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# HOW RAPID WAS THE ONSET OF XELJANZ IN SIGNIFICANTLY IMPROVING PAIN SYMPTOMS IN PATIENTS WITH RA IN A PHASE 3 CLINICAL TRIAL PROGRAMME?[1]

0 1 2 3 4 5 6 7 8 9

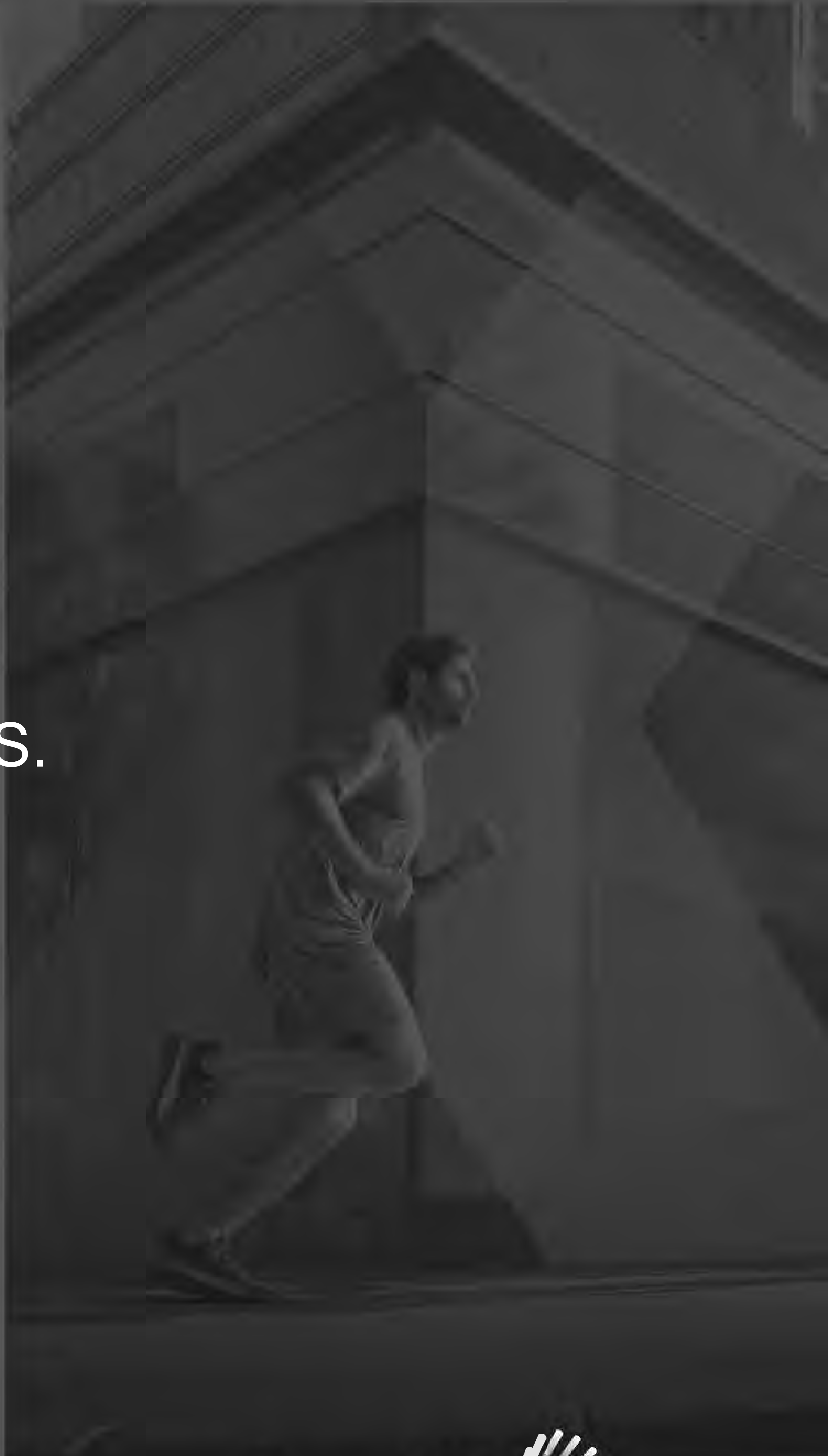
SLIDE BUTTON TO SELECT YOUR ANSWER.
PRESS 'VIEW ANSWER' TO SEE THE RESULTS.

TAP ANYWHERE TO BEGIN

RESET

VIEW ANSWER

RA, rheumatoid arthritis.





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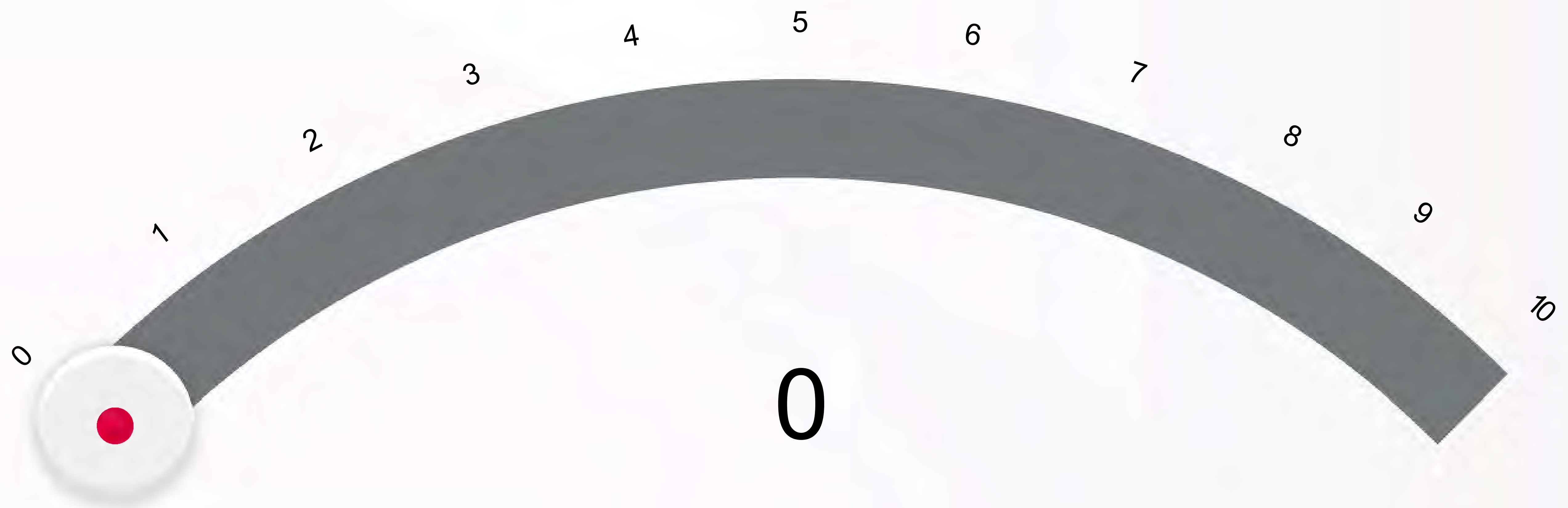


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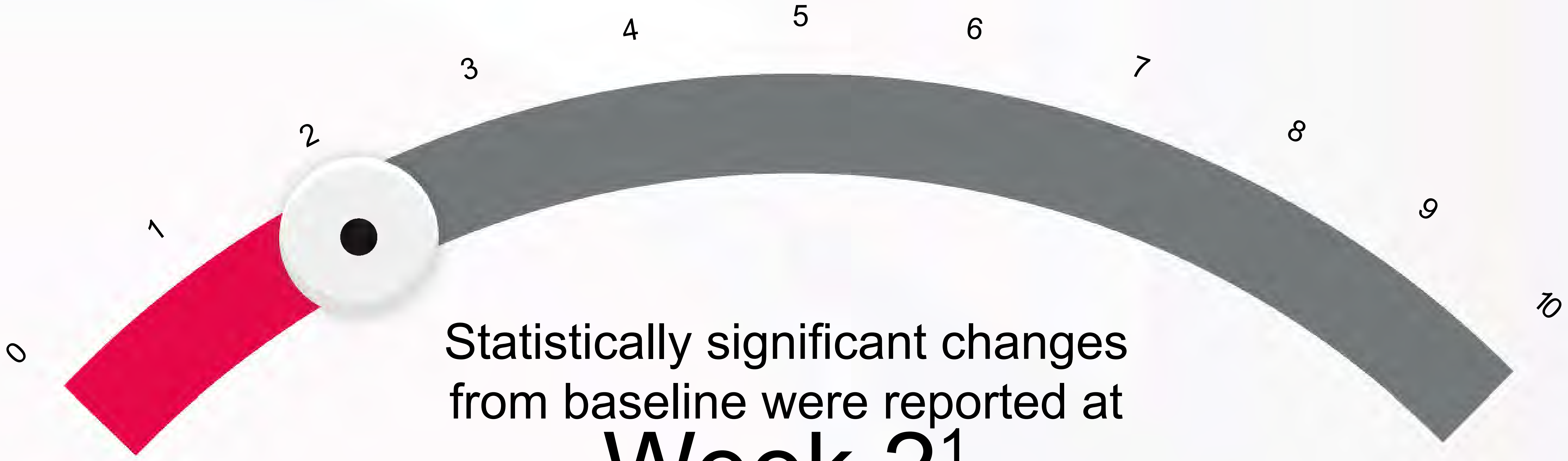


Statistically significant changes from baseline were reported at

**Week 2**[1]

XELJANZ 5 mg BID vs placebo:
mean change in pain from baseline:
–16.10 (1.47)** vs –6.32 (2.07), respectively;
**p<0.001 vs placebo[1,a]

Correct answer

Your answer
XXXX

ADDITIONAL INFORMATION

NEXT QUESTION

The recommended dose for rheumatoid arthritis is 5 mg film-coated tablets administered twice daily, which should not be exceeded. No dose adjustment is required when used in combination with

[a]Information from source Table S2, Ref 1. Please refer to the source materials for the original table.

ACR 20, at least a 20% improvement in the American College of Rheumatology scale; BID, twice daily; DAS28-4[ESR], Disease Activity Score in 28 joints with 4 variables, erythrocyte sedimentation rate; ESR, erythrocyte sedimentation rate; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire Disability Index; IR, inadequate response; MOS, Medical Outcomes Survey; MTX, methotrexate; PRO, patient reported outcome; PtGA, Patient Global Assessment of Disease Activity; RA, rheumatoid arthritis; RCT, randomised controlled trial;
SF-36, Short Form-36;VAS, visual analogue scale.

## Supporting information:

- **Primary endpoint:** The primary endpoints, assessed at month 3, were the percentage of patients with at least a 20% improvement in the American College of Rheumatology scale (ACR 20), the change from baseline in Health Assessment Questionnaire–Disability Index (HAQ-DI) scores (which range from 0 to 3, with higher scores indicating greater disability), and the percentage of patients with a Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate (DAS28-4[ESR]) of less than 2.6 (with scores ranging from 0 to 9.4 and higher scores indicating more disease activity)[2]
- In this 6-month, phase 3, randomized, placebo-controlled trial, 611 patients with inadequate response to DMARD-IR were randomized 4:4:1:1 to receive: tofacitinib 5 mg BID or tofacitinib 10 mg BID for the duration of the study, or placebo for 3 months followed by tofacitinib 5 mg BID or tofacitinib 10 mg BID. Patient-reported outcomes (PROs) included: Patient Global Assessment of Disease Activity (PtGA); Patient Assessment of Pain (Pain); Health Assessment Questionnaire-Disability Index (HAQ-DI); Medical Outcomes Survey (MOS) Short Form-36 (SF-36); Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F); and MOS Sleep Scale[1]

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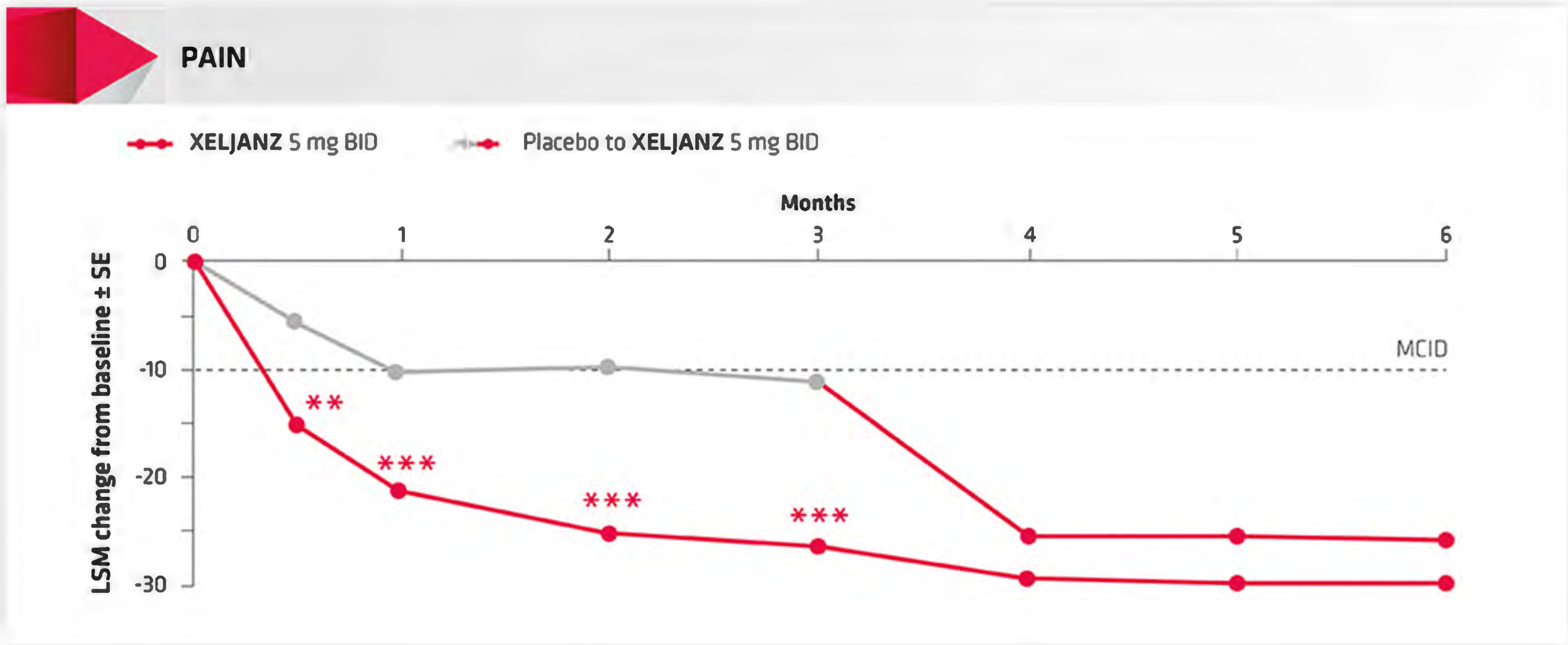
# ADDITIONAL INFORMATION

## PATIENT GLOBAL ASSESSMENT OF PAIN[1]

At month 3, LSM changes from baseline were statistically significant with tofacitinib 5 mg BID treatment versus placebo ($p < 0.0001$), and exceeded the MCID (≥10 points). Statistically significant changes from baseline were evident at week 2 and months 1 and 2 for bo doses of tofacitinib versus placebo.[1]

**b**




**P<0.01, ***P<0.0001 vs placebo.[1]

Patient Assessment of Pain (Pain) was evaluated using the 100 mm visual analogue scale (VAS).[1]

Patients assessed the severity of their arthritis pain in response to the statement ‘My pain at this time is’ using a VAS, ranging from 0 (‘no pain’) to 100 mm (‘most severe pain’).[4]

Changes from baseline were compared with published values for minimum clinically important differences (MCID) ≥10 points in VAS PfGA and Pain.[1]

Figure elaborated from Fig 2, Ref 1. Please refer to source materials for the original graph.

**The recommended dose for rheumatoid arthritis is 5 mg film-coated tablets administered twice daily, which should not be exceeded. No dose adjustmen**



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HOW RAPID WAS THE ONSET OF XELJANZ IN SIGNIFICANTLY

# ADDITIONAL INFORMATION

**The recommended dose for rheumatoid arthritis is 5 mg film-coated tablets administered twice daily, which should not be exceeded. No dose adjustmen is required when used in combination with MTX.[3]**

## PRIMARY EFFICACY ANALYSES[2]

At month 3, a total of 59.8% of patients in the 5 mg XELJANZ group, as compared with 26.7% in the combined placebo groups, met the criteria for an ACR 20 response (P<0.001).[2]

**a**


P<0.001 for the comparison of the 5 mg dose of tofacitinib with placebo at 2 weeks and at months 1, 2 and 3.[2]

Figure elaborated from Fig 1, Ref 2. Please refer to source materials for the original graph.

HOW RAPID WAS THE ONSET OF XELJANZ IN SIGNIFICANTLY

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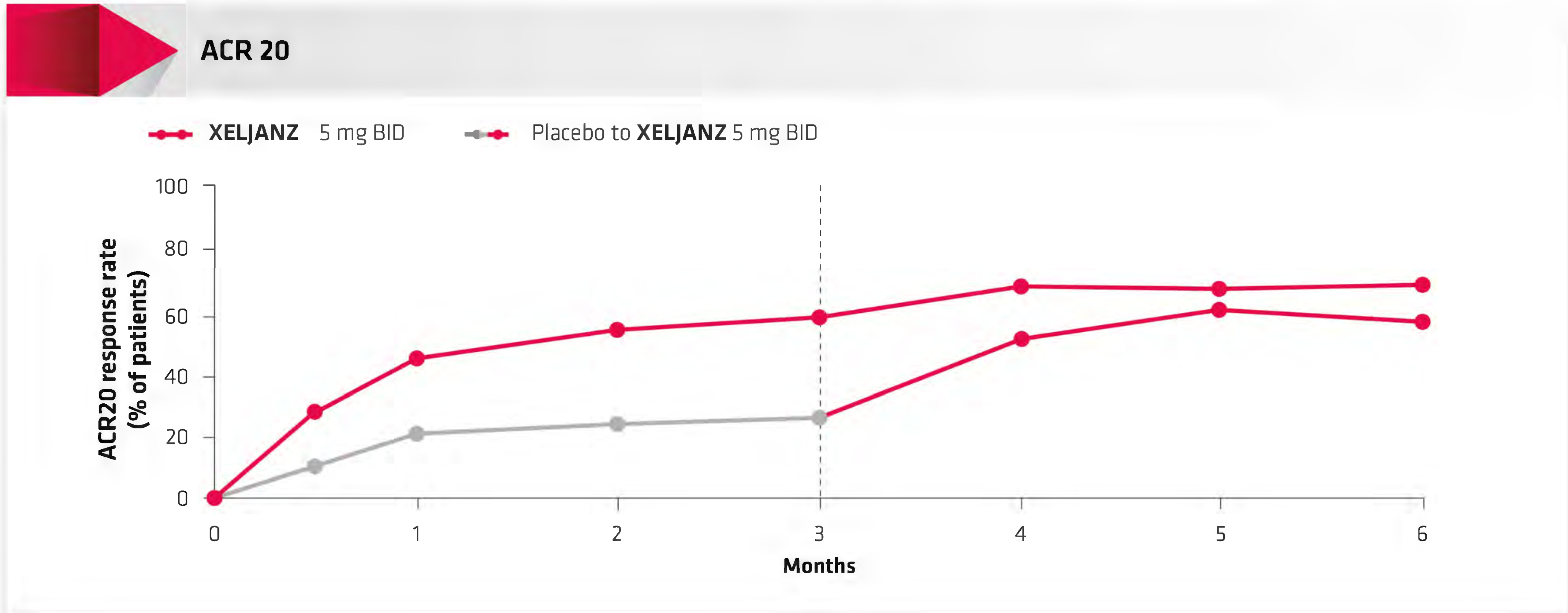


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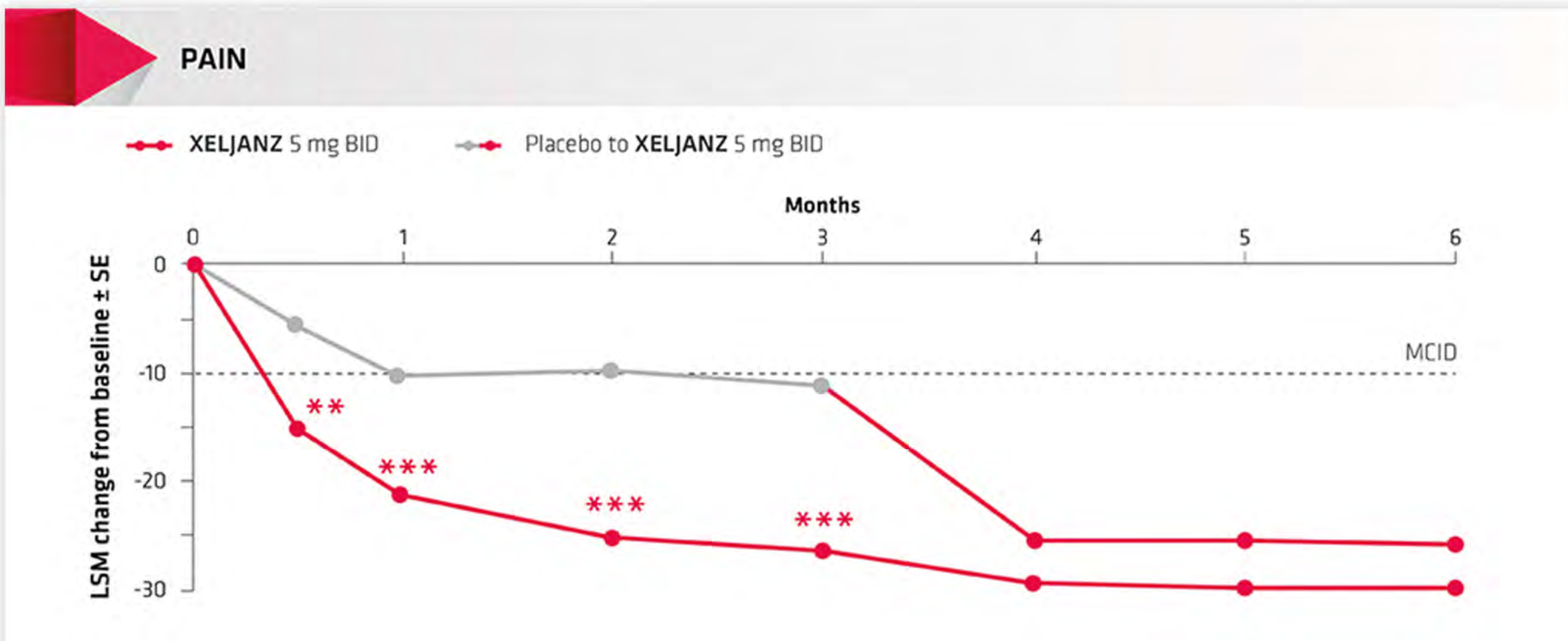


