nitrofurantoin, and 27% had not received any of the included drugs at the end of the 5-year follow-up for ILD and respiratory failure. MTX treatment was not associated with an increased risk of lung disease (≥ 1 redeemed prescription(s) compared to no prescriptions), HR 1.00 (95% CI 0.78 to 1.27) for ILD and 0.54 (95% CI 0.43 to 0.67) for respiratory failure at 5-year follow-up (Table). The SIR was 3-4 times increased for ILD in MTX-treated RA patients, but this was no different from the RA population in general compared to the background population.

Conclusion: RA patients had an increased risk of ILD compared to the general population, but that risk was not further increased in patients treated with MTX compared to non-MTX treated.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.1609

OP0233

EFFICACY, SAFETY, AND PHARMACODYNAMIC EFFECTS OF THE BRUTON'S TYROSINE KINASE INHIBITOR, FENEPRUTINIB (GDC-0853), IN MODERATE TO SEVERE SYSTEMIC LUPUS ERYTHEMATOSUS IN A PHASE 2 CONTROLLED STUDY

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Background: Feneprutinib (GDC-0853, FEN) is an oral, non-covalent, and selective inhibitor of Bruton's tyrosine kinase (BTK) in clinical development for autoimmune diseases.

Objectives: This was a randomized, placebo-controlled, multi-center study to evaluate the efficacy, safety, and pharmacodynamic effects of FEN in patients with moderate-to-severe systemic lupus erythematosus (SLE) activity.

Methods: Patients who met SLICC or revised ACR SLE criteria, had ≥ 1 serologic marker of SLE, SLEDAI ≥ 8 , and were on ≥ 1 standard of care (SOC) therapy were included; patients with renal or CNS involvement, or exposure to B cell depleting or calcineurin inhibitor therapy were excluded. Patients were randomized to placebo (PBO), FEN 150mg QD, or FEN 200mg BID, for 48 weeks. A corticosteroid taper was recommended, with burst and taper permitted from Week 0 (W0) to W12 and W24 to W36. The primary endpoint was SRI-4 at W48. Post hoc subgroup analyses were conducted based on patient baseline disease characteristics.

Results: This study enrolled 260 patients, with the majority recruited in Latin America, USA, and Western Europe. At W48, the SRI-4 response rates for FEN 150mg QD and FEN 200mg BID were 51% (95% CI: -8.5, 21.2; p value 0.37) and 52% (95% CI: -7.3, 22.4; p value 0.34), respectively, compared to 44% for PBO (Table 1). Post-hoc analysis showed larger responses in subgroups of patients with higher baseline disease activity (Table 1). Safety results were similar between FEN and PBO arms, although more serious adverse events were observed in the FEN 200mg BID arm. Study discontinuations were balanced across the 3 arms (24-26%). FEN treatment significantly reduced levels of CD19+ B cells, anti-dsDNA autoantibodies, IgG, and a BTK-dependent RNA signature highly expressed in plasmablasts by W48 compared to PBO; C4 levels modestly improved with FEN vs. PBO (Table 2).

Table 1. SRI-4 Response (%) at W48 in Primary Analysis and in Post-hoc Patient Subgroups

	PBO	FEN 150mg QD	FEN 200mg BID
SRI-4 Response (%) at W48	44 n=84	51 n=87	52 n=88
SRI-4 Response (%) in Baseline Subgroups			
At least 1 BILAG A	48 n=42	54 n=39	59 n=46
At least 1 BILAG A and SLEDAI	37 n=19	53 n=17	65 n=26
increased DNA binding	39 n=57	50 n=54	57 n=54
SLEDAI arthritis with at least 4 swollen joints	39 n=71	53 n=70	59 n=69
SLEDAI arthritis with at least 4 tender joints	21 n=14	36 n=11	31 n=16
CLASI ≥ 10			

Table 2. Key Biomarker Results

	PBO	FEN 150mg QD	FEN 200mg BID
Median (%) Change from Baseline at W48			
Plasmablast signature	-19.7% n=52	-54.3%* n=53	-51.7%* n=57
CD19+ B cells (cells/ μ l)	-0.50 n=38	-57.0* n=49	-57.5* n=48
Anti-dsDNA ^a (IU/ml)	+6.9 n=31	-38.3* n=36	-75.7* n=33
Total IgG (g/L)	-0.20 n=65	-1.25* n=64	-1.56* n=64
C3 (g/L)	-0.02 n=65	+0.01 n=67	-0.01 n=66
C4 (g/L)	0.00 n=65	+0.02* n=67	+0.01* n=66

^aPatients who were positive at baseline (>30 IU/mL)

*Denotes significant vs. PBO; Kruskal-Wallis false-discovery rate controlled two sided (p-value ≤ 0.05)

Conclusion: The primary endpoint of SRI-4 for FEN was not met despite evidence of strong BTK target and pathway inhibition. FEN had an acceptable safety profile. Several disease activity subgroups were suggestive of a greater treatment effect on SRI-4 compared to PBO

