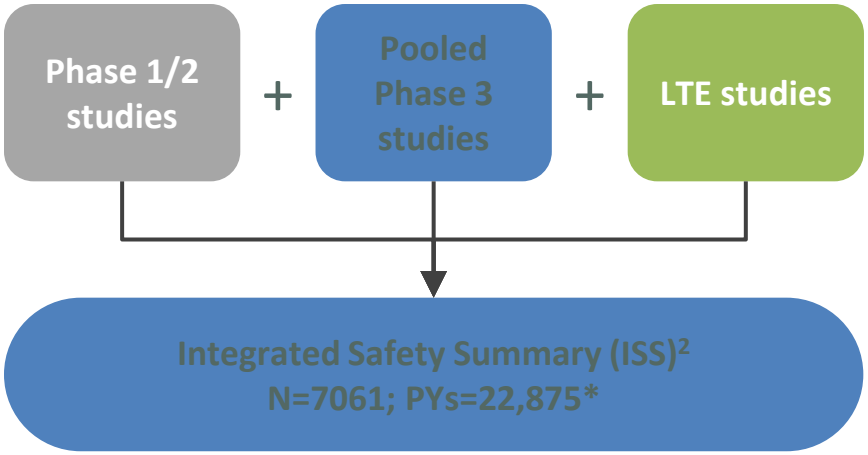
1. Strand V et al. *Rheumatology* (Oxford). 2016;55:1031-41.
2. van Vollenhoven RF, et al. *N Engl J Med*. 2012;367:508-19
3. Strand V et al. *Arthritis Res Ther*. 2015;17:307.

Tofacitinib LTE Programme

Tofacitinib long-term studies



- Efficacy, AEs, labs
- Data from two LTEs
- Tofacitinib 5 or 10 mg BID, as monotherapy or with background csDMARDs, predominantly MTX



- AEs only
- Data from RA Phase 1, 2, 3, and LTE studies
- Tofacitinib 5 mg, 10 mg and tofacitinib all populations

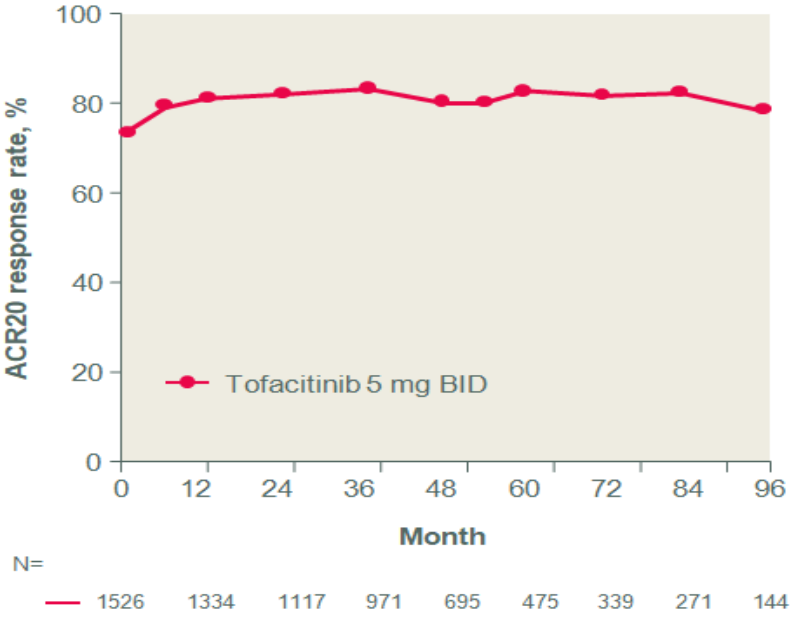
*Data cut-off: March 2017
Reasons for dose change: Safety: Dose reduction from 10 mg to 5 mg BID or temporary discontinuation of 5 mg BID. IR: Dose increase from 5 mg to 10 mg BID.
AE, adverse event; BID, twice daily; csDMARD, conventional synthetic disease-modifying antirheumatic drug; LTE, long-term extension; MTX, methotrexate; PY, patient-years; RA, rheumatoid arthritis.

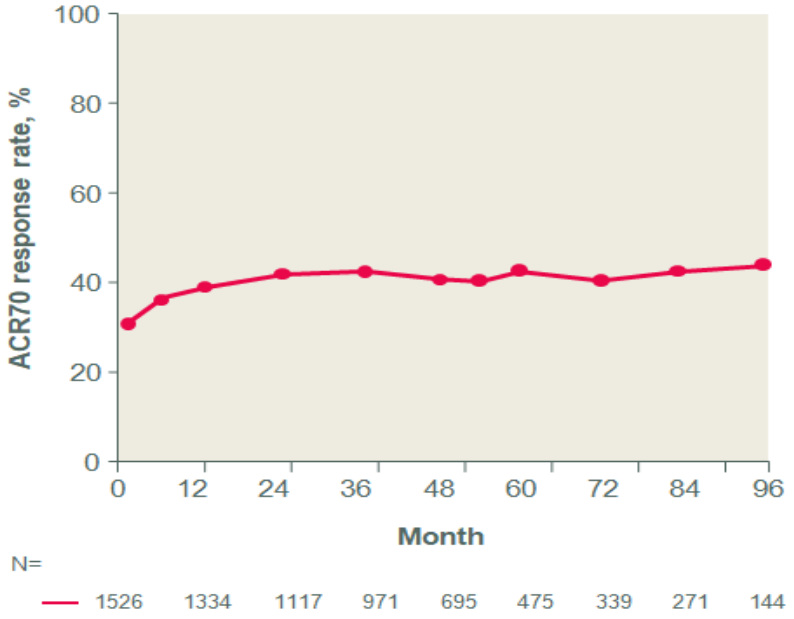
1.Wollenhaupt et al. Poster 522 presented at ACR 2017
2.Cohen et al. *Ann Rheum Dis* 2017;0:1–10

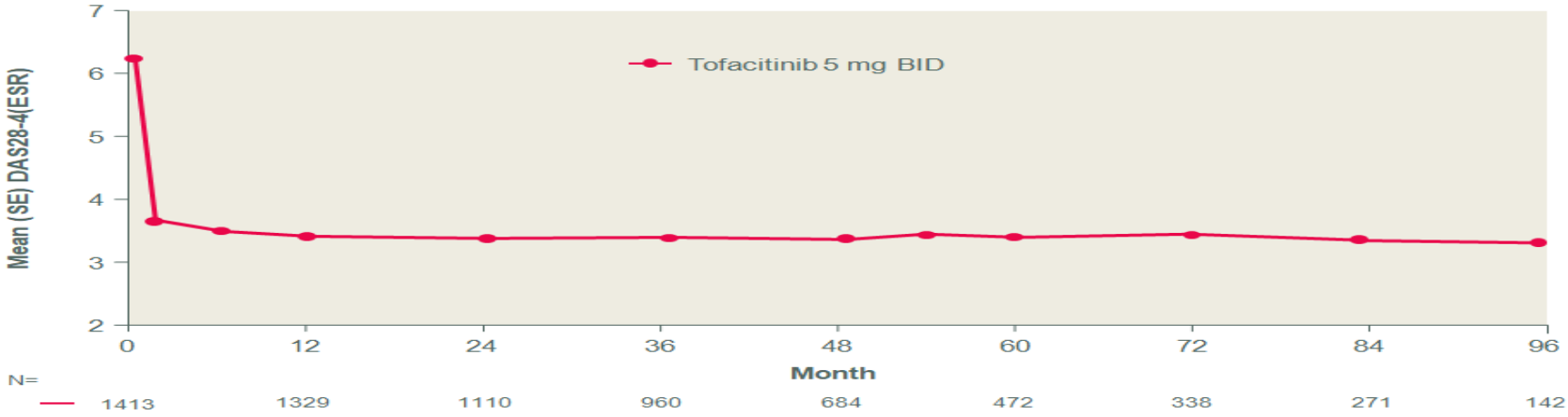
Tofacitinib, an Oral Janus Kinase Inhibitor, in the Treatment of Rheumatoid Arthritis: Safety and Efficacy in Open-Label, Long-Term Extension Studies over 9 Years

Jürgen Wollenhaupt[1], Joel Silverfield[2], Eun Bong Lee[3], Ketti Terry[4], Kenneth Kwok[5], Sander Strengholt[6], Ryan DeMasi[7] and Lisy Wang[4], [1]Schoen-Klinik Hamburg-Eilbek

4967 pts were treated (mean [max] duration: 3.5 [9.4] years). In total, 2518 pts (50.7%) discontinued (AEs: 1189 [23.9%]; insufficient clinical response: 179 [3.6%])







ACR 2017, POSTER 522

Tofacitinib and Real World Data (RWD)

