of patients in the liposomal prednisone groups reported AEs related to study drug administration, versus 6% in the methylprednisolone group. Serious adverse events (SAEs) were reported by 4 (8.2%), 1 (1.9%) and 2 patients (4.1%) resp for the liposomal prednisone 75 mg, liposomal prednisone 150 mg and methylprednisolone 120 mg groups. Five of the 7 SAEs were treatment related; these included 4 events of hypersensitivity in the liposomal prednisone arms and one event of viral upper respiratory tract infection in the methylprednisolone group.

Conclusion: In this phase III trial, liposomal prednisone 75 mg and 150 mg were significantly more effective than 120 mg -methylprednisolone in treating patients with a flare of their RA. The overall incidence of AEs was similar across treatment groups, although hypersensitivity appeared to be more common with liposomal prednisone.

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University Medical Center Utrecht, Utrecht University, Consultant for: SUN Pharma, Speakers bureau: Lilly, Roche, Bart Metselaar Shareholder of: Enceladus, Grant/research support from: SUN Pharma, Leonie Middelink Grant/research support from: SUN Pharma, Cees Wortel Shareholder of: Enceladus, Accelovance, Grant/research support from: SUN Pharma, Consultant for: SUN Pharma, Reinhard Bos Grant/research support from: SUN Pharma, Jacob M. van Laar Grant/research support from: Genentech, Consultant for: F. Hoffmann-La Roche, Harald Vonkeman: None declared, Rene Westhovens Grant/research support from: Bristol-Myers Squibb, Consultant for: Celltrion, Galapagos-Gilead, Siu Long Yao Shareholder of: SUN Pharma, Employee of: SUN Pharma, Mudgal Kothekar Shareholder of: SUN Pharma, Employee of: SUN Pharma, Atul Raut Shareholder of: SUN Pharma, Employee of: SUN Pharma

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FRI0136 THE EFFICACY AND SAFETY OF SIROLIMUS IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS: A RANDOMIZED AND PARALLEL-CONTROLLED CLINICAL TRIAL

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Background: We have reported previously that the insufficient absolute number or functional defects of regulatory T cells (Tregs) in patients with rheumatoid arthritis (RA)[1-3], challenging conventional unspecific immunosuppressive therapy. Sirolimus, a mTOR inhibitor, is reported to allow growth of functional Tregs, which would be able to provide new strategy and target for the treatment of RA[4].

Objectives: To investigate efficacy and safety of sirolimus combined with conventional immunosuppressants for RA treatment.

Methods: In this non-blinded and parallel-group trial, we randomly assigned 62 patients to receive conventional glucocorticoids and immunosuppressants with or without sirolimus at a dosage of 0.5 mg on alternate days for 24 weeks in a 2:1 ratio. The demographic features, clinical manifestations and laboratory indicators including peripheral blood lymphocyte subgroups and $CD4^+$T subsets were compared before and after the treatment.

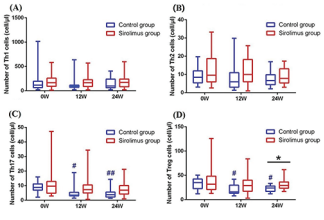

Figure 1: Changes of levels of $CD4^+T$ cells subsets after different treatments. Effects of treatments were assessed by repeated measures analysis using a mixed-effects model. Two-tailed unpaired t-test was used to compare the disease activity measures between sirolimus and conventional groups. #p< 0.05, ##p< 0.01 relative to baseline (week 0) in conventional group (blue); ‡p< 0.05 relative to baseline in sirolimus group (red).. * p< 0.05 compared between groups.

Results: Finally, 37 patients in sirolimus group and 18 in conventional treated group completed 6-month study. By 24 weeks, the patients with sirolimus experienced the significant reduction in disease activity indicators including DAS28, ESR, the number of tender joints and swollen joints (p<0.001). Notably, they had a higher level of Tregs as compared those with conventional therapy alone (p<0.05), indicating that sirolimus could partly restore the reduced Tregs. Concomitantly, their usages of immunosuppressants for controlling disease activity were decreased as compared with conventional group with no difference in blood routine, liver and renal functions both before and after the treatment of sirolimus and between two groups (p>0.05).

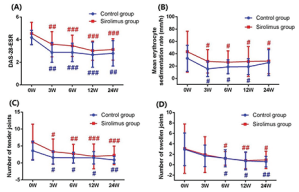

Figure 2: Efficacy of sirolimus in reducing disease activity. Mean DAS-28-ESR score (A), ESR (B), mean number of tender joints (C) and swollen joints(D). Overall changes during treatment were assessed by repeated measures analysis using a mixed-effects model. Two-tailed unpaired *t*-test was used to compare the disease activity measures between sirolimus and conventional groups. Error bars show SD. DAS28: 28-joint disease activity score; ESR: erythrocyte sedimentation rate. #p< 0.05, ##p< 0.01, ###p< 0.001 relative to baseline (week 0) in conventional group (blue); ‡p< 0.05, ‡‡p< 0.01, ‡‡‡p< 0.001 relative to baseline in sirolimus group (red).

