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ORIGINAL RESEARCH

Frequency and Duration of Early Non-serious Adverse Events in Patients with Rheumatoid Arthritis and Psoriatic Arthritis Treated with Tofacitinib

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ABSTRACT

Introduction: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA) and psoriatic arthritis (PsA). This post hoc analysis assessed frequency or duration of early select non-serious adverse events (AEs; excluding infections), and their impact on treatment discontinuation, in patients with RA or PsA treated with tofacitinib 5 or 10 mg twice daily, or placebo.

Methods: Data were pooled from five phase 3 and one phase 3b/4 studies in patients with moderate-to-severe RA, and two phase 3 studies in patients with active PsA. Select all-causality, non-serious AEs, reported to month 3 (placebo-controlled period), were headache, diarrhea, nausea, vomiting, and gastric discomfort (including dyspepsia, gastritis, epigastric discomfort, and abdominal discomfort or pain); incidence rates (unique patients with events per 100 patient-years of follow-up), duration of, and discontinuations due to these non-serious AEs were reported.

Results: We analyzed 3871 and 710 patients with RA and PsA, respectively. Incidence of non-serious AEs to month 3 was generally sim-

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ilar with tofacitinib and placebo. The most frequent non-serious AEs were headache and diarrhea with tofacitinib, and dyspepsia, nausea, and headache with placebo. Most events were mild or moderate in severity, lasting $\leq$ 4 weeks. Permanent discontinuations due to non-serious AEs were not observed in patients with PsA, and were < 1.0% in patients with RA across treatment groups. The most frequent cause of temporary discontinuation across all groups was gastric discomfort (0.3–0.8%).

Conclusions: Non-serious AE incidence was generally similar in patients with RA or PsA receiving tofacitinib or placebo. Most events were mild or moderate and generally resolved within 4 weeks.

Trial Registration: ClinicalTrials.gov identifiers: NCT00960440; NCT00847613; NCT00814307; NCT00856544; NCT00853385; NCT01877668; NCT01882439; NCT02187055.

PLAIN LANGUAGE SUMMARY

Tofacitinib is a medicine that can be taken by patients to treat rheumatoid arthritis (RA) or psoriatic arthritis (PsA). Serious side effects that might occur in patients taking tofacitinib are more frequently discussed than the mild, non-serious side effects that patients might consider to be more of a 'nuisance', which often occur shortly (< 3 months) after starting treatment. Here we looked at patients with RA or PsA who were taking tofacitinib or placebo (no medicine) during clinical trials, to find out how often they had certain non-serious side effects, how long they lasted, and whether they caused the patients to stop taking their medication. A similar number of patients with RA or PsA taking tofacitinib or placebo had non-serious side effects. The most common non-serious side effects in patients taking tofacitinib were a headache and diarrhea. The most common non-serious side effects in patients taking placebo (no medicine) were indigestion, a feeling of sickness, and/or headache. Most non-serious side effects were mild or moderate and stopped within about 4 weeks. Fewer than one in every 100 patients with RA, and no patients with PsA, stopped taking their medication because of non-serious side effects. Most patients who stopped taking their medication did so due to a feeling of gastrointestinal (stomach) discomfort.

Keywords: Adverse event; Antirheumatic agents; Autoimmune diseases; Psoriatic arthritis; Rheumatoid arthritis; Tofacitinib; Tolerability

Key Summary Points
Why carry out this study?
Serious adverse events (AEs) have been extensively investigated for tofacitinib; however, there has been less focus on non-serious AEs that patients may consider to be a 'nuisance', and which may impact treatment adherence.
This post hoc analysis demonstrated that the frequency of select non-serious, non-infectious AEs was generally similar for patients with rheumatoid arthritis (RA) or psoriatic arthritis (PsA) receiving tofacitinib versus placebo.
What was learned from the study?
Overall, these select non-serious, non-infectious AEs were mild/moderate in severity, and the majority resolved within 4 weeks.
These data demonstrate that early non-serious, non-infectious AEs had little impact on treatment continuation in tofacitinib clinical trials, as < 1.0% of patients with RA, and no patients with PsA, permanently discontinued due to these AEs.
These findings can help inform clinicians on the type and impact of early non-serious AEs that may occur following tofacitinib treatment; this has the potential to improve patient compliance and adherence and could prevent otherwise unnecessary early discontinuation of treatment.

INTRODUCTION

Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are chronic inflammatory diseases, for which long-term pharmacologic treatment is recommended to achieve and maintain remission or low disease activity, and to prevent disease progression [1–4]. Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA and PsA. In patients with moderately to severely active RA, the efficacy and safety of tofacitinib 5 and 10 mg twice daily (BID) administered as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), mainly methotrexate (MTX), have been demonstrated in phase 2 [5–9], phase 3 [10–15], and phase 3b/4 [16] studies of up to 24 months in duration, and in long-term extension studies with up to 114 months of observation [17–19]. In patients with active PsA, the efficacy and safety of tofacitinib 5 and 10 mg BID in combination with csDMARDs have been demonstrated in two phase 3 studies of up to 12 months in duration [20, 21], and in a long-term extension study (NCT01976364) [22].

Tolerability of a medical product, as defined by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), is "the degree to which overt adverse events (AEs) can be tolerated by the patient" [23, 24]. The FDA and the EMA define serious AEs as those that result in death, a life-threatening experience, inpatient hospitalization, a persistent or significant disability or incapacity, a congenital anomaly or birth defect, or require (based on a reasonable medical judgment) medical or surgical intervention to prevent any of these outcomes [25, 26]. Non-serious AEs are events that do not meet these criteria. Nevertheless, even mild non-serious AEs can negatively impact patients and potentially limit adherence to treatment [27].

The most frequently reported all-causality, treatment-emergent AEs in clinical trials of tofacitinib were upper respiratory tract infection (URTI), viral URTI, and urinary tract infection in RA, and nasopharyngitis, URTI, and headache in PsA [28, 29]. In clinical trials of patients with RA or PsA, and in post-marketing surveillance of patients with RA, the majority of AEs in patients receiving tofacitinib 5 or 10 mg BID were non-serious [20–22, 30, 31]. Data regarding infections and AEs of special interest, such as cardiovascular events and malignancies, from clinical trials of tofacitinib of patients with RA or PsA have been published previously [29, 31, 32]. However, there has been less focus on non-serious AEs that patients may consider to be a 'nuisance', but could also result in early discontinuation of tofacitinib.

This post hoc analysis describes the frequency and duration of the most commonly reported non-serious, non-infectious AEs in patients with RA or PsA treated with tofacitinib 5 or 10 mg BID, compared with placebo, in phase 3 and phase 3b/4 studies, and describes their impact on treatment discontinuation.

METHODS

Study Designs and Patients

Data were pooled from five phase 3 studies of tofacitinib in patients with moderate-to-severe RA (ORAL Step [NCT00960440] [10]; ORAL Solo [NCT00814307] [11]; ORAL Scan [NCT00847613] [14]; ORAL Sync [NCT00856544] [12]; ORAL Standard [NCT00853385] [15]) and one phase 3b/4 study (ORAL Strategy [NCT02187055] [16]), and, separately, from two phase 3 studies of tofacitinib in patients with active PsA (OPAL Broaden [NCT01877668] [20]; OPAL Beyond [NCT01882439] [21]). Patients included in this analysis received tofacitinib 5 or 10 mg BID, or placebo, and had a previous inadequate response to ≥ 1 csDMARD [11, 12, 14–16, 20] or ≥ 1 tumor necrosis factor inhibitor (TNFi) [10, 21].

Study designs and patient eligibility criteria for all studies included in this analysis have been published previously [10–12, 14–16, 20, 21], and are summarized in Table S1 in the electronic supplementary material. Briefly, patients with RA were aged ≥ 18 years, with a RA diagnosis based on the American College of Rheumatology 1987 or 2010 revised criteria [33, 34], and had active disease (≥ 6

tender/painful joints and ≥ 6 swollen joints [≥ 4 in each case for ORAL Sync and ORAL Strategy] at baseline, and erythrocyte sedimentation rate [ESR] > 28 mm/h or C-reactive protein [CRP] > 7 mg/l at screening). Patients with PsA were aged ≥ 18 years, with a PsA diagnosis of ≥ 6 months, fulfilled the Classification Criteria for Psoriatic Arthritis [35], and had active disease (≥ 3 tender/painful joints and ≥ 3 swollen joints at baseline, and active plaque psoriasis at screening).

Patients included in this analysis received tofacitinib 5 mg BID monotherapy (ORAL Solo, ORAL Strategy); tofacitinib 10 mg BID monotherapy (ORAL Solo); placebo alone (i.e., without background csDMARDs [only concomitant anti-malarial medications were allowed]; hereafter defined as 'placebo monotherapy' [ORAL Solo]); and tofacitinib 5 or 10 mg BID, or placebo, in combination with csDMARDs (all PsA studies, and all RA studies except ORAL Solo [patients received monotherapy only] and ORAL Strategy [no placebo arm]).