Double – blinded studies

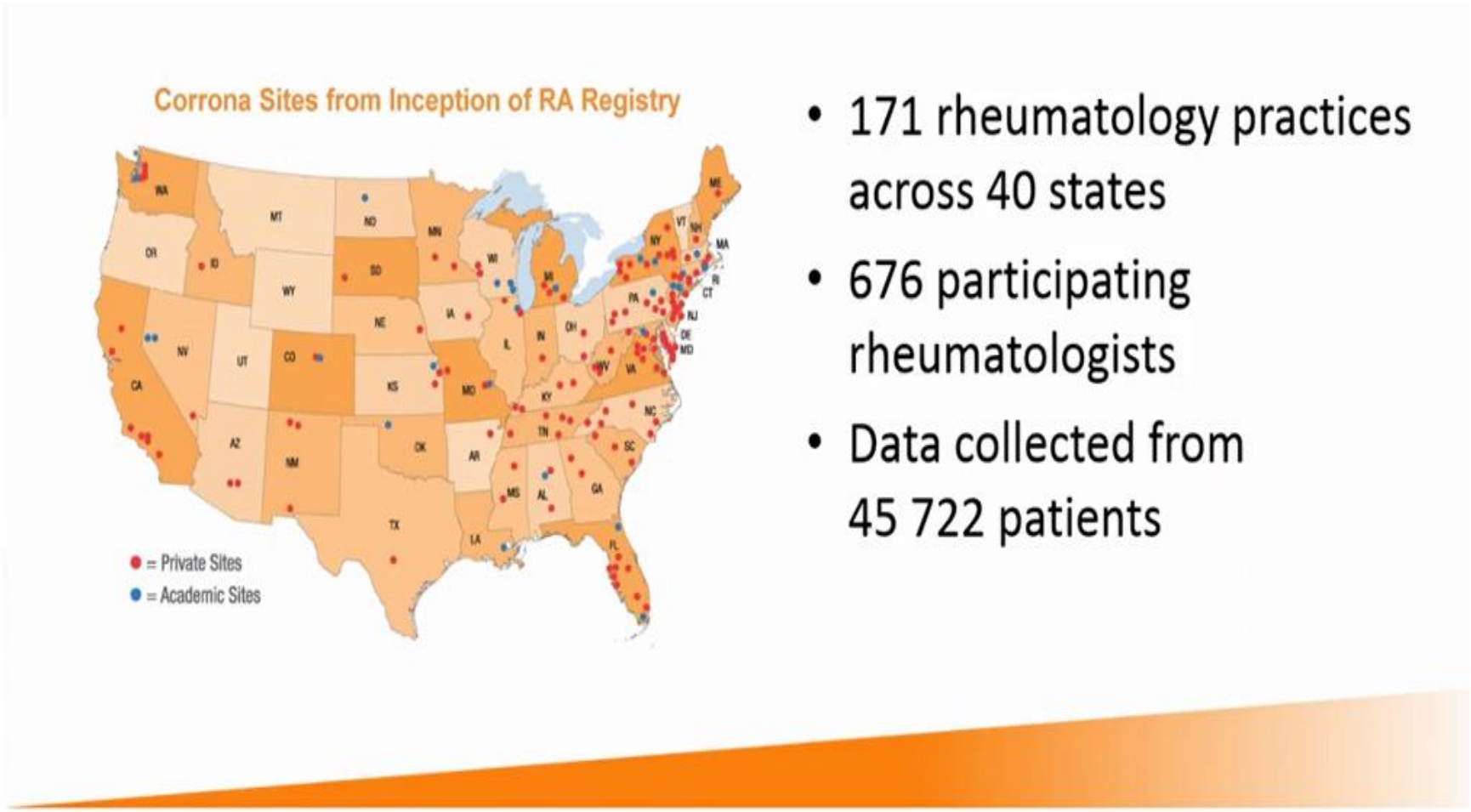
Real world

Oral Presentations

Still breaking news on TNF inhibitors in rheumatoid arthritis

OP0022 TNFI and TOFACITINIB monotherapy and comparative effectiveness in clinical practice: results from corrona registry

GW Reed[1,2], RA Gerber[3], Y Shan[1], L Takiya[4], KJ Dandreo[1], D Gruben[3], JM Kremer[5], GV Wallenstein[3]



Reed et al. Oral presentation OP0022 presented at: EULAR 2017, Madrid, Spain.

Oral Presentations

Still breaking news on TNF inhibitors in rheumatoid arthritis

OP0022 TNFI and TOFACITINIB monotherapy and comparative effectiveness in clinical practice: results from corrona registry

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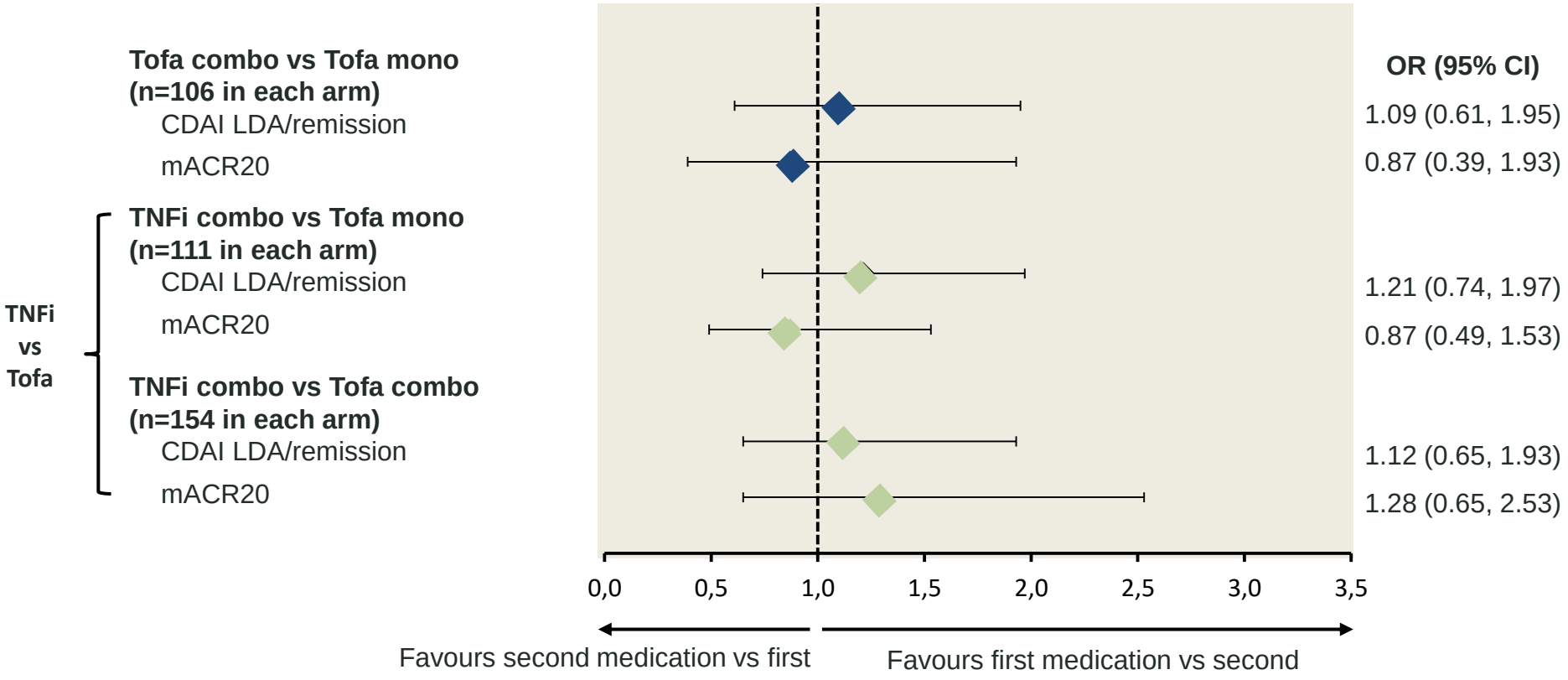


Similar effectiveness is seen with tofacitinib combination therapy vs tofacitinib monotherapy, and with TNFi combination therapy vs tofacitinib monotherapy and tofacitinib combination therapy

*Comparisons were in biologic-experienced patients

CDAI, Clinical Disease Activity Index; CI, confidence interval; mACR20, modified American College of Rheumatology 20; OR, odds ratio; TNFi, tumour necrosis factor inhibitor; tofa, tofacitinib

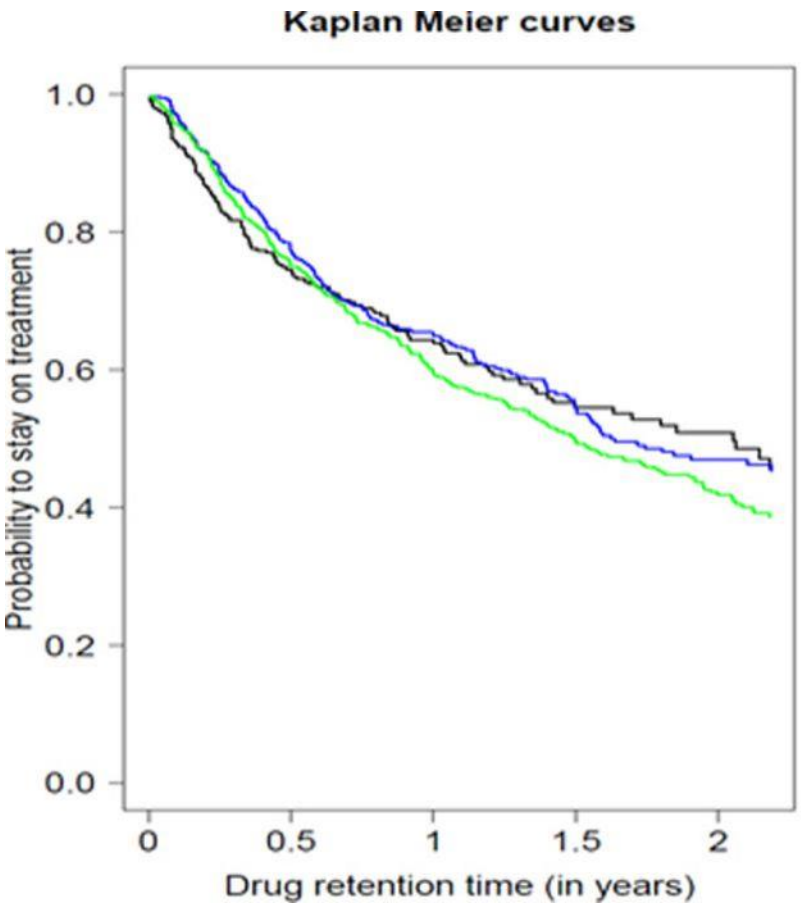
Reed et al. Oral presentation OP0022 presented at: EULAR 2017, Madrid, Spain.

