Efficacy and safety of tofacitinib modified-release 11 mg once daily + MTX in RA patients with an inadequate response to MTX: open-label phase results from a global Phase 3b/4 MTX withdrawal study

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Introduction

- Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA).
- A modified-release (MR) formulation of tofacitinib was developed to provide a once-daily (QD) dosing option, which may offer convenience and improve adherence for patients preferring treatments with less frequent administration, potentially improving disease control.[1,2]
- The tofacitinib MR 11 mg QD formulation was first approved in the US in 2016 for the treatment of patients with moderate to severe RA and an inadequate response, or intolerance, to methotrexate (MTX).
- ORAL Shift was the first global study of tofacitinib MR 11 mg QD + MTX.
  - Results of the 24-week, double-blind (DB) MTX withdrawal phase of ORAL Shift were reported previously,[3] and showed that the primary efficacy endpoint was met, in that non-inferiority of tofacitinib MR 11 mg QD monotherapy compared with tofacitinib MR 11 mg QD + MTX was demonstrated, with respect to change in disease activity (Disease Activity Score in 28 joints, erythrocyte sedimentation rate [DAS28-4[ESR]]) in the DB phase.
  - Overall, results from the DB phase indicated that patients with RA who achieve low disease activity (LDA) with a combination of tofacitinib MR 11 mg QD and background MTX may consider withdrawing MTX without significant worsening of disease activity or unexpected safety issues.

Objective

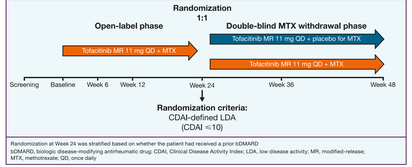
- To report the efficacy, patient-reported outcomes (PROs), and safety of tofacitinib MR 11 mg QD + MTX in patients with RA and an inadequate response to MTX over the 24-week open-label (OL) phase of ORAL Shift.

Methods

Study design and patients

- ORAL Shift (NCT02831855) was a global Phase 3b/4 study in adult patients with moderate to severe RA and an inadequate response to MTX.
- The study included a 24-week, OL run-in phase and a 24-week, randomized, DB MTX withdrawal phase (Figure 1).
  - During the OL phase, eligible patients received tofacitinib MR 11 mg QD + MTX.
  - Baseline was defined as Day 1 of the OL phase.
  - Patients who achieved LDA (defined as Clinical Disease Activity Index [CDAI] ≤10) at Week 24 entered the DB MTX withdrawal phase, and were randomized 1:1 to receive tofacitinib MR 11 mg QD + placebo (tofacitinib monotherapy; ie underwent blinded, immediate MTX withdrawal) or tofacitinib MR 11 mg QD + MTX (tofacitinib + MTX; ie continuation of OL phase treatment).

Figure 1. Study design



Randomization at Week 24 was stratified based on whether the patient had received a prior bDMARD
bDMARD, biologic disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; LDA, low disease activity; MR, modified-release; MTX, methotrexate; QD, once daily

- Patients eligible to enter the study were ≥18 years of age, met the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification Criteria for RA[4] at and/or prior to screening, had ≥4 tender/painful joints on motion and ≥4 swollen joints (based on 28 joint counts) at screening and baseline, and moderate to severe RA (moderate to high disease activity defined as CDAI >10 and DAS28-4[ESR] ≥3.2) at baseline.
- Patients must have received oral MTX (15–25 mg/week) continuously for ≥4 months before the screening visit and have taken a stable weekly dose of oral MTX with supplemental folic acid (≥5 mg/week) or folinic acid (≥2.5 mg/week) for ≥4 weeks before the baseline visit.
- Exclusion criteria included a history of insufficient response to ≥2 biologic disease-modifying antirheumatic drugs (bDMARDs) or previous treatment with ≥1 JAK inhibitor.
- The study involved 109 centers across 16 countries. It was conducted in accordance with the Guidelines for Good Clinical Practice (International Conference on Harmonization) and the Declaration of Helsinki, as well as local regulatory requirements and laws. The study protocol, any amendments, and informed consent documents were reviewed and approved by the Institutional Review Boards and the Independent Ethics Committees of the study centers. All patients provided written informed consent.