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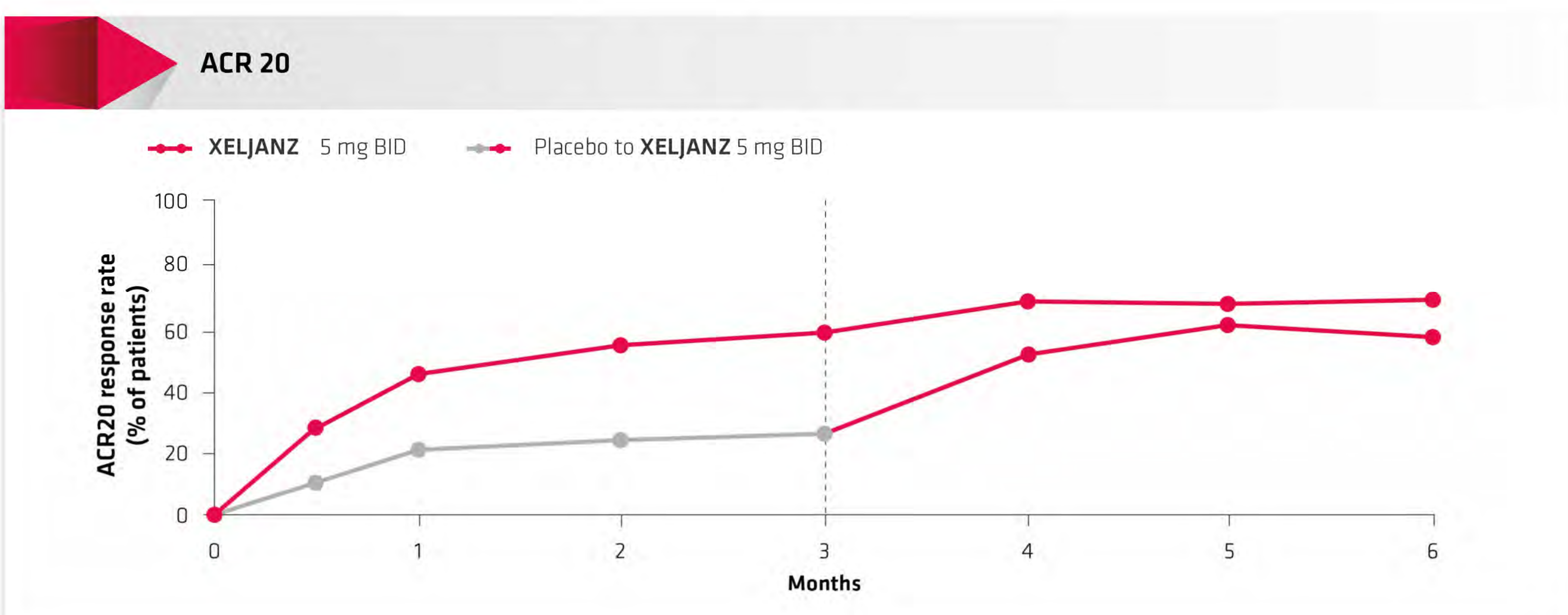


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# XELJANZ CLINICAL TRIAL PROGRAMME

## PHASE 3 CLINICAL STUDIES OF XELJANZ 5 MG AND 10 MG TWICE DAILY DOSES IN PATIENTS WITH RA[3]

| Studies | Study I (ORAL Solo) | Study II (ORAL Sync) | Study III (ORAL Standard) | Study IV (ORAL Scan) | Study V (ORAL Step) | Study VI (ORAL Start) | Study VII (ORAL Strategy) |
|---|---|---|---|---|---|---|---|
| Population | DMARD-IR | DMARD-IR | MTX-IR | MTX-IR | TNFi-IR | MTX-naïve[a] | MTX-IR |
| Control | Placebo | Placebo | Placebo | Placebo | Placebo | MTX | MTX, ADA |
| Background treatment | None[b] | csDMARDs | MTX | MTX | MTX | None[b] | 3 Parallel arms:<br>• Tofacitinib monotherapy<br>• Tofacitinib+MTX<br>• ADA+MTX |
| Key features | Monotherapy | Various csDMARDs | Active control (ADA) | X-Ray | TNFi-IR | Monotherapy, Active comparator (MTX), X-Ray | Tofacitinib with and without MTX or in comparison to ADA with MTX |
| Number of patients treated | 610 | 792 | 717 | 797 | 399 | 956 | 1,146 |
| Total study duration | 6 months | 1 year | 1 year | 2 years | 6 months | 2 years | 1 year |
| Co-primary efficacy endpoints[c] | Month 3:<br>ACR20<br>HAQ-DI<br>DAS28-4(ESR)<2.6 | Month 6:<br>ACR20<br>DAS28-4(ESR)<2.6<br>Month 3:<br>HAQ-DI | Month 6:<br>ACR20<br>DAS28-4(ESR)<2.6<br>Month 3:<br>HAQ-DI | Month 6:<br>ACR20<br>mTSS<br>DAS28-4(ESR)<2.6<br>Month 3:<br>HAQ-DI | Month 3:<br>ACR20<br>HAQ-DI<br>DAS28-4(ESR)<2.6 | Month 6:<br>mTSS<br>ACR70 | Month 6:<br>ACR50 |
| Time of mandatory placebo rescue to | Month 3 | Month 6 (placebo subjects with < 20% improvement in swollen | | | Month 3 | NA | NA |



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# XELJANZ CLINICAL TRIAL PROGRAMME

| | | | | | |
|---|---|---|---|---|---|
| Time of mandatory placebo rescue to tofacitinib 5 or 10 mg twice daily | Month 3 | Month 6 (placebo subjects with < 20% improvement in swollen and tender joint counts advanced to tofacitinib at month 3) | Month 3 | NA | NA |

Table 9, Ref 3.

The recommended dose for rheumatoid arthritis is 5 mg film-coated tablets administered twice daily, which should not be exceeded. No dose adjustment is required when used in combination with MTX.[3]

[a]≤3 weekly doses (MTX naïve).[3]
[b]Antimalarials were allowed.[3]
[C]Co-primary endpoints as follows: mean change from baseline in mTSS; percent of subjects achieving ACR20 or ACR70 responses; mean change from baseline in HAQ-DI; percent of subjects achieving a DAS28-4(ESR) <2.6 (remission). [3]

| | ORAL Sequel[5] |
|---|---|
| Study type | Long-term extension study |
| Patient type | Eligible patients[a] |
| Distinguishing feature of study | Long-term safety and tolerability |
| Study duration | 9.5 years |
| Treatment | Across qualifying studies, tofacitinib was dosed at 1, 3, 5, 10, 15 and 30 mg BID, or 20 mg once daily as monotherapy or in combination with background |

| | ORAL Surveillance[6] |
|---|---|
| Study type | Randomised, open-label, noninferiority, phase 3b-4 safety endpoint trial |
| Patient type | Active rheumatoid arthritis despite methotrexate treatment who were 50 years of age or older and had at least one additional cardiovascular risk factor |
| Distinguishing feature of study | Non-inferiority trial |
| Study duration | Up to 6 years |
| Treatment | Open-label oral tofacitinib at a dose of 5 mg or 10 mg twice daily, or a subcutaneous TNF inhibitor (adalimumab at a dose of 40 mg every 2 weeks [in North America, including the United States, Puerto Rico, and Canada] or etanercept at a dose of 50 mg once weekly [in the |

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| Patients randomised, n | 4481 |
| Primary endpoints | Long-term safety and tolerability |

From text, Ref 5.

| | |
|---|---|
| Patient type | Active rheumatoid arthritis despite methotrexate treatment who were 50 years of age or older and had at least one additional cardiovascular risk factor |
| Distinguishing feature of study | Non-inferiority trial |
| Study duration | Up to 6 years |
| Treatment | Open-label oral tofacitinib at a dose of 5 mg or 10 mg twice daily, or a subcutaneous TNF inhibitor (adalimumab at a dose of 40 mg every 2 weeks [in North America, including the United States, Puerto Rico, and Canada] or etanercept at a dose of 50 mg once weekly [in the rest of the world]); background methotrexate was continued |
| Patients randomised, n | 4362 |
| Primary endpoints | Adjudicated MACE (death from cardiovascular causes, non-fatal myocardial infarction, or nonfatal stroke) and cancers, excluding nonmelanoma skin cancer |

From text, Ref 6.

The recommended dose for rheumatoid arthritis is 5 mg film-coated tablets administered twice daily, which should not be exceeded. No dose adjustment is required when used in combination with MTX.[3]

[a]Eligible patients had previously completed a prior qualifying index study of tofacitinib, which included two phase 1 studies, eight phase 2 studies, and six phase 3 studies.[5]

ACR 20/50/70, at least a 20/50/70% improvement in the American College of Rheumatology scale; ADA, adalimumab; BID, twice daily; CRP, c-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-4[ESR], Disease Activity Score in 28 joints with 4 variables, erythrocyte sedimentation rate; DMARD, disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire Disability Index; IR, inadequate response; MACE, major adverse cardiovascular events; mTSS, modified Total Sharp Score; MTX, methotrexate; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

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| Time of mandatory placebo rescue to tofacitinib 5 or 10 mg twice daily | Month 3 | Month 6 (placebo subjects with < 20% improvement in swollen and tender joint counts advanced to tofacitinib at month 3) | | | Month 3 | NA | NA |

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# XELJANZ SAFETY PROFILE IN RA

## THE EFFICACY AND SAFETY OF TOFACITINIB FILM-COATED TABLETS WERE ASSESSED IN 6 RANDOMIZED, DOUBLE-BLIND, CONTROLLED MULTICENTRE STUDIES (PHASE 3 CLINICAL STUDIES)[3]

The most commonly reported adverse reactions during the first 3 months of the double-blind, placebo or MTX controlled clinical studies were headache (3.9%), upper respiratory tract infections (3.8%), viral upper respiratory tract infection (3.3%), diarrhoea (2.9%), nausea (2.7%), and hypertension (2.2%).[3]

**The recommended dose for rheumatoid arthritis is 5 mg film-coated tablets administered twice daily, which should not be exceeded. No dose adjustment is required when used in combination with MTX.[3]**

## ADVERSE EVENTS OF SPECIAL INTEREST IN THE RA CLINICAL TRIALS PROGRAMME (EXCLUDING ORAL

### IRS (95% CI) FOR AEs OF SPECIAL INTEREST[7]

| | RA (N=7964) |
|---|---|
| Total tofacitinib exposure, patient-years | 23,497 |
| Serious infections, IR (95% CI) (n) | 2.5 (2.3 to 2.7) (592) |
| All HZ (nonserious and serious), IR (95% CI) (n) | 3.6 (3.3 to 3.8) (795) |
| Adjudicated tuberculosis, IR (95% CI) (n) | 0.2 (0.1 to 0.2) (38) |



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# XELJANZ SAFETY PROFILE IN RA

| | |
|---|---|
| Adjudicated OIs excluding tuberculosis, IR (95% CI) (n) | 0.4 (0.3 to 0.5) (95) |
| Adjudicated malignancies excluding all NMSC, IR (95% CI) (n)<br>n1 (%) | 0.7 (0.6 to 0.9) (179)<br>211 (2.6) |
| Adjudicated NMSC, IR (95% CI) (n)<br>n1 (%) | 0.6 (0.5 to 0.7) (133)<br>135 (1.7) |
| Adjudicated lymphoma/lymphoproliferative disorders, IR (95% CI) (n) n1 (%)[9] | 0.1 (0.0 to 0.1) (12)<br>19 (0.2) |
| Adjudicated MACE,[a] IR (95% CI) (n) | 0.4 (0.3 to 0.5) (85)[b] |
| DVT[c] IR (95% CI) (n) | 0.2 (0.1 to 0.2) (37) |
| PE[c] IR (95% CI) (n) | 0.1 (0.1 to 0.2) (31) |
| Adjudicated gastrointestinal perforation, IR (95% CI) (n) | 0.1 (0.1 to 0.2) 27 |

Table elaborated from Table 3, Ref 7. Please refer to source materials for the original table.

**The recommended dose for rheumatoid arthritis is 5 mg film-coated tablets administered twice daily, which should not be exceeded. No dose adjustment is required when used in combination with MTX.[3]**

**XELJANZ is not approved in the European Union for the treatment of plaque psoriasis.**

[a]Composite MACE defined as any myocardial infarction, stroke, or cardiovascular death.[7]

[b]N=7311.[7]



XELJANZ (tofacitinib citrate)

# XELJANZ SAFETY PROFILE IN RA

[c]Previously reported in Mease et al. Ann Rheum Dis 2020;79:1400-13 (excludes Study A3921133) and Sandborn et al. J Crohns Colitis 2020;14:S498-500.

- The objectives of this analysis were to provide a comparison of adverse events (AEs) of special interest from integrated pooled studies of the tofacitinib clinical programmes[7]
- Patients received tofacitinib 0.5, 1, 2, 3, 5, 10, 15 or 30 mg two times per day, or 20 mg once a day in phase 1/2 studies, and tofacitinib 5 or 10 mg two times per day, or 11 mg extended-release once a day in phase 3 and phase 3b/4 studies. In LTE studies, the tofacitinib dose could be switched for efficacy or safety reasons. Data are reported for the following treatment groups: tofacitinib 5 mg two times per day (average total daily dose <15 mg); tofacitinib 10 mg two times per day (average total dose ≥15 mg); and all tofacitinib doses (i.e., average tofacitinib 5 mg two times per day and average tofacitinib 10 mg two times per day populations pooled)[7]
- The five most common SIEs per cohort were pneumonia (n=131), herpes zoster (HZ; n=44), urinary tract infection (n=31), cellulitis (n=31) and gastroenteritis (n=24) for RA[7]

**The recommended dose for rheumatoid arthritis is 5 mg film-coated tablets administered twice daily, which should not be exceeded. No dose adjustment is required when used in combination with MTX.[3]**

**XELJANZ is not approved in the European Union for the treatment of plaque psoriasis.**

**Major adverse cardiovascular events (including myocardial infarction)[3]**

- Major adverse cardiovascular events (MACE) have been observed in patients taking tofacitinib
- In a randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of myocardial infarctions was observed with tofacitinib compared with TNF inhibitors. In patients over 65 years of age, patients who are current or past smokers, and patients with other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available



XELJANZ® (tofacitinib citrate)

# XELJANZ SAFETY PROFILE IN RA

**Malignancy and lymphoproliferative disorder**[3]

- Tofacitinib may affect host defences against malignancies
- In a randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies excluding NMSC, particularly lung cancer and lymphoma, was observed with tofacitinib compared to TNF inhibitors
- Lung cancers and lymphoma in patients treated with tofacitinib have also been observed in other clinical studies and in the post-marketing setting
- Other malignancies in patients treated with tofacitinib were observed in clinical studies and the post-marketing setting, including, but not limited to, breast cancer, melanoma, prostate cancer, and pancreatic cancer
- In patients over 65 years of age, patients who are current or past smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer), tofacitinib should only be used if no suitable treatment alternatives are available

**Venous thromboembolism (VTE)**[3]

- Serious VTE events including pulmonary embolism (PE), some of which were fatal, and deep vein thrombosis (DVT), have been observed in patients taking tofacitinib
- In a large, randomised post-authorisation safety surveillance study of rheumatoid arthritis patients who were 50 years of age and older and had at least one additional cardiovascular (CV) risk factor, VTE was observed at an increased and dose-dependent incidence in patients treated with tofacitinib compared to TNF inhibitors. The majority of these events were serious and some resulted in death

**PRAC recommendations on JAK inhibitors**[8]

- These medicines should be used in the following patients only if no suitable treatment alternatives are available: those aged 65

# XELJANZ SAFETY PROFILE IN RA

**PRAC recommendations on JAK inhibitors[8]**

- These medicines should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past, and those at increased risk of cancer
- JAK inhibitors should be used with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE) other than those listed above. Further, the doses should be reduced in patient groups who are at risk of VTE, cancer or major cardiovascular problems, where possible

# ORAL SURVEILLANCE: FOR MACE AND CANCERS (COPRIMARY ENDPOINTS), NONINFERIORITY WAS NOT SHOWN FOR THE COMBINED TOFACITINIB DOSES AS COMPARED WITH A TNF

**For adjudicated MACE and cancers, noninferiority was not shown for the combined XELJANZ doses as compared with a TNF inhibitor (MACE: hazard ratio 1.33; 95% CI 0.91–1.94; cancers: hazard ratio 1.48; 95% CI 1.04–2.09), because the upper boundary of the 95% CI was more than 1.8.[6]**

- ORAL Surveillance was a randomised, open-label, noninferiority, postauthorisation safety endpoint trial involving patients with active rheumatoid arthritis despire methotrexate treatment who were 50 years of age or older and had at least one additional cardiovascular risk factor[6]
- MACE and cancers occurred more often with tofacitinib than with a TNF inhibitor[6]



XELJANZ® (tofacitinib citrate)

# XELJANZ SAFETY PROFILE IN RA

- MACE and cancers occurred more often with tofacitinib than with a TNF inhibitor[6]

## DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PATIENTS AT BASELINE[6]

| | Total (N=4362) |
|---|---|
| **Female sex – no. (%)** | 3410 (78.2) |
| **Ever smoked – no. (%)** | 2103 (48.2) |
| **History of coronary heart disease – no. (%)** | 497 (11.4) |
| **History of diabetes mellitus – no. (%)** | 759 (17.4) |
| **History of hypertension – no. (%)** | 2878 (66.0) |
| **History of extraarticular disease – no. (%)** | 1605 (36.8) |

Table elaborated from Table 1, Ref 6. Please refer to source materials for the original table.

## ADDITIONAL PATIENT DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS (SAFETY ANALYSIS SET)[6]

| | Total (N=4362) |
|---|---|
| **Age (years), median (range)** | 60.0 (50.0–88.0) |
| **Duration of RA (years), mean (SD)** | 10.4 (9.1) |
| **BMI (kg/m²), mean (SD)** | 29.8 (6.5) |

Table elaborated from Table S2, Ref 6. Please refer to source materials for the original table.

## ADVERSE EVENTS (SAFETY ANALYSIS POPULATION, 28-DAY ON-TREATMENT TIME)[6,a]

## ADVERSE EVENTS (SAFETY ANALYSIS POPULATION, 28-DAY ON-TREATMENT TIME)[6,a]



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# XELJANZ SAFETY PROFILE IN RA

## ADVERSE EVENTS (SAFETY ANALYSIS POPULATION, 28-DAY ON-TREATMENT TIME)[6,a]

| | Tofacitinib, 5 mg Twice Daily (N=1455) | TNF inhibitor[b] (N=1451) |
|---|---|---|
| Serious adverse event – no. (%) | 351 (24.1) | 306 (21.1) |
| Serious infection – no. (%)<br>Hazard ratio vs. TNF inhibitor (95% CI) | 141 (9.7)<br>1.17 (0.92–1.50) | 119 (8.2)<br>Referent |
| Adjudicated opportunistic infection – no. (%)[c]<br>Hazard ratio vs. TNF inhibitor (95% CI) | 39 (2.7)<br>1.82 (1.07–3.09) | 21 (1.4)<br>Referent |
| All herpes zoster, serious and nonserious – no. (%)[d]<br>Hazard ratio vs. TNF inhibitor (95% CI) | 180 (12.4)<br>3.28 (2.44–4.41) | 58 (4.0)<br>Referent |
| Adjudicated hepatic event – no. (%)<br>Hazard ratio vs. TNF inhibitor (95% CI) | 46 (3.2)<br>1.29 (0.83–2.00) | 35 (2.4)<br>Referent |
| Adjudicated NMSC – no. (%)<br>Hazard ratio vs. TNF inhibitor (95% CI) | 31 (2.1)<br>1.90 (1.04–3.47) | 16 (1.1)<br>Referent |
| Adjudicated pulmonary embolism – no. (%)<br>Hazard ratio vs. TNF inhibitor (95% CI) | 9 (0.6)<br>2.93 (0.79–10.83) | 3 (0.2)<br>Referent |
| Adjudicated DVT – no. (%)<br>Hazard ratio vs. TNF inhibitor (95% CI) | 11 (0.8)<br>1.54 (0.60–3.97) | 7 (0.5)<br>Referent |
| Adjudicated VTE – no. (%)<br>Hazard ratio vs. TNF inhibitor (95% CI) | 17 (1.2)<br>1.66 (0.76–3.63) | 10 (0.7)<br>Referent |
| Adjudicated death from any cause – no. (%)<br>Hazard ratio vs. TNF inhibitor (95% CI) | 26 (1.8)<br>[illegible] | 17 (1.2)<br>[illegible] |

## ADVERSE EVENTS (SAFETY ANALYSIS POPULATION, 28-DAY ON-TREATMENT TIME)[6,a]

| | Tofacitinib, 5 mg Twice Daily (N=1455) | TNF inhibitor[b] (N=1451) |
|---|---|---|
| Incidence rate for MACE<br>No. of patients with first event/total no. (%) | 47/1455 (3.2) | 37/1451 (2.5) |

Table elaborated from Fig 1, Ref 6. Please refer to source materials for the original figure.

## ADVERSE EVENTS (SAFETY ANALYSIS POPULATION, 28-DAY ON-TREATMENT TIME)[6,a]

| | Tofacitinib, 5 mg Twice Daily (N=1455) | TNF inhibitor[b] (N=1451) |
|---|---|---|
| Incidence rate for cancers, excluding NMSC<br>No. of patients with first event/total no. (%) | 62/1455 (4.3) | 42/1451 (2.9) |

Table elaborated from Fig 2, Ref 6. Please refer to source materials for the original figure.

# XELJANZ SAFETY PROFILE IN RA

| | | |
|---|---|---|
| Hazard ratio vs. TNF inhibitor (95% CI) | 1.90 (1.04–3.47) | Referent |
| **Adjudicated pulmonary embolism – no. (%)**<br>**Hazard ratio vs. TNF inhibitor (95% CI)** | 9 (0.6)<br>2.93 (0.79–10.83) | 3 (0.2)<br>Referent |
| **Adjudicated DVT – no. (%)**<br>**Hazard ratio vs. TNF inhibitor (95% CI)** | 11 (0.8)<br>1.54 (0.60–3.97) | 7 (0.5)<br>Referent |
| **Adjudicated VTE – no. (%)**<br>**Hazard ratio vs. TNF inhibitor (95% CI)** | 17 (1.2)<br>1.66 (0.76–3.63) | 10 (0.7)<br>Referent |
| **Adjudicated death from any cause – no. (%)**<br>**Hazard ratio vs. TNF inhibitor (95% CI)** | 26 (1.8)<br>1.49 (0.81–2.74) | 17 (1.2)<br>Referent |

Table elaborated from Table 2, Ref 6. Please refer to source materials for the original table.

| | (N=1455) | |
|---|---|---|
| **Incidence rate for cancers, excluding NMSC**<br>**No. of patients with first event/total no. (%)** | 62/1455 (4.3) | 42/1451 (2.9) |

Table elaborated from Fig 2, Ref 6. Please refer to source materials for the original figure.