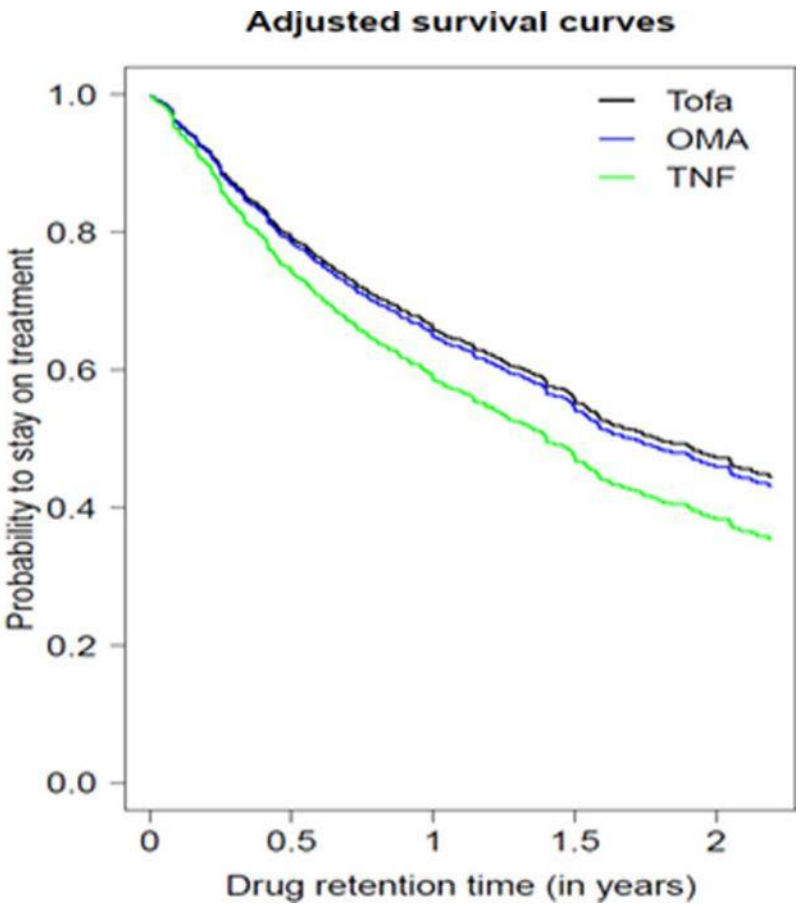
Poster Presentations

Rheumatoid arthritis - non biologic treatment

THU0174 Drug retention of tofacitinib versus biologic antirheumatic agents in rheumatoid arthritis: observational data from the swiss scqm registry

A Finckh[1], L Herzog[2], A Scherer[2], J Dudler[3], B Moeller[4], A Ciurea[5], R Mueller[6], P Hasler[7], P Exer[8], I von Muehlenen[8], D Kyburz[9], C Gabay[1], P Zufferey[10], on behalf of the Physicians of the SCQM





A Finckh et al. Ann Rheum Dis 2017;76:267

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

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

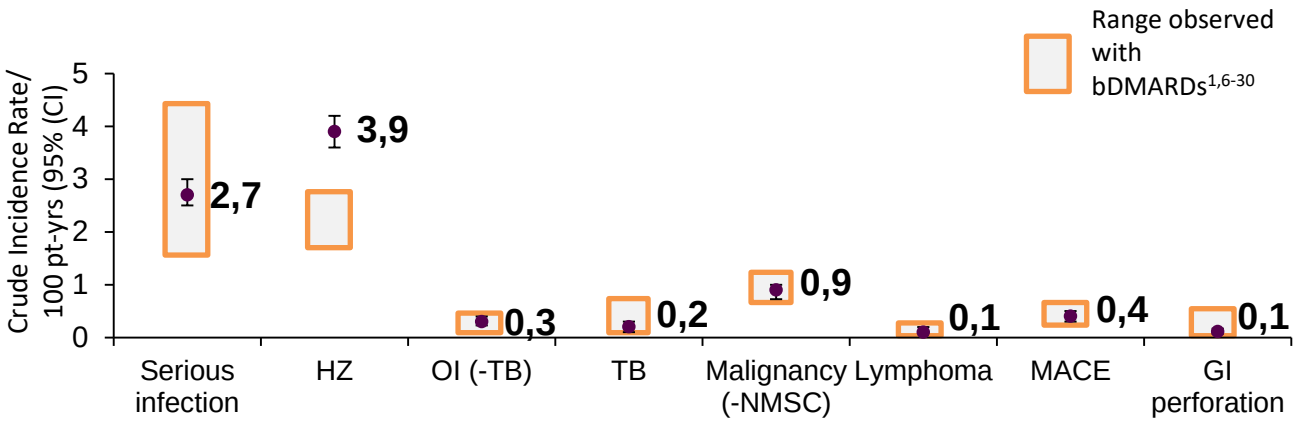
Incidence rate Is **stable over time**[1–4]

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.

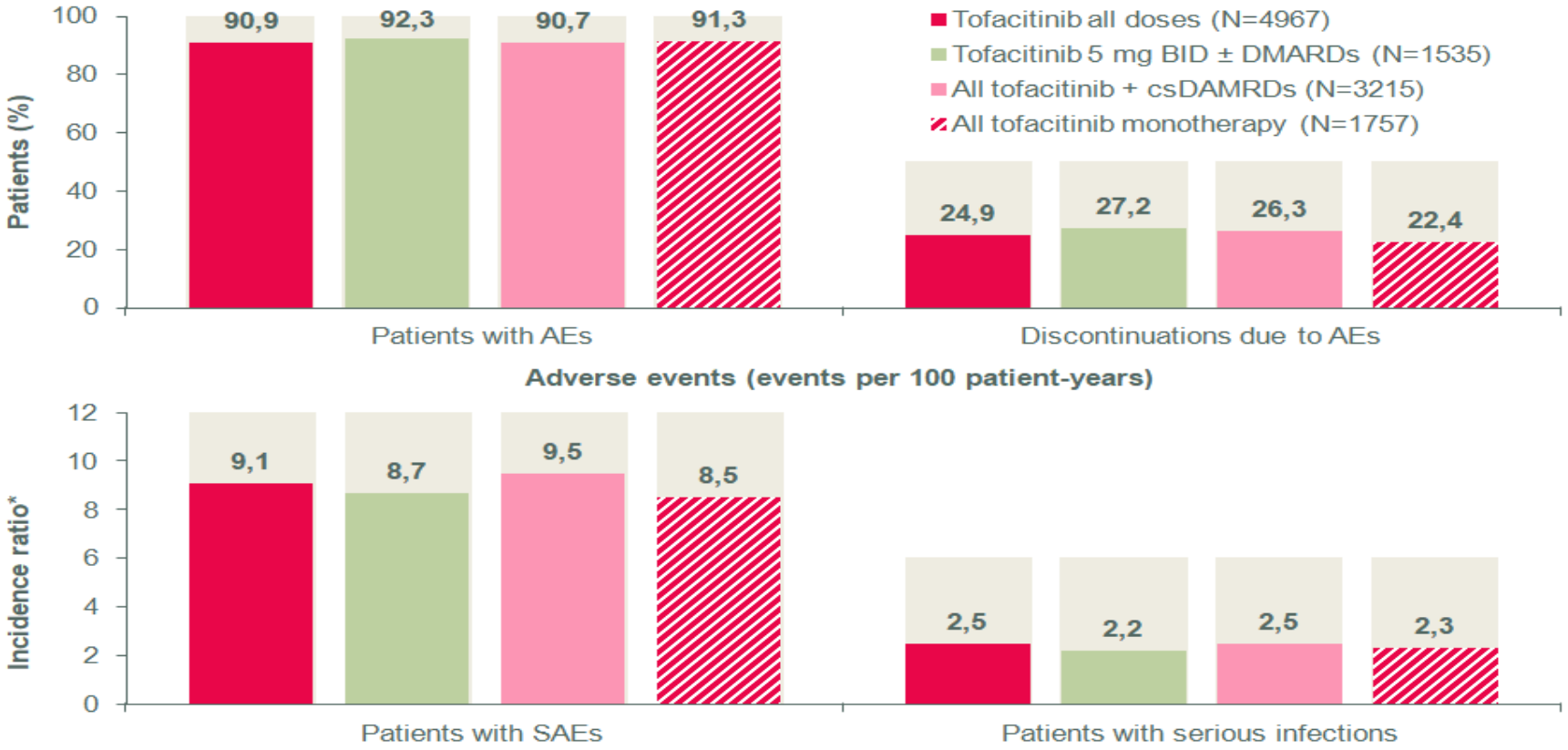
The approved dose of tofacitinib is 5 mg twice daily

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.

Tofacitinib, an Oral Janus Kinase Inhibitor, in the Treatment of Rheumatoid Arthritis: Safety and Efficacy in Open-Label, Long-Term Extension Studies over 9 Years

Jürgen Wollenhaupt[1], Joel Silverfield[2], Eun Bong Lee[3], Ketti Terry[4], Kenneth Kwok[5], Sander Strengholt[6], Ryan DeMasi[7] and Lisy Wang[4], [1]Schoen-Klinik Hamburg-Eilbek Teaching Hospital of the University of Hamburg, Hamburg, Germany, [2]Healthpoint Medical Group, Tampa, FL, [3]Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea, Republic of (South), [4]Pfizer Inc, Groton, CT, [5]Pfizer Inc, New York, NY, [6]Pfizer Inc, Capelle aan den IJssel, Netherlands, [7]Pfizer Inc, Collegeville, PA

4967 pts were treated (mean [max] duration: 3.5 [9.4] years). In total, 2518 pts (50.7%) discontinued (AEs: 1189 [23.9%]; insufficient clinical response: 179 [3.6%])

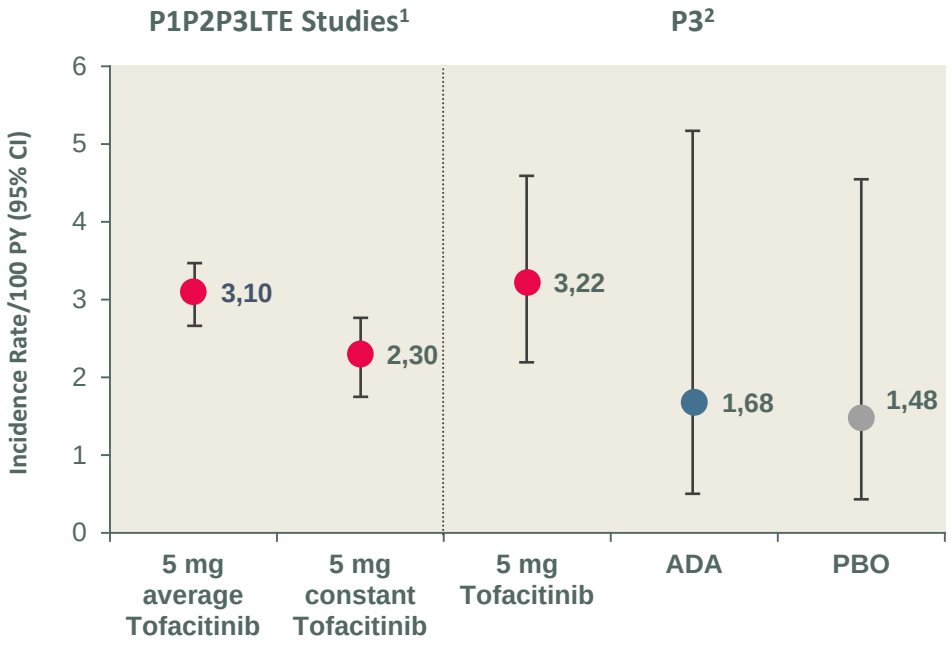


Wollenhaupt J, et al. Poster 522 presented at ACR 2017

The approved dose of tofacitinib is 5 mg twice daily

*IR, Patients with events per 100 patient-years [95% CI]); **Serious infections were those requiring hospitalization or parenteral administration of antibiotics. AEs, adverse events; BID, twice daily;
csDMARDS, conventional synthetic disease-modifying anti-rheumatic drugs