Outcomes

- Efficacy endpoints and PROs assessed at Weeks 12 and 24 of the OL phase included:
  - Mean change from baseline in DAS28-4(ESR), DAS28-4(C-reactive protein [CRP]), CDAI, Simplified Disease Activity Index (SDAI), Health Assessment Questionnaire-Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), patient assessment of arthritis pain (Pain Visual Analog Scale [VAS]), and Patient Global Assessment of arthritis (PtGA)
  - The proportion of patients achieving the following:
    - ACR20/50/70 response
    - HAQ-DI response (decrease of ≥0.22, relative to baseline)
    - LDA, defined by DAS28-4(ESR) ≤3.2, DAS28-4(CRP) ≤3.2, CDAI ≤10, and SDAI ≤11
    - Remission, defined by ACR/EULAR Boolean remission criteria,[5] DAS28-4(ESR) <2.6, DAS28-4(CRP) <2.6, CDAI ≤2.8, and SDAI ≤3.3.
- Safety endpoints included all treatment-emergent adverse events (TEAEs), serious AEs (SAEs), discontinuations due to TEAEs, TEAEs of special interest, and deaths reported during the OL phase.

Statistical analyses

- The full analysis set comprised all patients who received ≥1 dose of tofacitinib + MTX during the OL phase; efficacy, PROs, and safety were assessed in this set.
- Efficacy, PROs, and safety were summarized descriptively in the OL phase as observed.
- Binary endpoints (ACR20/50/70 and HAQ-DI response rates, and LDA/remission rates) were also analyzed using non-responder imputation (NRI; data not shown).

Results

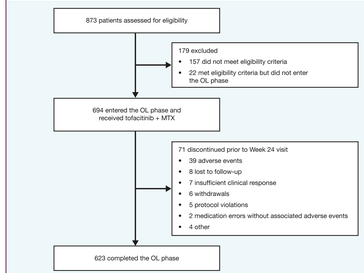
Patients

- Between September 1, 2016 and November 1, 2017, 694 patients received tofacitinib + MTX in the OL phase of ORAL Shift (Figure 2).
  - Most patients were female (76.7%), white (85.6%), with a mean age of 56.8 years, mean RA duration of 8.8 years, and had DAS28-4(ESR)- and CDAI-defined high disease activity (79.8% and 84.0%, respectively) (Table 1).
  - Mean MTX dose at baseline was 16.7 mg/week, and 37.5% of patients were receiving concomitant oral steroids at a mean dose of 5.7 mg/day.

Efficacy and patient-reported outcomes

- In patients treated with tofacitinib + MTX, improvements from baseline in disease activity (measured by DAS28-4[ESR], DAS28-4[CRP], CDAI, and SDAI) were seen at Week 12 and 24 (Table 2).
- Consistent with improvements in disease activity, improvements from baseline in PROs (HAQ-DI, FACIT-F, Pain VAS, and PtGA) were seen at Week 12 and 24 (Table 2).
- ACR20/50/70 and HAQ-DI (≥0.22) response rates increased between Week 12 and 24 (Figure 3).
- Similarly, increased LDA and remission rates were observed between Week 12 and 24 (Figure 4).
  - At Week 24, 84.5% of patients achieved CDAI-defined LDA.
- In general, similar results were seen when ACR20/50/70 and HAQ-DI response rates, and LDA/remission rates, were analyzed using NRI (data not shown).