All studies were conducted in accordance with the Declaration of Helsinki, International Council for Harmonisation Guidelines for Good Clinical Practice, and local regulations. Study protocols were reviewed and approved by the Institutional Review Board or Independent Ethics Committee. Patients provided informed consent.

Assessments and Safety Endpoints

In all studies, except ORAL Strategy, patients were randomized at baseline to receive tofacitinib 5 or 10 mg BID, or placebo. An adalimumab arm was also included in ORAL Standard (control), ORAL Strategy (comparator), and OPAL Broaden (control), with patients randomized at baseline to receive adalimumab 40 mg once every 2 weeks. Data for patients receiving adalimumab (injected subcutaneously) in these studies were excluded from this analysis to focus on the comparison of tofacitinib versus placebo, both of which were administered as oral formulations. There was no placebo arm in ORAL Strategy; all patients were randomized to receive tofacitinib or adalimumab from baseline. In ORAL Step, ORAL Solo, OPAL Broaden, and OPAL Beyond, patients receiving placebo advanced to tofacitinib 5 or 10 mg BID at month 3. In ORAL Standard, ORAL Scan, and ORAL Sync, placebo-treated patients who did not achieve ≥ 20% reduction from baseline in tender or swollen joint counts advanced to tofacitinib 5 or 10 mg BID at month 3, and all remaining patients receiving placebo advanced to tofacitinib 5 or 10 mg BID at month 6. To compare early select non-serious AEs in patients who were randomized to receive tofacitinib or placebo, this analysis was limited to data collected to month 3 (i.e., end of placebo-controlled period).

For this analysis, non-serious, all-causality, treatment-emergent AEs were defined as AEs that did not meet the definition of a serious AE [25, 26], and started (or increased in severity, leading to a new AE start date) after treatment initiation. Non-serious AEs meeting these criteria included: the Medical Dictionary for Regulatory Activities (MedDRA, v19.1) higher-level group term (HLGT) headache; MedDRA preferred terms diarrhea, nausea, and vomiting; and gastric discomfort (a composite term comprised of selected preferred terms, including dyspepsia, gastritis, epigastric discomfort, and abdominal discomfort or pain). A full list of the preferred terms included for headache (HLGT) and gastric discomfort (composite term) is provided in the Supplementary Methods in the electronic supplementary material. Severity of AEs was reported by investigators and was defined as "mild" (does not interfere with patient's usual function), "moderate" (interferes to some extent with patient's usual function), or "severe" (interferes significantly with patient's usual function). Laboratory test abnormalities and musculoskeletal or skin and subcutaneous tissue events likely to be due to underlying disease were excluded from the analysis. Non-serious infections have been reported previously, and were therefore also excluded [29, 31, 32].

Statistical Analyses

Analyses included all patients treated with ≥ 1 dose of study medication. The percentage of

patients experiencing select non-serious AEs that started within 3 months after treatment initiation was calculated for tofacitinib 5 mg BID, tofacitinib 10 mg BID, and placebo (monotherapy, combination therapy, or overall [i.e., monotherapy and combination therapy combined for RA studies] in each case). Incidence rates (IRs; unique patients with events per 100 patient-years [PY] of follow-up) and 95% confidence intervals (CIs; exact Poisson) were calculated for non-serious AEs, by MedDRA preferred term. The total follow-up time from baseline was calculated up to the day of the first event, subject to a 28-day risk period or 90 days post baseline (whichever came first). Events were counted up to 28 days beyond the last dose or 90 days post baseline (whichever came first). Data are presented for non-serious AEs that had an IR ≥ 5 (unique patients with events per 100 PY of follow-up) in at least one treatment group per cohort. The durations of non-serious AEs that started during months 0–3 were categorized as ≤ 1 week, > 1–≤ 2 weeks, > 2–≤ 3 weeks, > 3–≤ 4 weeks, or > 4 weeks. AE end date was used to calculate duration (if the end date was missing and the event was ongoing, the date of last treatment was used) with a 90-day cut off. For composite terms, AE duration was calculated by excluding any overlap in individual preferred terms. The proportions of patients who discontinued treatment (permanently or temporarily) due to non-serious AEs that started during months 0–3 were determined, regardless of the timing of discontinuation. Duration was also calculated for those non-serious AEs (that started during months 0–3) leading to treatment discontinuation, including end dates after month 3. All analyses were descriptive with no formal comparisons between groups.

RESULTS

Patient Demographics and Baseline Characteristics

Overall, 3871 patients with RA and 710 patients with PsA were included in the analysis. Patient demographics and baseline characteristics were generally similar across treatment groups within each cohort (Table 1).

The majority of patients with RA were female (> 80%) and aged < 65 years (> 80%). Mean weight and disease duration were generally similar across treatment groups. Baseline disease activity (measured by Disease Activity Score in 28 joints, ESR [DAS28-4(ESR)] and DAS28-3[CRP]) and physical impairment (measured by Health Assessment Questionnaire-Disability Index [HAQ-DI]) were generally comparable across groups. Prior TNFi exposure was less frequent among patients with RA receiving tofacitinib or placebo as monotherapy, compared with combination therapy. This is likely due to one of the combination therapy studies (ORAL Step) requiring previous inadequate response to TNFi [10]. Additionally, fewer patients receiving tofacitinib 5 mg BID had prior TNFi exposure, compared with those receiving placebo, in monotherapy and combination therapy groups. Prior exposure to csDMARDs, excluding MTX, was also lower in patients receiving tofacitinib 5 mg BID, compared with those receiving tofacitinib 10 mg BID or placebo, as monotherapy. Prior use of non-TNFi biologic DMARDs (bDMARDs) and non-steroidal anti-inflammatory drugs (NSAIDs) was generally similar across treatment groups. Numerically fewer patients receiving tofacitinib 10 mg BID or placebo monotherapy had previously used MTX, compared with other treatment groups. Fewer patients receiving tofacitinib 5 mg BID combination therapy received concomitant MTX at baseline, compared with tofacitinib 10 mg BID or placebo combination therapy. At baseline, a similar proportion of patients in each group received concomitant corticosteroids and concomitant NSAIDs.

In the PsA studies, 55.4% of patients were female and > 89% were aged < 65 years. Mean weight and disease duration were similar across treatment groups. Baseline disease activity (measured by DAS28-3[CRP] and PsA Disease Activity Score [PASDAS]) and physical impairment (measured by HAQ-DI) were generally comparable. A similar proportion of patients in each treatment group had prior exposure to csDMARDs (including MTX), bDMARDs

Table 1 Patient demographics and baseline disease characteristics

	RA									PsA		
	Monotherapy			Combination therapy[a]			Overall			Combination therapy[a]		
	Tofacitinib 5 mg BID *N* = 627	Tofacitinib 10 mg BID *N* = 245	PBO[b] *N* = 122	Tofacitinib 5 mg BID *N* = 1349	Tofacitinib 10 mg BID *N* = 969	PBO[c] *N* = 559	Tofacitinib 5 mg BID *N* = 1976	Tofacitinib 10 mg BID *N* = 1214	PBO[b,c] *N* = 681	Tofacitinib 5 mg BID *N* = 238	Tofacitinib 10 mg BID *N* = 236	PBO[c] *N* = 236
Female, *n* (%)	526 (83.9)	216 (88.2)	105 (86.1)	1131 (83.8)	814 (84.0)	448 (80.1)	1657 (83.9)	1030 (84.8)	553 (81.2)	121 (50.8)	136 (57.6)	136 (57.6)
Age (years), mean (SD)	50.7 (12.0)	52.4 (11.7)	49.7 (12.4)	52.5 (12.3)	52.6 (11.6)	53.1 (11.8)	51.9 (12.2)	52.5 (11.6)	52.5 (12.0)	49.5 (12.4)	49.4 (11.7)	48.4 (12.5)
Race, *n* (%)												
White	449 (71.6)	168 (68.6)	88 (72.1)	870 (64.5)	573 (59.1)	351 (62.8)	1319 (66.8)	741 (61.0)	439 (64.5)	226 (95.0)	221 (93.6)	222 (94.1)
Black	23 (3.7)	10 (4.1)	6 (4.9)	52 (3.9)	25 (2.6)	18 (3.2)	75 (3.8)	35 (2.9)	24 (3.5)	1 (0.4)	1 (0.4)	1 (0.4)
Asian	82 (13.1)	32 (13.1)	15 (12.3)	324 (24.0)	282 (29.1)	151 (27.0)	406 (20.6)	314 (25.9)	166 (24.4)	2 (0.8)	10 (4.2)	9 (3.8)
Other	73 (11.6)	35 (14.3)	13 (10.7)	103 (7.6)	89 (9.2)	39 (7.0)	176 (8.9)	124 (10.2)	52 (7.6)	9 (3.8)	4 (1.7)	4 (1.7)
Weight (kg), mean (SD)	73.6 (19.6)	71.6 (19.6)	72.5 (18.7)	71.5 (19.3)	71.1 (19.0)	72.3 (21.7)	72.1 (19.4)	71.2 (19.1)	72.3 (21.2)	86.1 (20.4)	85.1 (19.1)	82.1 (17.0)
Smoking status, *n* (%)[d]												
Current smoker	86 (13.7)	44 (18.0)	22 (18.0)	183 (13.6)	168 (17.3)	108 (19.3)	269 (13.6)	212 (17.5)	130 (19.1)	37 (15.5)	45 (19.1)	39 (16.5)
Ex-smoker	97 (15.5)	40 (16.3)	27 (22.1)	232 (17.2)	154 (15.9)	97 (17.4)	329 (16.7)	194 (16.0)	124 (18.2)	62 (26.1)	51 (21.6)	39 (16.5)
Never smoked	444 (70.8)	161 (65.7)	73 (59.8)	934 (69.2)	647 (66.8)	352 (63.0)	1378 (69.7)	808 (66.6)	425 (62.4)	139 (58.4)	140 (59.3)	158 (66.9)
Disease duration (years), mean (SD)	8.3 (7.9)	8.6 (8.3)	7.7 (7.2)	8.5 (7.8)	9.2 (8.2)	9.6 (8.7)	8.4 (7.8)	9.1 (8.2)	9.3 (8.5)	8.6 (7.9)	7.5 (6.6)	8.1 (7.5)
DAS28-4(ESR), mean (SD)[e]	6.6 (0.9)	6.7 (0.9)	6.6 (0.9)	6.4 (1.0)	6.4 (1.0)	6.3 (1.0)	6.5 (1.0)	6.4 (1.0)	6.4 (1.0)	NA	NA	NA