Conclusion: Low-dose sirolimus immunoregulatory therapy selectively up-regulated Tregs and partly replaced the usage of immunosuppressants to control disease activity without over-treatment and evaluable side effect. The further study is required using a large sample of RA patients treated with sirolimus for longer period.

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FRI0137 UPADACITINIB IMPROVES PATIENT-REPORTED OUTCOMES IN PATIENTS WITH RHEUMATOID ARTHRITIS AND INADEQUATE RESPONSE TO METHOTREXATE: RESULTS FROM SELECT-COMPARE

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Background: Upadacitinib (UPA), a selective JAK1 inhibitor, has demonstrated superior improvement in the clinical signs and symptoms of rheumatoid arthritis (RA) compared with placebo (PBO) and adalimumab (ADA).[1]

Objectives: To evaluate the effect of UPA vs PBO and vs ADA on patient-reported outcomes (PROs) at Week 12 in SELECT-COMPARE (NCT02629159), a randomised controlled trial (RCT) in an active RA population with inadequate responses to methotrexate (MTX).

Methods: Patients in SELECT-COMPARE, a phase 3 RCT, received UPA (15 mg once daily), PBO, or ADA (40 mg every other week) while on background MTX therapy. The following PROs were collected prospectively: Patient Global Assessment of Disease Activity (PtGA) by visual analogue scale (VAS), pain by VAS, Health Assessment Questionnaire Disability Index (HAQ-DI), duration and severity of morning (AM) stiffness, health-related quality of life by Short Form-36 (SF-36), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and Work Instability Scale for RA (RA-WIS). Least squares mean (LSM) changes from baseline (BL) to Week 12 were based on mixed-effects repeated measures

models. The proportions of patients reporting improvements ≥ minimum clinically important differences (MCID) from BL to Week 12 or scores ≥ 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 ≥ MCID and scores ≥ normative values across all PROs with numbers needed to treat (NNTs) <10. The proportions of UPA-treated patients reporting improvements ≥ MCID were similar or numerically higher than ADA-treated patients. Importantly, the proportion of UPA vs ADA treated patients reporting improvements ≥ 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.

LSM Changes from Baseline and Percentage of Responders at Week 12 After UPA Initiation

PRO	Baseline Mean	LSM Changes from Baseline			Patients Reporting Improvements ≥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*§	−15.2	−23.6¥	474 (73.4)*	332 (51.1)	219 (67.6)
Pain VAS	65.5	−31.8*§	−15.5	−25.3¥	483 (74.8)*	347 (53.4)	227 (69.8)
HAQ-DI	1.6	−0.6*§	-0.3	-0.5¥	465 (72.1)*	330 (50.8)	231 (71.1)
FACIT-F	26.8	9.0*§	4.8	7.4¥	413 (64.0)*	299 (46.4)	202 (62.2)
Duration AM Stiffness[a]	142.8	−92.6*	−48.6	−82.7¥	194 (29.9)[b]*	144 (22.1)	93 (28.7)[b]
Severity AM Stiffness[c]	6.3	−3.4*§	−1.8	−2.9¥	526 (81.3)[b]*	424 (65.0)	260 (80.2)[b]
RA-WIS	14.7	−5.2*	−2.0	−4.5¥	120 (41.7)*	64 (24.4)	42 (32.1)
SF-36 PCS	32.5	7.9*§	3.6	6.3¥	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*§	3.6	6.2¥	479 (73.7)*	379 (58.2)	237 (72.5)
SF-36 RP	33.3	6.9*§	3.6	5.2	470 (72.3)*§	374 (57.5)	213 (65.1)
SF-36 BP	34.1	9.9*§	4.6	8.0¥	501 (77.1)*	390 (59.9)	239 (73.1)
SF-36 GH	37.8	7.3*§	3.1	5.7¥	458 (70.5)*	362 (55.6)	212 (64.8)
SF-36 VT	40.9	8.2*§	4.3	6.8¥	479 (73.7)*	372 (57.1)	225 (68.8)
SF-36 SF	38.1	7.2*§	3.4	5.8¥	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.
§$P<0.05$ for UPA vs ADA. LSM change from baseline P values represent statistical significance between groups.
¥LSM change from baseline differences statistically significant between groups based on non-overlapping 95% confidence intervals.
[a] Duration in minutes. [b] % responders reporting scores ≥ minimal important difference. [c] Assessed 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 ≥600×10^9/L, platelets >400×10^9/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).

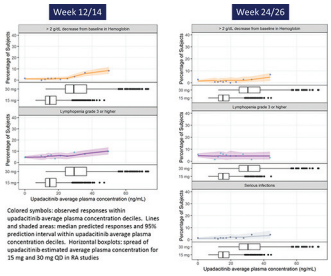

Figure 1. Observed and Model Predicted Percentage of Subjects Experiencing Laboratory Changes/Safety Events of Interest with Increasing UPA Plasma Exposures