**The recommended dose for rheumatoid arthritis is 5 mg film-coated tablets administered twice daily, which should not be exceeded. No dose adjustment is required when used in combination with MTX.[3]**

[a]Shown are adverse events that emerged or worsened during the 28-day on-treatment period, which was defined as the minimum of the date of last contact or the date of the last dose of a trial treatment plus 28 days.[6]

[b]Hazard ratios for each tofacitinib dose relative to a TNF inhibitor were estimated, with two-sided 95% confidence intervals, based on two Cox proportional-hazards models, with treatment as the covariate.[6]

[c]Also included are opportunistic herpes zoster and tuberculosis events.[6]

[d]Included are herpes zoster adjudicated as an opportunistic infection and non-adjudicated herpes zoster events.[6]

AE, adverse event; ATE, arterial thromboembolism; BID, twice daily; BMI, body mass index; CI, confidence interval; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, cardiovascular; DVT, deep vein thrombosis; HR, hazard ratio; HZ herpes zoster; IR, incidence rate; JAK, Janus kinase; LTE, long-term extension; MACE, major adverse cardiovascular event; MTX, methotrexate; NMSC, non-melanoma skin cancer; OI, opportunistic infection; PE, pulmonary embolism; PRAC, Pharmacovigilance Risk Assessment Committee; RA, rheumatoid arthritis; SD, standard deviation; SIE, serious infectious event; TNF, tumour necrosis factor; UTI, urinary tract infection; VTE, venous thromboembolism.



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# XELJANZ SAFETY PROFILE IN RA

## THE EFFICACY AND SAFETY OF TOFACITINIB FILM-COATED TABLETS WERE ASSESSED IN 6 RANDOMIZED, DOUBLE-BLIND, CONTROLLED MULTICENTRE STUDIES (PHASE 3 CLINICAL STUDIES)[3]

The most commonly reported adverse reactions during the first 3 months of the double-blind, placebo or MTX controlled clinical studies were headache (3.9%), upper respiratory tract infections (3.8%), viral upper respiratory tract infection (3.3%), diarrhoea (2.9%), nausea (2.7%), and hypertension (2.2%).[3]

**The recommended dose for rheumatoid arthritis is 5 mg film-coated tablets administered twice daily, which should not be exceeded. No dose adjustment is required when used in combination with MTX.[3]**

## ADVERSE EVENTS OF SPECIAL INTEREST IN THE RA CLINICAL TRIALS PROGRAMME (EXCLUDING ORAL

### IRS (95% CI) FOR AEs OF SPECIAL INTEREST[7]

| | RA (N=7964) |
|---|---|
| Total tofacitinib exposure, patient-years | 23,497 |
| Serious infections, IR (95% CI) (n) | 2.5 (2.3 to 2.7) (592) |
| All HZ (nonserious and serious), IR (95% CI) (n) | 3.6 (3.3 to 3.8) (795) |
| Adjudicated tuberculosis, IR (95% CI) (n) | 0.2 (0.1 to 0.2) (38) |
| Adjudicated OIs excluding tuberculosis, IR (95% CI) (n) | 0.4 (0.3 to 0.5) (95) |
| Adjudicated malignancies excluding all NMSC, IR (95% CI) (n)<br>n1 (%) | 0.7 (0.6 to 0.9) (179)<br>211 (2.6) |
| Adjudicated NMSC, IR (95% CI) (n)<br>n1 (%) | 0.6 (0.5 to 0.7) (133)<br>135 (1.7) |
| Adjudicated lymphoma/lymphoproliferative disorders, IR (95% CI) (n) n1 (%)[9] | 0.1 (0.0 to 0.1) (12)<br>19 (0.2) |
| Adjudicated MACE,[a] IR (95% CI) (n) | 0.4 (0.3 to 0.5) (85)[b] |
| DVT[c] IR (95% CI) (n) | 0.2 (0.1 to 0.2) (37) |
| PE[c] IR (95% CI) (n) | 0.1 (0.1 to 0.2) (31) |
| Adjudicated gastrointestinal perforation, IR (95% CI) (n) | 0.1 (0.1 to 0.2) 27 |

Table elaborated from Table 3, Ref 7. Please refer to source materials for the original table.

**The recommended dose for rheumatoid arthritis is 5 mg film-coated tablets administered twice daily, which should not be exceeded. No dose adjustment is required when used in combination with MTX.[3]**
**XELJANZ is not approved in the European Union for the treatment of plaque psoriasis.**

[a]Composite MACE defined as any myocardial infarction, stroke, or cardiovascular death.[7]
[b]N=7311.[7]
[c]Previously reported in Mease et al. Ann Rheum Dis 2020;79:1400-13 (excludes Study A3921133) and Sandborn et al. J Crohns Colitis 2020;14:S498-500.

- The objectives of this analysis were to provide a comparison of adverse events (AEs) of special interest from integrated pooled studies of the tofacitinib clinical programmes[7]
- Patients received tofacitinib 0.5, 1, 2, 3, 5, 10, 15 or 30 mg two times per day, or 20 mg once a day in phase 1/2 studies, and tofacitinib 5 or 10 mg two times per day, or 11 mg extended-release once a day in phase 3 and phase 3b/4 studies. In LTE studies, the tofacitinib dose could be switched for efficacy or safety reasons. Data are reported for the following treatment groups: tofacitinib 5 mg two times per day (average total daily dose <15 mg); tofacitinib 10 mg two times per day (average total dose ≥15 mg); and all tofacitinib doses (i.e., average tofacitinib 5 mg two times per day and average tofacitinib 10 mg two times per day populations pooled)[7]
- The five most common SIEs per cohort were pneumonia (n=131), herpes zoster (HZ; n=44), urinary tract infection (n=31), cellulitis (n=31) and gastroenteritis (n=24) for RA[7]

**The recommended dose for rheumatoid arthritis is 5 mg film-coated tablets administered twice daily, which should not be exceeded. No dose adjustment is required when used in combination with MTX.[3]**
**XELJANZ is not approved in the European Union for the treatment of plaque psoriasis.**

**Major adverse cardiovascular events (including myocardial infarction)[3]**

- Major adverse cardiovascular events (MACE) have been observed in patients taking tofacitinib
- In a randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of myocardial infarctions was observed with tofacitinib compared with TNF inhibitors. In patients over 65 years of age, patients who are current or past smokers, and patients with other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available

**Malignancy and lymphoproliferative disorder[3]**

- Tofacitinib may affect host defences against malignancies
- In a randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies excluding NMSC, particularly lung cancer and lymphoma, was observed with tofacitinib compared to TNF inhibitors
- Lung cancers and lymphoma in patients treated with tofacitinib have also been observed in other clinical studies and in the post-marketing setting
- Other malignancies in patients treated with tofacitinib were observed in clinical studies and the post-marketing setting, including, but not limited to, breast cancer, melanoma, prostate cancer, and pancreatic cancer
- In patients over 65 years of age, patients who are current or past smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer), tofacitinib should only be used if no suitable treatment alternatives are available

**Venous thromboembolism (VTE)[3]**

- Serious VTE events including pulmonary embolism (PE), some of which were fatal, and deep vein thrombosis (DVT), have been observed in patients taking tofacitinib
- In a large, randomised post-authorisation safety surveillance study of rheumatoid arthritis patients who were 50 years of age and older and had at least one additional cardiovascular (CV) risk factor, VTE was observed at an increased and dose-dependent incidence in patients treated with tofacitinib compared to TNF inhibitors. The majority of these events were serious and some resulted in death

**PRAC recommendations on JAK inhibitors[8]**

- These medicines should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past, and those at increased risk of cancer
- JAK inhibitors should be used with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE) other than those listed above. Further, the doses should be reduced in patient groups who are at risk of VTE, cancer or major cardiovascular problems, where possible

## ORAL SURVEILLANCE: FOR MACE AND CANCERS (COPRIMARY ENDPOINTS), NONINFERIORITY WAS NOT SHOWN FOR THE COMBINED TOFACITINIB DOSES AS COMPARED WITH A TNF

**For adjudicated MACE and cancers, noninferiority was not shown for the combined XELJANZ doses as compared with a TNF inhibitor (MACE: hazard ratio 1.33; 95% CI 0.91–1.94; cancers: hazard ratio 1.48; 95% CI 1.04–2.09), because the upper boundary of the 95% CI was more than 1.8.[6]**

- ORAL Surveillance was a randomised, open-label, noninferiority, postauthorisation safety endpoint trial involving patients with active rheumatoid arthritis despire methotrexate treatment who were 50 years of age or older and had at least one additional cardiovascular risk factor[6]
- MACE and cancers occurred more often with tofacitinib than with a TNF inhibitor[6]

### DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PATIENTS AT BASELINE[6]

| | Total (N=4362) |
|---|---|
| Female sex – no. (%) | 3410 (78.2) |
| Ever smoked – no. (%) | 2103 (48.2) |
| History of coronary heart disease – no. (%) | 497 (11.4) |
| History of diabetes mellitus – no. (%) | 759 (17.4) |
| History of hypertension – no. (%) | 2878 (66.0) |
| History of extraarticular disease – no. (%) | 1605 (36.8) |

Table elaborated from Table 1, Ref 6. Please refer to source materials for the original table.

### ADDITIONAL PATIENT DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS (SAFETY ANALYSIS SET)[6]

| | Total (N=4362) |
|---|---|
| Age (years), median (range) | 60.0 (50.0–88.0) |
| Duration of RA (years), mean (SD) | 10.4 (9.1) |
| BMI ($kg/m^2$), mean (SD) | 29.8 (6.5) |

Table elaborated from Table S2, Ref 6. Please refer to source materials for the original table.

### ADVERSE EVENTS (SAFETY ANALYSIS POPULATION, 28-DAY ON-TREATMENT TIME)[6,a]

| | Tofacitinib, 5 mg Twice Daily (N=1455) | TNF inhibitor[b] (N=1451) |
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| Serious adverse event – no. (%) | 351 (24.1) | 306 (21.1) |
| Serious infection – no. (%)<br>Hazard ratio vs. TNF inhibitor (95% CI) | 141 (9.7)<br>1.17 (0.92–1.50) | 119 (8.2)<br>Referent |
| Adjudicated opportunistic infection – no. (%)[c]<br>Hazard ratio vs. TNF inhibitor (95% CI) | 39 (2.7)<br>1.82 (1.07–3.09) | 21 (1.4)<br>Referent |
| All herpes zoster, serious and nonserious – no. (%)[d]<br>Hazard ratio vs. TNF inhibitor (95% CI) | 180 (12.4)<br>3.28 (2.44–4.41) | 58 (4.0)<br>Referent |
| Adjudicated hepatic event – no. (%)<br>Hazard ratio vs. TNF inhibitor (95% CI) | 46 (3.2)<br>1.29 (0.83–2.00) | 35 (2.4)<br>Referent |
| Adjudicated NMSC – no. (%)<br>Hazard ratio vs. TNF inhibitor (95% CI) | 31 (2.1)<br>1.90 (1.04–3.47) | 16 (1.1)<br>Referent |
| Adjudicated pulmonary embolism – no. (%)<br>Hazard ratio vs. TNF inhibitor (95% CI) | 9 (0.6)<br>2.93 (0.79–10.83) | 3 (0.2)<br>Referent |
| Adjudicated DVT – no. (%)<br>Hazard ratio vs. TNF inhibitor (95% CI) | 11 (0.8)<br>1.54 (0.60–3.97) | 7 (0.5)<br>Referent |
| Adjudicated VTE – no. (%)<br>Hazard ratio vs. TNF inhibitor (95% CI) | 17 (1.2)<br>1.66 (0.76–3.63) | 10 (0.7)<br>Referent |
| Adjudicated death from any cause – no. (%)<br>Hazard ratio vs. TNF inhibitor (95% CI) | 26 (1.8)<br>1.49 (0.81–2.74) | 17 (1.2)<br>Referent |

Table elaborated from Table 2, Ref 6. Please refer to source materials for the original table.

### ADVERSE EVENTS (SAFETY ANALYSIS POPULATION, 28-DAY ON-TREATMENT TIME)[6,a]

| | Tofacitinib, 5 mg Twice Daily (N=1455) | TNF inhibitor[b] (N=1451) |
|---|---|---|
| Incidence rate for MACE<br>No. of patients with first event/total no. (%) | 47/1455 (3.2) | 37/1451 (2.5) |

Table elaborated from Fig 1, Ref 6. Please refer to source materials for the original figure.

### ADVERSE EVENTS (SAFETY ANALYSIS POPULATION, 28-DAY ON-TREATMENT TIME)[6,a]

| | Tofacitinib, 5 mg Twice Daily (N=1455) | TNF inhibitor[b] (N=1451) |
|---|---|---|
| Incidence rate for cancers, excluding NMSC<br>No. of patients with first event/total no. (%) | 62/1455 (4.3) | 42/1451 (2.9) |

Table elaborated from Fig 2, Ref 6. Please refer to source materials for the original figure.

**The recommended dose for rheumatoid arthritis is 5 mg film-coated tablets administered twice daily, which should not be exceeded. No dose adjustment is required when used in combination with MTX.[3]**

[a]Shown are adverse events that emerged or worsened during the 28-day on-treatment period, which was defined as the minimum of the date of last contact or the date of the last dose of a trial treatment plus 28 days.[6]

[b]Hazard ratios for each tofacitinib dose relative to a TNF inhibitor were estimated, with two-sided 95% confidence intervals, based on two Cox proportional-hazards models, with treatment as the covariate.[6]

[c]Also included are opportunistic herpes zoster and tuberculosis events.[6]

[d]Included are herpes zoster adjudicated as an opportunistic infection and non-adjudicated herpes zoster events.[6]

AE, adverse event; ATE, arterial thromboembolism; BID, twice daily; BMI, body mass index; CI, confidence interval; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, cardiovascular; DVT, deep vein thrombosis; HR, hazard ratio; HZ herpes zoster; IR, incidence rate; JAK, Janus kinase; LTE, long-term extension; MACE, major adverse cardiovascular event; MTX, methotrexate; NMSC, non-melanoma skin cancer; OI, opportunistic infection; PE, pulmonary embolism; PRAC, Pharmacovigilance Risk Assessment Committee; RA, rheumatoid arthritis; SD, standard deviation; SIE, serious infectious event; TNF, tumour necrosis factor; UTI, urinary tract infection; VTE, venous thromboembolism.

# KEY DIFFERENCES BETWEEN RANDOMISED CONTROLLED TRIALS AND REAL-WORLD EVIDENCE STUDIES

| | RCTS | RWE |
|---|---|---|
| **Patient population** | • Narrow, restricted, motivated[10]<br>• Internal validity due to unbiased methodology. For example, narrowly defined study population, randomisation, blinding, and inclusion of control groups[9] | • Larger and more diverse patient groups than RCTs[9]<br>• Unrestricted[10] |
| **Methodology** | • Different levels of hierarchies exist, with RCTs considered to provide higher quality evidence than observational studies because of their scientifically rigorous and robust methodology and randomised setting that eliminates both measured and unmeasured confounding[9]<br>• Standardised, controlled[10] | • Techniques such as propensity score matching (PSM) can be used to reduce selection bias by matching the characteristics of patients entering different arms of studies[10]<br>• Lack of standardisation across settings[9] |
| **Study design** | • Prospective design[9]<br>• Generally short follow-up period[10]<br>• Controlled trials and other interventional studies[9] | • Real-world studies may use information from electronic health and claims databases, which provide large datasets from diverse patient populations, and/or may be observational, collecting prospective or retrospective data over a long period of time[10] |

RCT, randomised controlled trial; RWE, real-world evidence.

TAP ANYWHERE TO CONTINUE

# KEY DIFFERENCES BETWEEN RANDOMISED CONTROLLED TRIALS AND REAL-WORLD EVIDENCE STUDIES

RCTs

Patient population

Methodology

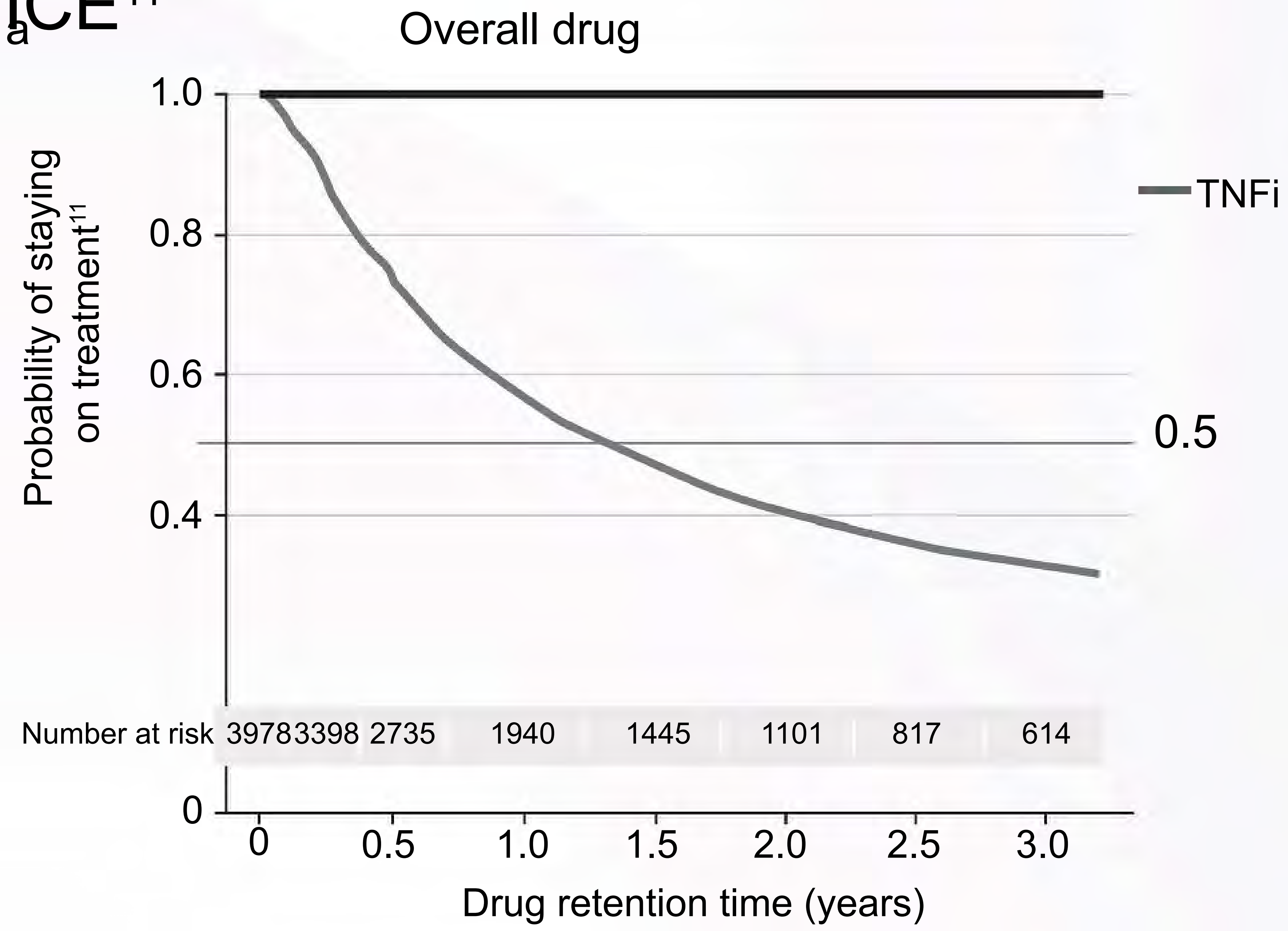
Study design

USING THE TOUCHSCREEN, MOVE THE SLIDER ON THE RIGHT HAND SIDE TO PLACE THE CURVE CORRECTLY

TAP ANYWHERE TO BEGIN

TAP ANYWHERE TO CONTINUE

# PLACE A LINE TO REFLECT HOW YOU THINK DRUG MAINTENANCE OF XELJANZ OVER A 3-YEAR PERIOD COMPARES WITH TNFis IN REAL-WORLD CLINICAL PRACTICE[11]




RESET

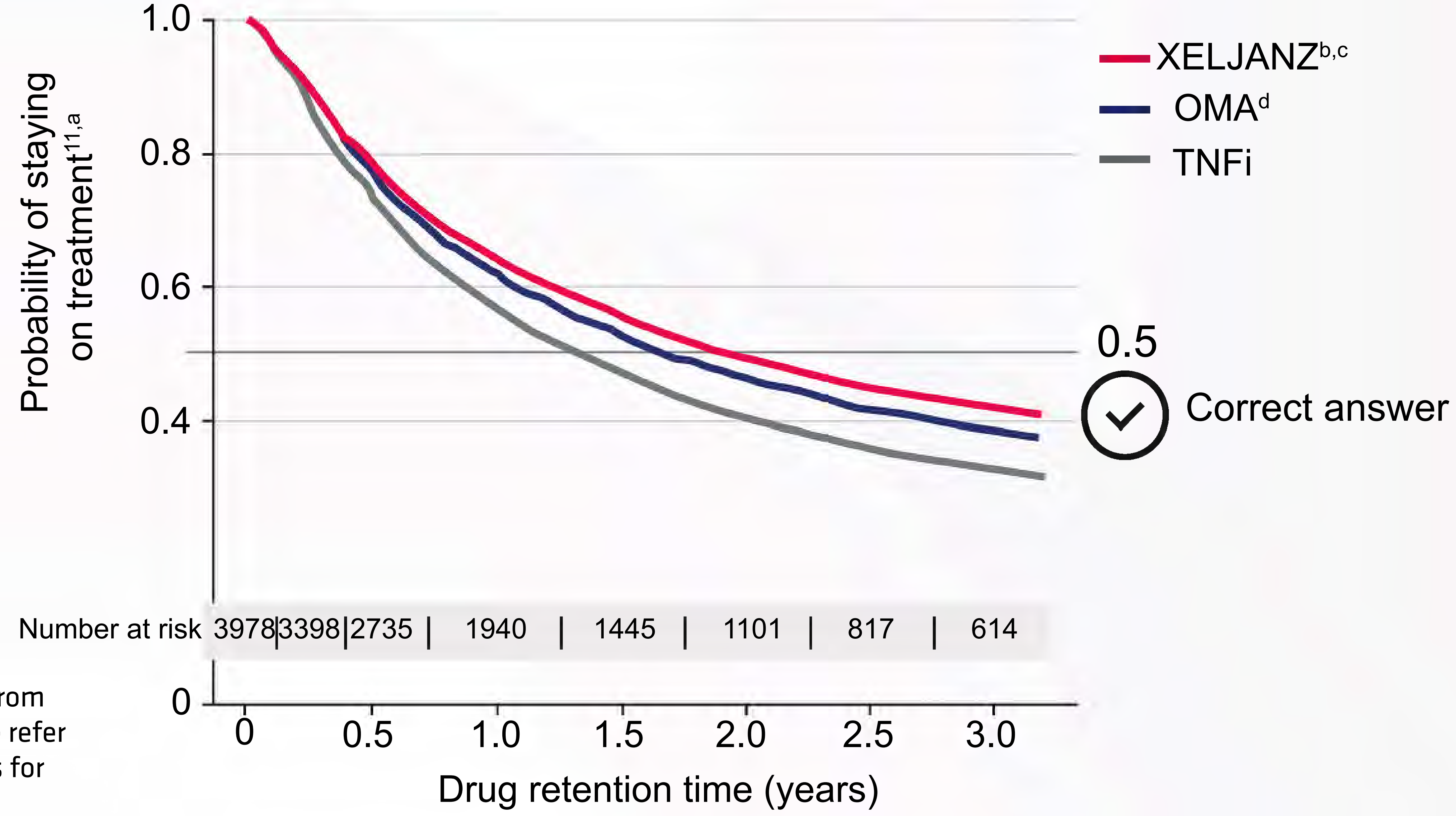
VIEW ANSWER

Graph elaborated from Fig 1, Ref 11. Please refer to source materials for the original graph.

