according to protocol. The peficitinib concentration-time profiles from dosing to 72 h (**Fig. 1**), extrapolated to infinity (AUC_{inf}), and maximum concentration (C_{max}) were similar in subjects with normal and mildly impaired hepatic function; however, AUC_{inf} and C_{max} were increased in subjects with moderate hepatic impairment (**Table 2**). There was a trend of greater exposure to H1, H2 and H4 metabolites in subjects with mild or moderate hepatic impairment, except for H2 in moderate hepatic impairment, although geometric mean ratios versus subjects with normal function were variable (**Table 2**). One subject in each group experienced a total of 5 TEAEs (**Table 3**), all of which were considered drug-related except back pain. No serious TEAEs, deaths or clinically significant mean changes from baseline in clinical laboratory parameters were reported during the study.

Table 1 Demographic characteristics (PKAS)

Parameter	Normal hepatic function (n=8)	Mild hepatic impairment[2] (n=8)	Moderate hepatic impairment[2] (n=8)	Total (n=24)
Male, n (%)	6 (75.0)	5 (62.5)	6 (75.0)	17 (70.8)
Median (min, max) age, y	60.0 (55, 68)	69.0 (48, 75)	60.5 (49, 67)	63.0 (48, 75)
Median (min, max) weight, kg	69.3 (48.8, 76.3)	69.0 (51.7, 81.2)	73.0 (43.3, 75.1)	71.3 (43.3, 81.2)
Median (min, max) BMI, kg/m^2	24.2 (20.8, 28.4)	27.3 (20.0, 29.7)	23.8 (18.6, 29.2)	24.5 (18.6, 29.7)
Median (min, max) prothrombin time, %	-	97.0 (70.2, 120.0)	65.2 (52.2, 101.0)	86.0 (52.2, 120.0)[2]

[1]Total number of subjects for which prothrombin time was calculated was 16.
[2]Hepatic impairment was defined at screening according to Child-Pugh classifications: Class A, mild, 5–6 points; or Class B, moderate, 7–9 points.

Table 2 Plasma PK parameters of peficitinib and its metabolites H1, H2 and H4 (PKAS)

Parameter		Normal hepatic function (n=8)[1]	Mild hepatic impairment[2] (n=8)	Moderate hepatic impairment[2] (n=8)
Peficitinib				
AUC_{inf}, ng.h/mL	Mean (SD)	1149 (231.1)	1435 (525.1)	2332 (895.6)
	GMR (90% CI)	--	1.19 (0.86, 1.64)	1.92 (1.39, 2.66)
C_{max}, mg/mL	Mean (SD)	350.4 (129.1)	371.6 (146.5)	673.8 (331.6)
	GMR (90% CI)	--	1.04 (0.71, 1.53)	1.82 (1.24, 2.69)
$t_{1/2}$, h	Mean (SD)	10.43 (6.215)	13.70 (9.934)	11.16 (8.881)
H1				
AUC_{inf}, ng.h/mL	Mean (SD)	372.1 (111.8)	887.9 (453.0)	1138 (1259)
	GMR (90% CI)	--	2.15 (1.01, 4.56)	1.65 (0.78, 3.50)
C_{max}, ng/mL	Mean (SD)	44.79 (23.87)	90.64 (50.46)	110.3 (107.2)
	GMR (90% CI)	--	1.95 (0.97, 3.92)	1.71 (0.85, 3.45)
$t_{1/2}$, h	Mean (SD)	12.50 (7.983)	9.939 (5.496)	14.11 (7.024)
H2				
AUC_{inf}, ng.h/mL	Mean (SD)	2707 (557.4)	4393 (2075)	2489 (2358)
	GMR (90% CI)	--	1.52 (0.86, 2.68)	0.62 (0.35, 1.10)
C_{max}, ng/mL	Mean (SD)	641.3 (174.0)	808.9 (247.1)	485.0 (426.3)
	GMR (90% CI)	--	1.25 (0.75, 2.09)	0.55 (0.33, 0.91)
$t_{1/2}$, h	Mean (SD)	10.77 (6.098)	7.743 (5.093)	12.24 (9.027)
H4				
AUC_{inf}, ng.h/mL	Mean (SD)	357.2 (143.1)	571.8 (281.1)	1346 (1011)
	GMR (90% CI)	--	1.51 (0.91, 2.49)	3.17 (1.92, 5.24)
C_{max}, ng/mL	Mean (SD)	35.57 (26.23)	53.46 (34.03)	110.5 (80.01)
	GMR (90% CI)	--	1.55 (0.85, 2.83)	3.05 (1.67, 5.56)
$t_{1/2}$, h	Mean (SD)	12.24 (6.956)	10.71 (4.767)	15.13 (7.502)