Table 1 continued

	RA									PsA		
	Monotherapy			Combination therapy[a]			Overall			Combination therapy[a]		
	Tofacitinib 5 mg BID *N* = 627	Tofacitinib 10 mg BID *N* = 245	PBO[b] *N* = 122	Tofacitinib 5 mg BID *N* = 1349	Tofacitinib 10 mg BID *N* = 969	PBO[c] *N* = 559	Tofacitinib 5 mg BID *N* = 1976	Tofacitinib 10 mg BID *N* = 1214	PBO[b,c] *N* = 681	Tofacitinib 5 mg BID *N* = 238	Tofacitinib 10 mg BID *N* = 236	PBO[c] *N* = 236
DAS28-3(CRP), mean (SD)[e]	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)	5.4 (0.9)	5.3 (0.9)	5.3 (0.9)	5.4 (0.9)	5.3 (0.9)	5.3 (0.9)	4.5 (1.0)	4.6 (1.1)	4.4 (1.0)
PASDAS, mean (SD)[e]	NA	NA	NA	NA	NA	NA	NA	NA	NA	6.1 (1.2)	6.2 (1.2)	6.0 (1.2)
HAQ-DI, mean (SD)[e]	1.6 (0.6)	1.5 (0.6)	1.5 (0.7)	1.5 (0.7)	1.4 (0.7)	1.4 (0.7)	1.5 (0.7)	1.5 (0.7)	1.4 (0.7)	1.2 (0.7)	1.2 (0.6)	1.2 (0.7)
Treatment history, *n* (%)												
Prior MTX	593 (94.6)	207 (84.5)	102 (83.6)	1329 (98.5)	947 (97.7)	547 (97.9)	1922 (97.3)	1154 (95.1)	649 (95.3)	220 (92.4)	212 (89.8)	221 (93.6)
Prior csDMARDs excluding MTX	279 (44.5)	164 (66.9)	83 (68.0)	705 (52.3)	585 (60.4)	315 (56.4)	984 (49.8)	749 (61.7)	398 (58.4)	112 (47.1)	112 (47.5)	112 (47.5)
Prior TNFi	62 (9.9)	41 (16.7)	24 (19.7)	276 (20.5)	245 (25.3)	177 (31.7)	338 (17.1)	286 (23.6)	201 (29.5)	131 (55.0)	132 (55.9)	132 (55.9)
Prior bDMARDs excluding TNFi	31 (4.9)	19 (7.8)	10 (8.2)	78 (5.8)	53 (5.5)	36 (6.4)	109 (5.5)	72 (5.9)	46 (6.8)	14 (5.9)	18 (7.6)	14 (5.9)
Prior NSAIDs	490 (78.2)	193 (78.8)	98 (80.3)	991 (73.5)	770 (79.5)	430 (76.9)	1481 (75.0)	963 (79.3)	528 (77.5)	150 (63.0)	133 (56.4)	139 (58.9)
Concomitant MTX at baseline, *n* (%)	5 (0.8)[f]	0	0	902 (66.9)	895 (92.4)	513 (91.8)	907 (45.9)	895 (73.7)	513 (75.3)	190 (79.8)	184 (78.0)	193 (81.8)
Mean MTX dose at baseline, mg/week (SD)[g]	*N1* = 5 16.5 (4.2)	NA	NA	*N1* = 902 14.7 (4.7)	*N1* = 895 15.1 (4.8)	*N1* = 512 15.2 (4.7)	*N1* = 907 14.7 (4.7)	*N1* = 895 15.1 (4.8)	*N1* = 512 15.2 (4.7)	*N1* = 190 15.6 (4.2)	*N1* = 183 14.7 (4.4)	*N1* = 193 14.8 (4.3)
Concomitant corticosteroids at baseline, *n* (%)	367 (58.5)	140 (57.1)	71 (58.2)	797 (59.1)	551 (56.9)	325 (58.1)	1164 (58.9)	691 (56.9)	396 (58.2)	67 (28.2)	37 (15.7)	49 (20.8)
Mean corticosteroid dose at baseline, mg/day (SD)[h]	*N1* = 358 7.4 (10.9)	*N1* = 135 6.7 (2.4)	*N1* = 71 7.0 (2.9)	*N1* = 776 6.3 (2.8)	*N1* = 529 6.3 (2.8)	*N1* = 305 6.7 (2.8)	*N1* = 1134 6.7 (6.6)	*N1* = 664 6.4 (2.8)	*N1* = 376 6.8 (2.8)	*N1* = 67 7.0 (3.3)	*N1* = 37 6.3 (2.6)	*N1* = 49 6.7 (4.0)

Table 1 continued

	RA									PsA		
	Monotherapy			Combination therapy[a]			Overall			Combination therapy[a]		
	Tofacitinib 5 mg BID *N* = 627	Tofacitinib 10 mg BID *N* = 245	PBO[b] *N* = 122	Tofacitinib 5 mg BID *N* = 1349	Tofacitinib 10 mg BID *N* = 969	PBO[c] *N* = 559	Tofacitinib 5 mg BID *N* = 1976	Tofacitinib 10 mg BID *N* = 1214	PBO[b,c] *N* = 681	Tofacitinib 5 mg BID *N* = 238	Tofacitinib 10 mg BID *N* = 236	PBO[c] *N* = 236
Concomitant NSAIDs, *n* (%)[i]	469 (74.8)	177 (72.2)	86 (70.5)	955 (70.8)	737 (76.1)	419 (75.0)	1424 (72.1)	914 (75.3)	505 (74.2)	149 (62.6)	129 (54.7)	137 (58.1)

bDMARD biologic disease-modifying antirheumatic drug, *BID* twice daily, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *DAS28-3(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, *MTX* methotrexate, *N* total number of patients in each treatment group, *n* number of patients in each category, *N1* number of patients included in the calculation of mean dose, *NA* not applicable, *NSAID* non-steroidal anti-inflammatory drug, *PASDAS* Psoriatic Arthritis Disease Activity Score, *PBO* placebo, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *SD* standard deviation, *TNFi* tumor necrosis factor inhibitor

[a]Background csDMARDs

[b]PBO monotherapy is defined as patients receiving no active treatment in ORAL Solo

[c]PBO combination therapy is defined as patients receiving PBO with csDMARDs in phase 3 (RA and PsA) or phase 3b/4 studies (RA)

[d]Smoking status was unknown in two patients with RA receiving PBO as combination therapy

[e]The number of patients assessed was fewer than the total *N* in some treatment groups

[f]One patient stopped receiving MTX before receiving tofacitinib 5 mg BID and four patients stopped receiving MTX within the first week of tofacitinib 5 mg BID treatment; for all clinical purposes, none of these patients were categorized as receiving background MTX during the study

[g]Mean dose was calculated based on those patients receiving a known dose of MTX at baseline (dose was unknown for some patients)

[h]Mean dose was calculated based on those patients receiving a known dose of corticosteroids at baseline (dose was unknown for some patients); for patients with RA, corticosteroid doses that appeared to be outside the range of oral or systemic administration were excluded from the calculation of mean dose