**Data from a Swiss Registry.**[11]
TNFi, tumour necrosis factor inhibitor.

# PLACE A LINE TO REFLECT HOW YOU THINK DRUG MAINTENANCE OF XELJANZ OVER A 3-YEAR PERIOD COMPARES WITH TNFis IN REAL-WORLD CLINICAL PRACTICE[11]

Overall drug[a]




Graph elaborated from Fig 1, Ref 11. Please refer to source materials for the original graph.

**Data from a Swiss Registry.[11]**

Your answer
Black line

ADDITIONAL INFORMATION

NEXT QUESTION

[a]Adjusted survival curves based on 4023 treatment courses with 2103 events, representing the average patient in the SCQM population: a female seropositive, non-smoking patient with one prior b/tsDMARD, a female seropositive, non-smoking patients with one prior b/tsDMARD, mean age of 57, disease duration of 10.5 years, baseline DAS28 of 3.7, BMI of 26, who initiated her treatment before the launch of a second JAKi.[11] [b]In this analysis, patients took tofacitinib ≤5 mg bd (761) or tofacitinib >5-10 mg BID (27).[11] [c]The recommended dose for rheumatoid arthritis is 5 mg film-coated tablets administered twice daily, which should not be exceeded.[3] [d]bDMARD-OMA agents were abatacept (600), sarilumab (10), or tocilizumab (728).[11]
bDMARD, biologic disease-modifying antirheumatic drug; b/tsDMARD, targeted synthetic disease-modifying rheumatic drugs; bDMARD-OMA, biologic disease-modifying antirheumatic drug with other mode of actions; BID, twice daily; BMI, body mass index; CI, confidence interval; DAS28, disease activity 28; HR, hazard ratio; JAKi, Janus kinase inhibitor; LDA, low disease activity; RA, rheumatoid arthritis; SCQM-RA, Swiss Clinical Quality Management-Rheumatoid Arthritis; TNFi, tumour necrosis factor inhibitor.

## Supporting information:

- The effectiveness of three alternative treatment options for RA, including a JAKi, was compared in a large, observational, population-based cohort[11]
- Overall drug maintenance was significantly lower with TNFi compared with tofacitinib (HR 1.29 [95% CI 1.14 to 1.47]), but similar between bDMARD-OMA and tofacitinib (HR 1.09 [95% CI 0.96 to 1.24])[11]
- The likelihood of reaching LDA at 12 months was not significantly different between the three b/tsDMARDs[11]
- TNFi (n=1847), OMA (n=1338), Tofa (793)[11]



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# ADDITIONAL INFORMATION

## LIMITATIONS OF THE SCQM REGISTRY[11]

Missing data and incomplete follow-up is an issue in most registries; however, our primary outcome, drug retention, is a fairly robust outcome in this setting. All analyses were performed both with and without multiple imputations for missing baseline covariates. The results of complete case analysis yielded results consistent with analyses using multiple imputations and did not change the interpretations, suggesting that missing data points did not bias our results. Our effectiveness analysis at 1 year is limited by a reduced proportion of patients having an available disease activity assessment (CDAI) around 1 year. We used prediction (mixed-effects models) to attempt to recover the missing information; however, the response rates at 1 year need to be interpreted with caution. As with all non-randomised studies, confounding by indication may occur if the choice of a particular drug is linked to the outcome. To limit the risk of confounding by indication, we restricted the analysis to a time period when all treatment options were available, and adjusted the analysis by line of therapy and other potential confounding factors. Nevertheless, observational studies may be confounded by unmeasured factors. The strength of this observational study relies on the wide variety of RA patients, representative of the 'real world' and the statistical power stemming from a relatively large number of patients.

## EFFECTS OF CONCOMITANT csDMARD PRESCRIPTION[11]

In the multivariable adjusted model, TNFi maintenance was significantly decreased in MONO (HR 1.27 [95% CI 1.08–1.49]), but bDMARD-OMA and tofacitinib maintenance was not significantly different in MONO compared with csDMARD COMBI therapy (HR 1.03 [95% CI 0.89–1.20] and HR 1.11 [95% CI 0.91–1.35], respectively).

## REASONS FOR DISCONTINUATION[11]

The most common reason for stopping therapy was insufficient effectiveness (57%, 50%, and 46% for TNFi, bDMARD-OMA, and tofacitinib, respectively), followed by intolerance or adverse events (19%, 22%, and 30%, for TNFi, bDMARD-OMA, and tofacitinib,

# ADDITIONAL INFORMATION

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bDMARD-OMA, biologic disease-modifying antirheumatic drug with other mode of actions; CDAI, Clinical Disease Activity Index; CI, confidence interval; COMBI, combination therapy; csDMARD, conventional synthetic antirheumatic drug; HR, hazard ratio; MONO, monotherapy; RA, rheumatoid arthritis; SCQM, Swiss Clinical Quality Management; TNFi, tumour necrosis factor inhibitor.



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# IN REAL-WORLD CLINICAL PRACTICE, WHAT PERCENTAGE OF PATIENTS ACHIEVED DAS28(CRP) REMISSION WITH XELJANZ, COMPARED WITH bDMARDS?[12]

PULL UPWARDS WHERE INDICATED BY ARROWS, TO PLACE THE BARS AT THE DESIRED PERCENTAGE ON

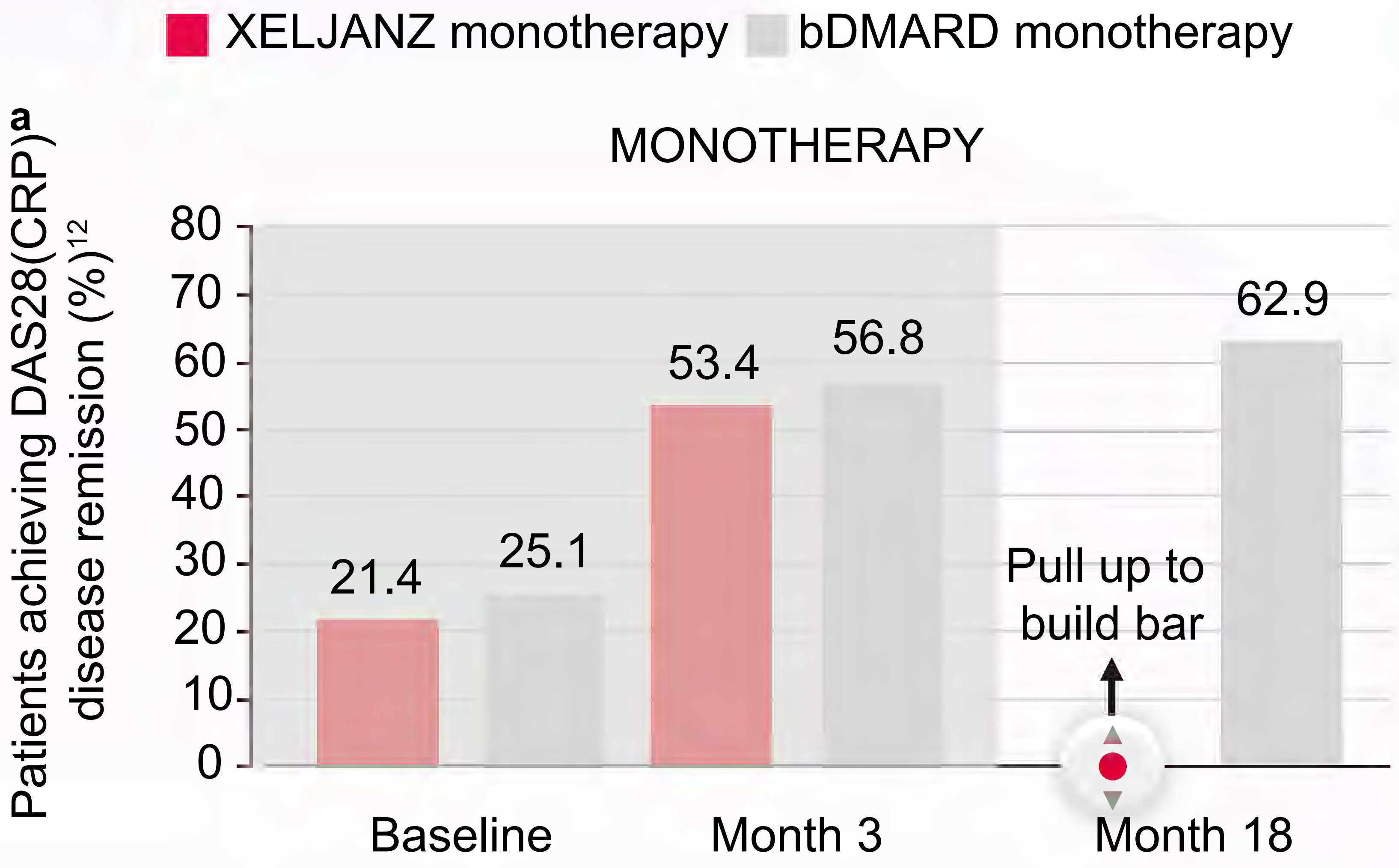
TAP ANYWHERE TO BEGIN

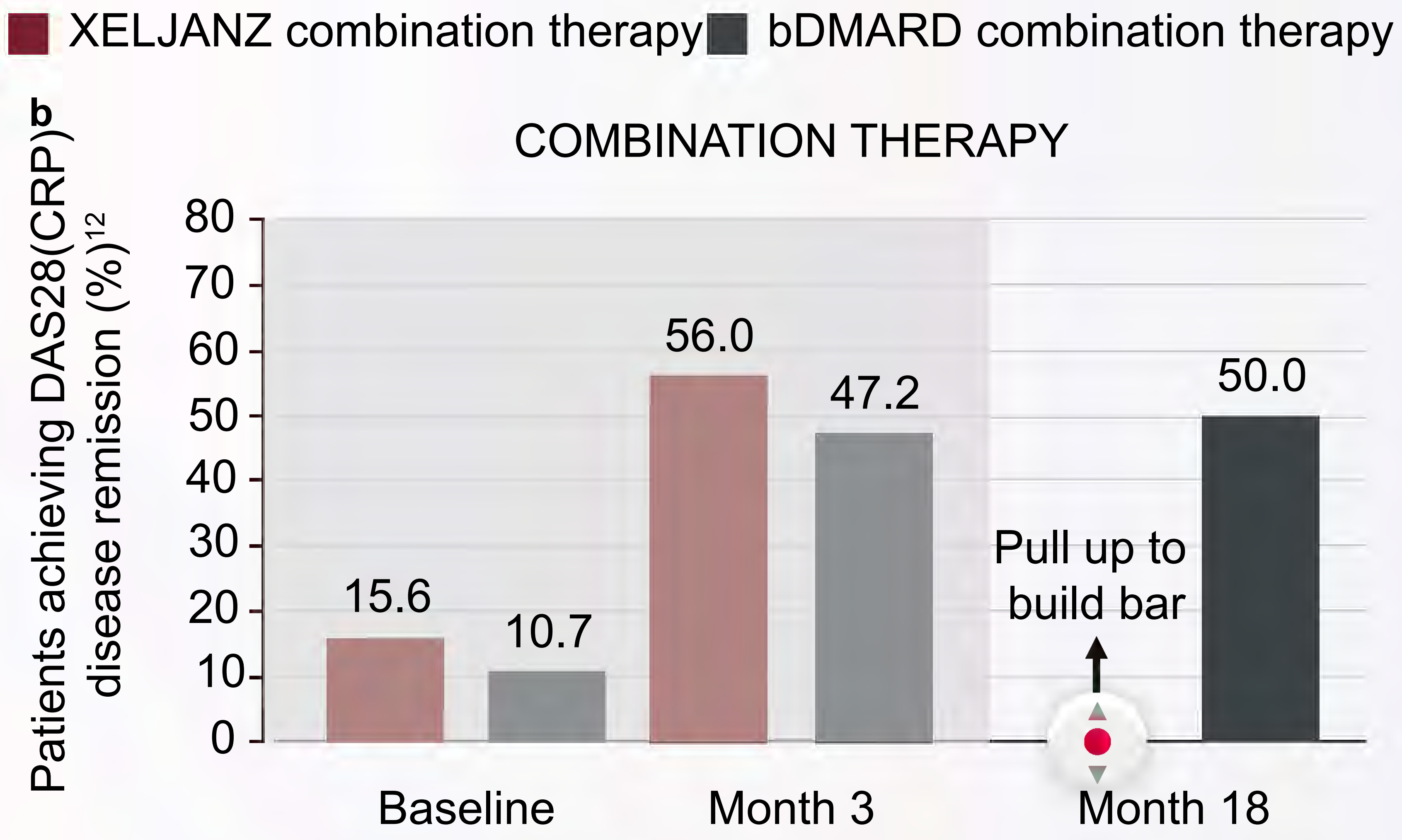
**Data were extracted from the Australian OPAL dataset.**



XELJANZ®
(tofacitinib citrate)

# IN REAL-WORLD CLINICAL PRACTICE, WHAT PERCENTAGE OF PATIENTS ACHIEVED DAS28(CRP) REMISSION WITH XELJANZ, COMPARED WITH bDMARDS?[12]



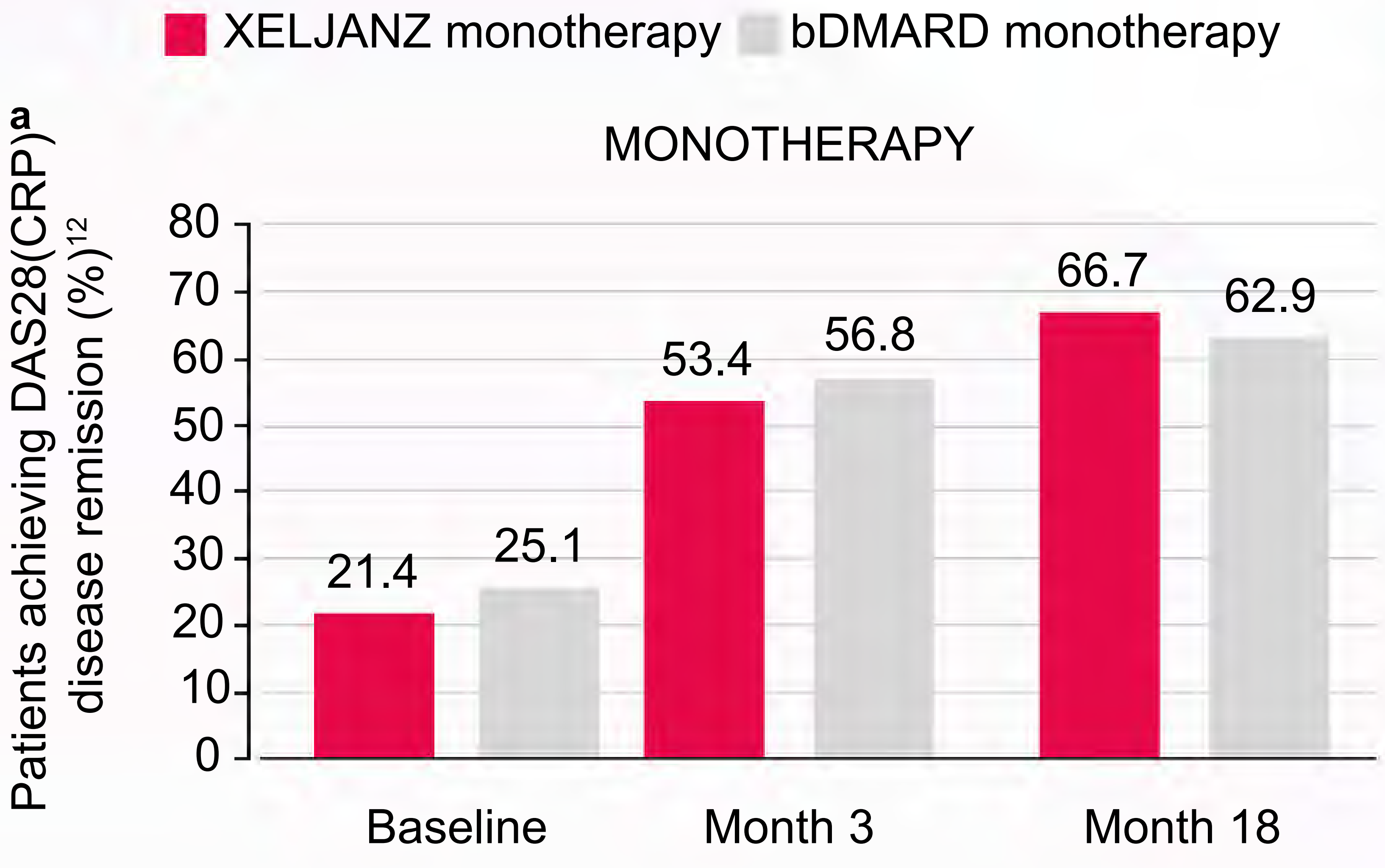

Graphs elaborated from Fig 2, Ref 12. Please refer to source materials for the original graphs.
Values above graph are sourced from Ref 12.

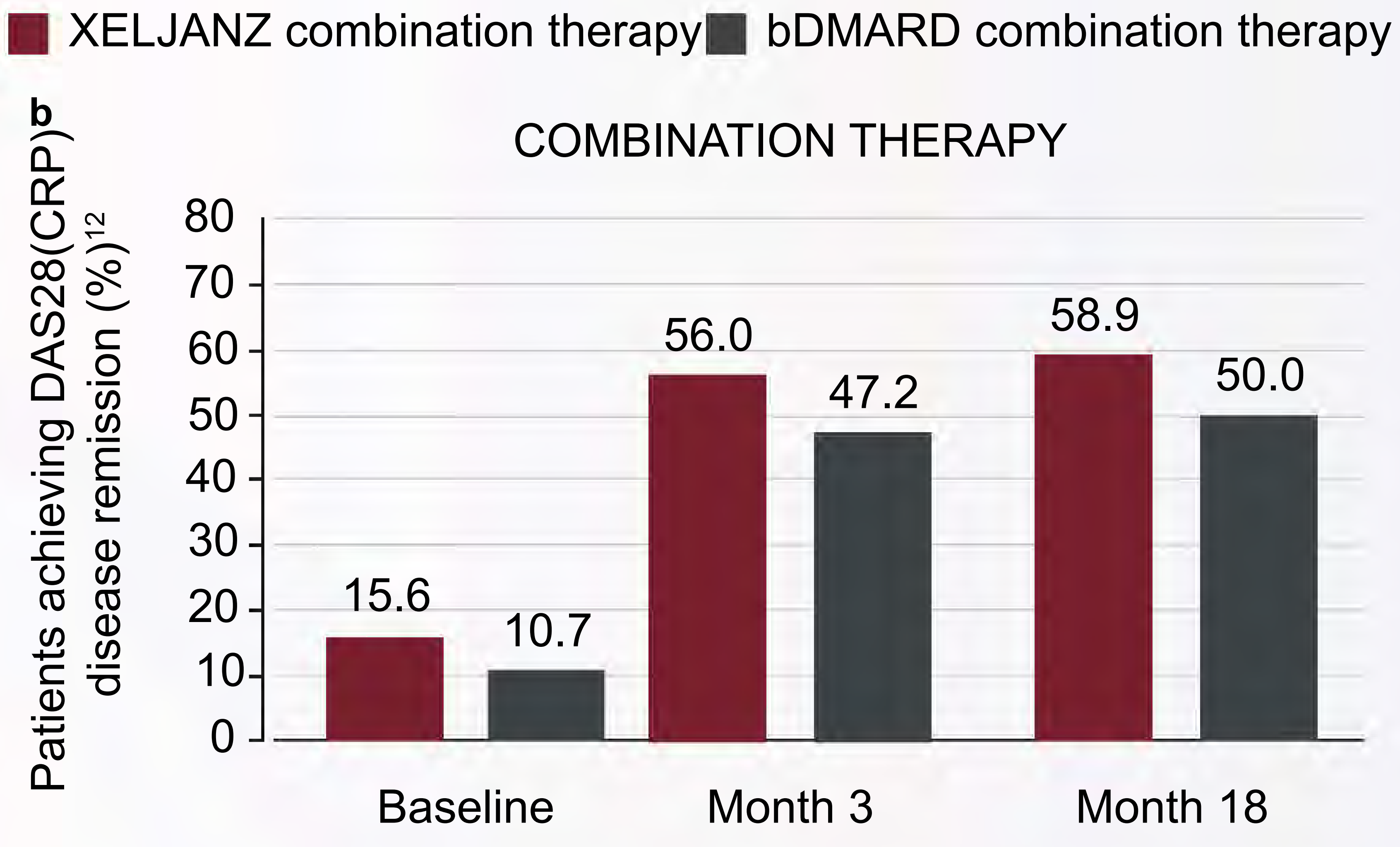
RESET

VIEW ANSWER

**Data were extracted from the Australian OPAL dataset.[12]**
bDMARD, biologic disease-modifying antirheumatic drug; CRP, C-reactive protein; DAS28, disease activity 28.