Incidence rate for serious infections in patients on tofacitinib



Unique pts with event	*	*	29	3	3
Exposure, pt years	6870	3623	900.87	178.66	202.46

pneumonia, cellulitis, HZ, urinary tract infection, diverticulitis, and appendicitis

Bars indicate 95% confidence limits; incidence rate of patients per 100 patient-years. Phase 3 data as of 19 April 2012. LTE data as of January 2016.
. *527 as reported across all tofacitinib doses

The infection incidence rate for tofacitinib was similar across studies

1. Cohen S, et al. *Ann Rheum Dis.* 2017;0:1–10.
2. Cohen S, et al. *Arthritis Rheumatol.* 2014;66:2924–37,

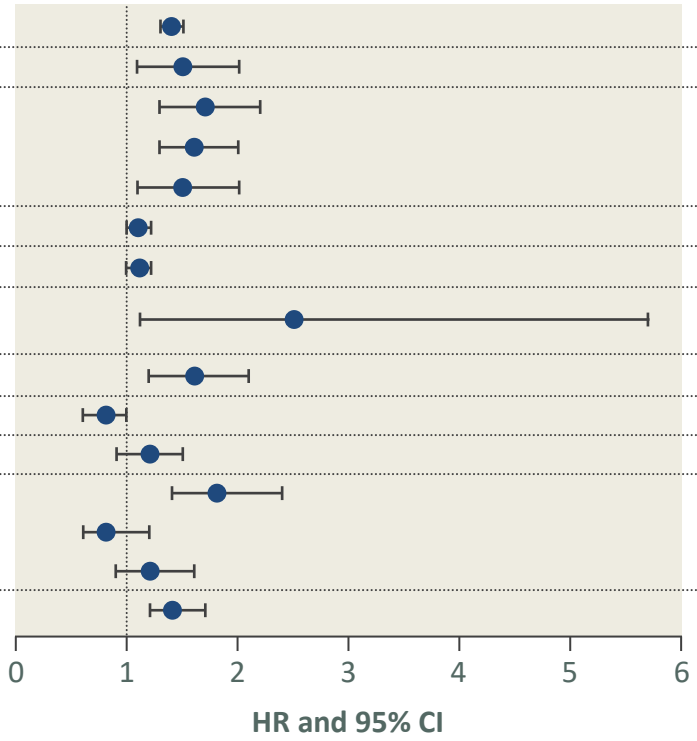
ADA, adalimumab; csDMARDS, conventional synthetic disease-modifying anti-rheumatic drugs; CI, confidence interval; LTE, long-term extension; PBO, placebo.

The approved dose of tofacitinib is 5 mg twice daily

Independent factors of serious infections

ISS 2015 data cut

Factors	Comparisons	HR	95% CI	Type 3 Wald p-value
Baseline age, years	Unit = 10†	1.4	1.3, 1.5	<0.0001
Baseline COPD*	Yes vs No	1.5	1.1, 2.0	0.0145
Baseline glucocorticoid use	≥7.5mg/day vs 0 mg/day	1.7	1.3, 2.2	
	0-<7.5mg/day vs 0 mg/day	1.6	1.3, 2.0	0.0001
	Unknown dose vs 0 mg/day	1.5	1.1, 2.0	
Baseline HAQ-DI score	Unit = 0.5†	1.1	1.0, 1.2	0.0078
Baseline body mass index	Unit = 5†	1.1	1.0, 1.2	0.0320
Prior confirmed post-baseline lymphopenia <500 cells/µL‡	Unit = 1†	2.5	1.1, 5.7	0.0249
Baseline diabetes	Yes vs No	1.6	1.2, 2.1	0.0009
Gender	Female vs Male	0.8	0.6, 1.0	0.0299
Line of therapy	3rd line vs 2nd line	1.2	0.9, 1.5	0.0399
Geographic region	Asia vs USA/Canada	1.8	1.4, 2.4	
	Europe vs USA/Canada	0.8	0.6, 1.0	<0.0001
	LA vs USA/Canada	1.2	0.9, 1.6	
Time-varying tofacitinib dose, mg BID	Unit = 5†	1.4	1.2, 1.7	0.0003



*Medical history and/or complication of chronic obstructive pulmonary disease.
†In Unit=x, 'x' is the change in the continuous variable corresponding to which the change in hazards is observed.
‡Based on exposure period before lymphopenia <500 cells/µL vs exposure period after lymphopenia <500 cells/µL.

Higher age, COPD, corticosteroid dose >7.5 mg and diabetes were identified as independent factors associated with a risk of SIE

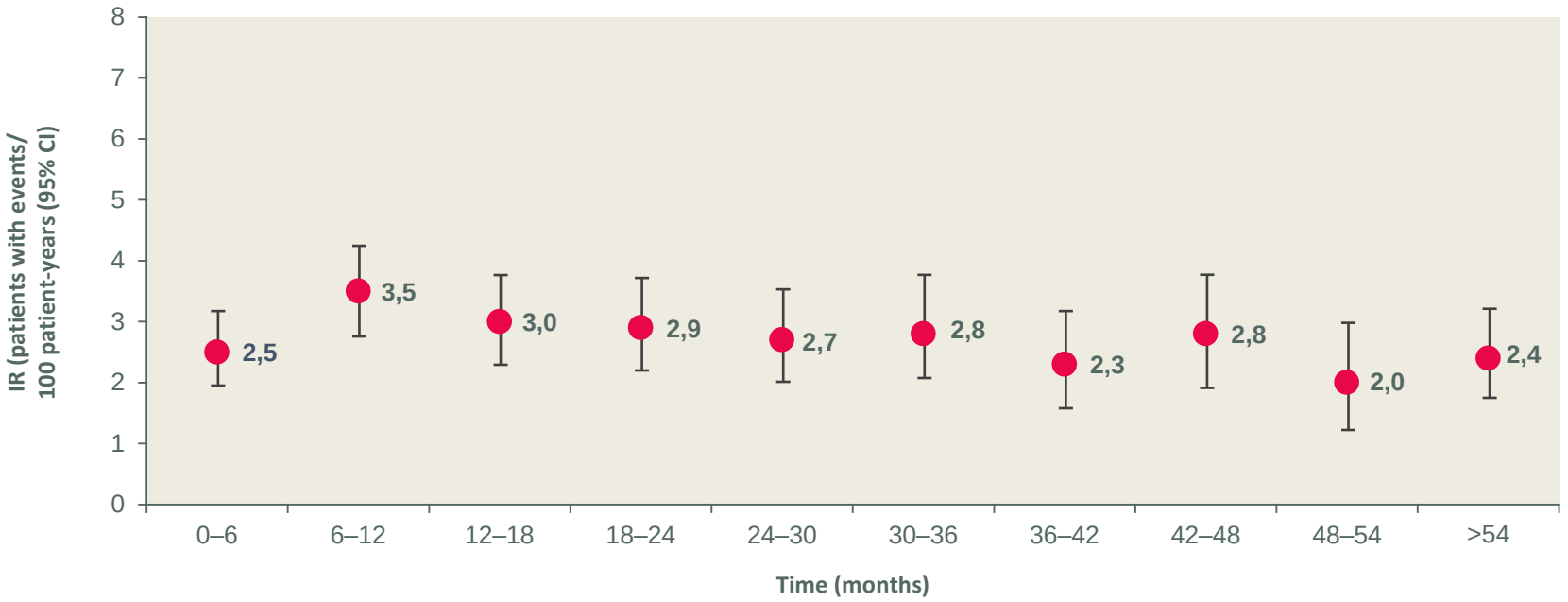
Cohen S, et al. *Ann Rheum Dis* 2017;0:1–10.

BID, twice daily; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DMARD, disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire – Disability Index; IR, inadequate responder; HR, hazard ratio; LA, Latin America; SIE, serious infection event.