Figure 2. Patient disposition in the OL phase



MTX, methotrexate; OL, open-label

Table 1. Demographics and baseline disease characteristics of patients treated in the OL phase

	Tofacitinib MR 11 mg QD + MTX (N=694)
Female, n (%)	532 (76.7)
Age, mean (SD), years	56.8 (11.8)
Race, n (%)	
White	594 (85.6)
Black or African American	33 (4.8)
Asian	37 (5.3)
Other	30 (4.3)
Region, n (%)	
Europe	355 (51.2)
United States	276 (39.8)
Latin America	25 (3.6)
Rest of the World	38 (5.5)
Disease duration, mean (SD), years	8.8 (8.8)
DAS28-4(ESR)-defined disease activity, n (%)	
Moderate[a]	140 (20.2)
High[b]	554 (79.8)
CDAI-defined disease activity, n (%)	
Moderate[c]	110 (15.9)
High[d]	583 (84.0)
Previous drug use, n (%)	
csDMARD excluding MTX	178 (25.6)
bDMARD excluding TNFi	100 (14.4)
TNFi	206 (30.0)
tsDMARD[e]	5 (0.7)
Concomitant drug use	
MTX dose, mean (SD), mg/week	16.7 (3.9)
Glucocorticoid use, n (%)	260 (37.5)
Glucocorticoid dose, mean (SD), mg/day	5.7 (2.7)
DAS28-4(ESR), mean (SD)	6.1 (1.0)
DAS28-4(CRP), mean (SD)	5.3 (0.9)
CDAI, mean (SD)	34.7 (11.9)
SDAI, mean (SD)	35.8 (12.2)
HAQ-DI, mean (SD)	1.4 (0.6)
Pain VAS, mean (SD)	57.5 (22.5)
PtGA, mean (SD)	57.7 (22.9)

[a]DAS28-4(ESR) >3.2 to ≤5.1
[b]DAS28-4(ESR) >5.1
[c]CDAI >10 to ≤22
[d]CDAI >22
[e]Two patients were enrolled prior to protocol amendment excluding prior JAK inhibitors; other patients received fostamatinib, apremilast, and a Bruton's tyrosine kinase inhibitor

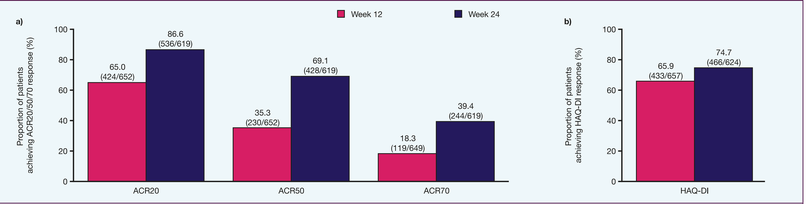
bDMARD, biologic disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-4(CRP), Disease Activity Score in 28 joints, C-reactive protein; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; MR, modified-release; MTX, methotrexate; OL, open-label; QD, once daily; PtGA, Patient Global Assessment of arthritis; SD, standard deviation; SDAI, Simplified Disease Activity Index; TNFi, tumor necrosis factor inhibitor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug; VAS, Visual Analog Scale

Table 2. Change from baseline in efficacy and patient-reported outcomes during the OL phase

	Tofacitinib MR 11 mg QD + MTX (N=694)	
Change from baseline, mean (SD)	Week 12	Week 24
DAS28-4(ESR)	-2.0 (1.2)	-2.7 (1.3)
DAS28-4(CRP)	-1.9 (1.2)	-2.6 (1.2)
CDAI	-19.6 (12.1)	-26.2 (12.6)
SDAI	-20.3 (12.5)	-27.0 (13.1)
HAQ-DI	-0.5 (0.5)	-0.6 (0.6)
FACIT-F	6.9 (9.3)	9.3 (10.1)
Pain VAS	-26.5 (26.0)	-36.1 (27.0)
PtGA	-26.8 (27.5)	-37.5 (27.1)