# IN REAL-WORLD CLINICAL PRACTICE, WHAT PERCENTAGE OF PATIENTS ACHIEVED DAS28(CRP) REMISSION WITH XELJANZ, COMPARED WITH bDMARDS?[12]




Graphs elaborated from Fig 2, Ref 12. Please refer to source materials for the original graphs.
Values above graph are sourced from Ref 12.
**Data were extracted from the Australian OPAL dataset.[12]**

Correct answer

Your answer
Black line

ADDITIONAL INFORMATION

NEXT QUESTION

## Supporting information:

- Post hoc analysis describing the effect monotherapy or concomitant csDMARD therapy has on the clinical effectiveness, treatment persistence, and treatment patterns in patients prescribed tofacitinib or bDMARDs[12,a]
- After 3 months of treatment, 56.8% and 53.4% were in DAS-28 CRP disease remission and after 18 months of treatment, 62.9% and 66.7% had reached DAS-28 CRP disease remission in the bDMARD monotherapy and tofacitinib
  - There were no significant differences in remission rates between monotherapy bDMARD and monotherapy tofacitinib groups[12]
  - After 3 months of treatment, 47.2% and 56.0% had achieved DAS-28 CRP disease remission and after 18 months of treatment, 50.0% and 58.9% had reached DAS-28 CRP disease remission in the bDMARD combination and tofacitinib combination therapy[b]
  - There were no significant differences in remission rates between the combination therapy bDMARD and combination therapy tofacitinib groups at any of these time points[12]

[a]The bDMARDs approved for use in Australia that were included in this study were abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tocilizumab.[12] [b]The baseline treatment combination covariates were methotrexate monotherapy, methotrexate in combination with other csDMARD(s), csDMARD(s) other than methotrexate and neither methotrexate nor other csDMARD(s) (bDMARD monotherapy).[12]
bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic antirheumatic drug; CRP, C-reactive protein; DAS28, disease activity 28; MTX, methotrexate; OPAL, Optimizing Patient outcome in Australian rheumatology.



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# ADDITIONAL INFORMATION

## LIMITATIONS OF THE OPAL-QUMI REGISTRY[12]

- This was a retrospective study of observational data, and as such there are a number of limitations including a large proportion of missing data
  - The variables, sample size, and study duration were selected in order to minimise the impact of this
- There may have also been confounding factors due to differences in the duration of disease at the commencement of the index b/tsDMARD, with those treated with tofacitinib had longer disease duration at index compared to the bDMARD

## PATIENT DEMOGRAPHICS AND DISEASE CHARACTERISTICS AT INDEX FOR THE PROPENSITY SCORE MATCHED POPULATION OF bDMARD AND TOFACITINIB MONOTHERAPY AND COMBINATION THERAPY[12]

| | Monotherapy | | Combination therapy[a] | |
|---|---|---|---|---|
| | bDMARDs[b] | Tofacitinib | bDMARDs[b] | Tofacitinib |
| *N* (%) | 564 | 282 | 736 | 368 |
| Age at index (years) Mean (SD) | 62.1 (12.8) | 62.0 (12.2) | 59.8 (13.3) | 60.2 (13.0) |
| Gender, *n* (% of column) Female | 452 (80.1) | 226 (80.1) | 604 (82.1) | 302 (82.1) |
| Disease duration in months, median | 125.4 [*N*=323] | 138.5 [*N*=170] | 90.9 [*N*=465] | 113.1 [*N*=241] |
| Line of therapy<br>1st line | 393 (69.7%) | 141 (50.0%) | 530 (72.0%) | 205 (55.7%) |



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IN REAL-WORLD CLINICAL PRACTICE, WHAT PERCENTAGE OF PATIEN…

COMPA…

# ADDITIONAL INFORMATION

| | | | | |
|---|---|---|---|---|
| Line of therapy | | | | |
| 1st line | 393 (69.7%) | 141 (50.0%) | 530 (72.0%) | 205 (55.7%) |
| 2nd line | 169 (30.0%) | 140 (49.6%) | 203 (27.6%) | 159 (43.2%) |
| 3rd line | 2 (0.4%) | 1 (0.4%) | 2 (0.4%) | 4 (1.1%) |
| Disease status | | | | |
| DAS28-CRP, *n* (% of column) | Rem: 52 (25.1%)<br>Low: 24 (11.6%)<br>Mod: 71 (34.3%)<br>High: 60 (29.0%) | Rem: 24 (21.4%)<br>Low: 12 (10.7%)<br>Mod: 40 (35.7%)<br>High: 36 (32.1%) | Rem: 36 (10.7%)<br>Low: 24 (7.2%)<br>Mod: 114 (34.0%)<br>High: 161 (48.1%) | Rem: 30 (15.6%)<br>Low: 14 (7.3%)<br>Mod: 69 (35.9%)<br>High: 79 (41.1%) |
| CDAI, *n* (% of column) | Rem: 25 (12.4%)<br>Low: 46 (22.8%)<br>Mod: 53 (26.2%)<br>High: 78 (38.6%) | Rem: 9 (7.8%)<br>Low: 28 (24.1%)<br>Mod: 26 (22.4%)<br>High: 53 (45.7%) | Rem: 12 (3.6%)<br>Low: 36 (10.9%)<br>Mod: 78 (23.6%)<br>High: 205 (61.9%) | Rem: 11 (5.7%)<br>Low: 25 (13.0%)<br>Mod: 52 (27.1%)<br>High: 104 (54.2%) |
| TJC28, mean (SD) | 6.6 (7.5) [*N*=314] | 7.3 (7.7) [*N*=168] | 10.9 (8.9) [*N*=469] | 9.2 (8.5) [*N*=234] |
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Table adapted from Bird, et al. 2022.

Table 2, Ref 12.

- In both the overall and matched populations, patients prescribed bDMARDs[b] or tofacitinib in combination with csDMARD(s)[a] had higher disease activity at index than those prescribed monotherapy bDMARD or tofacitinib[12]



XELJANZ®
(tofacitinib citrate)

IN REAL-WORLD CLINICAL PRACTICE, WHAT PERCENTAGE OF

# ADDITIONAL INFORMATION

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UP TO HOW MANY YEARS DOES XELJANZ OFFER LONG-TERM SAFETY DATA IN RA?[11]

SLIDE BUTTON TO SELECT YOUR ANSWER.
PRESS 'VIEW ANSWER' TO SEE THE RESULTS.

TAP ANYWHERE TO BEGIN



XELJANZ®
(tofacitinib citrate)

0 questions remaining

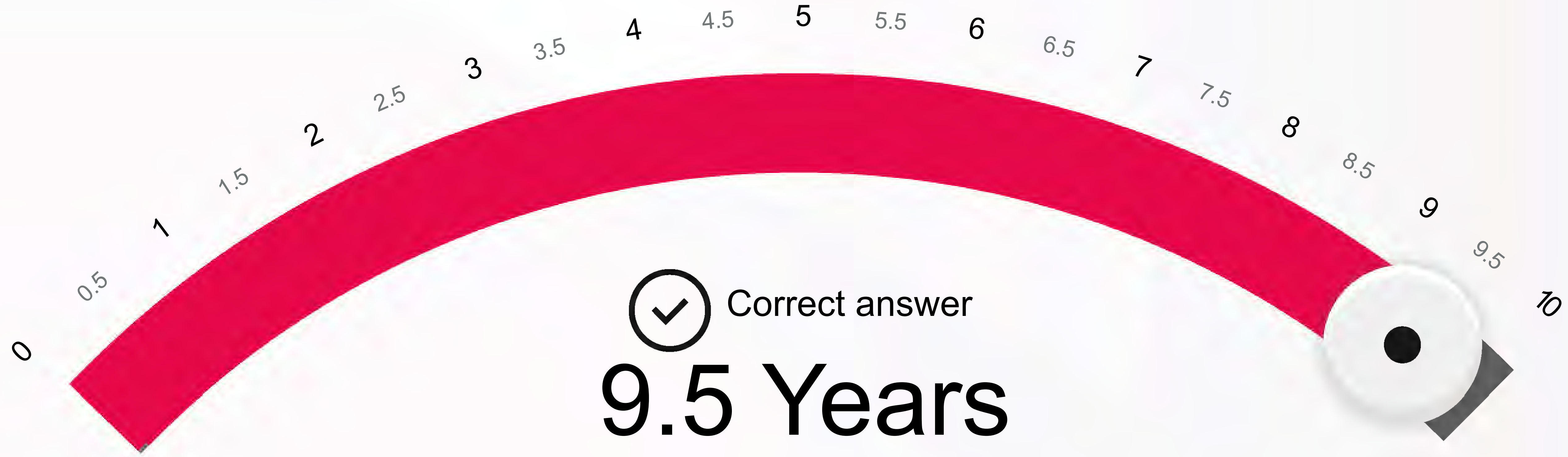
# UP TO HOW MANY YEARS DOES XELJANZ OFFER LONG-TERM SAFETY DATA IN RA?[13]


RESE
T

VIEW
ANSWER

RA, rheumatoid arthritis.

# UP TO HOW MANY YEARS DOES XELJANZ OFFER LONG-TERM SAFETY DATA IN RA?[13]




Correct answer

**9.5 Years**

(median exposure of 3.1 years)[13]

Your answer
XXXX

JAK, Janus kinase; PY, patient years; RA, rheumatoid arthritis.

COMPLETE

## Supporting information:

- This long-term integrated safety summary of tofacitinib with up to 9.5 years of follow-up in >7000 patients with RA worldwide, with a combined tofacitinib exposure of 22,875 PY, represents the largest clinical dataset for a JAK inhibitor in RA to date[13]



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# SOURCE MATERIALS

**The recommended dose for rheumatoid arthritis is 5 mg film-coated tablets administered twice daily, which should not be exceeded. No dose adjustment is required when used in combination with MTX.[3]**

TABLE S2, REF 1

**Additional file 2: Table S2.** Baseline and changes from baseline by visit prior to month 3 for patient-reported outcome measures

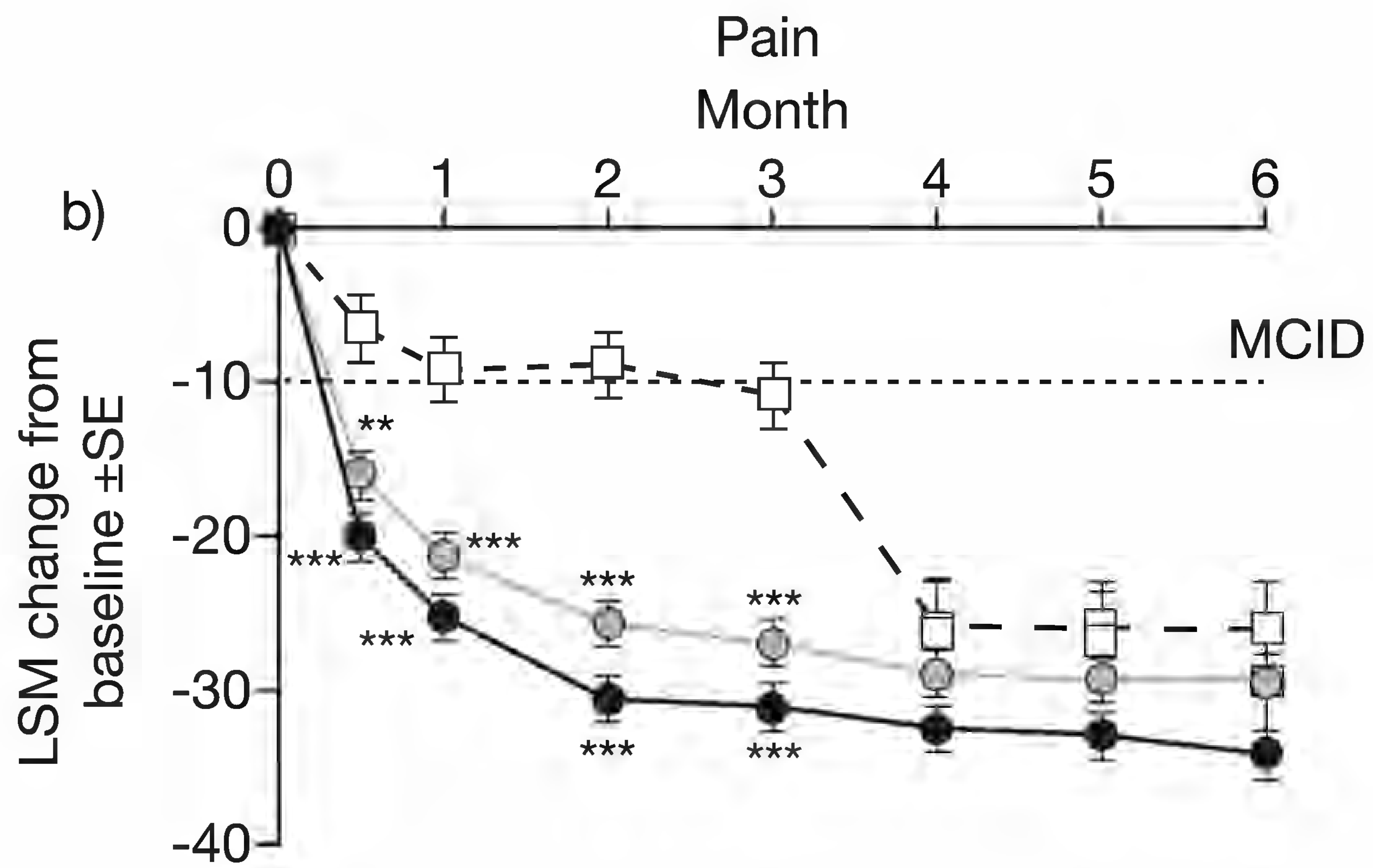
| | **Baseline mean (SD)** | | | **Week 2 LSM change from baseline (SE)** | | | **Month 1 LSM change from baseline (SE)** | | | **Month 2 LSM change from baseline (SE)** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Placebo (n=122)** | **Tofacitinib 5 mg BID (n=243)** | **Tofacitinib 10 mg BID (n=245)** | **Placebo (n=119)** | **Tofacitinib 5 mg BID (n=239)** | **Tofacitinib 10 mg BID (n=239)** | **Placebo (n=116)** | **Tofacitinib 5 mg BID (n=236)** | **Tofacitinib 10 mg BID (n=240)** | **Placebo (n=110)** | **Tofacitinib 5 mg BID (n=239)** | **Tofacitinib 10 mg BID (n=233)** |
| **PtGA** | 62.63 (21.91) | 61.66 (22.00)$^{b}$ | 63.46 (23.23)$^{g}$ | -7.02 (2.04) | -16.64 (1.44)$^{**}$ | -22.01 (1.46)$^{***}$ | -9.44 (2.06) | -23.26 (1.45)$^{***}$ | -25.62 (1.45)$^{***}$ | -9.22 (2.09) | -26.61 (1.44)$^{***}$ | -30.81 (1.47)$^{***}$ |
| **Pain** | 61.79 (21.27) | 61.35 (22.27)$^{f}$ | 62.03 (23.63)$^{g}$ | -6.32 (2.07) | -16.10 (1.47)$^{**}$ | -20.03 (1.48)$^{***}$ | -9.13 (2.09) | -21.28 (1.47)$^{***a}$ | -25.25 (1.48)$^{***}$ | -8.79 (2.13) | -25.65 (1.46)$^{***b}$ | -30.58 (1.49)$^{***}$ |
| **HAQ-DI** | 1.53 [illegible] | 1.53 [illegible]$^{h}$ | 1.50 [illegible]$^{f}$ | -0.12 [illegible] | -0.28 [illegible]$^{*}$ | -0.33 [illegible]$^{**c}$ | -0.14 [illegible] | -0.37 [illegible]$^{***}$ | -0.44 [illegible]$^{***d}$ | -0.14 [illegible] | -0.50 [illegible]$^{***}$ | -0.56 [illegible]$^{***e}$ |

# SOURCE MATERIALS

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HAQ-DI** | 1.53 (0.65) | 1.53 (0.66)[b] | 1.50 (0.64)[f] | -0.12 (0.05) | -0.28 (0.03)* | -0.33 (0.03)**[c] | -0.14 (0.05) | -0.37 (0.03)*** | -0.44 (0.03)***[d] | -0.14 (0.05) | -0.50 (0.03)*** | -0.56 (0.03)***[e] |

*p<0.01; **p<0.001; ***p<0.0001 vs placebo.
[a]n=237, [b]n=240, [c]n=237, [d]n=238, [e]n=231; [f]n=241; [g]n=243

FIGURE 2B, REF 1



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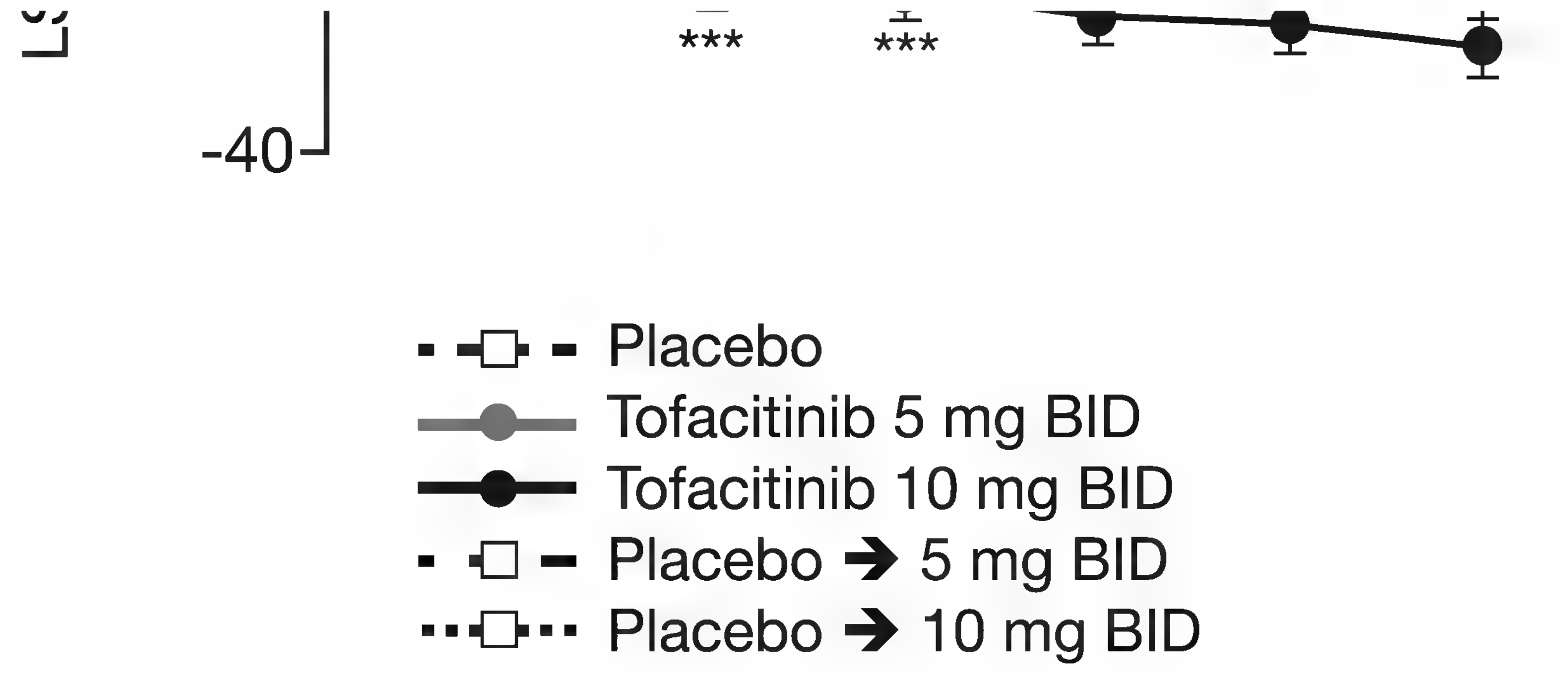
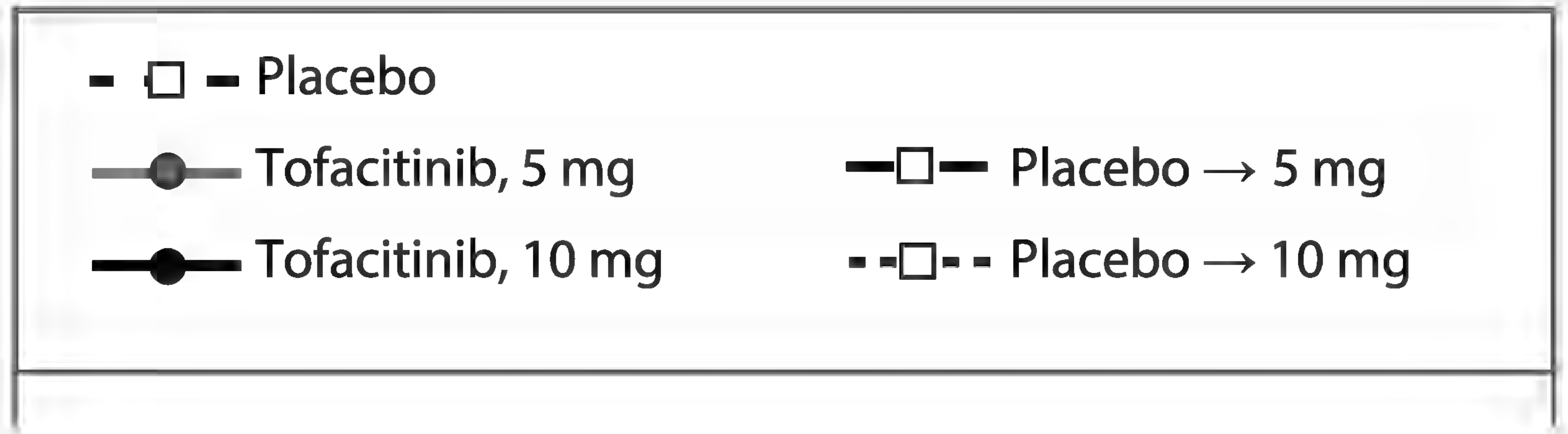
# SOURCE MATERIALS

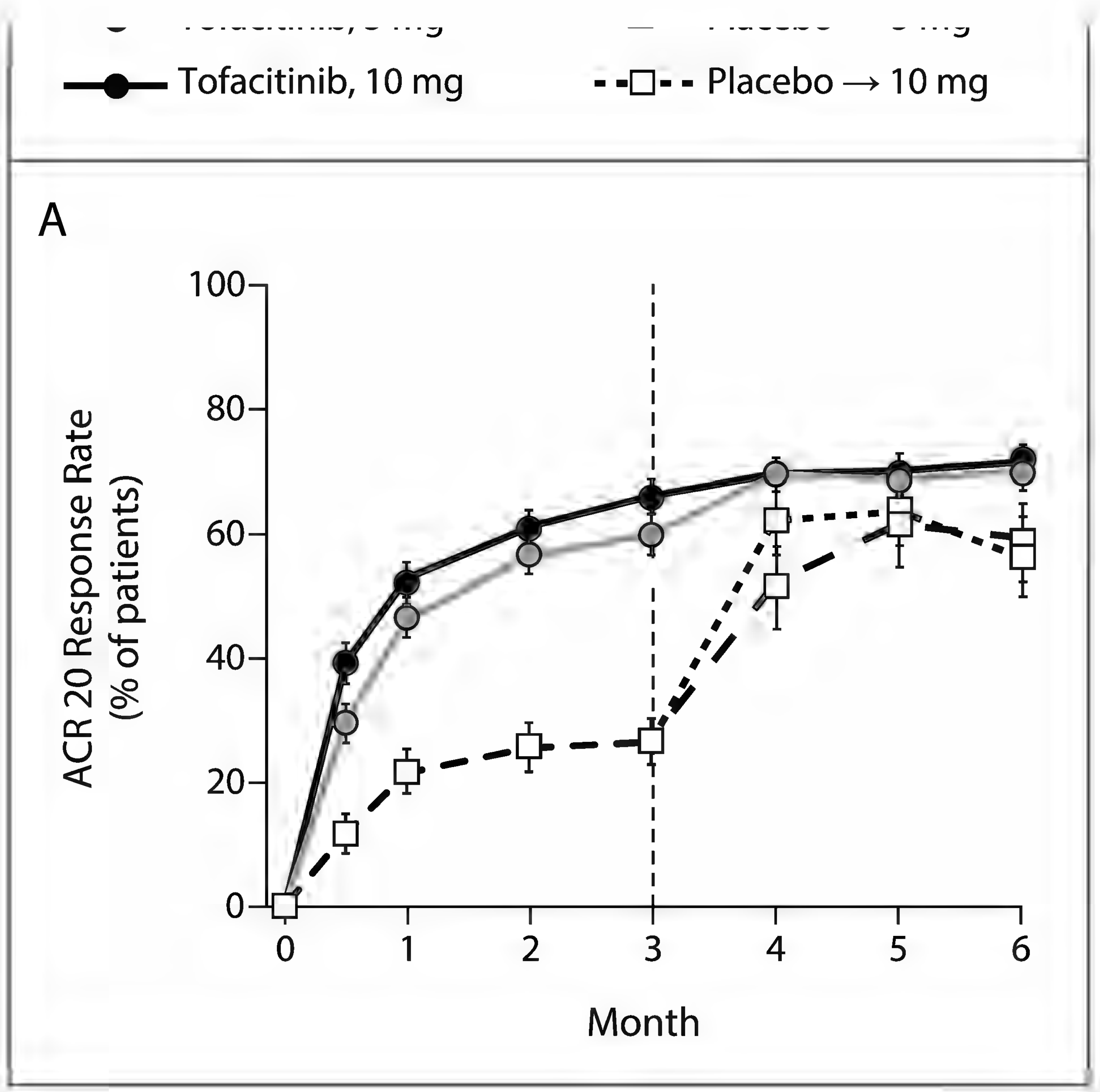



Least squares mean (LSM) changes from baseline: Patient Global Assessment of Pain (Pain). *p <0.05; **p <0.01; ***p <0.0001 vs placebo. MCID minimum clinically important difference.