The approved dose of tofacitinib is 5 mg twice daily

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

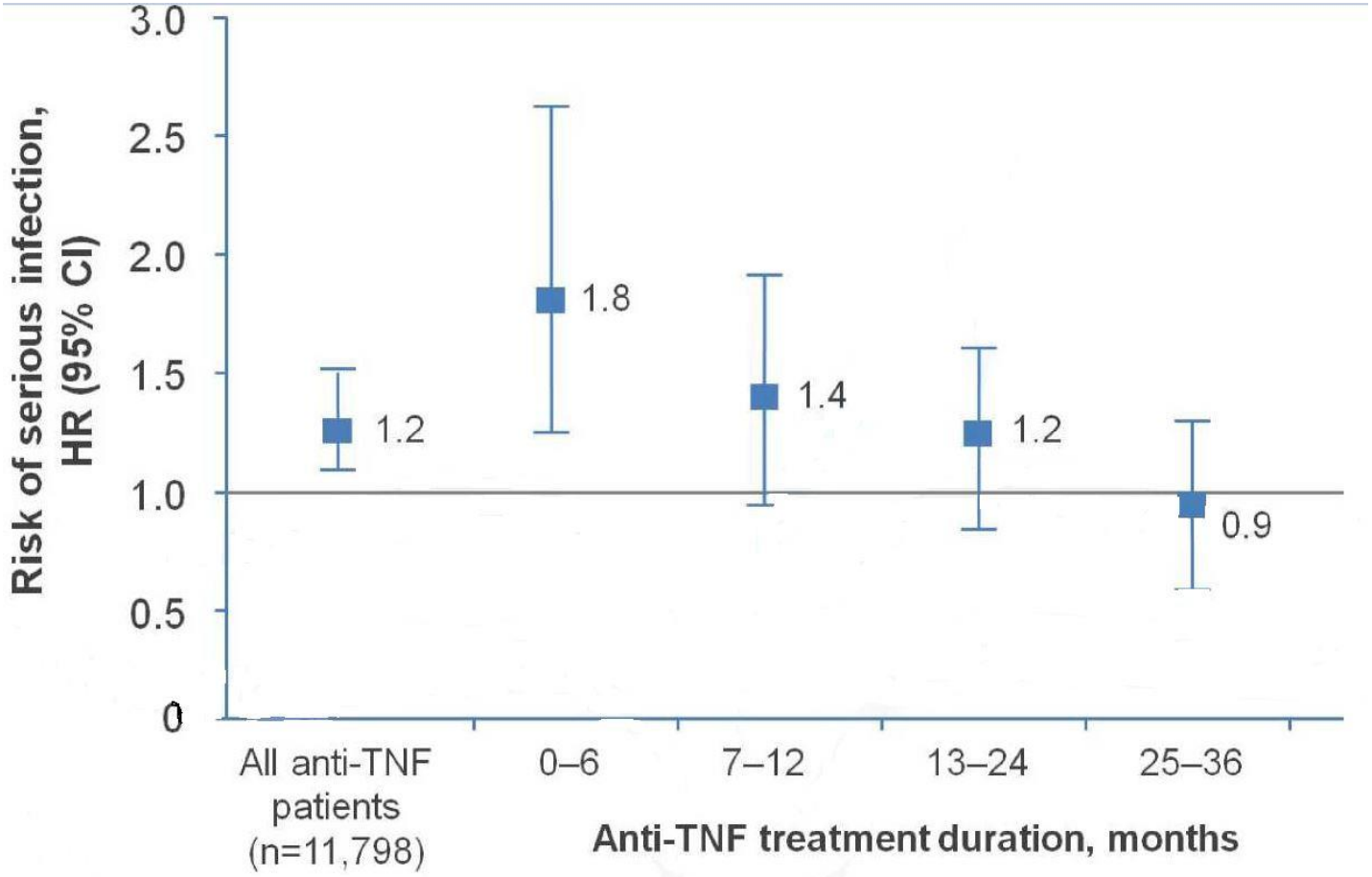
- The most common serious infection events were: pneumonia, HZ, urinary tract infection and cellulitis

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

Μεταβολή του κινδύνου σοβαρών λοιμώξεων με την πάροδο του χρόνου (BSRBR data)



Galloway *et al* Rheumatology 2011

RESEARCH ARTICLE Open Access

arthritis research&therapy

2015;17:362

Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials

Vibeke Strand[1], Sima Ahadieh[2], Jonathan French[3], Jamie Geier[4], Sriram Krishnaswami[2], Sujatha Menon[2], Tina Checchio[2], Thomas G. Tensfeldt[2], Elaine Hoffman[2], Richard Riese[2], Mary Boy[2] and Juan J. Gómez-Reino[5*]

66 randomized controlled trials and 22 long-term extension studies

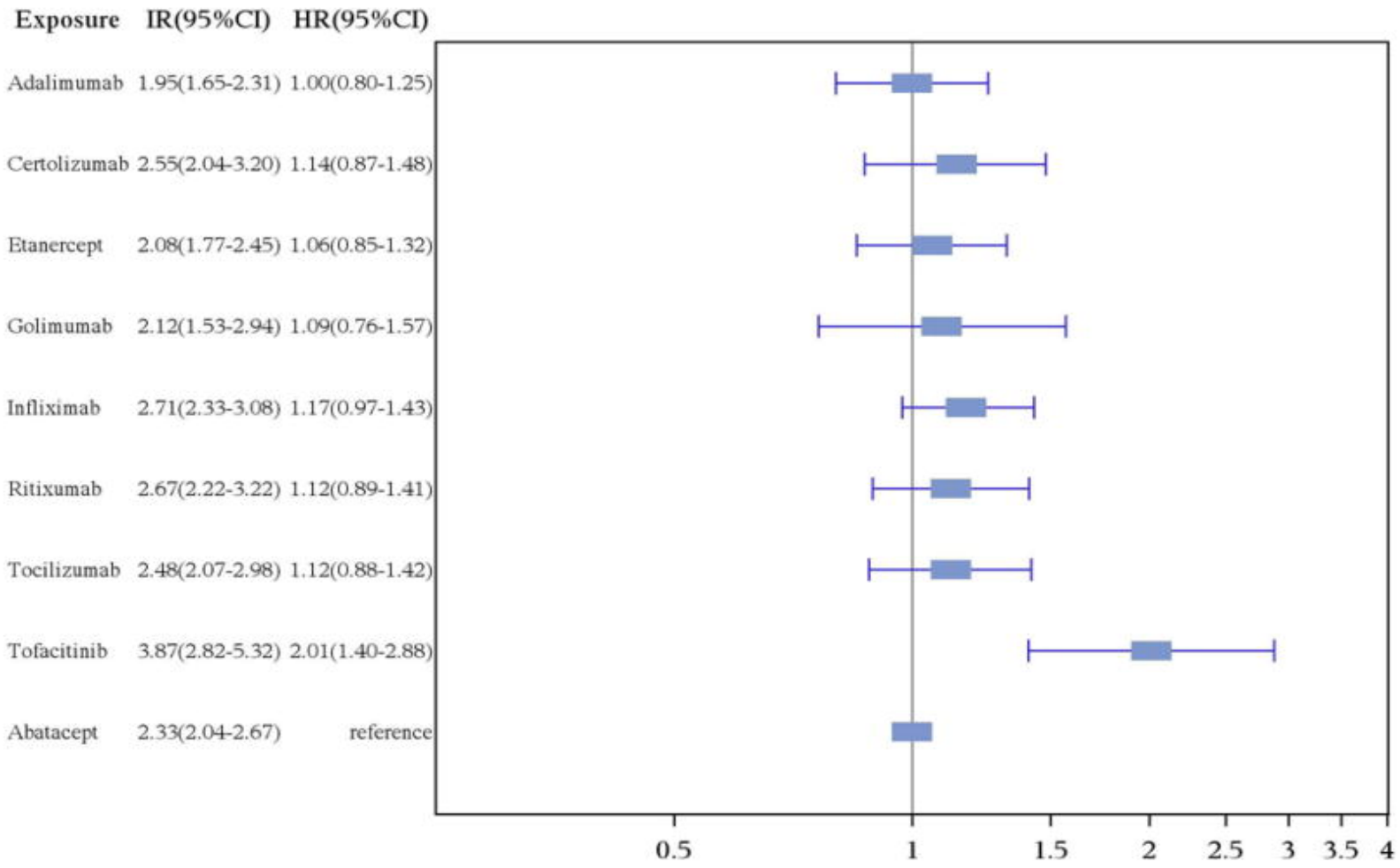
Drug	No. trials	Serious infection incidence rate, patients with events per 100 pt-yrs (95% CI)	Patients (N)	Cumulative exposure (pt-yrs)
Abatacept	11	3.04	5953	6070
Rituximab	8	3.72	2926	2687
Tocilizumab	13	5.45	5547	4522
Infliximab	11	6.11	4592	3555
Etanercept	17	4.06	7141	13037
Certolizumab pegol	5	7.59	3212	1339
Golimumab	6	5.31	2820	1648
Adalimumab	18	5.04	6570	7095
TNFi	57	4.90	26492	29429
Tofacitinib, Phase 3, 5 mg BID	6	3.02	1587	1464
Tofacitinib, Phase 3, 10 mg BID	6	3.00	1609	1501
Tofacitinib, LTE, 5 mg BID	1	2.50	1452	4005
Tofacitinib, LTE, 10 mg BID	1	3.19	3375	5191
Tofacitinib, Phase 2, Phase 3, LTE (all doses)	14	2.93	5671	12664
Adalimumab (tofacitinib, Phase 3, ORAL Standard)	1	1.68	204	179

Fig. 2 Incidence rates for serious infections with biologic DMARDs and tofacitinib across RCTs* and LTE studies. The results displayed did not include the continuity factor to account for zero incidence rates due to the low percentage of zero incidence rates for serious infections within these trials (<10 %). Tofacitinib data as of April 2013. *Clinical trial data published between 1999 and 2013. *BID* twice daily, *CI* confidence interval, *DMARD* disease-modifying antirheumatic drug, *LTE* long-term extension, *pt-yrs* patient-years, *RCT* randomized controlled trial, *TNFi* tumor necrosis factor inhibitors

Ann Rheum Dis. 2016 Oct;75(10):1843-7. doi: 10.1136/annrheumdis-2016-209131. Epub 2016 Apr 25.

