models. The proportions of patients reporting improvements $\geq$ minimum clinically important differences (MCID) from BL to Week 12 or scores $\geq$ normative values were determined with UPA, PBO, and ADA treatment; comparisons used chi-square tests.

Results: Data from 1629 patients (UPA: 651; PBO: 651; ADA: 327) were analysed. Mean age was 54 years; 79% were female; 54% had RA for ≥ 5 years. Baseline mean PRO scores were similar across treatment groups. At Week 12, UPA treatment resulted in statistically significant LSM changes from BL vs PBO across all PROs and statistically significant LSM changes from BL vs ADA in PtGA, pain, HAQ-DI, AM stiffness severity, FACIT-F, and SF-36 physical component summary (PCS) and 6/8 domain scores (**Table**). ADA treatment resulted in statistically significant LSM changes from baseline vs PBO in PtGA, pain, HAQ-DI, AM stiffness severity and duration, FACIT-F, and SF-36 PCS and 5/8 domain scores. Compared with PBO at Week 12, significantly more UPA-treated patients reported improvements $\geq$ MCID and scores $\geq$ normative values across all PROs with numbers needed to treat (NNTs) < 10 . The proportions of UPA-treated patients reporting improvements $\geq$ MCID were similar or numerically higher than ADA-treated patients. Importantly, the proportion of UPA vs ADA treated patients reporting improvements $\geq$ normative values were significantly greater (all $p < 0.05$) in PtGA (36% vs 26%), HAQ-DI (21% vs 14%), SF-36 PCS (16% vs 11%), and SF-36 bodily pain (29% vs 21%) and vitality (42% vs 35%) domains.

PRO	Baseline Mean	LSM Changes from Baseline			Patients Reporting Improvements $\geq$ MCID, n (%)		
	(n=1629)	UPA 15 mg (n=651)	PBO (n=651)	ADA 40 mg (n=327)	UPA 15 mg (n=651)	PBO (n=651)	ADA 40 mg (n=327)
PtGA	64.4	-30.4 ^a	-15.2	-23.6 ^a	474 (73.4)*	332 (51.1)	219 (67.6)
Pain VAS	65.5	-31.8 ^a	-15.5	-25.3 ^a	483 (74.8)*	347 (53.4)	227 (69.8)
HAQ-DI	1.6	-0.6 ^a	-0.3	-0.5 ^a	465 (72.1)*	330 (50.8)	231 (71.1)
FACIT-F	26.8	9.0 ^a	4.8	7.4 ^a	413 (64.0)*	299 (46.4)	202 (62.2)
Duration AM Stiffness ^b	142.8	-92.6*	-48.6	-82.7 ^a	194 (29.9)**	144 (22.1)	93 (28.7) ^b
Severity AM Stiffness ^c	6.3	-3.4 ^a	-1.8	-2.9 ^a	526 (81.3)**	424 (65.0)	260 (80.2) ^b
RA-WIS	14.7	-5.2*	-2.0	-4.5 ^a	120 (41.7)*	64 (24.4)	42 (32.1)
SF-36 PCS	32.5	7.9 ^a	3.6	6.3 ^a	469 (72.5)*	345 (53.2)	226 (69.1)
SF-36 MCS	42.9	6.4*	3.7	5.4	386 (59.7)*	309 (47.7)	192 (58.7)
SF-36 PF	31.5	7.3 ^a	3.6	6.2 ^a	479 (73.7)*	379 (58.2)	237 (72.5)
SF-36 RP	33.3	6.9 ^a	3.6	5.2	470 (72.3)* ^a	374 (57.5)	213 (65.1)
SF-36 BP	34.1	9.9 ^a	4.6	8.0 ^a	501 (77.1)*	390 (59.9)	239 (73.1)
SF-36 GH	37.8	7.3 ^a	3.1	5.7 ^a	458 (70.5)*	362 (55.6)	212 (64.8)
SF-36 VT	40.9	8.2 ^a	4.3	6.8 ^a	479 (73.7)*	372 (57.1)	225 (68.8)
SF-36 SF	38.1	7.2 ^a	3.4	5.8 ^a	418 (64.3)*	323 (49.6)	195 (59.6)
SF-36 RE	37.9	6.2*	3.6	5.2	368 (56.6)*	301 (46.2)	175 (53.5)
SF-36 MH	40.7	7.0*	4.0	5.9	449 (69.1)*	349 (53.6)	213 (65.1)

* $P < 0.05$ for UPA vs PBO. LSM change from baseline P values represent statistical significance between groups.
^a $P < 0.05$ for UPA vs ADA. LSM change from baseline P values represent statistical significance between groups.
^bLSM change from baseline differences statistically significant between groups based on non-overlapping 95% confidence intervals.
^cDuration in minutes. ^b% responders reporting scores $\geq$ minimal important difference. ^aAssessed on a numeric scale of 1–10, with 10 being the worst level.
ADA, adalimumab; AM, morning; BP, bodily pain; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; GH, general health; HAQ-DI, Health Assessment Questionnaire Disability Index; LSM, least squares mean; MCID, minimum clinically important difference; MCS, Mental Component Summary; MH, mental health; PBO, placebo; PCS, Physical Component Summary; PF, physical function; PRO, patient-reported outcome; PtGA, Patient Global Assessment of Disease Activity; RA-WIS, Work Instability Scale for Rheumatoid Arthritis (among employed patients); RE, role emotional; RP, role physical; SF, social function; SF-36, 36-Item Short Form Health Survey; UPA, upadacitinib; VAS, visual analogue scale; VT, vitality.