FIGURE 1A, REF 2



# SOURCE MATERIALS




The percentage of patients with at least a 20% improvement in the American College of Rheumatology scale (ACR 20).

# SOURCE MATERIALS

TABLE 3, REF 7

**Table 3** IRs (95% CI) for AEs of special interest

| | RA (N=7964) | PsA (N=783) | UC (N=1157) | PsO (N=3663) |
|---|---|---|---|---|
| Total tofacitinib exposure, patient-years | 23 497 | 2038 | 2581 | 8950 |
| Serious infections, IR (95% CI) (n) | 2.5 (2.3 to 2.7) (592) | 1.2 (0.7 to 1.7) (24) | 1.7 (1.2 to 2.3) (45) | 1.3 (1.1 to 1.5) (119) |
| All HZ (non-serious and serious), IR (95% CI) (n) | 3.6 (3.3 to 3.8) (795) | 1.8 (1.2 to 2.4) (36) | 3.5 (2.8 to 4.3) (87) | 2.4 (2.0 to 2.7) (209) |
| Adjudicated OIs excluding tuberculosis, IR (95% CI) (n) | 0.4 (0.3 to 0.5) (95) | 0.3 (0.1 to 0.7) (7) | 1.6 (1.1 to 2.1) (40)* | 0.3 (0.2 to 0.5) (29) |
| Adjudicated tuberculosis, IR (95% CI) (n) | 0.2 (0.1 to 0.2) (38) | 0.0 (0.0 to 0.2) (0) | 0.0 (0.0 to 0.1) (0)* | 0.0 (0.0 to 0.1) (1) |
| Adjudicated malignancies excluding all NMSC, IR (95% CI) (n)<br>n1 (%) | 0.7 (0.6 to 0.9) (179)<br>211 (2.6) | 0.7 (0.4 to 1.2) (15)<br>18 (2.3) | 0.6 (0.3 to 1.0) (16)*<br>20 (1.8)* | 0.7 (0.5 to 0.8) (60)<br>74 (2.0) |
| Adjudicated NMSC, IR (95% CI) (n)<br>n1 (%) | 0.6 (0.5 to 0.7) (133)<br>135 (1.7) | 0.8 (0.4 to 1.3) (16)<br>16 (2.0) | 0.7 (0.4 to 1.1) (19)*<br>19 (1.7)* | 0.7 (0.5 to 0.9) (63)<br>67 (1.8) |
| Adjudicated melanoma, IR (95% CI) (n)<br>n1 (%) | 0.1 (0.0 to 0.1) (14)<br>14 (0.2) | 0.0 (0.0 to 0.2) (0)<br>0 (0.0) | 0.1 (0.0 to 0.3) (2)*<br>2 (0.2)* | 0.1 (0.0 to 0.1) (5)<br>5 (0.1) |
| Adjudicated lymphoma/lymphoproliferative disorders, IR (95% CI) (n)<br>n1 (%) | 0.1 (0.0 to 0.1) (12)<br>19 (0.2) | 0.1 (0.0 to 0.3) (1)<br>1 (0.1) | 0.1 (0.0 to 0.3) (2)*<br>2 (0.2)* | 0.02 (0.0 to 0.1) (2)<br>4 (0.1) |
| Adjudicated gastrointestinal perforation, IR (95% CI) (n) | 0.1 (0.1 to 0.2) (27) | 0.1 (0.0 to 0.3)(1) | 0.2 (0.1 to 0.5) (6)* | 0.1 (0.0 to 0.2) (7) |
| Adjudicated MACE,† IR (95% CI) (n) | 0.4 (0.3 to 0.5) (85)‡ | 0.3 (0.1 to 0.6) (6) | 0.3 (0.1 to 0.5) (7)* | 0.3 (0.2 to 0.4) (23) |
| DVT,§ IR (95% CI) (n) | 0.2 (0.1 to 0.2) (37) | 0.1 (0.0 to 0.3) (1) | 0.0 (0.0 to 0.2) (1) | 0.1 (0.0 to 0.1) (6) |
| PE,§ IR (95% CI) (n) | 0.1 (0.1 to 0.2) (31) | 0.1 (0.0 to 0.3) (1) | 0.2 (0.0 to 0.4) (4) | 0.1 (0.0 to 0.2) (9) |

*N=1124.
†Composite MACE defined as any myocardial infarction, stroke or cardiovascular death.
‡N=7311.
§Previously reported in Mease *et al*[40] (excludes Study A3921133) and Sandborn *et al*.[44]
AE, adverse event; DVT, deep vein thrombosis; HZ, herpes zoster; IR, incidence rate (unique patients with events per 100 patient-years); MACE, major adverse cardiovascular events; N, number of

# SOURCE MATERIALS

| | | | | |
|---|---|---|---|---|
| PE,§ IR (95% CI) (n) | 0.1 (0.1 to 0.2) (31) | 0.1 (0.0 to 0.3) (1) | 0.2 (0.0 to 0.4) (4) | 0.1 (0.0 to 0.2) (9) |

*N=1124.
†Composite MACE defined as any myocardial infarction, stroke or cardiovascular death.
‡N=7311.
§Previously reported in Mease *et al*[40] (excludes Study A3921133) and Sandborn *et al*.[44]
AE, adverse event; DVT, deep vein thrombosis; HZ, herpes zoster; IR, incidence rate (unique patients with events per 100 patient-years); MACE, major adverse cardiovascular events; N, number of patients in the disease cohort; n, unique number of patients with event (events are counted up to 28 days beyond the last dose or to the data cut-off date, and are included in the calculation of IR); n1, all events, including those occurring outside the 28-day risk period; NMSC, non-melanoma skin cancer; OI, opportunistic infection; PE, pulmonary embolism; PsA, psoriatic arthritis; PsO psoriasis; RA, rheumatoid arthritis; UC, ulcerative colitis.

**XELJANZ is not approved in the European Union for the treatment of plaque psoriasis.**

TABLE 1, REF 6

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Safety Analysis Population).*

| Characteristic | Tofacitinib, 5 mg Twice Daily (N = 1455) | Tofacitinib, 10 mg Twice Daily (N = 1456)† | TNF Inhibitor (N = 1451) | Total (N = 4362) |
|---|---|---|---|---|
| Age | | | | |
| Mean — yr | 60.8±6.8 | 61.4±7.1 | 61.3±7.5 | 61.2±7.1 |
| ≥65 yr — no. (%) | 413 (28.4) | 478 (32.8) | 462 (31.8) | 1353 (31.0) |
| Female sex — no. (%) | 1169 (80.3) | 1124 (77.2) | 1117 (77.0) | 3410 (78.2) |



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| | | | | |
|---|---|---|---|---|
| Female sex — no. (%) | 1169 (80.3) | 1124 (77.2) | 1117 (77.0) | 3410 (78.2) |
| Race — no. (%)‡ | | | | |
| White | 1128 (77.5) | 1126 (77.3) | 1099 (75.7) | 3353 (76.9) |
| Black | 63 (4.3) | 65 (4.5) | 83 (5.7) | 211 (4.8) |
| Asian | 65 (4.5) | 56 (3.8) | 55 (3.8) | 176 (4.0) |
| Other | 199 (13.7) | 209 (14.4) | 214 (14.7) | 622 (14.3) |
| Smoking status — no. (%) | | | | |
| Never smoked | 735 (50.5) | 752 (51.6) | 772 (53.2) | 2259 (51.8) |
| Ever smoked | 720 (49.5) | 704 (48.4) | 679 (46.8) | 2103 (48.2) |
| History of hypertension — no. (%) | 955 (65.6) | 954 (65.5) | 969 (66.8) | 2878 (66.0) |
| History of diabetes mellitus — no. (%) | 243 (16.7) | 261 (17.9) | 255 (17.6) | 759 (17.4) |
| History of venous thromboembolism — no. (%)§ | 19 (1.3) | 33 (2.3) | 27 (1.9) | 79 (1.8) |
| History of extraarticular disease — no. (%)¶ | 532 (36.6) | 521 (35.8) | 552 (38.0) | 1605 (36.8) |
| History of coronary heart disease — no. (%) | 161 (11.1) | 172 (11.8) | 164 (11.3) | 497 (11.4) |
| Family history of coronary heart disease — no. (%) | | | | |
| First-degree male relative <55 yr of age | 154 (10.6) | 132 (9.1) | 151 (10.4) | 437 (10.0) |
| First-degree female relative <65 yr of age | 115 (7.9) | 107 (7.3) | 100 (6.9) | 322 (7.4) |
| Fasting HDL cholesterol <40 mg/dl — no. (%) | 172 (11.8) | 195 (13.4) | 173 (11.9) | 540 (12.4) |



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| | | | | |
|---|---|---|---|---|
| Fasting HDL cholesterol <40 mg/dl — no. (%) | 172 (11.8) | 195 (13.4) | 173 (11.9) | 540 (12.4) |

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. HDL denotes high-density lipoprotein, and TNF tumor necrosis factor.
† Patients assigned to receive tofacitinib at a dose of 10 mg twice daily who had their dose reduced to 5 mg twice daily or who discontinued the trial drug were counted in the group receiving 10 mg twice daily.
‡ Race was reported by the patient.
§ Venous thromboembolism included deep-vein thrombosis and pulmonary embolism.
¶ Extraarticular disease included nodules, Sjögren's syndrome, anemia of chronic disease, pulmonary manifestations, or other clinical features as identified by the site investigator.

TABLE S2, REF 6

**Table S2.** Additional Patient Demographics and Baseline Disease Characteristics (Safety Analysis Set)

| | Tofacitinib 5 mg BID (N=1455) | Tofacitinib 10 mg BID* (N=1456) | TNFi (N=1451) | Total (N=4362) |
|---|---|---|---|---|
| Age (years), median (range) | 60.0 (50.0–86.0) | 61.0 (50.0–85.0) | 60.0 (50.0–88.0) | 60.0 (50.0–88.0) |
| Duration of RA (years), mean (SD) | 10.4 (8.8) | 10.2 (9.0) | 10.6 (9.3) | 10.4 (9.1) |

# SOURCE MATERIALS

| | (N=1455) | (N=1456) | (N=1451) | (N=4362) |
|---|---|---|---|---|
| Age (years), median (range) | 60.0 (50.0–86.0) | 61.0 (50.0–85.0) | 60.0 (50.0–88.0) | 60.0 (50.0–88.0) |
| Duration of RA (years), mean (SD) | 10.4 (8.8) | 10.2 (9.0) | 10.6 (9.3) | 10.4 (9.1) |
| Geographical region, n (%) | | | | |
| US and Canada | 402 (27.6) | 409 (28.1) | 432 (29.8) | 1243 (28.5) |
| Latin America | 385 (26.5) | 414 (28.4) | 403 (27.8) | 1202 (27.6) |
| Europe | 43 (3.0) | 56 (3.8) | 48 (3.3) | 147 (3.4) |
| Rest of the world | 625 (43.0) | 577 (39.6) | 568 (39.1) | 1770 (40.6) |
| BMI (kg/m$^2$), mean (SD) [number of patients with missing values] | 29.7 (6.5) [7] | 29.7 (6.3) [3] | 29.8 (6.6) [7] | 29.8 (6.5) [17] |
| BMI ≥30 kg/m$^2$, n (%) | 606 (41.6) | 594 (40.8) | 617 (42.5) | 1817 (41.7) |
| Concomitant medication use at baseline (day 1), n (%) | | | | |
| Oral contraceptives or HRT | 51 (3.5) | 41 (2.8) | 45 (3.1) | 137 (3.1) |
| Corticosteroid | 836 (57.5) | 829 (56.9) | 830 (57.2) | 2495 (57.2) |
| Methotrexate | 1453 (99.9) | 1456 (100.0) | 1451 (100.0) | 4360 (>99.9) |

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| | | | | |
|---|---|---|---|---|
| Methotrexate | 1453 (99.9) | 1456 (100.0) | 1451 (100.0) | 4360 (>99.9) |
| Aspirin | 212 (14.6) | 231 (15.9) | 224 (15.4) | 667 (15.3) |
| Anticoagulants | 47 (3.2) | 66 (4.5) | 62 (4.3) | 175 (4.0) |
| Antidepressants | 218 (15.0) | 208 (14.3) | 223 (15.4) | 649 (14.9) |
| Methotrexate dose[†] (mg/week), mean SD [number of patients with missing values] | 17.4 (4.4) [21] | 17.4 (4.1) [33] | 17.3 (4.3) [16] | 17.3 (4.3) [70] |
| Prior medication use, n (%) | | | | |
| Methotrexate | 1455 (100.0) | 1456 (100.0) | 1451 (100.0) | 4362 (100.0) |
| Nonmethotrexate csDMARDs | 421 (28.9) | 395 (27.1) | 424 (29.2) | 1240 (28.4) |
| bDMARDs | 164 (11.3) | 138 (9.5) | 150 (10.3) | 452 (10.4) |
| TNFi | 115 (7.9) | 110 (7.6) | 105 (7.2) | 330 (7.6) |
| Non-TNFi bDMARDs | 71 (4.9) | 53 (3.6) | 62 (4.3) | 186 (4.3) |
| Number of prior csDMARDs, mean (SD) | 1.4 (0.7) | 1.4 (0.7) | 1.4 (0.7) | 1.4 (0.7) |
| Number of prior bDMARDs,[‡] mean (SD) | 1.3 (0.6) | 1.3 (0.6) | 1.2 (0.5) | 1.3 (0.6) |

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| | | | | |
|---|---|---|---|---|
| Number of prior bDMARDs,‡ mean (SD) | 1.3 (0.6) | 1.3 (0.6) | 1.2 (0.5) | 1.3 (0.6) |
| Medical history, n (%) | | | | |
| Depression | 176 (12.1) | 178 (12.2) | 183 (12.6) | 537 (12.3) |
| Myocardial infarction | 60 (4.1) | 59 (4.1) | 48 (3.3) | 167 (3.8) |
| Unstable angina | 17 (1.2) | 14 (1.0) | 7 (0.5) | 38 (0.9) |
| Coronary artery procedures | 63 (4.3) | 69 (4.7) | 63 (4.3) | 195 (4.5) |
| Other coronary heart disease | 84 (5.8) | 95 (6.5) | 101 (7.0) | 280 (6.4) |
| Alcohol use within last 7 days, n (%) | 187 (12.9) | 193 (13.3) | 183 (12.6) | 563 (12.9) |
| Fasting HDL-C (mg/dL), mean (SD) | 58.1 (16.8) | 57.6 (17.3) | 57.9 (16.8) | 57.9 (17.0) |
| Fasting total cholesterol/HDL-C ratio >4, n (%) | 433 (29.8) | 439 (30.2) | 430 (29.6) | 1302 (29.8) |
| CRP >2.87 mg/L, n (%) | 1279 (87.9) | 1270 (87.2) | 1266 (87.3) | 3815 (87.5) |
| SDAI,§ mean (SD) [number of patients with missing values] | 41.5 (12.5) [45] | 41.5 (12.6) [52] | 41.4 (12.5) [65] | 41.5 (12.5) [162] |
| HAQ-DI,¶ mean (SD) [number of patients with missing values] | 1.6 (0.6) [11] | 1.6 (0.6) [18] | 1.6 (0.6) [25] | 1.6 (0.6) [54] |
| TJC28, mean (SD) [number of patients with missing values] | 15.7 (6.3) [1] | 15.7 (6.4) | 15.6 (6.2) [2] | 15.7 (6.3) [3] |



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| | | | | |
|---|---|---|---|---|
| TJC28, mean (SD) [number of patients with missing values] | 15.7 (6.3) [1] | 15.7 (6.4) | 15.6 (6.2) [2] | 15.7 (6.3) [3] |
| SJC28, mean (SD) [number of patients with missing values] | 11.8 (5.1) [1] | 12.0 (5.2) | 11.7 (5.0) [2] | 11.8 (5.1) [3] |
| Rheumatoid factor positive, n (%) | 1243 (85.4) | 1261 (86.6) | 1264 (87.1) | 3768 (86.4) |
| Anti-CCP positive, n (%) | 1093 (75.1) | 1129 (77.5) | 1119 (77.1) | 3341 (76.6) |

*Patients randomized to the tofacitinib 10 mg BID group who had their dose of tofacitinib reduced to 5 mg BID, or discontinued from the trial drug, were counted in the tofacitinib 10 mg BID group. †Based on use on day 1. ‡For patients who were previously treated with either TNFi or non-TNFi bDMARDs. §Scores range from 0 to 100, with the maximum score dependent on the maximum reasonably assumable C-reactive protein level in RA; higher scores are indicative of worse disease activity.[2-4] ¶Scores range from 0 to 3, with increasing scores indicative of worse functioning (0 indicating no functional impairment and 3 indicating complete impairment).[5] bDMARD, biologic disease-modifying antirheumatic drug; BID, twice daily; BMI, body mass index; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire-Disability Index; HDL-C, high-density lipoprotein cholesterol; HRT, hormone replacement therapy; n, number of patients meeting baseline criteria; N, number of patients in each treatment group in the safety population; RA, rheumatoid arthritis; SD, standard deviation; SDAI, Simplified Disease Activity Index; SJC28, swollen joint count out of 28 joints; TJC28, tender joint count out of 28 joints; TNFi, tumor necrosis factor inhibitors.

TABLE S2, REF 6

# SOURCE MATERIALS

TABLE S2, REF 6

Table 2. Adverse Events (Safety Analysis Population, 28-Day On-Treatment Time).*

| Event | Tofacitinib, 5 mg Twice Daily (N = 1455) | Tofacitinib, 10 mg Twice Daily (N = 1456)† | TNF Inhibitor (N = 1451) |
|---|---|---|---|
| Adverse event — no. (%) | 1333 (91.6) | 1344 (92.3) | 1308 (90.1) |
| Serious adverse event — no. (%) | 351 (24.1) | 390 (26.8) | 306 (21.1) |
| Discontinuation of trial treatment due to adverse event — no. (%) | | | |
| Permanent discontinuation‡ | 210 (14.4) | 304 (20.9) | 210 (14.5) |
| Temporary discontinuation§ | 665 (45.7) | 736 (50.5) | 576 (39.7) |
| Adverse events of special interest | | | |
| Serious infection — no. (%) | 141 (9.7) | 169 (11.6) | 119 (8.2) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 1.17 (0.92–1.50) | 1.48 (1.17–1.87) | Referent |
| Adjudicated opportunistic infection — no. (%)¶ | 39 (2.7) | 44 (3.0) | 21 (1.4) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 1.82 (1.07–3.09) | 2.17 (1.29–3.66) | Referent |
| All herpes zoster, serious and nonserious — no. (%)⊠ | 180 (12.4) | 178 (12.2) | 58 (4.0) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 3.28 (2.44–4.41) | 3.39 (2.52–4.55) | Referent |

# SOURCE MATERIALS

| | | | |
|---|---|---|---|
| Hazard ratio vs. TNF inhibitor (95% CI) | 3.28 (2.44–4.41) | 3.39 (2.52–4.55) | Referent |
| Adjudicated hepatic event — no. (%) | 46 (3.2) | 72 (4.9) | 35 (2.4) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 1.29 (0.83–2.00) | 2.14 (1.43–3.21) | Referent |
| Adjudicated NMSC — no. (%) | 31 (2.1) | 33 (2.3) | 16 (1.1) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 1.90 (1.04–3.47) | 2.16 (1.19–3.92) | Referent |
| Adjudicated pulmonary embolism — no. (%) | 9 (0.6) | 24 (1.6) | 3 (0.2) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 2.93 (0.79–10.83) | 8.26 (2.49–27.43) | Referent |
| Adjudicated DVT — no. (%) | 11 (0.8) | 15 (1.0) | 7 (0.5) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 1.54 (0.60–3.97) | 2.21 (0.90–5.43) | Referent |
| Adjudicated VTE — no. (%) | 17 (1.2) | 34 (2.3) | 10 (0.7) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 1.66 (0.76–3.63) | 3.52 (1.74–7.12) | Referent |
| Adjudicated death from any cause — no. (%) | 26 (1.8) | 39 (2.7) | 17 (1.2) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 1.49 (0.81–2.74) | 2.37 (1.34–4.18) | Referent |

* Shown are adverse events that emerged or worsened during the 28-day on-treatment period, which was defined as the minimum of the date of last contact or the date of the last dose of a trial treatment plus 28 days. DVT denotes deep-vein thrombosis, NMSC nonmelanoma skin cancer, and VTE venous thromboembolism.

† For patients assigned to receive tofacitinib at a dose of 10 mg twice daily who had their dose reduced to 5 mg twice daily, the data collected after patients had been switched to 5 mg twice daily were counted in the group receiving 10 mg twice daily.