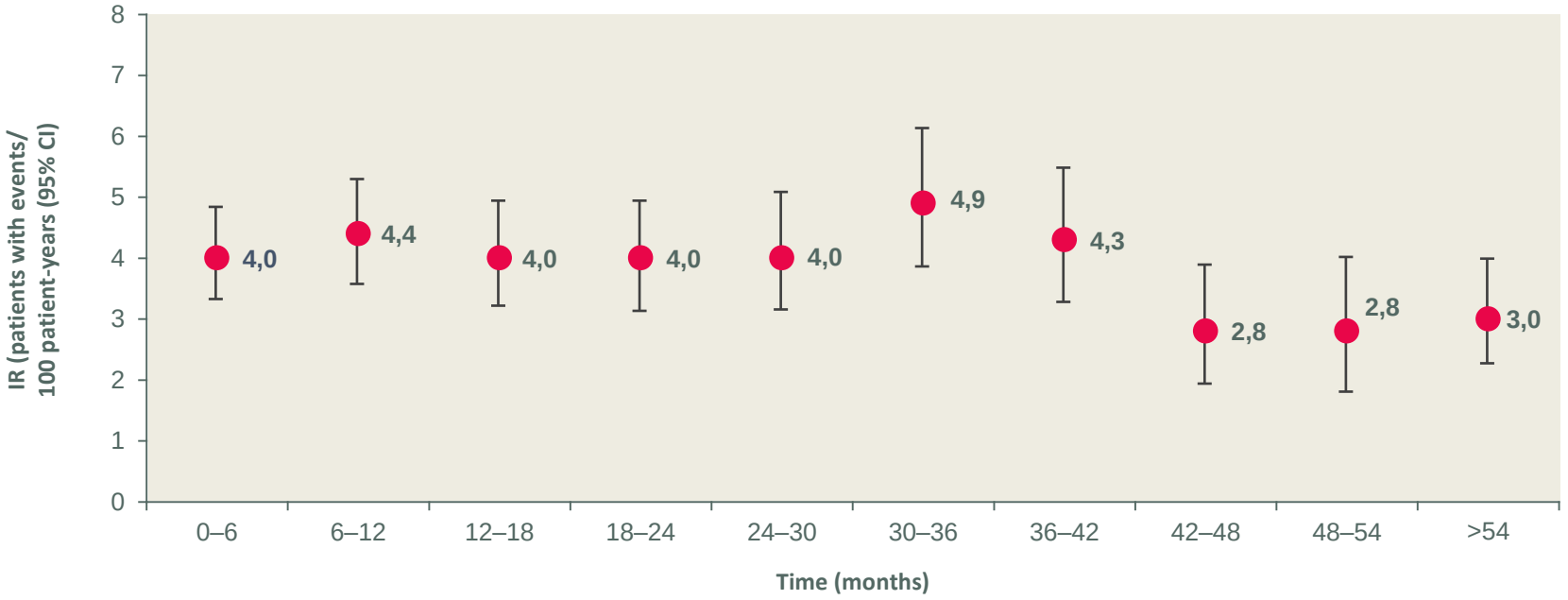
Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis.

Curtis JR[1], Xie F[2], Yun H[1], Bernatsky S[3], Winthrop KL[4].



Incidence rates for serious and non-serious herpes zoster infection over time

ISS 2015 data cut



Patients with HZ (n)	112	106	87	79	71	77	60	34	27	50
Total pt exposure (N)	6,194	5,222	4,677	4,217	3,858	3,361	3,043	2,656	2,303	1,727

Herpes zoster rates remain stable over time

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

CI, confidence interval; HZ, herpes zoster

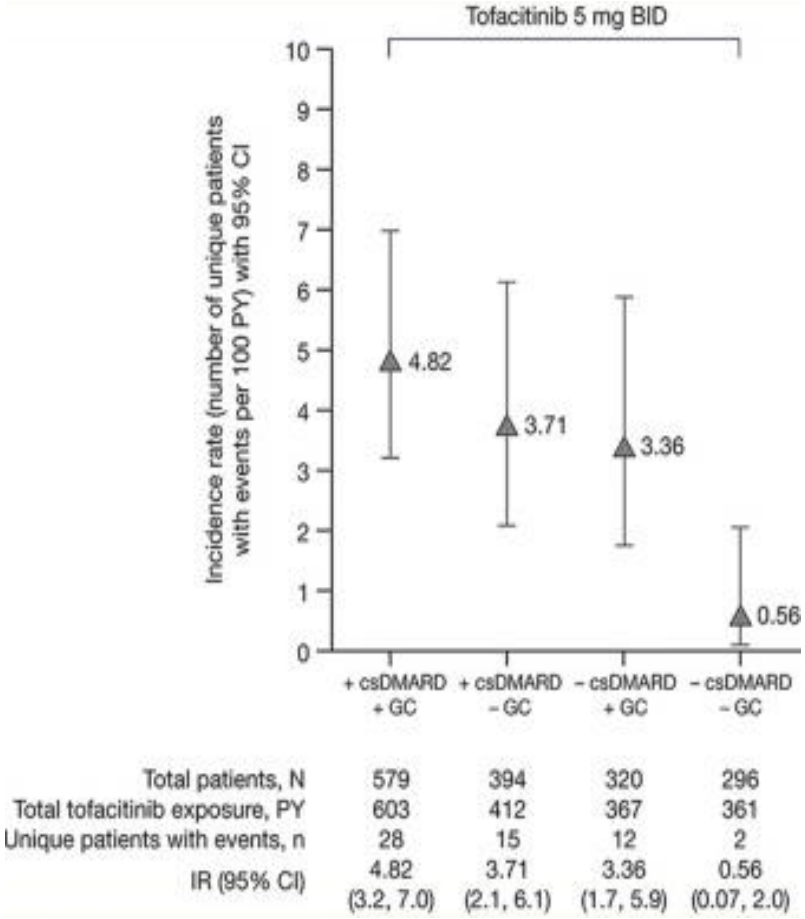
The approved dose of tofacitinib is 5 mg twice daily

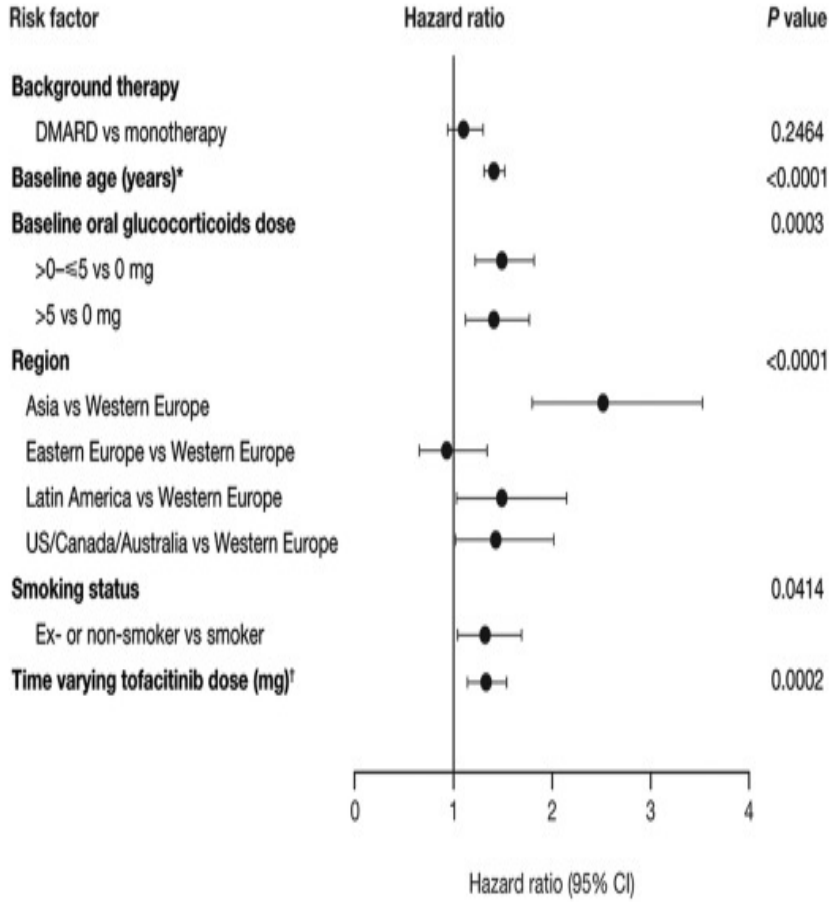
Arthritis Rheumatol. 2017 Oct; 69(10): 1960–1968.
Published online 2017 Sep 6. doi: 10.1002/art.40189
PMCID: PMC5656820
PMID: 28845604

Arthritis & Rheumatology

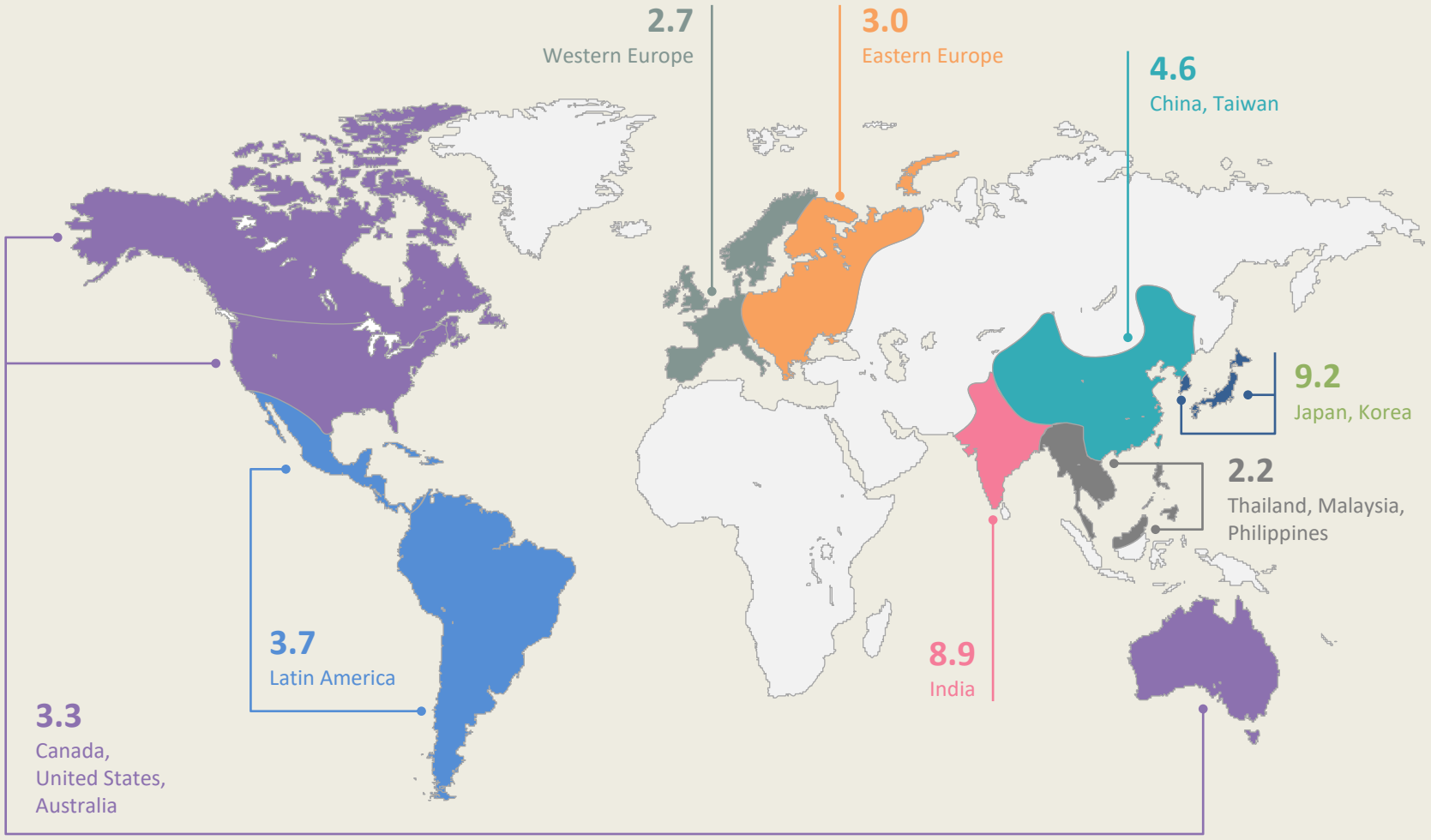
Herpes Zoster and Tofacitinib: Clinical Outcomes and the Risk of Concomitant Therapy