Conclusion: Among patients with active RA, treatment with UPA 15 mg QD on background MTX therapy for 12 weeks resulted in statistically significant and clinically meaningful improvements in PROs compared with PBO. Overall, PRO improvements with UPA treatment met or were superior to treatment with ADA, especially in key domains of pain, function and vitality.

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FRI0138 EXPOSURE-RESPONSE ANALYSES OF UPADACITINIB EFFICACY AND SAFETY IN RHEUMATOID ARTHRITIS – ANALYSES OF PHASE 2 AND 3 STUDIES

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Background: Upadacitinib (UPA), an oral selective JAK1 inhibitor, demonstrated favorable efficacy and acceptable safety in two Phase 2 and five Phase 3 global studies in subjects with moderately to severely active rheumatoid arthritis (RA).

Objectives: To characterize relationships between UPA plasma exposures and different efficacy and safety endpoints using data from Phase 2 and Phase 3 RA studies.

Methods: Analyses were conducted using data from 3685 (for efficacy) and 4577 (for safety) subjects with RA enrolled in the Phase 2 and 3 studies. Relationships between UPA plasma concentrations and efficacy and selected clinically relevant safety endpoints were analyzed using Markov Chain models and logistic regression analyses, respectively.

Results: Percentage of subjects achieving ACR20, ACR50, AC70, DAS28 (CRP) ≤ 3.2 , and DAS28(CRP) < 2.6 increased with increasing UPA exposures, with maximum efficacy reached at exposures of 15 mg to 30 mg QD. Model-estimated efficacy responses are presented in Table 1. No relationships were observed between UPA exposure and pneumonia, herpes zoster infection, changes in platelet count (platelets $\geq 600 \times 10^9/L$, platelets $> 400 \times 10^9/L$), lymphopenia (Grade 4 or higher), and neutropenia (Grade 3 or higher) at Week 12/14 or Week 24/26. Shallow trends for exposure-response relationships were observed for > 2 g/dL decrease in hemoglobin from baseline at Week 12/14 and Week 24/26, lymphopenia Grade 3 or higher at Week 12/14, and serious infections at Week 24/26. No relationship with UPA exposure was observed for Grade 3 or higher lymphopenia at Week 24/26 (Figure 1).

Figure 1. Observed and Model Predicted Percentage of Subjects Experiencing Laboratory Changes/Safety Events of Interest with Increasing UPA Plasma Exposures

Table 1. Model-Estimated Efficacy Responses Following Placebo and UPA 15 mg and 30 mg QD Dosing Regimens Based on Exposure-Response Analyses of Phase 2 and 3 Studies

Population	Clinical Efficacy Response Variable ^a	Upadacitinib Dose		
		Placebo	15 mg QD	30 mg QD
csDMARD-IR on	ACR20	40 (34, 47)	66 (59, 71)	68 (63, 74)
Background csDMARDs	ACR50	17 (12, 22)	41 (35, 47)	45 (39, 51)
	ACR70	6 (3, 11)	23 (17, 29)	26 (21, 33)
	DAS28(CRP) ≤ 3.2	19 (13, 24)	45 (40, 52)	50 (44, 57)
	DAS28(CRP) < 2.6	11 (8, 16)	31 (25, 36)	34 (29, 41)
	ACR20	36 (30, 43)	58 (52, 65)	61 (54, 67)
bDMARD-IR on	ACR50	14 (8, 19)	34 (27, 41)	37 (31, 45)
Background csDMARDs	ACR70	5 (2, 9)	18 (12, 24)	21 (16, 26)
	DAS28(CRP) ≤ 3.2	18 (14, 24)	40 (34, 47)	45 (39, 51)
	DAS28(CRP) < 2.6	11 (7, 15)	27 (21, 33)	31 (25, 36)
	ACR20	36 (29, 44)	66 (58, 71)	68 (61, 75)
	ACR50	12 (8, 16)	42 (36, 49)	45 (37, 51)
csDMARDs-IR on	ACR70	3 (1, 7)	24 (18, 31)	27 (20, 34)
Upadacitinib Monotherapy	DAS28(CRP) ≤ 3.2	17 (12, 23)	50 (44, 58)	55 (48, 62)
	DAS28(CRP) < 2.6	11 (7, 16)	36 (31, 44)	40 (34, 47)