[1]Number of subjects available for AUC_{inf} and $t_{1/2}$ was 7.
[2]Hepatic impairment was defined at screening according to Child-Pugh classifications: Class A, mild, 5–6 points; or Class B, moderate, 7–9 points.
AUC_{inf}, area under the concentration–time curve from the time of dosing extrapolated to infinity; C_{max}, maximum concentration; GMR, geometric mean ratio; PKAS, pharmacokinetic analysis set (all subjects who received the study drug and provided at least one estimable PK parameter); SD, standard deviation; $t_{1/2}$, terminal elimination half-life; t_{max}, time of C_{max}.

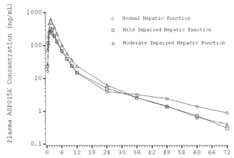
Table 3 Treatment-emergent adverse events (SAF), by Preferred Term

n (%)	Normal hepatic function (n=8)	Mild hepatic impairment[1] (n=8)	Moderate hepatic impairment[1] (n=8)	Total (n=24)
Overall	1 (12.5)[2]	1 (12.5)[3]	1 (12.5)	3 (12.5)
Diarrhoea	0	1 (12.5)	0	1 (4.2)
Nausea	1 (12.5)	0	0	1 (4.2)
Blood urine present	0	1 (12.5)	0	1 (4.2)
Back pain	1 (12.5)	0	0	1 (4.2)
Hypotension	0	0	1 (12.5)	1 (4.2)

[1]Hepatic impairment was defined at screening according to Child-Pugh classifications: Class A, mild, 5–6 points; or Class B, moderate, 7–9 points.
[2]Adverse events of nausea and back pain were observed in a single subject with normal hepatic function.
[3]Adverse events of diarrhoea and presence of blood urine were observed in a single subject with mild hepatic impairment.
SAF, safety analysis set (all subjects who received the study drug)

Conclusion: Peficitinib exposure in subjects with mild hepatic impairment was similar to that in subjects with normal hepatic function; subjects with moderate hepatic impairment had greater exposure. A single dose of peficitinib was well tolerated.

Figure 1 Mean plasma peficitinib concentration over time by degree of hepatic impairment (semi-log scale; PKAS)



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FRI0162

BASELINE CHARACTERISTICS AND OUTCOMES IN PATIENTS WITH ANAEMIA IN CLINICAL STUDIES OF TOFACITINIB IN RHEUMATOID ARTHRITIS