[i]Includes patients receiving NSAIDs at baseline and during the study

Table 2 Incidence of non-serious AEs[a] (preferred terms) up to month 3

Non-serious AE, *n* (%) IR (95% CI)[b]	RA									PsA		
	Monotherapy			Combination therapy			Overall			Combination therapy		
	Tofacitinib 5 mg BID *N* = 627	Tofacitinib 10 mg BID *N* = 245	PBO[c] *N* = 122	Tofacitinib 5 mg BID *N* = 1349	Tofacitinib 10 mg BID *N* = 969	PBO[d] *N* = 559	Tofacitinib 5 mg BID *N* = 1976	Tofacitinib 10 mg BID *N* = 1214	PBO[c,d] *N* = 681	Tofacitinib 5 mg BID *N* = 238	Tofacitinib 10 mg BID *N* = 236	PBO[d] *N* = 236
Headache	21 (3.3)	11 (4.5)	3 (2.5)	50 (3.7)	29 (3.0)	13 (2.3)	71 (3.6)	40 (3.3)	16 (2.3)	9 (3.8)	20 (8.5)	11 (4.7)
	13.7	18.6	10.1	15.3	12.3	9.5	14.8	13.5	9.6	16.9	39.2	21.3
	(8.5–21.0)	(9.3–33.2)	(2.1–29.4)	(11.3–20.1)	(8.2–17.6)	(5.1–16.3)	(11.5–18.6)	(9.7–18.4)	(5.5–15.6)	(7.7–32.1)	(24.0–60.6)	(10.6–38.1)
Migraine	IR < 5[e]	IR < 5[e]	IR < 5[e]	IR < 5[e]	IR < 5[e]	IR < 5[e]	IR < 5[e]	IR < 5[e]	IR < 5[e]	3 (1.3)	2 (0.8)	0
										5.6	3.7	0
										(1.1–16.2)	(0.5–13.3)	(0–6.9)
Diarrhea	18 (2.9)	9 (3.7)	3 (2.5)	41 (3.0)	26 (2.7)	13 (2.3)	59 (3.0)	35 (2.9)	16 (2.3)	8 (3.4)	9 (3.8)	1 (0.4)
	11.7	15.1	10.0	12.5	10.9	9.5	12.2	11.8	9.6	15.0	17.0	1.9
	(7.0–18.5)	(6.9–28.6)	(2.1–29.2)	(8.9–16.9)	(7.1–16.0)	(5.1–16.3)	(9.3–15.8)	(8.2–16.4)	(5.5–15.6)	(6.5–29.5)	(7.8–32.3)	(0.1–10.4)
Nausea	15 (2.4)	8 (3.3)	3 (2.5)	29 (2.1)	16 (1.7)	15 (2.7)	44 (2.2)	24 (2.0)	18 (2.6)	6 (2.5)	5 (2.1)	7 (3.0)
	9.8	13.4	10.0	8.8	6.7	11.0	9.1	8.1	10.8	11.2	9.4	13.4
	(5.5–16.1)	(5.8–26.5)	(2.1–29.2)	(5.9–12.6)	(3.8–10.9)	(6.2–18.2)	(6.6–12.2)	(5.2–12.0)	(6.4–17.1)	(4.1–24.4)	(3.0–21.8)	(5.4–27.6)
Vomiting	7 (1.1)	3 (1.2)	2 (1.6)	18 (1.3)	5 (0.5)	8 (1.4)	25 (1.3)	8 (0.7)	10 (1.5)	IR < 5[e]	IR < 5[e]	IR < 5[e]
	4.5	5.0	6.6	5.4	2.1	5.8	5.1	2.7	6.0			
	(1.8–9.3)	(1.0–14.5)	(0.8–24.0)	(3.2–8.6)	(0.7–4.9)	(2.5–11.4)	(3.3–7.6)	(1.2–5.2)	(2.9–11.0)			
Gastritis	5 (0.8)	6 (2.4)	3 (2.5)	IR < 5[e]	IR < 5[e]	IR < 5[e]	16 (0.8)	16 (1.3)	7 (1.0)	IR < 5[e]	IR < 5[e]	IR < 5[e]
	3.2	10.0	10.0				3.3	5.3	4.2			
	(1.1–7.5)	(3.7–21.8)	(2.1–29.4)				(1.9–5.3)	(3.1–8.7)	(1.7–8.6)			
Dyspepsia	4 (0.6)	6 (2.4)	4 (3.3)	20 (1.5)	20 (2.1)	7 (1.3)	24 (1.2)	26 (2.1)	11 (1.6)	5 (2.1)	2 (0.8)	2 (0.8)
	2.6	10.0	13.6	6.0	8.4	5.1	4.9	8.7	6.6	9.3	3.7	3.7
	(0.7–6.6)	(3.7–21.8)	(3.7–34.7)	(3.7–9.3)	(5.1–13.0)	(2.1–10.5)	(3.2–7.3)	(5.7–12.8)	(3.3–11.8)	(3.0–21.7)	(0.5–13.4)	(0.5–13.5)

Table 2 continued

Non-serious AE, *n* (%) IR (95% CI)[b]	RA									PsA		
	Monotherapy			Combination therapy			Overall			Combination therapy		
	Tofacitinib 5 mg BID *N* = 627	Tofacitinib 10 mg BID *N* = 245	PBO[c] *N* = 122	Tofacitinib 5 mg BID *N* = 1349	Tofacitinib 10 mg BID *N* = 969	PBO[d] *N* = 559	Tofacitinib 5 mg BID *N* = 1976	Tofacitinib 10 mg BID *N* = 1214	PBO[c,d] *N* = 681	Tofacitinib 5 mg BID *N* = 238	Tofacitinib 10 mg BID *N* = 236	PBO[d] *N* = 236
Abdominal pain	4 (0.6)	4 (1.6)	1 (0.8)	IR < 5[e]	IR < 5[e]	IR < 5[e]	IR < 5[e]	IR < 5[e]	IR < 5[e]	3 (1.3)	3 (1.3)	1 (0.4)
	2.6	6.6	3.3							5.5	5.6	1.9
	(0.7–6.6)	(1.8–17.0)	(0.1–18.4)							(1.1–16.2)	(1.2–16.3)	(0.1–10.4)
Abdominal discomfort	2 (0.3)	1 (0.4)	2 (1.6)	IR < 5[e]	IR < 5[e]	IR < 5[e]	IR < 5[e]	IR < 5[e]	IR < 5[e]	IR < 5[e]	IR < 5[e]	IR < 5[e]
	1.3	1.6	6.6									
	(0.2–4.6)	(0–9.2)	(0.8–23.8)									
Abdominal pain upper	7 (1.1)	4 (1.6)	0	17 (1.3)	9 (0.9)	6 (1.1)	IR < 5[e]	IR < 5[e]	IR < 5[e]	2 (0.8)	3 (1.3)	0
	4.5	6.7	0	5.1	3.8	4.4				3.7	5.6	0
	(1.8–9.3)	(1.8–17.0)	(0–12.1)	(3.0–8.2)	(1.7–7.1)	(1.6–9.5)				(0.5–13.3)	(1.2–16.3)	(0–6.9)

AE adverse event, *BID* twice daily, *CI* confidence interval, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *IR* incidence rate, *N* total number of patients in each treatment group, *n* number of patients experiencing the specified AE in each category, *PBO* placebo, *PsA* psoriatic arthritis, *PY* patient-years, *RA* rheumatoid arthritis

[a]Defined as AEs (individual preferred AE terms) with an IR (unique patients with events per 100 PY of follow-up) ≥ 5 in at least one treatment group under monotherapy, combination therapy, or overall therapy per cohort

[b]Total follow-up time was calculated up to the day of the first event, subject to a risk period up to 28 days beyond the last dose or 90 days (whichever came first). IR was a naïve estimate without adjusting for study. Exact Poisson 95% CIs are provided for the IR. Events were counted up to 28 days beyond the last dose or 90 days (whichever came first)

[c]PBO monotherapy is defined as patients receiving no active treatment in ORAL Solo

[d]PBO combination therapy is defined as patients receiving PBO with csDMARDs in phase 3 (RA and PsA) or phase 3b/4 studies (RA)