MTX-IR = Methotrexate inadequate responder; csDMARDs-IR = conventional synthetic disease-modifying anti-rheumatic drug inadequate responders; bDMARD-IR = Biologic disease-modifying anti-rheumatic drug inadequate responder

a. Data are presented as median (5th, 95th percentiles)

Conclusion: Exposure-efficacy analyses demonstrate that UPA 15 mg QD dose maximizes efficacy in RA while 30 mg QD dose provides only a small (≤ 5%) additional incremental efficacy benefit. This was consistent across RA populations and whether UPA is used as monotherapy or on background treatment of csDMARDs. UPA plasma exposures associated with 15 mg and 30 mg QD dosing are predicted to have limited effects on the evaluated safety endpoints after 24 to 26 weeks of treatment.

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FRI0139

IMPROVEMENT SOLUBILITY OF AMPHIPHILIC NAPROXEN-NIOSOME FOR INFLAMMATORY ARTHRITIS TREATMENT

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Background: Naproxen (S-6-methoxy-a-methyl-2-naphthaleneacetic acid) is a nonsteroidal anti-inflammatory drug (NSAID), which is used to treat rheumatoid arthritis, osteoarthritis, chronic juvenile arthritis, ankylosing spondylitis. Niosomes or nonionic surfactant vesicles (NSVs) are known as biocompatible, non-immunogenic systems and present potential applications in the delivery of hydrophilic and hydrophobic drugs in order to higher chemical stability and less production cost characteristics. Niosomes are now broadly investigated as other drug vehicles to the encapsulation and controlled release of the different drug molecules. Many studies showed micronized NSAIDs, at low dosages using nanotechnology, can increase the drug level and increase absorption and can have the best effect at the lowest dose and reduce the risk of side effects. Because insufficiently soluble and insoluble drugs exhibit low absorption and poor bioavailability, improvements in solubility and solubility are important for developing various drug preparation methods.

Objectives: The purpose of the present study was to investigate the formulations of micellar/niosomal vesicles prepared from the biocompatible

surfactant tween 80 (polysorbate 80) and the squalene as an excipient, through film hydration method and their potential as a drug delivery system for NPX.

Methods: We prepared niosomal Naproxen from the biocompatible surfactant tween 80 (polysorbate 80) and the squalene as an excipient, through thin-film hydration method and their potential as a drug delivery system for NPX. The prepared system was characterized by Fourier transform infrared spectroscopy (FT-IR), UV-visible, photoluminescence (PL), field emission scanning electron microscopy (FE-SEM), and transmission electron microscopy (TEM).

Results: By using this method, the percent drug loading that resulted by the encapsulation of niosomes was found to be 99.5 ± 0.2% for 5% of NPX weight in total ingredients weight of niosomal vesicles (w/w). It was also seen that a slower rate of release of the NPX from the drug encapsulated niosome over 7 days, suggesting stable complexation of NPX. Cell toxicity assay was carried out by A549 and HeLa cancer cell lines and showed the half maximal inhibitory concentration (IC₅₀) of NPX increased about 8.25 folds for A549 (from 3300 μM to 400 μM) and it decreases about 5.5 folds for HeLa (from 1920 μM to 350 μM by nanoformulation).

Conclusion: Niosomal formulation has been evaluated as a safe drug delivery system. In this study, we showed that niosomal naproxen has more stability and more efficiently affect the cells. It can be explained by increasing the bioavailability of naproxen by niosomal nanocarriers which probably is based on more water solubility and more efficient cell entrance of drug. It seems that niosomal naproxen is a great candidate for future in vitro and in vivo researches for evaluating potential clinical applications.

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FRI0140

EVALUATION OF EFFECTIVENESS AND USAGE PATTERNS OF TOFACITINIB IN TREATMENT OF RHEUMATOID ARTHRITIS IN AUSTRALIA: AN ANALYSIS FROM THE OPAL-QUMI REAL WORLD DATASET

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Background: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Limited data from large real-world patient populations exist to describe treatment outcomes of patients who receive tofacitinib for the management of RA in Australia.

Objectives: To evaluate effectiveness and treatment patterns of tofacitinib in a large real-world cohort of Australian adult patients with RA.

Methods: Routinely collected, de-identified clinical data were sourced from the OPAL-QUMI dataset. Data from adult patients with a diagnosis of RA, who initiated treatment with tofacitinib or a bDMARD and had at least 12 months of follow-up between March 2015 and September 2018, were included. Descriptive analyses were performed on overall and propensity score matched populations. Treatment effectiveness was evaluated from baseline to month 18 by DAS28-ESR, SDAI and CDAI measures. Treatment persistence, in part a surrogate for efficacy, was estimated by Kaplan-Meier methods. Treatment pattern evaluation included percentage