Kevin L. Winthrop,[1] Jeffrey R. Curtis,[2] Stephen Lindsey,[3] Yoshiya Tanaka,[4] Kunihiro Yamaoka,[5] Hernan Valdez,[6] Tomohiro Hirose,[7] Chudy I. Nduaka,[8] Lisy Wang,[9] Alan M. Mendelsohn,[8] Haiyun Fan,[8] Connie Chen,[6] and Eustratios Bananis[8]





Herpes zoster incidence rates by region in tofacitinib clinical trials



Winthrop KL, et al. *Arthritis Rheum* 2014;66(10):2675–84.

Incidence rates per 100 patient-years.
Data cutoff as of March 2011 using P2P3 LTE data.

HZ Events Are Medically Manageable

Severity of HZ Events[1,2,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

8% Rates of **postherpetic neuralgia** (PHN); **comparable to rates in general population**[3]

Vaccination recommendation[31,32]

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

1. Data on file. Pfizer Inc, New York, NY.
2. Cohen SB et al. Ann Rheum Dis. 2017 Jul;76(7):1253-1262
3. Sampathkumar P et al. *Mayo Clin Proc.* 2009;84(3):274-280.
4. Singh JA et al. *Arthritis Care Res (Hoboken)*. 2016;68(1):1-25.
5. Harpaz R et al. *MMWR Morb Mortal Wkly Rep.* 2008;57(RR-5). 1-30; quiz CE2-4.
6. 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.
7. Kivitz AJ et al. Presented at: American College of Rheumatology Annual Meeting; November 6-11, 2015; San Francisco, CA. Poster 2143.

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

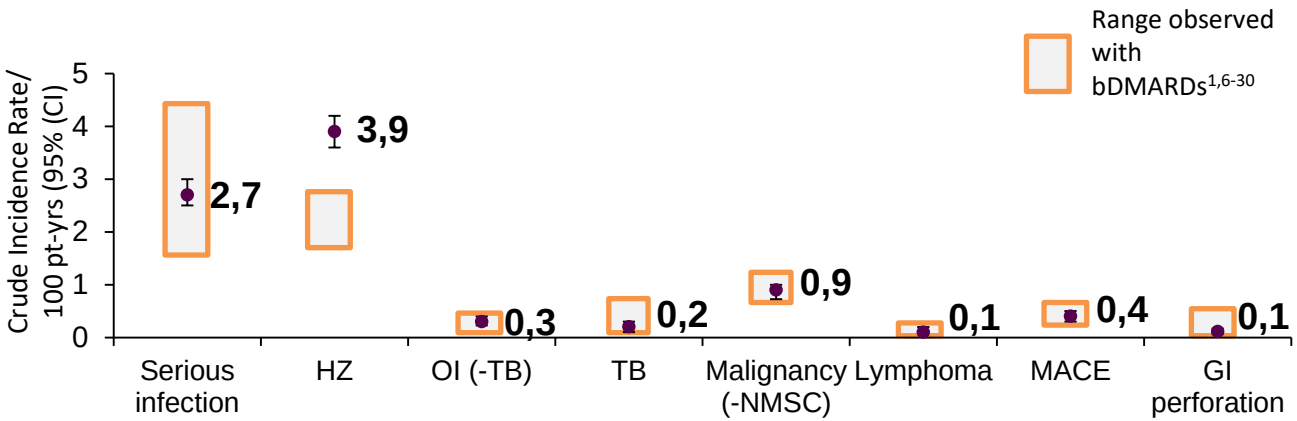
Incidence rate Is **stable over time**[1–4]

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.

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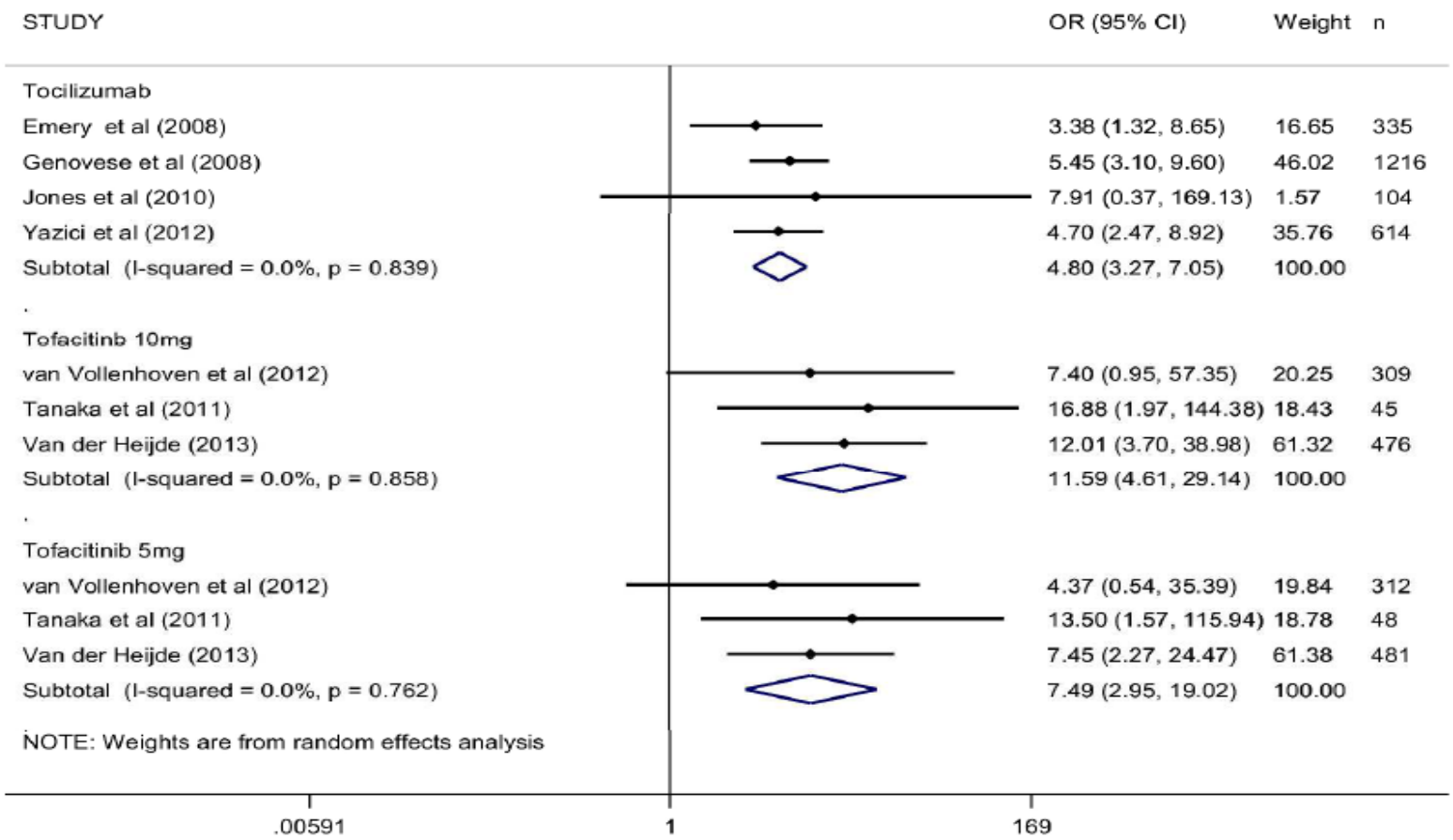
Arthritis & Rheumatology
AN OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF RHEUMATOLOGY
American College of Rheumatology

Lipid Profile Changes in Patients With Chronic Inflammatory Arthritis Treated With Biologic Agents and Tofacitinib in Randomized Clinical Trials: A Systematic Review and Meta-Analysis

Alejandro Souto ✉, Eva Salgado, José Ramón Maneiro, Antonio Mera, Loreto Carmona, Juan J. Gómez-Reino