‡ Data are based on the adverse-event and disposition case-report forms.



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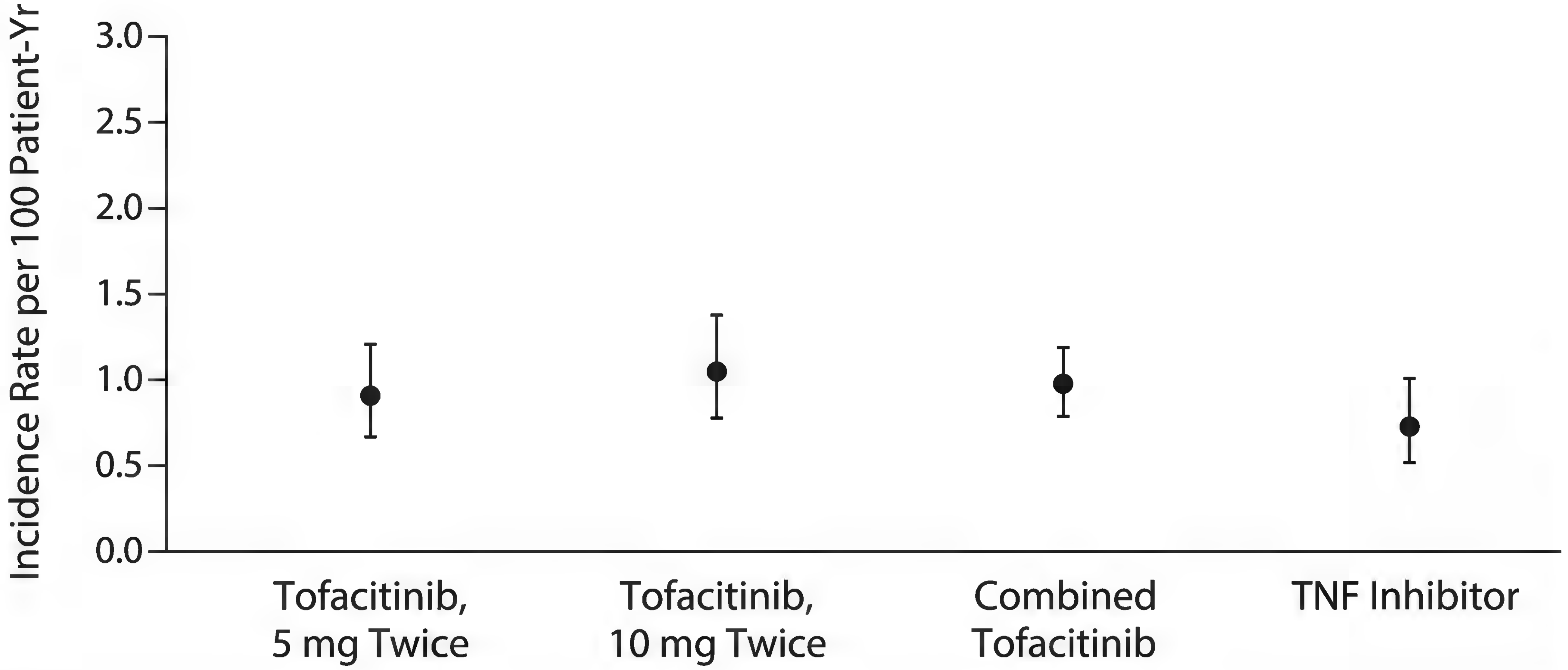
‡ Data are based on the adverse-event and disposition case-report forms.
§ At the discretion of the investigator, discontinuations of trial medication were allowed, not to exceed 2 months, for safety issues.
¶ Also included are opportunistic herpes zoster and tuberculosis events.
 Included are herpes zoster adjudicated as an opportunistic infection and nonadjudicated herpes zoster events.

FIG 1B, REF 6

B Incidence Rate for MACE

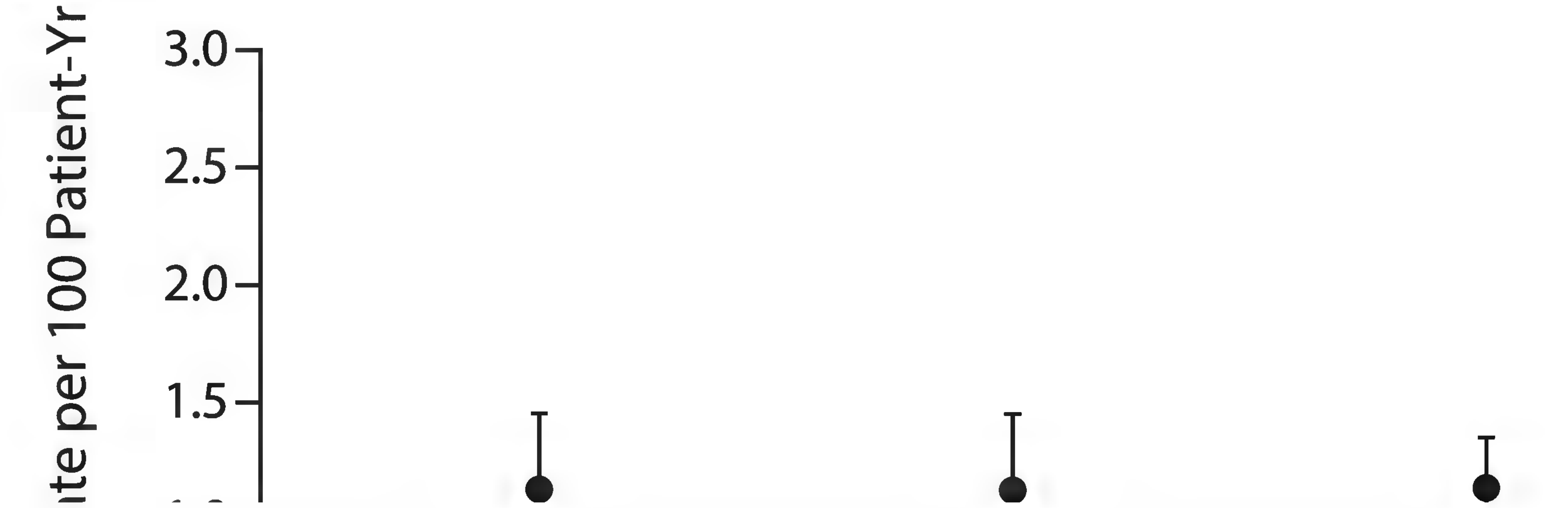


# SOURCE MATERIALS


| | Tofacitinib, 5 mg Twice Daily | Tofacitinib, 10 mg Twice Daily | Combined Tofacitinib Doses | TNF Inhibitor |
|---|---|---|---|---|
| No. of Patients with First Event/Total No. (%) | 47/1455 (3.2) | 51/1456 (3.5) | 98/2911 (3.4) | 37/1451 (2.5) |
| No. of Patient-Yr | 5166.32 | 4871.96 | 10,038.28 | 5045.27 |
| Incidence Rate per 100 Patient-Yr (95% CI) | 0.91 (0.67–1.21) | 1.05 (0.78–1.38) | 0.98 (0.79–1.19) | 0.73 (0.52–1.01) |
| NNH (patient-yr) vs. TNF Inhibitor | 567 | 319 | — | — |
| NNH (over 5-yr period) vs. TNF Inhibitor | 113 | 64 | — | — |

FIG 2B REF 6

B Incidence Rate for Cancers, Excluding NMSC



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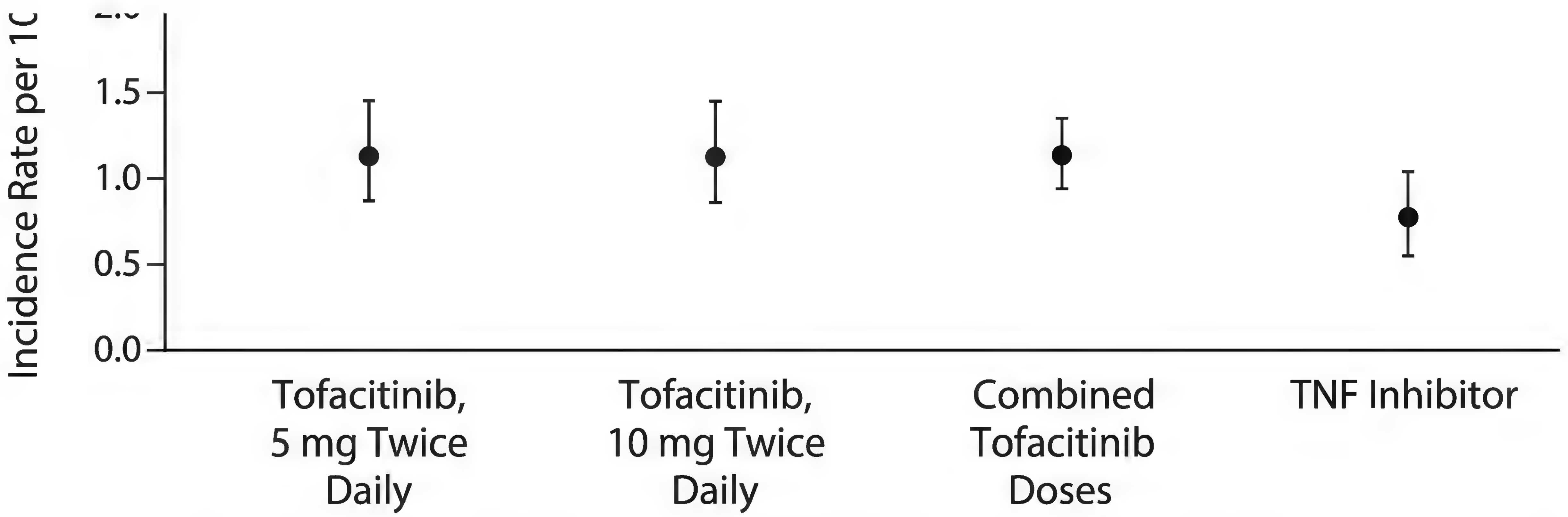
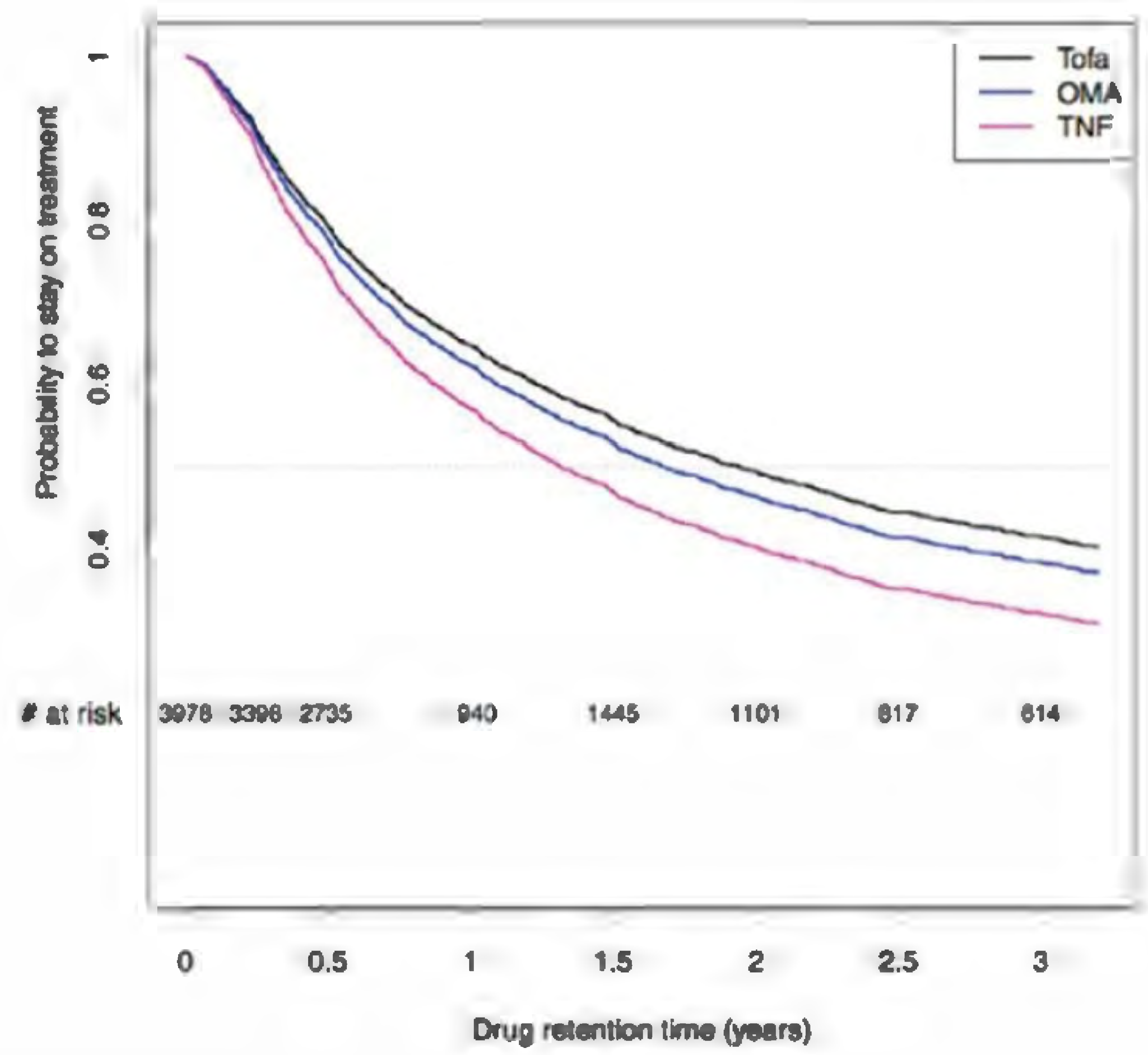



| | Tofacitinib, 5 mg Twice Daily | Tofacitinib, 10 mg Twice Daily | Combined Tofacitinib Doses | TNF Inhibitor |
|---|---|---|---|---|
| No. of Patients with First Event/Total No. (%) | 62/1455 (4.3) | 60/1456 (4.1) | 122/2911 (4.2) | 42/1451 (2.9) |
| No. of Patient-Yr | 5491.48 | 5311.71 | 10,803.19 | 5482.30 |
| Incidence Rate per 100 Patient-Yr (95% CI) | 1.13 (0.87–1.45) | 1.13 (0.86–1.45) | 1.13 (0.94–1.35) | 0.77 (0.55–1.04) |
| NNH (patient-yr) vs. TNF Inhibitor | 276 | 275 | — | — |
| NNH (over 5-yr period) vs. TNF Inhibitor | 55 | 55 | — | — |

FIG 1A, REF 11

**A: Overalldrugdiscontinuation**

# SOURCE MATERIALS



# SOURCE MATERIALS

FIG 2A, FIG 2B, REF 12

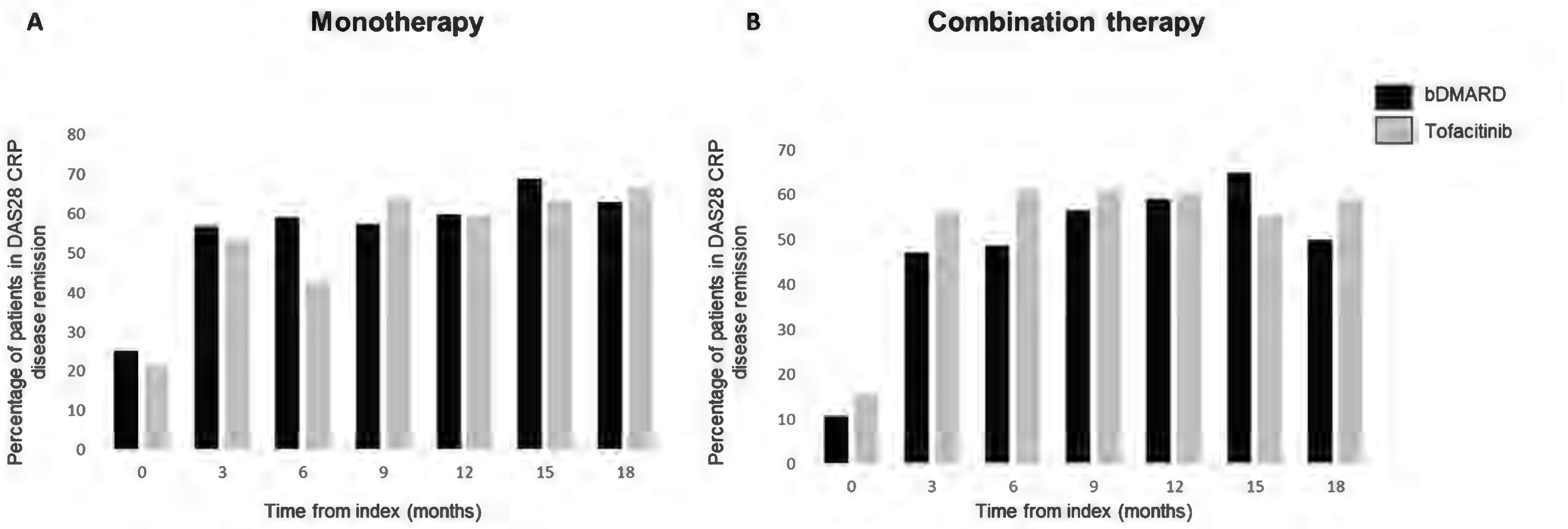



**Fig. 2** Percentage of patients in DAS28-CRP disease remission in the **A** bDMARD and tofacitinib monotherapy population and **B** the bDMARD and tofacitinib combination therapy population

# SOURCE MATERIALS

**The recommended dose for rheumatoid arthritis is 5 mg film-coated tablets administered twice daily, which should not be exceeded. No dose adjustment is required when used in combination with MTX.[1]**

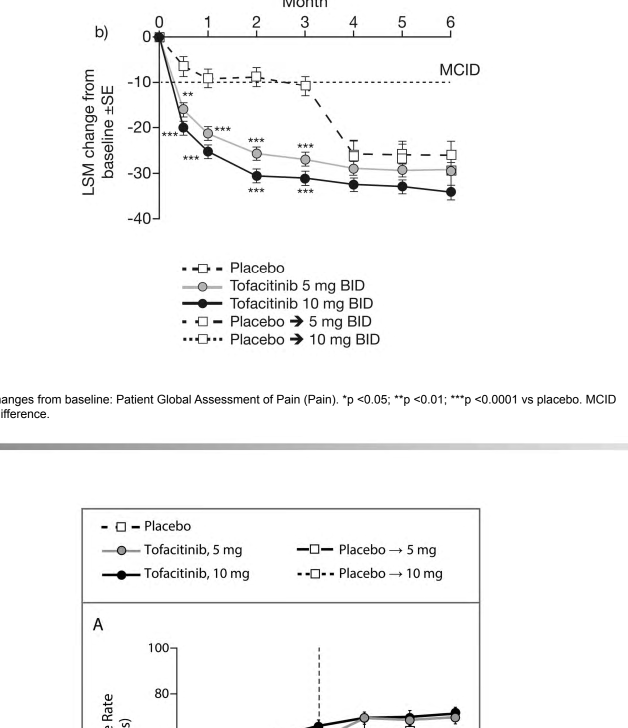
TABLE S2, REF 1

**Additional file 2: Table S2.** Baseline and changes from baseline by visit prior to month 3 for patient-reported outcome measures

| | Baseline mean (SD) | | | Week 2 LSM change from baseline (SE) | | | Month 1 LSM change from baseline (SE) | | | Month 2 LSM change from baseline (SE) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo (n=122) | Tofacitinib 5 mg BID (n=243) | Tofacitinib 10 mg BID (n=245) | Placebo (n=119) | Tofacitinib 5 mg BID (n=239) | Tofacitinib 10 mg BID (n=239) | Placebo (n=116) | Tofacitinib 5 mg BID (n=238) | Tofacitinib 10 mg BID (n=240) | Placebo (n=115) | Tofacitinib 5 mg BID (n=229) | Tofacitinib 10 mg BID (n=233) |
| PtGA | 62.63 (21.91) | 61.66 (22.00)[a] | 63.46 (23.23)[b] | −7.92 (2.04) | −18.64 (1.47)*** | −22.01 (1.46)*** | −9.44 (2.08) | −23.26 (1.45)*** | −25.62 (1.45)*** | −9.22 (2.11) | −26.01 (1.46)*** | −30.81 (1.47)*** |
| Pain | 61.79 (21.27) | 61.35 (22.27)[a] | 62.03 (23.63)[b] | −6.12 (2.07) | −16.16 (1.47)*** | −20.03 (1.46)*** | −9.13 (2.09) | −21.28 (1.45)*** | −25.25 (1.46)*** | −8.79 (2.13) | −25.65 (1.46)*** | −30.58 (1.46)*** |
| HAQ-DI | 1.53 (0.58) | 1.53 (0.64)[c] | 1.50 (0.64)[d] | −0.12 (0.05) | −0.28 (0.03)* | −0.33 (0.03)*** | −0.14 (0.05) | −0.37 (0.03)*** | −0.44 (0.03)*** | −0.14 (0.05) | −0.50 (0.03)*** | −0.56 (0.03)*** |

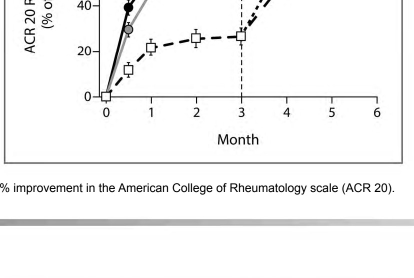
*p<0.05; **p<0.001; ***p<0.0001 vs placebo. [a]n=241; [b]n=244; [c]n=242; [d]n=243.

FIGURE 2B, REF 1




Least squares mean (LSM) changes from baseline: Patient Global Assessment of Pain (Pain). *p <0.05; **p <0.01; ***p <0.0001 vs placebo. MCID minimum clinically important difference.

FIGURE 1A, REF 2




The percentage of patients with at least a 20% improvement in the American College of Rheumatology scale (ACR 20).

