SAT0234 TOFACITINIB, AN ORAL JANUS KINASE INHIBITOR, IN THE TREATMENT OF RHEUMATOID ARTHRITIS: SAFETY AND EFFICACY IN OPEN-LABEL, LONG-TERM EXTENSION STUDIES OVER 9 YEARS

J. Wollenhaupt[1], J. Silverfield[2], E. B. Lee[3], K. Terry[4], K. Kwok[5], S. Strengholt[6], R. DeMasi[7], L. Wang[4]. *[1]Schön-Klinik Hamburg-Eilbek Teaching Hospital of the University of Hamburg, Hamburg, Germany, [2]Healthpoint Medical Group, Tampa, FL, United States, [3]Seoul National University, Seoul, Korea, Republic Of, [4]Pfizer Inc, Groton, CT, [5]Pfizer Inc, New York, NY, United States, [6]Pfizer Inc, Capelle aan den IJssel, Netherlands, [7]Pfizer Inc, Collegeville, PA, United States*

Background: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA).
Objectives: To report tofacitinib safety and tolerability up to 114 months and clinical efficacy up to 96 months in long-term extension (LTE) studies.
Methods: Data were pooled from 2 open-label studies (NCT00413699 [database locked as of March 2017]; and NCT00661661) of patients with RA who had participated in qualifying Phase 1/2/3 studies of tofacitinib. Patients received tofacitinib 5 or 10 mg twice daily (BID) as monotherapy or with background conventional synthetic (cs)DMARDs. As patients in the LTE studies were allowed to switch doses, they were assigned to the 5 mg BID group if the total daily dose (TDD) was <15 mg/day, and to the 10 mg BID group if TDD was ≥15 mg/day. Primary endpoints were adverse events (AEs) and confirmed laboratory safety data. Other endpoints included clinical efficacy measures (ACR20/50/70 response rates, mean DAS28–4[ESR] score, mean HAQ-DI score and mean change from baseline in Clinical Disease Activity Index score). Safety data were included up to Month 114 and completer-analyzed efficacy data up to Month 96 (n≤100 post-Month 96).

Table 1 Safety data (Month 114) and clinical efficacy outcomes (up to Month 96; as observed) in LTE studies of tofacitinib in patients with RA

Table. Safety data (Month 114) and clinical efficacy outcomes (up to Month 96; as observed) in LTE studies of tofacitinib in patients with RA

	Tofacitinib (5 and 10 mg BID) ± background csDMARDs N=4967		
AEs of interest	**IR per 100 py (95% CI)**		
Serious adverse events	9.13 (8.67, 9.61)		
Serious infections	2.46 (2.23, 2.70)		
Malignancies (excluding NMSC)	0.83 (0.71, 0.98)		
Confirmed laboratory abnormalities	**n (%)**	**IR per 100 py (95% CI)**	
Decrease from baseline in hemoglobin ≥3 g/dL or hemoglobin ≤7 g/dL	104 (2.1)	0.59 (0.48, 0.71)	
Neutropenia, ANC <0.5 x 10^3/mm^3	0 (0.0)	0 (0.0, 0.0)	
Lymphopenia, ALC <0.5 x 10^3/mm^3	70 (1.4)	0.39 (0.30, 0.49)	
Aminotransferases			
ALT >3 x ULN	285 (5.7)	1.62 (1.44, 1.82)	
AST >3 x ULN	166 (3.3)	0.93 (0.79, 1.08)	
Serum creatinine increase >50% from baseline	138 (2.8)	0.77 (0.65, 0.91)	
Clinical efficacy outcomes	**Baseline**	**Month 1**	**Month 96**
ACR response rates, %		N=4907	N=163
ACR20	NA	73.7	77.9
ACR50	NA	49.9	59.5
ACR70	NA	29.2	41.7
DAS28-4(ESR) score, mean (SE)	N=4782 6.32 (0.01)	N=4776 3.75 (0.02)	N=161 3.34 (0.09)
HAQ-DI score, mean (SE)	N=4924 1.42 (0.01)	N=4880 0.82 (0.01)	N=163 0.77 (0.05)
CDAI score, mean change from baseline (SE)	NA	N=4802 -24.5 (0.21)	N=161 -30.7 (1.05)

ACR20/50/70, American College of Rheumatology 20%/50%/70% improvement; AE, adverse event; ALC, absolute lymphocyte count, ALT, alanine aminotransferase, ANC, absolute neutrophil count, AST, aspartate aminotransferase; BID, twice daily; CDAI, Clinical Disease Activity Index; CI, confidence interval; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ DI, Health Assessment Questionnaire-Disability Index; IR, incidence rate; LTE, long-term extension; N, number of evaluable patients; NA, not applicable, NMSC, non-melanoma skin cancer, py, patient-years, RA, rheumatoid arthritis, SE, standard error; ULN, upper limit of normal