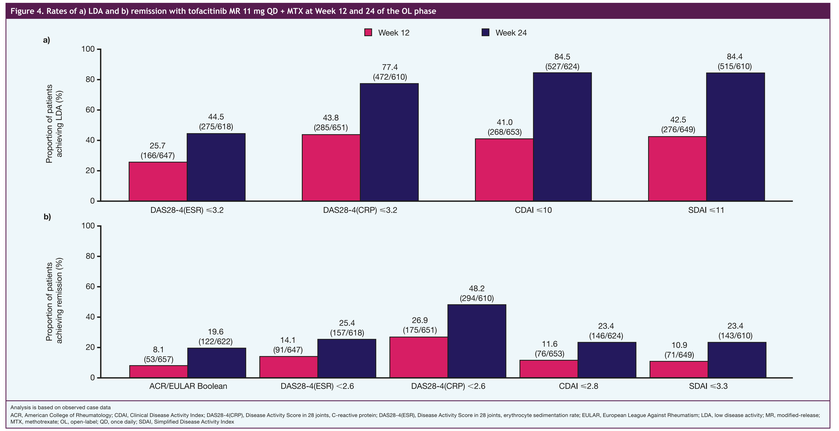
The number of patients assessed for each efficacy outcome measure may be less than the overall N. The value at baseline is defined as the last non-missing measurement on, or prior to, the first dosing date in the OL phase
CDAI, Clinical Disease Activity Index; DAS28-4(CRP), Disease Activity Score in 28 joints, C-reactive protein; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; MR, modified-release; MTX, methotrexate; OL, open-label; QD, once daily; PtGA, Patient Global Assessment of arthritis; SD, standard deviation; SDAI, Simplified Disease Activity Index; VAS, Visual Analog Scale

Figure 3. Rates of a) ACR20/50/70[a] and b) HAQ-DI[b] response with tofacitinib MR 11 mg QD + MTX at Week 12 and 24 of the OL phase



[a]20/50/70% improvement in tender and swollen joint counts and 20/50/70% improvement in at least three of the five other criteria (PtGA, PGA, HAQ-DI, Pain VAS, and CRP), relative to baseline
[b]HAQ-DI decrease of ≥0.22, relative to baseline
Analysis is based on observed case data
ACR, American College of Rheumatology; CRP, C-reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index; MR, modified-release; MTX, methotrexate; OL, open-label; PGA, Physician Global Assessment of arthritis; PtGA, Patient Global Assessment of arthritis; QD, once daily; VAS, Visual Analog Scale

Figure 4. Rates of a) LDA and b) remission with tofacitinib MR 11 mg QD + MTX at Week 12 and 24 of the OL phase



Analysis is based on observed case data
ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; DAS28-4(CRP), Disease Activity Score in 28 joints, C-reactive protein; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; LDA, low disease activity; MR, modified-release; MTX, methotrexate; OL, open-label; QD, once daily; SDAI, Simplified Disease Activity Index

Safety

- Safety data are reported in Table 3.
- TEAEs, SAEs, and discontinuations due to TEAEs were reported by 52.2%, 2.9%, and 5.9% of patients, respectively; no deaths were reported.
- The most common TEAEs were nasopharyngitis and upper respiratory tract infections.
- TEAEs of special interest were infrequent:
  - The following occurred in <1% of patients: serious infections, herpes zoster (HZ), malignancies excluding non-melanoma skin cancer (NMSC), and NMSC
    - All HZ events involved one or two adjacent dermatomes and were non-serious
  - There were no cases of major adverse cardiovascular events, opportunistic infections, gastrointestinal perforation, pulmonary embolism, or deep vein thrombosis.