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Background: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA).
Objectives: To describe the profile of patients (pts) with RA and clinically significant anaemia and the impact of treatment with tofacitinib on those with anaemia.
Methods: In this post hoc analysis, data were pooled from Phase (P)2, P3 and P3b/4 studies across the tofacitinib RA clinical programme. Pts received tofacitinib 5 or 10 mg twice daily (BID) with/without background conventional synthetic disease-modifying antirheumatic drugs, or placebo (PBO). Pts with grade ≥2 anaemia (G2A; haemoglobin [Hgb] <10 g/dL) at baseline (BL) were compared with pts without G2A (Hgb ≥10 g/dL) at BL. Demographic and BL characteristics, Hgb levels and efficacy (Disease Activity Score in 28 joints, erythrocyte sedimentation rate [DAS28-4(ESR)]) at Month (M)6 and treatment-emergent adverse events (TEAEs) were summarised descriptively.
Results: The proportion of pts with G2A at BL was similar for tofacitinib (3.2%, 152 of 4736 pts) and PBO (2.4%, 27 of 1125 pts) groups. Pts with G2A at BL were more often female, Asian, younger, had never smoked and had a lower body mass index (BMI) and higher C-reactive protein (CRP) and ESR vs pts without G2A at BL; RA duration was generally similar across groups (Table). Tofacitinib seemed to improve anaemia more rapidly than PBO: in pts with G2A at BL, a lower proportion of those receiving tofacitinib had G2A at M1 and M3 vs those receiving PBO (48.8% vs 75.0%, respectively, at M1 and 36.1% vs 57.1%, respectively, at M3), while the proportions were similar at M6 (28.9% vs 30.6%, respectively). In pts receiving tofacitinib, mean Hgb levels gradually increased from BL to M6 in those with G2A at BL (1.25 g/dL change), but were relatively stable in those without G2A at BL (0.15 g/dL change). In tofacitinib-treated pts, DAS28-4(ESR) scores decreased from BL to M6 by -2.40 in those with G2A at BL and -2.42 in those without G2A at BL. DAS28-4(ESR) low disease activity (≤3.2) rate at M6 was lower in tofacitinib-treated pts with G2A at BL vs those without G2A at BL (18.3% vs 28.4%, respectively). Among pts receiving tofacitinib,

those with BL G2A had a higher incidence of TEAEs vs those without BL G2A in the following MedDRA system organ classes (with incidence >20% in pts who were either with or without BL G2A): gastrointestinal disorders (30.9% vs 22.5%, respectively) and infections and infestations (44.1% vs 39.0%, respectively).

Conclusion: In this post hoc analysis, more pts with BL G2A were female, Asian, younger, had never smoked, and had lower BMI and elevated ESR and CRP vs those without BL G2A. G2A resolved within 6 months in most pts with RA receiving tofacitinib, while inflammation and disease activity (assessed by DAS28-4[ESR]) decreased. G2A appeared to resolve more rapidly in pts receiving tofacitinib vs those receiving PBO. These data suggest that tofacitinib for the treatment of RA can be an option for pts who have anaemia, within prescribing guidelines.[1]

Table. Demographics and disease characteristics at baseline

	With baseline G2A (Hgb <10 g/dL)		Without baseline G2A (Hgb ≥10 g/dL)	
	Tofacitinib (N=152)	Placebo (N=27)	Tofacitinib (N=4584)	Placebo (N=1098)
Age group, years (%)				
18–45	40.8	63.0	27.3	24.3
>45–<65	46.1	25.9	58.6	59.7
≥65	13.2	11.1	14.1	16.0
Age, years (mean [SD])	48.9 (13.1)	45.1 (13.7)	52.0 (12.0)	53.1 (12.0)
Female (%)	96.1	96.3	82.7	81.2
BMI, kg/m^2 (mean [SD])	23.9 (5.3)	24.7 (7.1)	27.3 (6.5)	27.5 (6.7)
Race (%)				
White	39.5	37.0	64.4	66.9
Black	3.3	14.8	3.4	3.2
Asian	47.4	33.3	21.7	22.1
Other	9.9	14.8	10.5	7.7
Smoking status (%)				
Never smoked	85.5	85.2	65.2	56.0
Previous or current smoker	13.8	14.8	33.5	37.9
Unknown	<1.0	0.0	1.3	6.1
HAQ-DI (mean [SD])	1.7 (0.7)	1.6 (0.7)	1.5 (0.7)	1.4 (0.7)
DAS28-4(ESR; mean [SD])	6.9 (0.9)	7.0 (0.9)	6.4 (1.0)	6.3 (1.0)
Disease duration, years (mean [SD])	7.1 (7.8)	7.3 (7.0)	7.7 (7.9)	9.4 (8.6)
ESR, mm/hr (mean [SD])	77.8 (31.5)	69.7 (31.1)	49.5 (26.6)	45.4 (24.7)
CRP, mg/L (mean [SD])	39.1 (37.7)	34.7 (27.6)	17.7 (22.4)	16.0 (18.2)
RF+ (%)	73.4	65.2	72.3	68.6
Anti-CCP+ (%)	61.8	51.9	52.4	47.5
Hgb, g/dL (mean [SD])	9.4 (0.4)	9.3 (0.6)	12.8 (1.4)	12.9 (1.3)