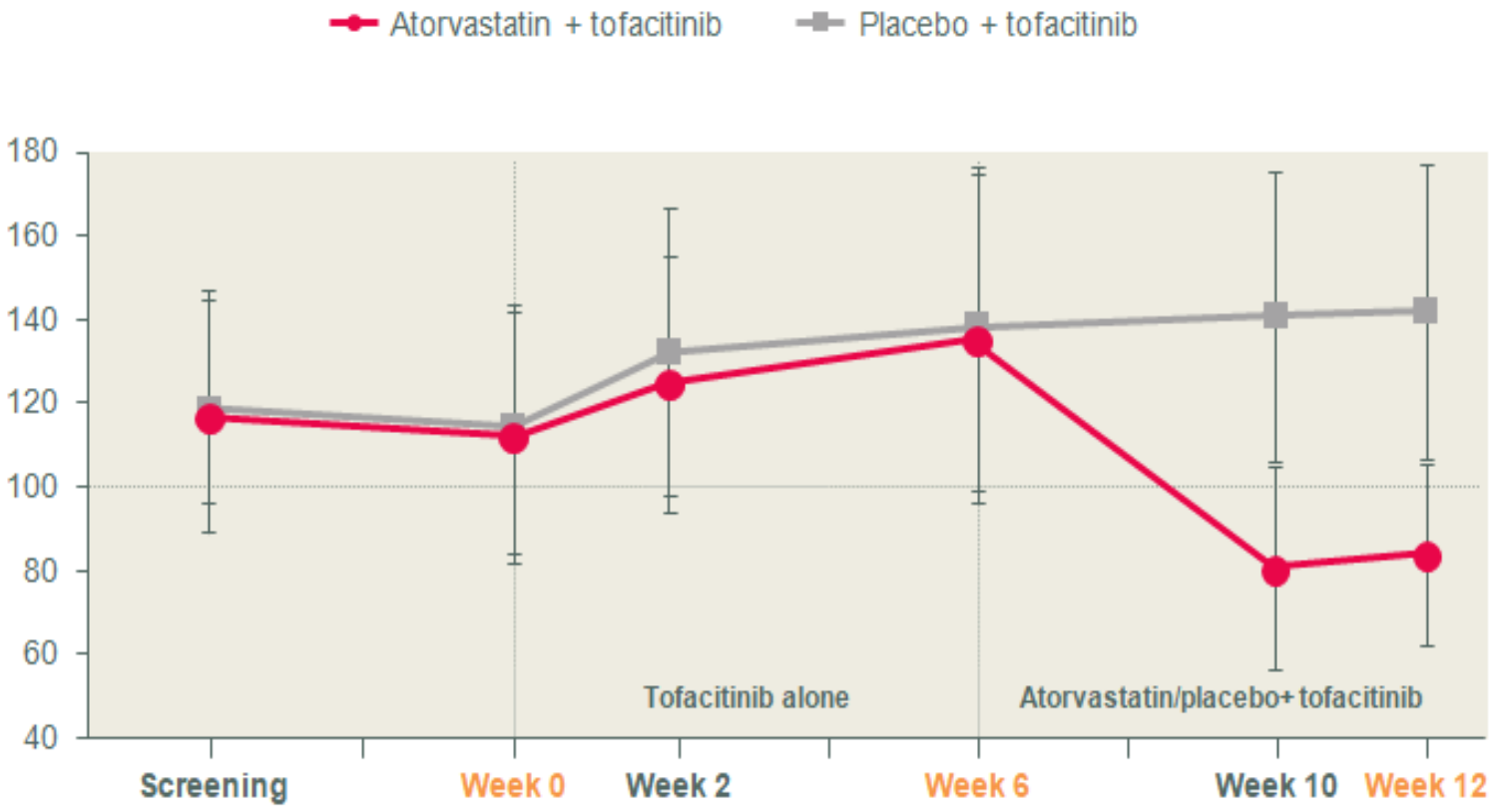
LDL values

Clinical and epidemiological research
Extended report

Annals of the
Rheumatic Diseases

Open-label tofacitinib and double-blind atorvastatin in rheumatoid arthritis patients: a randomised study*

Iain B McInnes[1], Ho-Youn Kim[2], Sang-Heon Lee[3], David Mandel[4], Yeong-Wook Song[5], Carol A Connell[6], Zhen Luo[7], M Julia Brosnan[6], Andrea Zuckerman[6], Samuel H Zwillich[6], John D Bradley[6]



The approved dose of tofacitinib is 5 mg twice daily

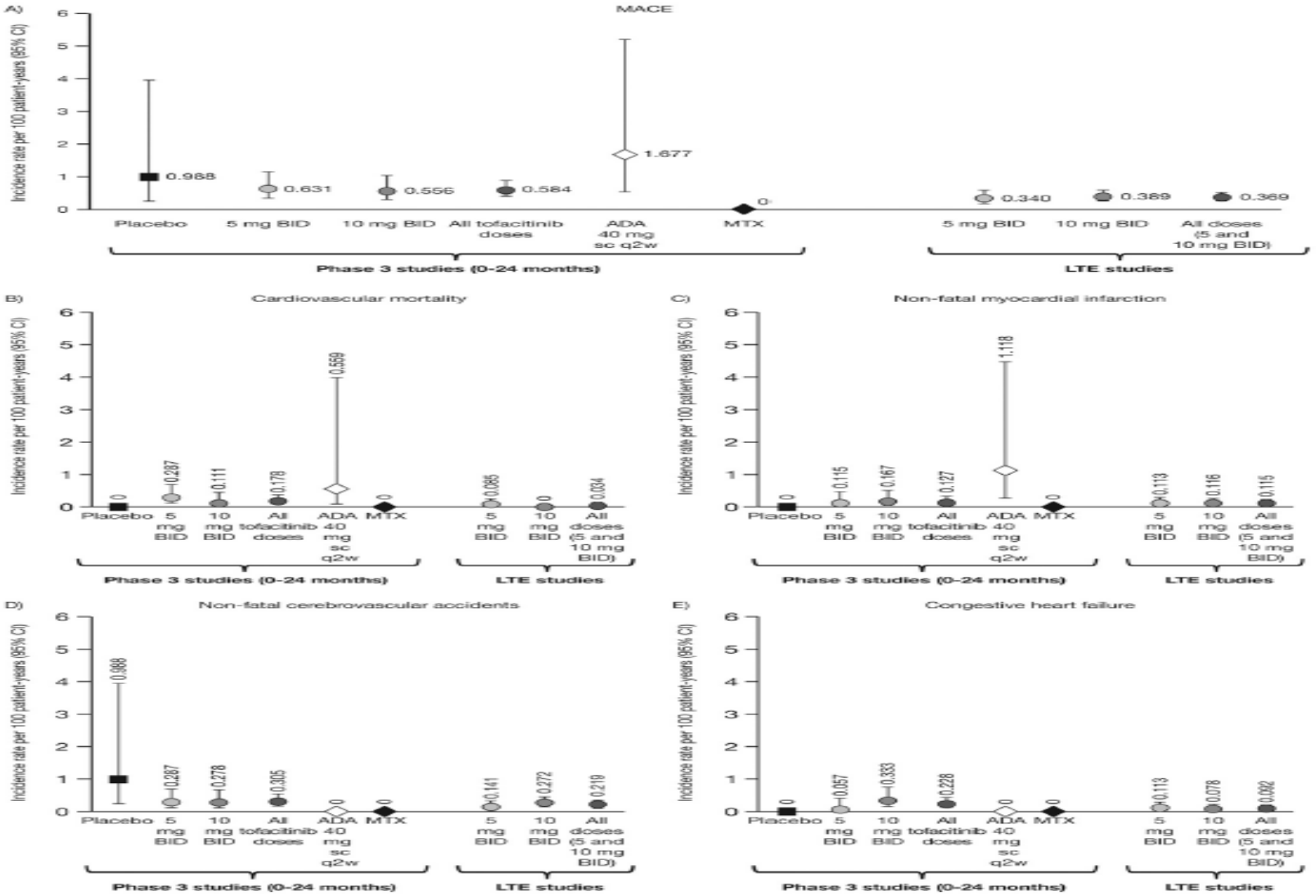
McInnes IB, et al. *Ann Rheum Dis* 2014;73:124–31.

Cardiovascular safety findings in patients with rheumatoid arthritis treated with tofacitinib, an oral Janus kinase inhibitor☆,☆☆

Christina Charles-Schoeman, MD[a,*], Pierre Wicker, MD[b], Miguel A. Gonzalez-Gay, MD, PhD[c], Mary Boy, MD[d], Andrea Zuckerman, MD[e], Koshika Soma, MD[d], Jamie Geier, PhD[f], Kenneth Kwok, MSc[f], Richard Riese, MD, PhD[d]

Seminars in Arthritis and Rheumatism 46 (2016) 261–271

3942 patient- years of follow-up in the Phase 3 studies and 8699 patient-years of follow-up in the LTE studies



ΣΥΜΠΕΡΑΣΜΑΤΑ

Το tofacitinib αποτελεί μία νέα θεραπευτική προσέγγιση στη ΡΑ με διαφορετικό μηχανισμό δράσης

Έχει καλά δεδομένα σε RTC αλλά και στην καθημερινή κλινική πράξη σε αντιπροσωπευτικούς πληθυσμούς με ΡΑ που καλύπτουν όλο το φάσμα των ασθενών

Η μακροχρόνια αποτελεσματικότητα και η ασφάλεια είναι επιβεβαιωμένες σε μελέτες και καταγραφές

Υπάρχει αυξημένος κίνδυνος λοίμωξης με HZ σε σχέση με άλλα βιολογικά φάρμακα αλλά οι σοβαρές λοιμώξεις αφορούν έναν περιορισμένο αριθμό ασθενών με συγκεκριμένα χαρακτηριστικά

Tofacitinib is a JAK Inhibitor

- A synthetic, per os, small molecule
- 300-fold smaller than etanercept
- Tofacitinib acts inside the cell by preferentially inhibiting signaling by cytokine receptors associated with JAK1 or JAK3 over receptors that signal via pairs of JAK2
- Inhibition of JAK1 and JAK3 by tofacitinib attenuates signaling of interleukines (IL-2, IL-4, IL-6, IL-7, IL-9, IL-15, IL-21) and type I and II interferons, resulting in modulation of immune and inflammatory response

Θεραπευτική ένδειξη

«Το XELJANZ σε συνδυασμό με μεθοτρεξάτη (MTX) ενδείκνυται για τη θεραπεία της μέτριας έως σοβαρής μορφής, ενεργής ρευματοειδούς αρθρίτιδας (PA), σε ενήλικες ασθενείς που παρουσίασαν ανεπαρκή ή όχι καλά ανεκτή ανταπόκριση σε ένα ή περισσότερα τροποποιητικά της νόσου αντιρρευματικά φάρμακα.
Το XELJANZ μπορεί να χορηγηθεί ως μονοθεραπεία σε περίπτωση δυσανεξίας στη MTX ή όταν η θεραπεία με MTX είναι ακατάλληλη.»

Hodge JA, Kawabata TT, Krishnaswami S, Clark JD, Telliez JB, Dowty ME, Menon S, Lamba M, Zwillich S. The mechanism of action of tofacitinib - an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2016;34(2):318-28
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