TABLE 3, REF 7

**Table 3** IRs (95% CI) for AEs of special interest

| | RA (N=7964) | PsA (N=783) | UC (N=1157) | PsO (N=3663) |
|---|---|---|---|---|
| Total tofacitinib exposure, patient-years | 23 497 | 2038 | 2581 | 8950 |
| Serious infections, IR (95% CI) (n) | 2.5 (2.3 to 2.7) (592) | 1.2 (0.7 to 1.7) (24) | 1.7 (1.2 to 2.3) (45) | 1.3 (1.1 to 1.5) (119) |
| All HZ (non-serious and serious), IR (95% CI) (n) | 3.6 (3.3 to 3.8) (795) | 1.8 (1.2 to 2.4) (36) | 3.5 (2.8 to 4.3) (87) | 2.4 (2.0 to 2.7) (209) |
| Adjudicated OIs excluding tuberculosis, IR (95% CI) (n) | 0.4 (0.3 to 0.5) (95) | 0.3 (0.1 to 0.7) (7) | 1.6 (1.1 to 2.1) (40)* | 0.3 (0.2 to 0.5) (29) |
| Adjudicated tuberculosis, IR (95% CI) (n) | 0.2 (0.1 to 0.2) (38) | 0.0 (0.0 to 0.2) (0) | 0.0 (0.0 to 0.1) (0)* | 0.0 (0.0 to 0.1) (1) |
| Adjudicated malignancies excluding all NMSC, IR (95% CI) (n)<br>n1 (%) | 0.7 (0.6 to 0.9) (179)<br>211 (2.6) | 0.7 (0.4 to 1.2) (15)<br>18 (2.3) | 0.6 (0.3 to 1.0) (16)*<br>20 (1.8)* | 0.7 (0.5 to 0.8) (60)<br>74 (2.0) |
| Adjudicated NMSC, IR (95% CI) (n)<br>n1 (%) | 0.6 (0.5 to 0.7) (133)<br>135 (1.7) | 0.8 (0.4 to 1.3) (16)<br>16 (2.0) | 0.7 (0.4 to 1.1) (19)*<br>19 (1.7)* | 0.7 (0.5 to 0.9) (63)<br>67 (1.8) |
| Adjudicated melanoma, IR (95% CI) (n)<br>n1 (%) | 0.1 (0.0 to 0.1) (14)<br>14 (0.2) | 0.0 (0.0 to 0.2) (0)<br>0 (0.0) | 0.1 (0.0 to 0.3) (2)*<br>2 (0.2)* | 0.1 (0.0 to 0.1) (5)<br>5 (0.1) |
| Adjudicated lymphoma/lymphoproliferative disorders, IR (95% CI) (n)<br>n1 (%) | 0.1 (0.0 to 0.1) (12)<br>19 (0.2) | 0.1 (0.0 to 0.3) (1)<br>1 (0.1) | 0.1 (0.0 to 0.3) (2)*<br>2 (0.2)* | 0.02 (0.0 to 0.1) (2)<br>4 (0.1) |
| Adjudicated gastrointestinal perforation, IR (95% CI) (n) | 0.1 (0.1 to 0.2) (27) | 0.1 (0.0 to 0.3)(1) | 0.2 (0.1 to 0.5) (6)* | 0.1 (0.0 to 0.2) (7) |
| Adjudicated MACE,† IR (95% CI) (n) | 0.4 (0.3 to 0.5) (85)‡ | 0.3 (0.1 to 0.6) (6) | 0.3 (0.1 to 0.5) (7)* | 0.3 (0.2 to 0.4) (23) |
| DVT,§ IR (95% CI) (n) | 0.2 (0.1 to 0.2) (37) | 0.1 (0.0 to 0.3) (1) | 0.0 (0.0 to 0.2) (1) | 0.1 (0.0 to 0.1) (6) |
| PE,§ IR (95% CI) (n) | 0.1 (0.1 to 0.2) (31) | 0.1 (0.0 to 0.3) (1) | 0.2 (0.0 to 0.4) (4) | 0.1 (0.0 to 0.2) (9) |

*N=1124.
†Composite MACE defined as any myocardial infarction, stroke or cardiovascular death.
‡N=7311.
§Previously reported in Mease *et al*[40] (excludes Study A3921133) and Sandborn *et al*.[44]
AE, adverse event; DVT, deep vein thrombosis; HZ, herpes zoster; IR, incidence rate (unique patients with events per 100 patient-years); MACE, major adverse cardiovascular events; N, number of patients in the disease cohort; n, unique number of patients with event (events are counted up to 28 days beyond the last dose or to the data cut-off date, and are included in the calculation of IR); n1, all events, including those occurring outside the 28-day risk period; NMSC, non-melanoma skin cancer; OI, opportunistic infection; PE, pulmonary embolism; PsA, psoriatic arthritis; PsO psoriasis; RA, rheumatoid arthritis; UC, ulcerative colitis.

**XELJANZ is not approved in the European Union for the treatment of plaque psoriasis.**

TABLE 1, REF 6

**Table 1.** Demographic and Clinical Characteristics of the Patients at Baseline (Safety Analysis Population).*

| Characteristic | Tofacitinib, 5 mg Twice Daily (N = 1455) | Tofacitinib, 10 mg Twice Daily (N = 1456)† | TNF Inhibitor (N = 1451) | Total (N = 4362) |
|---|---|---|---|---|
| Age | | | | |
| Mean — yr | 60.8±6.8 | 61.4±7.1 | 61.3±7.5 | 61.2±7.1 |
| ≥65 yr — no. (%) | 413 (28.4) | 478 (32.8) | 462 (31.8) | 1353 (31.0) |
| Female sex — no. (%) | 1169 (80.3) | 1124 (77.2) | 1117 (77.0) | 3410 (78.2) |
| Race — no. (%)‡ | | | | |
| White | 1128 (77.5) | 1126 (77.3) | 1099 (75.7) | 3353 (76.9) |
| Black | 63 (4.3) | 65 (4.5) | 83 (5.7) | 211 (4.8) |
| Asian | 65 (4.5) | 56 (3.8) | 55 (3.8) | 176 (4.0) |
| Other | 199 (13.7) | 209 (14.4) | 214 (14.7) | 622 (14.3) |
| Smoking status — no. (%) | | | | |
| Never smoked | 735 (50.5) | 752 (51.6) | 772 (53.2) | 2259 (51.8) |
| Ever smoked | 720 (49.5) | 704 (48.4) | 679 (46.8) | 2103 (48.2) |
| History of hypertension — no. (%) | 955 (65.6) | 954 (65.5) | 969 (66.8) | 2878 (66.0) |
| History of diabetes mellitus — no. (%) | 243 (16.7) | 261 (17.9) | 255 (17.6) | 759 (17.4) |
| History of venous thromboembolism — no. (%)§ | 19 (1.3) | 33 (2.3) | 27 (1.9) | 79 (1.8) |
| History of extraarticular disease — no. (%)¶ | 532 (36.6) | 521 (35.8) | 552 (38.0) | 1605 (36.8) |
| History of coronary heart disease — no. (%) | 161 (11.1) | 172 (11.8) | 164 (11.3) | 497 (11.4) |
| Family history of coronary heart disease — no. (%) | | | | |
| First-degree male relative <55 yr of age | 154 (10.6) | 132 (9.1) | 151 (10.4) | 437 (10.0) |
| First-degree female relative <65 yr of age | 115 (7.9) | 107 (7.3) | 100 (6.9) | 322 (7.4) |
| Fasting HDL cholesterol <40 mg/dl — no. (%) | 172 (11.8) | 195 (13.4) | 173 (11.9) | 540 (12.4) |

* Plus-minus values are means ±SD. Percentages may not total 100 because of rounding. HDL denotes high-density lipoprotein, and TNF tumor necrosis factor.
† Patients assigned to receive tofacitinib at a dose of 10 mg twice daily who had their dose reduced to 5 mg twice daily for whom the data collected after the trial drug was switched were counted in the group receiving 10 mg twice daily.
‡ Race was reported by the patients.
§ Venous thromboembolism included deep-vein thrombosis and pulmonary embolism.
¶ Extraarticular disease included nodules, Sjögren's syndrome, anemia of chronic disease, pulmonary manifestations, or other clinical features, as identified by the site investigator.

TABLE S2, REF 6

**Table S2.** Additional Patient Demographics and Baseline Disease Characteristics (Safety Analysis Set)

| | Tofacitinib 5 mg BID (N=1455) | Tofacitinib 10 mg BID* (N=1456) | TNFi (N=1451) | Total (N=4362) |
|---|---|---|---|---|
| Age (years), median (range) | 60.0 (50.0–86.0) | 61.0 (50.0–83.0) | 60.0 (50.0–84.0) | 60.0 (50.0–86.0) |
| Duration of RA (years), mean (SD) | 10.4 (8.8) | 10.2 (9.0) | 10.6 (9.1) | 10.4 (9.0) |
| Geographical region, n (%) | | | | |
| US and Canada | 402 (27.6) | 409 (28.1) | 432 (29.8) | 1243 (28.5) |
| Latin America | 383 (26.3) | 414 (28.4) | 405 (27.9) | 1202 (27.6) |
| Europe | 43 (3.0) | 56 (3.8) | 48 (3.3) | 147 (3.4) |
| Rest of the world | 625 (43.0) | 577 (39.6) | 566 (39.0) | 1770 (40.6) |
| BMI (kg/m²), mean (SD) [number of patients with missing values] | 29.7 (6.5) [7] | 29.7 (6.3) [3] | 29.8 (6.4) [7] | 29.7 (6.4) [17] |
| BMI ≥30 kg/m², n (%) | 606 (41.6) | 594 (40.8) | 617 (42.5) | 1817 (41.7) |
| Concomitant medication use at baseline (day 1), n (%)† | | | | |
| Oral contraceptives or HRT | 51 (3.5) | 41 (2.8) | 45 (3.1) | 137 (3.1) |
| Corticosteroid | 836 (57.5) | 829 (56.9) | 830 (57.2) | 2495 (57.2) |
| Methotrexate | 1453 (99.9) | 1456 (100.0) | 1451 (100.0) | 4360 (99.9) |
| Aspirin | [illegible] | [illegible] | [illegible] | [illegible] |
| Anticoagulants | [illegible] | [illegible] | [illegible] | [illegible] |
| Antidepressants | 218 (15.0) | 208 (14.3) | 223 (15.4) | 649 (14.9) |
| Methotrexate dose‡ (mg/week), mean (SD) [number of patients with missing values] | [illegible] | [illegible] | [illegible] | [illegible] |
| Prior medication use, n (%) | | | | |
| Methotrexate | 1455 (100.0) | 1456 (100.0) | 1451 (100.0) | 4362 (100.0) |
| Nonmethotrexate csDMARDs | 421 (28.9) | 395 (27.1) | 424 (29.2) | 1240 (28.4) |
| bDMARDs | 164 (11.3) | 158 (10.9) | 150 (10.3) | 472 (10.8) |
| TNFi | 115 (7.9) | 110 (7.6) | 105 (7.2) | 330 (7.6) |
| Non-TNFi bDMARDs | 71 (4.9) | 73 (5.0) | 62 (4.3) | 206 (4.7) |
| Number of prior csDMARDs, mean (SD) | 1.4 (0.7) | 1.4 (0.7) | 1.4 (0.7) | 1.4 (0.7) |
| Number of prior bDMARDs‡, mean (SD) | 1.3 (0.6) | 1.3 (0.6) | 1.2 (0.5) | 1.3 (0.6) |
| Medical history, n (%) | | | | |
| Depression | 176 (12.1) | 178 (12.2) | 183 (12.6) | 537 (12.3) |
| Myocardial infarction | [illegible] | [illegible] | [illegible] | [illegible] |
| Unstable angina | 17 (1.2) | 14 (1.0) | 7 (0.5) | 38 (0.9) |
| Coronary artery procedures | 63 (4.3) | 69 (4.7) | 63 (4.3) | 195 (4.5) |
| Other coronary heart disease | 84 (5.8) | 95 (6.5) | 101 (7.0) | 280 (6.4) |
| Alcohol use within last 7 days, n (%) | 187 (12.9) | 193 (13.3) | 183 (12.6) | 563 (12.9) |
| Fasting HDL-C (mg/dL), mean (SD) | 58.1 (16.8) | 57.6 (17.3) | 57.9 (16.8) | 57.9 (17.0) |
| Fasting total cholesterol/HDL-C ratio >4, n (%) | [illegible] | [illegible] | [illegible] | [illegible] |
| CRP >2.87 mg/L, n (%) | [illegible] | [illegible] | [illegible] | [illegible] |
| SDAI,§ mean (SD) [number of patients with missing values] | [illegible] | [illegible] | [illegible] | [illegible] |
| HAQ-DI,¶ mean (SD) [number of patients with missing values] | 1.6 (0.6) [11] | 1.6 (0.6) [18] | 1.6 (0.6) [25] | 1.6 (0.6) [54] |
| TJC28, mean (SD) [number of patients with missing values] | 15.7 (6.3) [1] | 15.7 (6.4) | 15.6 (6.2) [2] | 15.7 (6.3) [3] |
| SJC28, mean (SD) [number of patients with missing values] | 11.8 (5.1) [1] | 12.0 (5.2) | 11.7 (5.0) [2] | 11.8 (5.1) [3] |
| Rheumatoid factor positive, n (%) | 1243 (85.4) | 1261 (86.6) | 1264 (87.1) | 3768 (86.4) |
| Anti-CCP positive, n (%) | 1093 (75.1) | 1129 (77.5) | 1119 (77.1) | 3341 (76.6) |

*Patients randomized to the tofacitinib 10 mg BID group who had their dose of tofacitinib reduced to 5 mg BID, or discontinued from the trial drug, were counted in the tofacitinib 10 mg BID group. †Based on use on day 1. ‡For patients who were previously treated with either TNFi or non-TNFi bDMARDs. §Scores range from 0 to 100, with the maximum score dependent on the maximum reasonably assumable C-reactive protein level in RA; higher scores are indicative of worse disease activity.[2-4] ¶Scores range from 0 to 3, with increasing scores indicative of worse functioning (0 indicating no functional impairment and 3 indicating complete impairment).[5] bDMARD, biologic disease-modifying antirheumatic drug; BID, twice daily; BMI, body mass index; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire-Disability Index; HDL-C, high-density lipoprotein cholesterol; HRT, hormone replacement therapy; n, number of patients meeting baseline criteria; N, number of patients in each treatment group in the safety population; RA, rheumatoid arthritis; SD, standard deviation; SDAI, Simplified Disease Activity Index; SJC28, swollen joint count out of 28 joints; TJC28, tender joint count out of 28 joints; TNFi, tumor necrosis factor inhibitors.

TABLE S2, REF 6

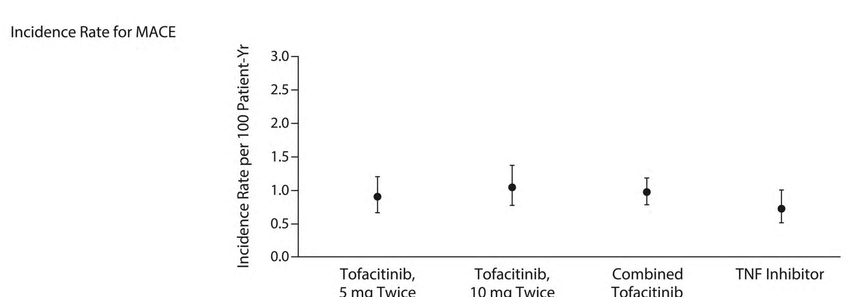
**Table 2.** Adverse Events (Safety Analysis Population, 28-Day On-Treatment Time).*

| Event | Tofacitinib, 5 mg Twice Daily (N = 1455) | Tofacitinib, 10 mg Twice Daily (N = 1456)† | TNF Inhibitor (N = 1451) |
|---|---|---|---|
| Adverse event — no. (%) | 1333 (91.6) | 1344 (92.3) | 1308 (90.1) |
| Serious adverse event — no. (%) | 351 (24.1) | 390 (26.8) | 306 (21.1) |
| Discontinuation of trial treatment due to adverse event — no. (%) | | | |
| Permanent discontinuation‡ | 210 (14.4) | 304 (20.9) | 210 (14.5) |
| Temporary discontinuation§ | 665 (45.7) | 736 (50.5) | 576 (39.7) |
| Adverse events of special interest | | | |
| Serious infection — no. (%) | 141 (9.7) | 169 (11.6) | 119 (8.2) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 1.17 (0.92–1.50) | 1.48 (1.17–1.87) | Referent |
| Adjudicated opportunistic infection — no. (%)¶ | 39 (2.7) | 44 (3.0) | 21 (1.4) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 1.82 (1.07–3.09) | 2.17 (1.29–3.66) | Referent |
| All herpes zoster, serious and nonserious — no. (%)‖ | 180 (12.4) | 178 (12.2) | 58 (4.0) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 3.28 (2.44–4.41) | 3.39 (2.52–4.55) | Referent |
| Adjudicated hepatic event — no. (%) | 46 (3.2) | 72 (4.9) | 35 (2.4) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 1.29 (0.83–2.00) | 2.14 (1.43–3.21) | Referent |
| Adjudicated NMSC — no. (%) | 31 (2.1) | 33 (2.3) | 16 (1.1) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 1.90 (1.04–3.47) | 2.16 (1.19–3.92) | Referent |
| Adjudicated pulmonary embolism — no. (%) | 9 (0.6) | 24 (1.6) | 3 (0.2) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 2.93 (0.79–10.83) | 8.26 (2.49–27.43) | Referent |
| Adjudicated DVT — no. (%) | 11 (0.8) | 15 (1.0) | 7 (0.5) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 1.54 (0.60–3.97) | 2.21 (0.90–5.43) | Referent |
| Adjudicated VTE — no. (%) | 17 (1.2) | 34 (2.3) | 10 (0.7) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 1.66 (0.76–3.63) | 3.52 (1.74–7.12) | Referent |
| Adjudicated death from any cause — no. (%) | 26 (1.8) | 39 (2.7) | 17 (1.2) |
| Hazard ratio vs. TNF inhibitor (95% CI) | 1.49 (0.81–2.74) | 2.37 (1.34–4.18) | Referent |

* Shown are adverse events that emerged or worsened during the 28-day on-treatment period, which was defined as the minimum of the date of last contact or the date of the last dose of a trial treatment plus 28 days. DVT denotes deep-vein thrombosis, NMSC nonmelanoma skin cancer, and VTE venous thromboembolism.
† For patients assigned to receive tofacitinib at a dose of 10 mg twice daily who had their dose reduced to 5 mg twice daily, the data collected after patients had been switched to 5 mg twice daily were counted in the group receiving 10 mg twice daily.
‡ Data are based on the adverse-event and disposition case-report forms.
§ At the discretion of the investigator, discontinuations of trial medication were allowed, not to exceed 2 months, for safety issues.
¶ Also included are opportunistic herpes zoster and tuberculosis events.
‖ Included are herpes zoster adjudicated as an opportunistic infection and nonadjudicated herpes zoster events.

FIG 1B, REF 6

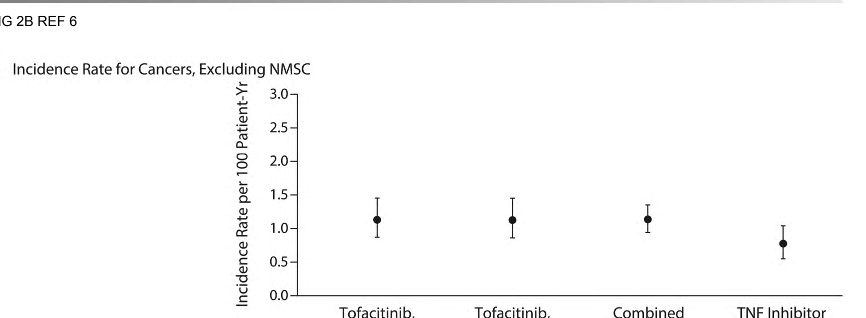
B Incidence Rate for MACE




| | Tofacitinib, 5 mg Twice Daily | Tofacitinib, 10 mg Twice Daily | Combined Tofacitinib Doses | TNF Inhibitor |
|---|---|---|---|---|
| No. of Patients with First Event/Total No. (%) | 47/1455 (3.2) | 51/1456 (3.5) | 98/2911 (3.4) | 37/1451 (2.5) |
| No. of Patient-Yr | 5166.32 | 4871.96 | 10,038.28 | 5045.27 |
| Incidence Rate per 100 Patient-Yr (95% CI) | 0.91 (0.67–1.21) | 1.05 (0.78–1.38) | 0.98 (0.79–1.19) | 0.73 (0.52–1.01) |
| NNH (patient-yr) vs. TNF Inhibitor | 567 | 319 | — | — |
| NNH (over 5-yr period) vs. TNF Inhibitor | 113 | 64 | — | — |

FIG 2B REF 6

B Incidence Rate for Cancers, Excluding NMSC




| | Tofacitinib, 5 mg Twice Daily | Tofacitinib, 10 mg Twice Daily | Combined Tofacitinib Doses | TNF Inhibitor |
|---|---|---|---|---|
| No. of Patients with First Event/Total No. (%) | 62/1455 (4.3) | 60/1456 (4.1) | 122/2911 (4.2) | 42/1451 (2.9) |
| No. of Patient-Yr | 5491.48 | 5311.71 | 10,803.19 | 5482.30 |
| Incidence Rate per 100 Patient-Yr (95% CI) | 1.13 (0.87–1.45) | 1.13 (0.86–1.45) | 1.13 (0.94–1.35) | 0.77 (0.55–1.04) |
| NNH (patient-yr) vs. TNF Inhibitor | 276 | 275 | — | — |
| NNH (over 5-yr period) vs. TNF Inhibitor | 55 | 55 | — | — |

FIG 1A, REF 11

A: Overalldrugdiscontinuation

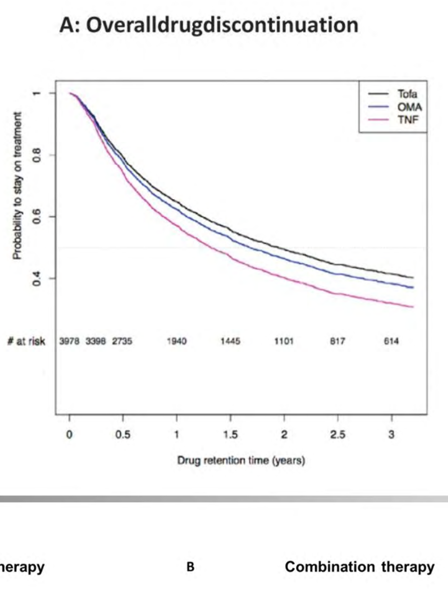



FIG 2A, FIG 2B, REF 12

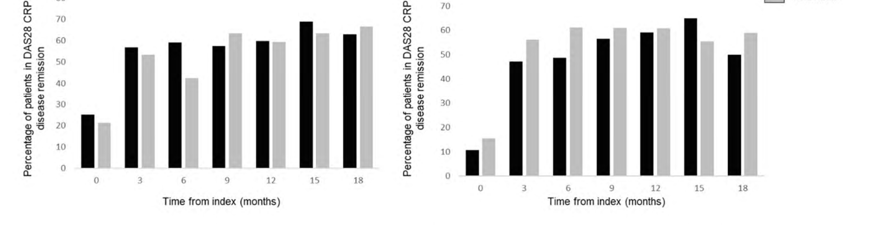



**Fig. 2** Percentage of patients in DAS28-CRP disease remission in the **A** bDMARD and tofacitinib monotherapy population and **B** the bDMARD and tofacitinib combination therapy population

# PRESCRIBING INFORMATION

For any further information on efficacy and side effects of XELJANZ, please refer to the Summary of Product Characteristics available at the booth.

XELJANZ 5 mg compresse rivestite con film

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