Data were pooled from the following Phase 2, Phase 3 and Phase 3b/4 studies across the tofacitinib clinical programme: NCT00147498; NCT00413660; NCT00960440; NCT00550446; NCT00603512; NCT00687193; NCT00847613; NCT00814307; NCT00856544; NCT00853385; NCT01164579; NCT01039688; NCT00976599; NCT01059864; NCT01359150; NCT02147587; NCT02187055

Treatment groups are based on initial randomised study drug; tofacitinib was dosed at 5 or 10 mg BID

BID, twice daily; BMI, body mass index; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; G2A, grade ≥2 anaemia; HAQ-DI, Health Assessment Questionnaire-Disability Index; Hgb, haemoglobin; RF, rheumatoid factor; SD, standard deviation

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TIME TO DISCONTINUATION OF TOFACITINAB IN PATIENTS WITH RHEUMATOID ARTHRITIS WITH AND WITHOUT METHOTREXATE: RESULTS FROM THE ONTARIO BEST PRACTICES RESEARCH INITIATIVE (OBRI) COHORT

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Background: Tofacitinib (TOFA) is an oral, small molecule drug which can be used as an alternative to biologic disease modifying antirheumatic drugs (bDMARDs) for rheumatoid arthritis (RA) treatment and is prescribed alone or with methotrexate (MTX).

Objectives: We aimed to evaluate the discontinuation rate of this drug, with and without concurrent MTX, with and without prior biologic use, in patients with RA using real world data from a Canadian (Ontario) observational cohort.

Methods: Patients enrolled in the Ontario Best Practices Research Initiative (OBRI) who started TOFA after its approval in Canada (June 2014) were included in the analysis. Patients were followed from TOFA initiation until discontinuation, death, lost to follow-up, or last visit, whichever came first. Time to discontinuation of TOFA, due to any reason, in patients 1) with or without concurrent MTX use; 2) with or without prior biologic use was assessed using Kaplan-Meier survival analysis.

Results: Among the 131 patients, 70 (53.4%) received TOFA without MTX and 61 (46.6%) TOFA with MTX. Mean (SD) age and disease duration were 60.2 (0.90) years and 13.7 (0.80) years, respectively. The majority were females (89.3%) and most had prior biologic use history (74.0%). At baseline, no significant differences in disease activity and sociodemographic profiles were found between the two groups of patients with and without concurrent MTX use. Discontinuation was reported in 44 (33.6%) of all TOFA patients with a median survival of 31.3 months. Overall retention of TOFA at 6, 12 and 24 months was 80.5%, 63.1% and 53.5% respectively. These findings are very similar to the results reported from the RHUMADATA registry at ACR 2018.[1] Fifteen (34.0%) patients stopped their TOFA due to non-response/loss of response, 22 (50.0%) due to adverse events, and 7 (16%) due to other reasons.

At 6 and 12 months' follow-up, more patients remained on TOFA in the 'TOFA with MTX' group (88.3% and 73.1%, respectively) compared to the 'TOFA without MTX" group (73.9% and 54.6%, respectively) (Logrank p=0.05). There was no significant difference in TOFA discontinuation between the two groups of patients with and without prior biologic use (Logrank p=0.77).

Conclusion: We found that half of the RA patients remained on TOFA 31 months after initiation. Patients also stayed on TOFA longer when they concurrently used MTX compared to TOFA without MTX.

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