Results: Overall, 4967 patients were treated (mean [max] duration: 3.5 [9.4] years). Total tofacitinib exposure was 17,738.5 patient-years (py); 76.4% of patients maintained their initial dose. In total, 2518 patients (50.7%) discontinued (AEs: 1189 [23.9%]; insufficient clinical response: 179 [3.6%]). The most common classes of AE were infections and infestations (69.6%; exposure adjusted event rate [EAER; events per 100 py], 19.71) and musculoskeletal/connective tissue disorders (40.3%; EAER, 11.40). The most common AEs were nasopharyngitis (19.1%; EAER, 5.41), upper respiratory tract infection (17.9%; EAER, 5.07), bronchitis (12.6%; EAER, 3.58) and urinary tract infection (12.5%; EAER, 3.55). Serious AEs occurred in 29.4% of patients and serious infections (SIEs) in 8.9% of patients. Malignancies, excluding non-melanoma skin cancer, were reported in 3.0% of patients. Incidence rates (IR; patients with events per 100 py) for AEs of interest, with 95% confidence intervals, are provided in the table 1. IRs for SAEs, SIEs and malignancies through Month 114 did not increase vs reported data through Month 105.[1] Confirmed laboratory data are provided in the table 1. No new safety risks were identified. Clinical responses were sustained from Month 1 to Month 96 (table 1).
Conclusions: In patients with RA who remained in the LTE studies, tofacitinib (5 or 10 mg BID), with or without background csDMARDs, was associated with consistent safety through Month 114 and sustained clinical efficacy through Month 96.

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SAT0235 SUBCUTANEOUS METHOTREXATE IS SAFER AND MORE EFFECTIVE THAN ORAL METHOTREXATE ALONE AND IN COMBINATION

K. H. C. Li[1], T. Jones[2], M. Grove[3], A. Roberts[4], F. Birrell[1]. *[1]Newcastle University, Newcastle Upon Tyne, [2]Sunderland University, Sunderland, [3]Northumbria Healthcare NHS Foundation Trust, Newcastle Upon Tyne, [4]Therapy Audit Ltd, Shrewsbury, United Kingdom*

Background: Methotrexate (MTX) is established as both first line therapy and combination therapy anchor drug for Rheumatoid Arthritis (RA) and other peripheral inflammatory arthritis such as Psoriatic Arthritis (PsA). There is evidence subcutaneous (sc) MTX is more effective than oral MTX, with fewer treatment failures[1–3], but it is not known if this holds true in routine practice and in combination.
Objectives: To show the safety & efficacy of sc MTX therapy in routine practice, compared to oral MTX, alternate monotherapy and combination therapies.
Methods: The Therapy Audit Monitoring System (TAMS, www.therapyaudit.com/tamonitor) was installed Jan 2014. Since then all new patients starting disease modifying therapy and existing patients are entered. The database was queried for diagnosis, dose and response, together with adverse events (defined as ALT>80U/l or neutrophils<2.0x10^9/l). Statistical comparisons used the two proportion Z test, T-test or exact rate ratio test, as appropriate: significance threshold p<0.05.
Results:

Patient groups	Oral MTX only	sc MTX only	Biologics only	Conventional Combination	Biologic Combination
Total patients ever exposed – n	2093	949	570	1596	552
Patients affected by abnormal LFTs n (%)	198 (10%)	100 (10%)	47 (8%)	154 (10%)	72 (13%)
Patients affected by low neutrophils n (%)	140 (7%)	64 (7%)	66 (12%)	219 (14%)	115 (21%)
Current patients	920	425	345	921	384

8394 patients had received one or more therapies with 4109 current patients identified. Including combinations, 2650 started oral MTX (1463 current) and 1343 sc MTX (911 current). Mean (range) oral MTX dose was 17 (2.5–30) mg and sc MTX was 21 (5–40) mg (p<0.0001). 4356 adverse events were observed over follow-up in 2382 patients, with 1710 (39%) due to ALT>80U/l and 2646 (61%) to neutrophils<2.0x10^9/l. Abnormal ALT events by drug: oral MTX 486, sc MTX 222 (p=0.92 sc vs. oral). Similarly, low neutrophil count (<2.0x10^9/l): oral MTX 491, sc MTX 151 (p<0.00001 sc vs. oral). Rate ratios (RR) for low neutrophils for oral MTX-only vs. sc MTX-only showed highly significant differences (RR=1.40, 95% CI: 1.17–1.70; p=0.0002). 14% (1197/8294) of all patients had post-treatment DAS28 scores. Of these 59% (67/113) patients on sc MTX only, and 72% (273/377) on conventional combination achieved DAS<5.1 compared to 69% (69/98) biologic-only and 78% (102/131) biologic-combination. Sensitivity analyses examined response & toxicity by group (data not included).
Conclusions: sc MTX is safe and effective in routine practice at doses up to 40 mg. It has lower toxicity than oral MTX in monotherapy and combination, despite a higher mean dose with highly significant reduction in neutropenia rate and the same rate of liver problems compared to oral. This is the largest study of sc MTX yet reported and supports use of higher doses in selected patients and aggregation or replication of data like this may support license extension for sc MTX beyond 30 mg. If patients are usually switched to sc MTX when oral MTX is ineffective or not tolerated, many do not progress to biologic therapy: delivering good care at lower cost.

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