[e]Data are not shown for AEs with IRs < 5 across treatment groups per cohort

Table 3 Severity of non-serious AEs[a,b] up to month 3

Non-serious AE, *n/N1* (%)[c]	RA (overall)[d]									PsA (combination therapy)								
	Tofacitinib 5 mg BID *N* = 1976			Tofacitinib 10 mg BID *N* = 1214			PBO[e,f] *N* = 681			Tofacitinib 5 mg BID *N* = 238			Tofacitinib 10 mg BID *N* = 236			PBO[f] *N* = 236		
	Mild	Mod	Severe	Mild	Mod	Severe	Mild	Mod	Severe	Mild	Mod	Severe	Mild	Mod	Severe	Mild	Mod	Severe
HLGT headache[g]	47/82 (57.3)	30/82 (36.6)	5/82 (6.1)	30/44 (68.2)	14/44 (31.8)	0/44 (0.0)	13/18 (72.2)	4/18 (22.2)	1/18 (5.6)	8/11 (72.7)	3/11 (27.3)	0/11 (0.0)	16/21 (76.2)	4/21 (19.0)	1/21 (4.8)	9/12 (75.0)	2/12 (16.7)	1/12 (8.3)
Diarrhea	48/59 (81.4)	9/59 (15.3)	2/59 (3.4)	29/35 (82.9)	5/35 (14.3)	1/35 (2.9)	10/16 (62.5)	6/16 (37.5)	0/16 (0.0)	6/8 (75.0)	2/8 (25.0)	0/8 (0.0)	8/9 (88.9)	1/9 (11.1)	0/9 (0.0)	1/1 (100.0)	0/1 (0.0)	0/1 (0.0)
Nausea	32/44 (72.7)	12/44 (27.3)	0/44 (0.0)	18/24 (75.0)	3/24 (12.5)	3/24 (12.5)	14/18 (77.8)	4/18 (22.2)	0/18 (0.0)	4/6 (66.7)	2/6 (33.3)	0/6 (0.0)	4/5 (80.0)	1/5 (20.0)	0/5 (0.0)	6/7 (85.7)	1/7 (14.3)	0/7 (0.0)
Vomiting	18/25 (72.0)	7/25 (28.0)	0/25 (0.0)	4/8 (50.0)	3/8 (37.5)	1/8 (12.5)	9/10 (90.0)	1/10 (10.0)	0/10 (0.0)	1/1 (100.0)	0/1 (0.0)	0/1 (0.0)	2/2 (100.0)	0/2 (0.0)	0/2 (0.0)	2/2 (100.0)	0/2 (0.0)	0/2 (0.0)
Gastric discomfort (composite term)[h]	62/99 (62.6)	34/99 (34.3)	3/99 (3.0)	55/83 (66.3)	28/83 (33.7)	0/83 (0.0)	28/41 (68.3)	10/41 (24.4)	3/41 (7.3)	8/13 (61.5)	5/13 (38.5)	0/13 (0.0)	9/11 (81.8)	2/11 (18.2)	0/11 (0.0)	6/6 (100.0)	0/6 (0.0)	0/6 (0.0)

AE adverse event, *BID* twice daily, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *HLGT* higher-level group term, *MedDRA* Medical Dictionary for Regulatory Activities, *Mod* moderate, *N* total number of patients in each treatment group, *n* number of patients experiencing the specified AE in each severity category, *N1* total number of patients experiencing the specified AE in each treatment group, *PBO* placebo, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis

[a]MedDRA HLGT (headache), MedDRA preferred terms (diarrhea, nausea, vomiting) and composite term (gastric discomfort)

[b]Only the most severe occurrence is taken if the same patient in a given treatment group had more than one occurrence in the same preferred term event category. Missing severities were imputed as severe unless the patient experienced another occurrence of the same event in a given treatment for which severity was recorded

[c]Percentages were calculated as proportions of the total number of patients experiencing the specified AE in each treatment group

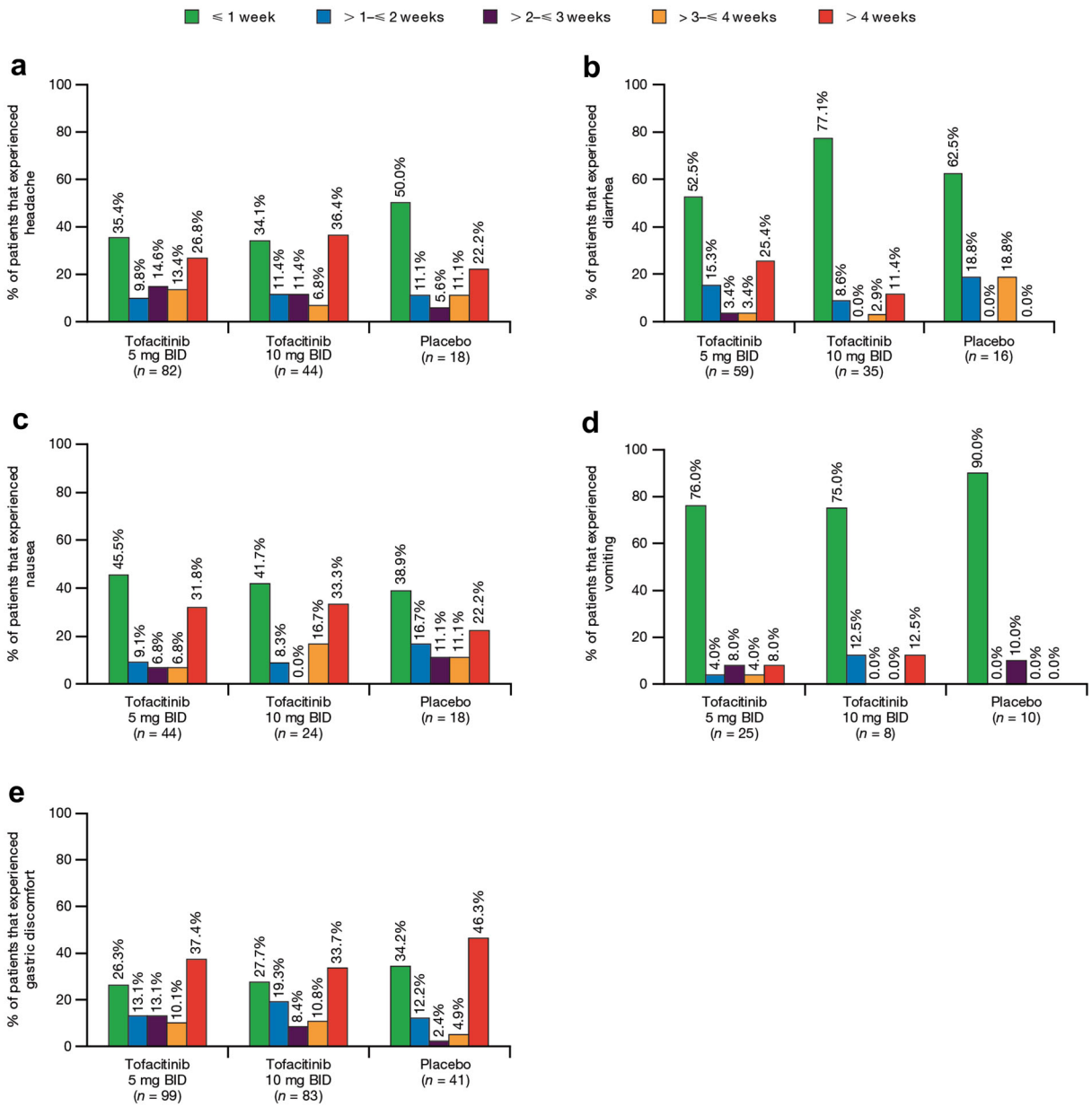
[d]Data are shown for overall treatment groups, i.e., combined data for patients with RA receiving tofacitinib or placebo as monotherapy and in combination with csDMARDs

[e]PBO monotherapy is defined as patients receiving no active treatment in ORAL Solo

[f]PBO combination therapy is defined as patients receiving PBO with csDMARDs in phase 3 (RA and PsA) or phase 3b/4 studies (RA)

[g]MedDRA HLGT, including all types of headache (see the Supplementary Methods in the electronic supplementary material for a full list of preferred terms included)

[h]A composite term comprised of selected preferred terms, including dyspepsia, gastritis, epigastric discomfort, and abdominal discomfort or pain (see the Supplementary Methods in the electronic supplementary material for a full list of preferred terms included)