Table 3. Safety during the OL phase[a]

	Tofacitinib MR 11 mg QD + MTX (N=694)[a]
TEAEs, n (%)	362 (52.2)
SAEs, n (%)	20 (2.9)
Discontinuations due to TEAEs, n (%)	41 (5.9)
Deaths, n (%)	0
Most common (≥2%) TEAEs by MedDRA PT, n (%)	
Nasopharyngitis	35 (5.0)
Upper respiratory tract infection	33 (4.8)
Nausea	20 (2.9)
Urinary tract infection	19 (2.7)
Headache	17 (2.4)
Hypertension	17 (2.4)
Diarrhea	16 (2.3)
ALT increased	16 (2.3)
Dizziness	15 (2.2)
TEAEs of special interest, n (%)	
Serious infections	5 (0.7)
Herpes zoster[a]	4 (0.6)
Malignancies excluding NMSC[b]	2 (0.3)
NMSC[b]	1 (0.1)
MACE[b]	0
Opportunistic infections[b]	0
GI perforation[b]	0
PE	0
DVT	0

[a]Includes data up to 28 days after last dose of study medication in the OL phase for patients who were not randomized into the DB phase
[b]Reviewed by an independent adjudication committee
ALT, alanine aminotransferase; DB, double-blind; DVT, deep vein thrombosis; GI, gastrointestinal; MACE, major adverse cardiovascular event; MedDRA, Medical Dictionary for Regulatory Activities; MR, modified-release; MTX, methotrexate; NMSC, non-melanoma skin cancer; OL, open-label; PE, pulmonary embolism; PT, preferred term; QD, once daily; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Limitations

- The rate of CDAI-defined LDA observed was higher than expected, compared with a previous study with a similar patient population,[6] possibly because this phase of the study was OL and both patients and investigators knew patients were receiving active treatment. Similarly, other composite measure-definitions of LDA were higher than expected.
- As patients were not eligible for inclusion in the DB phase if they did not achieve CDAI ≤10, there may have been an artificial improvement caused by an incentive to stay in the study by both the patient and investigator.

Conclusions

- **Tofacitinib MR 11 mg QD + MTX reduced disease activity and improved PROs in adult patients with moderate to severe RA and an inadequate response to MTX, with no new safety risks observed.**
- **The reductions in disease activity, improved PROs, and safety outcomes observed in the OL phase were consistent with those seen in the DB phase of ORAL Shift.[3]**
- **Together, these observations suggest that tofacitinib MR 11 mg QD + MTX could be an alternative to tofacitinib 5 mg BID + MTX for patients with RA who are inadequate responders to MTX, and who prefer, or are suitable for, QD dosing over BID dosing.**

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Disclosure of interest

SB Cohen has served as a consultant and investigator for AbbVie, Eli Lilly, Genentech, Gilead, and Pfizer Inc. J Pope has received grants and/or research support from Bristol-Myers Squibb, Roche, Seattle Genetics, and UCB, and has acted as a consultant for AbbVie, Acteion, Amgen, Bayer, Bristol-Myers Squibb, Eli Lilly, Merck, Novartis, Pfizer Inc, Roche, Sandoz, Sanofi, and UCB. B Haraoui has received research grants, or honoraria for advisory board membership or speaking engagements, from AbbVie, Amgen, Celgene, Eli Lilly, Merck, Pfizer Inc, Sandoz, and UCB. E Mysler has received research grants from Eli Lilly, Pfizer Inc, and Roche, and has been a member of the speakers' bureau for AbbVie, Bristol-Myers Squibb, Eli Lilly, Pfizer Inc, Roche, and Sanofi. A Diehl, T Lukic, S Liu, L Stockert, and S Menon are employees and stockholders of Pfizer Inc. EC Keystone has received research support from AbbVie, Amgen, Eli Lilly, Pfizer Inc, PureTech, and Sanofi-Aventis, has consultancy agreements or advisory board membership with AbbVie, Amgen, AstraZeneca, Biotest, Bristol-Myers Squibb, Celltrion, Crescendo Bioscience, Eli Lilly, F. Hoffmann-La Roche, Genentech, Gilead, Janssen, Merck, Pfizer Inc, Samsung Bioepis, Sanofi-Genzyme, Samsung Bioepis, and UCB, and has speaker honoraria agreements with Amgen, AbbVie, Bristol-Myers Squibb Canada, F. Hoffmann-La Roche, Janssen, Merck, Pfizer Inc, Sanofi Genzyme, and UCB.

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