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 Background csDMARDs	ACR20	40 (34, 47)	66 (59, 71)	68 (63, 74)
	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)
bDMARD-IR on Background csDMARDs	ACR20	36 (30, 43)	58 (52, 65)	61 (54, 67)
	ACR50	14 (8, 19)	34 (27, 41)	37 (31, 45)
	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)
csDMARDs-IR on Upadacitinib Monotherapy	ACR20	36 (29, 44)	66 (58, 71)	68 (61, 75)
	ACR50	12 (8, 16)	42 (36, 49)	45 (37, 51)
	ACR70	3 (1, 7)	24 (18, 31)	27 (20, 34)
	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 (NSV's) 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

of patients receiving monotherapy or combination therapy at treatment initiation.

Results: 1950 patients were included in the matched population (1300 bDMARD initiators; 650 tofacitinib initiators). Patients were predominantly aged 55 to 74 years (57.8%), and female (81.2%). At baseline, median disease duration was 107 and 120 months, with 16.1% and 17.3% of patients in DAS28-ESR defined disease remission for the bDMARD and tofacitinib groups respectively. After three months of treatment, 49.1% and 49.7% had achieved DAS remission and after 18 months of treatment, 52.4% and 57.8% of patients had achieved DAS remission in the bDMARD and tofacitinib groups respectively. At 18 months the percentage of patients achieving CDAI/SDAI remission was similar with 29.2%/29.0% bDMARD patients and 30.9%/30.5% tofacitinib patients reporting CDAI/SDAI remission respectively. The median persistence of treatment was similar for bDMARD and tofacitinib groups: 33.8 (95% CI 28.8 to 40.4) and 34.2 (95% CI 32.2 to not reached) months respectively. In the overall population, more patients were prescribed tofacitinib as monotherapy (43.4%) compared to bDMARD monotherapy (33.4%).

Conclusion: In this analysis of a large real world dataset, tofacitinib demonstrated treatment effectiveness and persistence that was similar to bDMARDs. Overall, there was a trend for more use of tofacitinib as monotherapy than bDMARDs.

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FRI0141 EFFICACY OF JAK-INHIBITORS VERSUS BIOLOGIC DMARDs ON QUALITY OF LIFE IN RHEUMATOID ARTHRITIS :A META ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: Recent studies comparing JAK-inhibitors (Jak-i) and adalimumab seem to show a better efficacy of JAK-i on patient-reported outcomes in rheumatoid arthritis (RA).

Objectives: As there is no study comparing directly the JAK-i with other biologic DMARDs (bDMARDs), we performed a meta-analysis and compared the effect size of JAK-i and bDMARD versus synthetic DMARDs (sDMARDs) on quality of life.

Methods: We performed a systematic review of the literature until May 2018 using database including : MEDLINE (via PUBMED), EMBASE and abstracts from the ACR and EULAR congresses 2015-2017. We selected all randomized controlled trials (RCT) comparing quality of life (evaluated by SF36) in patient with rheumatoid arthritis treated with bDMARD or JAK-i versus sDMARDs. We performed meta-analysis comparing the effect size of JAK-i (versus sDMARDs) and bDMARD (versus sDMARDs) on PCS SF36 and MCS SF36 at 12 weeks.

Statistical analysis determined in each study effect size.

Pooled ES were computed by meta-analysis. Data were analyzed using the inverse variance approach.

Results: The literature search identified 240 articles plus one found by manual search and no congress abstract. Finally, 44 articles met the inclusion criteria.

JAK-i and bDMARD showed higher level of quality of life than conventional therapies:

- For the SF36 PCS at 12 weeks: JAK-i: +4.82 IC95% [3.88, 5.77] and bDMARDs: +3.99 IC95% [2.81, 5.18]
- For the SF36 MCS at 12 weeks: JAK-i: +3.42 IC95% [2.24, 4.60] and bDMARD: 2.99 IC95% [2.02, 3.96]

The range of the confidence intervals seems similar between JAK-I and bDMARDs.

SF36 PCS at 12 weeks:

Results for JAK-i:

Results. for bDMARDs:

SF36 MCS at 12 weeks:

-Results for JAK-i:

-Results for bDMARDs:

Conclusion: In this meta-analysis, JAK-i and bDMARD showed better SF36 PCS and MCS at 12 weeks in comparison with sDMARDs. Although there is no significant difference, there seems to be a trend toward a better efficacy of JAK-I compared to bDMARD on quality of life.

The range of the confidence intervals seems similar between JAK-I and bDMARDs, suggesting a similar efficiency on the components of the SF36. More head-to-head studies are needed to draw definitive conclusions on potential efficacy differences between JAK-inhibitor and bDMARDs in RA.

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FRI0142 SAFETY OF THE METHOTREXATE-LEFLUNOMIDE COMBINATION IN THE BRAZILIAN REGISTRY OF BIOLOGICAL THERAPIES IN RHEUMATIC DISEASES (BIOBADABRASIL)

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Background: The combination of methotrexate (MTX) with leflunomide (LEF), despite being effective in the therapy of rheumatoid arthritis (RA) [1], has not been widely accepted [2,3]. In spite of evidence that the MTX-LEF combination is generally safe [1,4,5], the relatively small number of patients and treatment courses have not permitted firm conclusions.

Objectives: To evaluate the safety of the combination MTX-LEF in Brazilian patients with RA included in BiobadaBrasil.

Methods: BiobadaBrasil is a multicentric prospective cohort study involving patients with rheumatic diseases who started the first biologic or a synthetic disease modifying anti-rheumatic drug (DMARD) [6]. This analysis includes RA (2010 criteria) patients recruited from Jan 2009 to Aug 2018, followed-up for one or multiple courses of treatment until censoring (latest date, September 03, 2018) or occurrence of the outcome of interest. The primary outcome was the incidence of any serious AE (SAE). Secondary outcomes were infectious, non-mycobacterial pulmonary infectious, hepatic, hematologic and cardiovascular SAE. Multivariate Cox proportional hazards models (with DMARDs included as time-varying covariates) were used to estimate hazard ratios (HR) and 95% confidence intervals (CI); analyses were performed with the Survival package of R.