≤ 1 week
> 1–≤ 2 weeks
> 2–≤ 3 weeks
> 3–≤ 4 weeks
> 4 weeks
a
% of patients that experienced headache
35.4% 9.8% 14.6% 13.4% 26.8%
34.1% 11.4% 11.4% 6.8% 36.4%
50.0% 11.1% 5.6% 11.1% 22.2%
Tofacitinib 5 mg BID (n = 82)
Tofacitinib 10 mg BID (n = 44)
Placebo (n = 18)
b
% of patients that experienced diarrhea
52.5% 15.3% 3.4% 3.4% 25.4%
77.1% 8.6% 0.0% 2.9% 11.4%
62.5% 18.8% 0.0% 18.8% 0.0%
Tofacitinib 5 mg BID (n = 59)
Tofacitinib 10 mg BID (n = 35)
Placebo (n = 16)
c
% of patients that experienced nausea
45.5% 9.1% 6.8% 6.8% 31.8%
41.7% 8.3% 0.0% 16.7% 33.3%
38.9% 16.7% 11.1% 11.1% 22.2%
Tofacitinib 5 mg BID (n = 44)
Tofacitinib 10 mg BID (n = 24)
Placebo (n = 18)
d
% of patients that experienced vomiting
76.0% 4.0% 8.0% 4.0% 8.0%
75.0% 12.5% 0.0% 0.0% 12.5%
90.0% 0.0% 10.0% 0.0% 0.0%
Tofacitinib 5 mg BID (n = 25)
Tofacitinib 10 mg BID (n = 8)
Placebo (n = 10)
e
% of patients that experienced gastric discomfort
26.3% 13.1% 13.1% 10.1% 37.4%
27.7% 19.3% 8.4% 10.8% 33.7%
34.2% 12.2% 2.4% 4.9% 46.3%
Tofacitinib 5 mg BID (n = 99)
Tofacitinib 10 mg BID (n = 83)
Placebo (n = 41)

◀**Fig. 1** Duration of non-serious AEs up to month 3 in patients with RA: HLGT headache[a] (**a**), diarrhea[b] (**b**), nausea[b] (**c**), vomiting[b] (**d**), and gastric discomfort (composite term)[c] (**e**). AEs are shown as percentages of the total number of patients experiencing the specified AE in each treatment group. Data are shown for patients receiving tofacitinib 5 or 10 mg BID, or placebo, as monotherapy or in combination with csDMARDs in phase 3 and phase 3b/4 studies. [a]MedDRA HLGT, including all types of headache (see the Supplementary Methods in the electronic supplementary material for a full list of preferred terms included). [b]Preferred term. [c]A composite term comprised of selected preferred terms, including dyspepsia, gastritis, epigastric discomfort, and abdominal discomfort or pain (see the Supplementary Methods in the electronic supplementary material for a full list of preferred terms included). *AE* adverse event, *BID* twice daily, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *HLGT* higher-level group term, *MedDRA* Medical Dictionary for Regulatory Activities, *n* total number of patients experiencing the specified AE in each treatment group, *RA* rheumatoid arthritis

(including TNFi), and NSAIDs. More patients receiving tofacitinib 5 mg BID received concomitant corticosteroids, compared with tofacitinib 10 mg BID or placebo. Across treatment groups, a similar proportion of patients received concomitant MTX at baseline and concomitant NSAIDs.

Non-serious AEs

Among patients with RA, the most frequent non-serious AEs that started during months 0–3 (preferred terms with an IR $\geq$ 5 per 100 PY of follow-up) were headache (IR = 12.3–18.6) and diarrhea (IR = 10.9–15.1) for all tofacitinib treatment groups (Table 2). For placebo as monotherapy and combination therapy, dyspepsia (IR = 13.6) and nausea (IR = 11.0), respectively, were most common. The IR for headache was numerically higher in patients with RA receiving tofacitinib, compared with placebo, both as monotherapy and combination therapy; however, differences were not significant.

For patients with PsA, the most frequent non-serious AEs that started during months 0–3 (preferred terms with an IR $\geq$ 5) were headache (IR = 16.9–39.2) and diarrhea (IR = 15.0–17.0) for both tofacitinib 5 and 10 mg BID combination therapy, and headache (IR = 21.3) and nausea (IR = 13.4) for placebo combination therapy. Migraine, dyspepsia, abdominal pain, and upper abdominal pain also had an IR $\geq$ 5 in at least one tofacitinib group (Table 2). IRs for migraines, diarrhea, abdominal pain, and upper abdominal pain were numerically higher in patients with PsA receiving tofacitinib, compared with placebo; however, differences were not significant. Headache was more frequent in patients receiving tofacitinib 10 mg BID (IR = 39.2) with background csDMARDs, compared with both tofacitinib 5 mg BID and placebo (IR = 16.9 and 21.3, respectively); however, differences were not significant. In total, > 85% of non-serious AEs were mild or moderate in severity (Table 3).

Duration of Non-serious AEs

For the majority of patients with RA or PsA experiencing HLGT headache, diarrhea, nausea, vomiting, or gastric discomfort (composite term) with onset during months 0–3, the duration of these non-serious AEs was $\leq$ 4 weeks (Figs. 1, 2).

Generally, the proportion of patients with RA experiencing AEs for $\leq$ 2 weeks was similar across treatment groups (Fig. 1). The majority of patients with RA reporting diarrhea or vomiting experienced these for $\leq$ 1 week, regardless of treatment group. In general, > 60% of patients with RA experiencing headache, gastric discomfort, and nausea, reported a duration of $\leq$ 4 weeks across treatment groups, with the majority lasting $\leq$ 2 weeks. In patients with PsA, non-serious AEs were generally $\leq$ 4 weeks in duration across treatment groups; however, the number of patients was low ($n \leq 21$; Fig. 2). In patients with PsA receiving tofacitinib 5 mg BID who experienced headaches, > 50% of cases lasted > 4 weeks. However, there were only 11 headache events in this group, and 4 of these lasted $\leq$ 2 weeks.

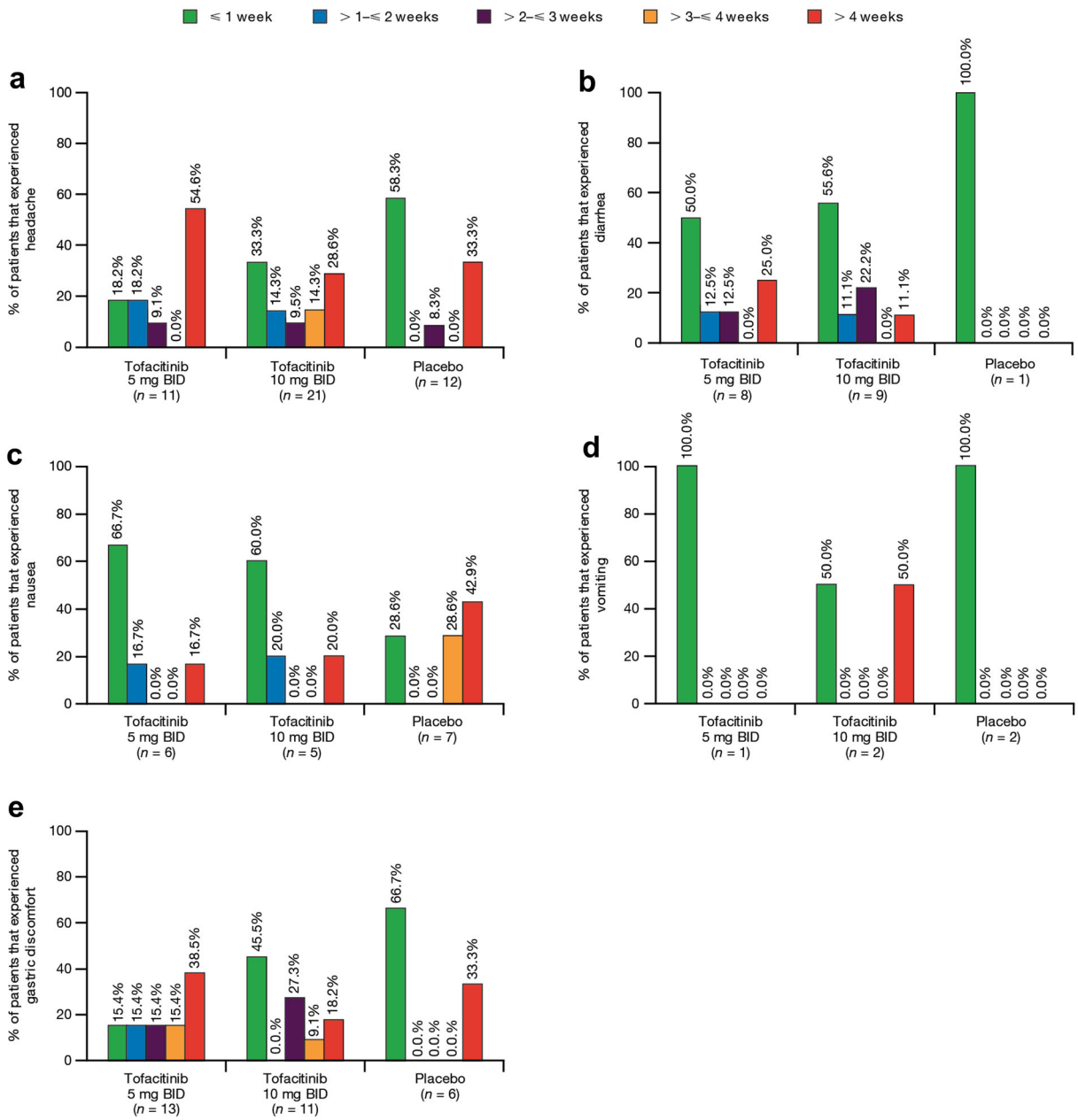


Fig. 2 Duration of non-serious AEs up to month 3 in patients with PsA: HLGT headache[a] (**a**), diarrhea[b] (**b**), nausea[b] (**c**), vomiting[b] (**d**), and gastric discomfort (composite term)[c] (**e**). AEs are shown as percentages of the total number of patients experiencing each AE in each treatment group. Data are shown for patients receiving tofacitinib 5 or 10 mg BID, or placebo, in combination with csDMARDs in phase 3 studies. [a]MedDRA HLGT, including all types of headache (see the Supplementary Methods in the electronic supplementary material for a full list of preferred terms included). [b]Preferred term. [c]A composite term comprised of selected preferred terms, including dyspepsia, gastritis, epigastric discomfort, and abdominal discomfort or pain (see the Supplementary Methods in the electronic supplementary material for a full list of preferred terms included). *AE* adverse event, *BID* twice daily, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *HLGT* higher-level group term, *MedDRA* Medical Dictionary for Regulatory Activities, *n* total number of patients experiencing the specified AE in each treatment group, *PsA* psoriatic arthritis

Discontinuations Due to Non-serious AEs

The numbers of patients with RA receiving overall therapy (i.e., monotherapy and combination therapy groups combined) and patients with PsA receiving combination therapy who temporarily or permanently discontinued treatment due to non-serious AEs that started during months 0–3, and the duration of these AEs, are shown in Table 4. Data for patients with RA receiving monotherapy or combination therapy are shown in Table S2 in the electronic supplementary material.

Overall, among patients with RA receiving tofacitinib 5 mg BID as monotherapy, 1 (0.2%) patient permanently discontinued (cause: nausea and gastric discomfort [composite term]) and 11 (1.8%) patients temporarily discontinued, due to non-serious AEs. The most common causes of temporary discontinuations of tofacitinib 5 mg BID monotherapy were HGLT headache and gastric discomfort (composite term; $n = 4$ [0.6%] for each AE). For patients with RA receiving tofacitinib 5 mg BID as combination therapy, there were 9 (0.7%) permanent discontinuations and 22 (1.6%) temporary discontinuations, due to non-serious AEs. The most common causes of permanent or temporary discontinuations of tofacitinib 5 mg BID combination therapy were HGLT headache ($n = 6$ [0.4%]) and gastric discomfort (composite term; $n = 11$ [0.8%]), respectively.

For patients with RA receiving tofacitinib 10 mg BID as monotherapy, 1 (0.4%) patient permanently discontinued with nausea, and 7 (2.9%) patients temporarily discontinued due to non-serious AEs. Diarrhea, vomiting, and gastric discomfort (composite term; $n = 2$ [0.8%] for each AE) were reported as the most common causes for temporary discontinuation of tofacitinib 10 mg BID monotherapy. For patients with RA receiving tofacitinib 10 mg BID as combination therapy, 3 (0.3%) patients permanently discontinued and 12 (1.2%) patients temporarily discontinued, due to non-serious AEs. Vomiting ($n = 2$ [0.2%]) was the most common cause for permanent discontinuations of tofacitinib 10 mg BID combination therapy, while the most common causes of temporary discontinuations of 10 mg BID combination therapy were diarrhea and gastric discomfort (composite term; $n = 4$ [0.4%] for each AE). The majority of AEs leading to temporary or permanent discontinuation of tofacitinib were mild or moderate in severity.

Among patients with RA receiving placebo monotherapy, 1 (0.8%) patient permanently discontinued (cause: gastric discomfort [composite term]), and 3 (2.5%) patients temporarily discontinued, due to non-serious AEs. Diarrhea ($n = 2$ [1.6%]) was the most common cause of temporary discontinuations of placebo monotherapy. There were 3 (0.5%) permanent discontinuations among patients with RA receiving placebo with csDMARDs, and 6 (1.1%) temporary discontinuations, due to non-serious AEs. For patients receiving placebo combination therapy, the most common cause of permanent discontinuations was diarrhea ($n = 2$ [0.4%]), while nausea and vomiting were the most common causes of temporary discontinuations ($n = 3$ [0.5%] for each AE).

There were no permanent discontinuations due to non-serious AEs in patients with PsA. Among patients with PsA receiving combination therapy with tofacitinib 5 mg BID, tofacitinib 10 mg BID, and placebo, 3 (1.3%), 3 (1.3%), and 4 (1.7%) patients temporarily discontinued treatment due to non-serious AEs, respectively. For patients receiving tofacitinib 5 mg BID combination therapy, nausea ($n = 2$ [0.8%]) and gastric discomfort (composite term; $n = 2$ [0.8%]) were the most common causes of temporary discontinuation. The most common causes of temporary discontinuation of tofacitinib 10 mg BID or placebo combination therapy were gastric discomfort (composite term; $n = 2$ [0.8%]) and vomiting ($n = 2$ [0.8%]), respectively. All AEs leading to temporary discontinuation of tofacitinib were mild or moderate in severity.

Table 4 Permanent and temporary discontinuations[a] due to HLGT headache, diarrhea, nausea, vomiting, or gastric discomfort (composite term) in patients with RA or PsA

	RA (overall)[b]			PsA (combination therapy)		
	Tofacitinib 5 mg BID *N* = 1976	Tofacitinib 10 mg BID *N* = 1214	PBO[c] *N* = 681	Tofacitinib 5 mg BID *N* = 238	Tofacitinib 10 mg BID *N* = 236	PBO[d] *N* = 236
HLGT headache[e]						
Temporary DC, *n* (%)	8 (0.4)	3 (0.3)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.4)
Duration (days), median (IQR)[f]	5.0 (1.5–16.0)	6.0 (5.0–36.0)	5.0 (5.0–5.0)	73.0 (73.0–73.0)	NA	3.0 (3.0–3.0)
Permanent DC, *n* (%)	6 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Duration (days), median (IQR)[f]	12.0 (10.0–21.0)	NA	NA	NA	NA	NA
Diarrhea[g]						
Temporary DC, *n* (%)	3 (0.2)	6 (0.5)	2 (0.3)	0 (0.0)	1 (0.4)	1 (0.4)
Duration (days), median (IQR)[f]	22.0 (3.0–342.0)	3.0 (2.0–14.0)	1.5 (1.0–2.0)	NA	9.0 (9.0–9.0)	2.0 (2.0–2.0)
Permanent DC, *n* (%)	1 (0.1)	1 (0.1)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Duration (days), median (IQR)[f]	163.0 (163.0–163.0)	4.0 (4.0–4.0)	9.5 (5.0–14.0)	NA	NA	NA
Nausea[g]						
Temporary DC, *n* (%)	6 (0.3)	3 (0.3)	3 (0.4)	2 (0.8)	1 (0.4)	1 (0.4)
Duration (days), median (IQR)[f]	4.0 (3.0–5.0)	4.0 (4.0–24.0)	6.0 (3.0–10.0)	30.0 (9.0–51.0)	4.0 (4.0–4.0)	2.0 (2.0–2.0)
Permanent DC, *n* (%)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Duration (days), median (IQR)[f]	72.0 (72.0–72.0)	7.0 (4.0–10.0)	NA	NA	NA	NA
Vomiting[g]						
Temporary DC, *n* (%)	7 (0.4)	4 (0.3)	3 (0.4)	0 (0.0)	0 (0.0)	2 (0.8)
Duration (days), median (IQR)[f]	3.0 (2.0–9.0)	4.5 (2.5–34.0)	3.0 (3.0–4.0)	NA	NA	3.5 (2.0–5.0)
Permanent DC, *n* (%)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Duration (days), median (IQR)[f]	NA	7.0 (4.0–10.0)	NA	NA	NA	NA

Table 4 continued

	RA (overall)[b]			PsA (combination therapy)		
	Tofacitinib 5 mg BID *N* = 1976	Tofacitinib 10 mg BID *N* = 1214	PBO[c] *N* = 681	Tofacitinib 5 mg BID *N* = 238	Tofacitinib 10 mg BID *N* = 236	PBO[d] *N* = 236
Gastric discomfort (composite term)[h]						
Temporary DC, *n* (%)	15	6	2	2	2	1
	(0.8)	(0.5)	(0.3)	(0.8)	(0.8)	(0.4)
Duration (days), median (IQR)[f]	13.0	6.0	149.0	39.5	4.0	1.0
	(4.0–163.0)	(2.0–24.0)	(4.0–294.0)	(6.0–73.0)	(4.0–4.0)	(1.0–1.0)
Permanent DC, *n* (%)	5	1	2	0	0	0
	(0.3)	(0.1)	(0.3)	(0.0)	(0.0)	(0.0)
Duration (days), median (IQR)[f]	14.0	7.0	5.5	NA	NA	NA
	(10.0–26.0)	(7.0–7.0)	(3.0–8.0)			

AE adverse event, *BID* twice daily, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *DC* discontinuation, *HLGT* higher-level group term, *IQR* interquartile range, *MedDRA* Medical Dictionary for Regulatory Activities, *N* total number of patients in each treatment group, *n* number of patients that discontinued due to each AE, *NA* not applicable, *PBO* placebo, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis

[a]Data for permanent discontinuations did not include temporary discontinuations

[b]Data are shown for overall treatment groups, i.e., combined data for patients with RA receiving tofacitinib or placebo as monotherapy and in combination with csDMARDs (see Table S2 in the electronic supplementary material)

[c]PBO monotherapy is defined as patients receiving no active treatment in ORAL Solo

[d]PBO combination therapy is defined as patients receiving PBO with csDMARDs in phase 3 (RA and PsA) or phase 3b/4 studies (RA)

[e]MedDRA HLGT, including all types of headache (see the Supplementary Methods in the electronic supplementary material for a full list of preferred terms included)

[f]Duration of AE leading to discontinuation was based on the duration of the actual AE or AEs that led to discontinuation

[g]Preferred term

[h]A composite term comprised of selected preferred terms, including dyspepsia, gastritis, epigastric discomfort, and abdominal discomfort or pain (see the Supplementary Methods in the electronic supplementary material for a full list of preferred terms included)

DISCUSSION

This post hoc analysis evaluated early non-serious AEs (excluding non-serious infections, laboratory abnormalities, and musculoskeletal or skin and subcutaneous tissue events likely to be due to underlying disease) reported by patients with RA or PsA within 3 months of initiating tofacitinib 5 or 10 mg BID, or placebo, in phase 3 or phase 3b/4 clinical trials. As non-serious infections, laboratory test abnormalities, serious AEs, and AEs of special interest in patients with RA and PsA have been reported previously [29, 31, 32], the focus of this analysis was to characterize and assess the impact of select non-serious AEs that patients may consider to be 'nuisance' side effects of tofacitinib. Most events were mild or moderate in severity and of short duration ($\leq$ 4 weeks), with few leading to permanent discontinuation.

The frequency and severity of early select non-serious AEs were comparable for patients with RA receiving tofacitinib as monotherapy or in combination with csDMARDs, and were generally similar to patients receiving placebo

with or without csDMARDs. In patients with PsA, the frequency of some non-serious AEs, most notably diarrhea, was numerically higher, but not statistically significant, in those receiving tofacitinib compared with placebo. In patients with RA or PsA, the most frequent non-serious AEs reported across all tofacitinib treatment groups were headache and diarrhea. This is consistent with safety data for patients with RA (up to 9.5 years of follow-up) or PsA (up to 4 years of follow-up) in the tofacitinib clinical trial program, in which either headache or diarrhea, or both, were among the most commonly reported AEs [19, 22, 29]. Headache was also among the most common AEs in patients with ulcerative colitis receiving tofacitinib 5 or 10 mg BID in phase 3 induction and maintenance trials [36]. In the present analysis, in patients with RA, IR estimates for both headache and diarrhea were similar to those observed in the placebo groups. Overall, gastric discomfort was the most frequent non-serious AE causing tofacitinib discontinuation in both cohorts. Among patients with RA receiving tofacitinib, 0.5–0.8% temporarily discontinued, and 0.1–0.3% permanently discontinued, due to gastric discomfort. In patients with PsA, 0.8% temporarily discontinued due to gastric discomfort in each tofacitinib treatment group. Diarrhea is a possible side effect experienced by patients receiving MTX, and may occasionally require treatment interruption [37]. In this analysis, the incidence of diarrhea and rates of temporary discontinuation due to diarrhea were similar across treatment groups; permanent discontinuation due to diarrhea was only observed in two patients with RA receiving tofacitinib and two receiving placebo, all in combination with csDMARDs. There were no permanent discontinuations among patients with PsA due to the non-serious AEs reported here.

The influence of non-serious AEs on treatment discontinuation may vary in patients enrolled in clinical trials, compared with patients receiving treatment in real-world settings, and will differ depending on each patient's tolerance to, and the severity and duration of, AEs. During clinical trials, patients may be more likely to report and tolerate non-serious AEs, and rates and severity of AEs may be affected by restrictions on use of concomitant medications. Additionally, patients enrolled in clinical trials for advanced treatments, such as tofacitinib, have generally already tolerated background therapies, such as csDMARDs, with known AE profiles [38], and are therefore likely to tolerate these treatments. Analysis of 3-year post-marketing surveillance data for tofacitinib 5 mg BID in patients with RA identified that 83% of reported AEs were non-serious [30]. Consistent with our analysis, headache (9.0%), nausea (6.0%), and diarrhea (5.8%) were among the most commonly reported non-serious AEs [30]. In a retrospective analysis of real-world data from a European cohort of patients with RA, 18/50 patients who discontinued tofacitinib reported gastrointestinal symptoms as a causative factor [39].

Other RA and PsA treatments are associated with non-serious AEs [38], which may affect tolerability; for example, MTX and sulfasalazine can be associated with nausea, diarrhea, vomiting, and skin reactions [38]. Treatment tolerability in patients with RA may also be influenced by patient-related factors such as ageing, comorbidities, and polypharmacy [38]. In the present analysis, incidence of nausea was similar or numerically higher in patients with RA receiving tofacitinib as monotherapy versus in combination with csDMARDs. In contrast, a previous phase 3 study of patients with RA found an approximately threefold higher rate of nausea in patients receiving MTX monotherapy versus tofacitinib monotherapy over 24 months [13], in contrast to 3 months in the current analysis. The individual studies included in this analysis reported rates of tofacitinib discontinuation ranging from 0.8–8% due to all AEs up to month 3 [10–12, 14–16, 20, 21]. Similar rates have been observed in studies of other oral RA and PsA treatments, including apremilast, upadacitinib, and baricitinib [40–48]. However, AEs leading to discontinuation of apremilast, upadacitinib, and baricitinib have not been differentiated as serious or non-serious; thus, these results are not directly comparable with those of the present analysis. Diarrhea, nausea, and headache were the most common AEs leading to discontinuation in patients with PsA

receiving apremilast for 52 weeks, with discontinuations due to AEs occurring in 2.3–3.4% of patients through week 24, and 4.8–7.9% of patients through week 52 [40, 41]. In several phase 3 trials in patients with RA, 2–4.6% of patients receiving upadacitinib 15 mg, and 3–9% of patients receiving upadacitinib 30 mg, over 12–24 weeks, discontinued treatment due to AEs [42–45]. Rates of discontinuation due to AEs in patients with RA receiving baricitinib 2 mg over 12–24 weeks ranged from 3–4%, while in patients receiving baricitinib 4 mg over 12–52 weeks the discontinuation rates ranged from 4–7% [46–48].

In clinical practice, patients are monitored less rigorously than in clinical trials and may have different disease characteristics and comorbidities which affect tolerability. Awareness of the type and duration of potential AEs associated with therapy may better inform patients and lead to improved persistence on therapy. However, knowledge of potential AEs can lead to AEs triggered by patients' negative expectations, referred to as nocebo effects [49, 50]. Framing information regarding AEs in a positive manner (e.g., if AE duration is limited) may reduce these effects [50]. Outside of trials, physicians have greater flexibility to minimize AEs by adapting treatment regimens and prescribing additional medications, and patients are less restricted in using over-the-counter medications, such as analgesics, to alleviate symptoms of non-serious AEs.

Limitations of this analysis include the use of data pooled from studies with different study designs and patient populations, and these studies were not powered for comparative analysis of AEs. Additionally, the PsA cohort was limited by small patient numbers. Differences in treatment history between groups in both cohorts may affect the results, e.g., prior TNFi exposure was less frequent in patients with RA receiving tofacitinib 5 mg BID, compared with placebo. The findings may not represent real-world populations who may have more comorbidities that affect adherence and tolerability. Additionally, the duration of AEs prior to discontinuation was based on the final event that led to discontinuation; therefore, it is unknown whether patients might have tolerated these non-serious AEs for a cumulatively longer period before stopping or interrupting therapy.

CONCLUSIONS

In conclusion, data from the tofacitinib clinical trial program in RA demonstrated that early non-serious, non-infectious AEs were generally mild or moderate in severity, generally resolved within 4 weeks, had a limited impact on continuation of tofacitinib treatment, and were generally similar in patients treated with placebo. Generally similar results were observed for PsA, although the incidence of some AEs was numerically higher in patients with PsA receiving tofacitinib, compared with placebo. Assessment of real-world data on types of, severity of, and discontinuations due to, AEs in patients with RA or PsA receiving tofacitinib will further characterize the tolerability profile of tofacitinib and elucidate the occurrence and impact of early non-serious AEs.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from Pfizer via Vivli on reasonable request. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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