Disclosure of Interests: David Isenberg Consultant of: Study Investigator and Consultant to Genentech, Richard Furie Grant/research support from: AstraZeneca, Biogen, Consultant of: AstraZeneca, Biogen, Nicholas S. Jones Shareholder of: Genentech/Roche, Employee of: Genentech/Roche, Pascal Guibord Shareholder of: Roche, Employee of: Roche, Joshua Galanter Shareholder of: Genentech/Roche, Employee of: Genentech/Roche, Chin Lee Shareholder of: Genentech/Roche and Eli Lilly, Employee of: Genentech/Roche, Anna McGregor Employee of: Genentech/Roche, Balazs Toth Shareholder of: Genentech/Roche, Employee of: Genentech/Roche, Julie Rae Shareholder of: Genentech/Roche, Employee of: Genentech/Roche, Olivia Hwang Shareholder of: Genentech/Roche, Employee of: Genentech/Roche, Armend Lokku Shareholder of: Roche, Employee of: Roche, Pedro Miranda Consultant of: Study Investigator for Genentech, Viviane de Souza Consultant of: Study investigator for Genentech, Juan Jaller-Raad Consultant of: Study investigator for Genentech, Anna Maura Fernandes Consultant of: Study investigator for Genentech, Rodrigo Garcia Salinas Consultant of: Study investigator for Genentech, Leslie Chinn Shareholder of: Genentech/Roche, Employee of: Genentech/Roche, Michael J. Townsend Shareholder of: Genentech/Roche, Employee of: Genentech/Roche, Alyssa Morimoto Shareholder of: Genentech/Roche, Employee of: Genentech/Roche, Katie Tuckwell Shareholder of: Genentech/Roche, Employee of: Genentech/Roche

DOI: 10.1136/annrheumdis-2020-eular.2949

OP0234

MBS2320, A NOVEL SELECTIVE MODULATOR OF IMMUNE METABOLISM, IN PATIENTS WITH SEVERE RHEUMATOID ARTHRITIS: SAFETY, TOLERABILITY AND EFFICACY RESULTS OF A PHASE 2 STUDY

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Background: Despite the availability of several treatment options for Rheumatoid Arthritis (RA), many patients are classed as 'non-responders' who show little or no improvement. Hence, there remains a need for new therapies with a differentiated mechanism of action, to be used alone or in combination. MBS2320 is a selective modulator of immune metabolism displaying distinctive dual pharmacology: strong anti-inflammatory activity as well as a broader spectrum of osteoprotection than TNF α inhibition in preclinical models¹.

Objectives: To evaluate the safety, tolerability and efficacy of MBS2320 in patients receiving a stable dose of methotrexate (MTX).

Methods: Patients with active RA on a stable dose of MTX were randomised 2:1 to receive MBS2320 (80mg) or matching placebo once daily for 4 weeks. Subject to a satisfactory safety and tolerability assessment, patients were escalated to a dose of 120mg qd or remained on 80mg qd for a further 8 weeks. Safety, efficacy, pharmacokinetics and pharmacodynamics were evaluated.

Results: 121 patients were randomised (Safety analysis set) to MBS2320 or matching placebo and 96 completed the study. Sixteen subjects were excluded from the efficacy analysis set due to evidence of poor compliance or absence of efficacy evaluations. Enrolled patients were mostly female (86.8%), white and with a mean (range) age at baseline (BL) of 52 (19-69) years.

The study population had hard-to-treat, severe, active and erosive disease as indicated by high BL DAS28-CRP and DAS28-ESR, low Week-12 placebo ACR50 and DAS28-CRP responder rates (2.5% and 5% respectively) and a low ratio of synovitis-to-erosion volume despite treatment with DMARD(s).

There were no serious treatment emergent adverse events (TEAEs). 15 patients (19%) randomised to MBS2320 withdrew due to TEAEs, predominantly of nausea. TEAEs were typically reported soon after dosing, were mostly mild in severity and resolved without treatment. Onset of TEAEs reduced as the study proceeded.

Gastrointestinal disorders were the most frequently reported TEAEs (all causalities) with a higher incidence in patients receiving MBS2320 (68.8%) than placebo (14.6%). Nausea was most frequently reported during Week 1 (27.3% patients). Asthenia and/or fatigue was reported more frequently in the MBS2320 treatment group (23.8% patients) than with placebo (7.3% patients), with the majority being considered related to study drug. Infections were more frequently reported by patients receiving placebo (22.0%) than those receiving MBS2320 (12.5%). There were no clinically relevant treatment-related trends in the biochemistry, haematology, urinalysis, vital signs or ECG data.

Higher ACR20 response rates were observed in patients receiving MBS2320 versus those receiving placebo at all time points and increased with time. At Week 12, ACR50 response rates with MBS2320 treatment were increased by >4-fold compared with placebo (11.6% vs 2.5%). Greater mean reductions from baseline in DAS28-CRP were also observed in patients receiving MBS2320 versus those receiving placebo at Week 12 (-18.6% vs -8.4%). DAS28-CRP responder rates were more than doubled with MBS2320 treatment compared to placebo (5% vs 14%). These changes were mirrored by improvements in tender joint counts, reduced hsCRP and improvements in Patient Reported Outcomes of pain VAS, Patients' and Clinicians' Global Assessments of Disease Activity and Patients' Global Impression of Change.

Conclusion: MBS2320 was generally well tolerated for up to 12 weeks in this RA study population. Nausea was the most common TEAE, was generally mild in severity and resolved without treatment. In this population of patients with hard-to-treat, severe, active, erosive disease MBS2320 showed evidence of a clinical benefit on both ACR20 responses and DAS28-CRP.

References:

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Acknowledgments: Louise Jopling, Ian Anderson, Ian Gourley, Devenini Damayanthi,

Disclosure of Interests: Lisa Patel Shareholder of: Istesso Ltd, Employee of: Istesso Ltd, Laurence Skillern Consultant of: Istesso Ltd, Martyn Foster Shareholder of: Istesso Ltd, Consultant of: Istesso Ltd, Andy Gray Shareholder of: Istesso Ltd, Consultant of: Istesso Ltd, Richard Leff Consultant of: Istesso Ltd, Sam Williams Shareholder of: Istesso Ltd, Employee of: Istesso Ltd

DOI: 10.1136/annrheumdis-2020-eular.3804

OP0235

ACHIEVING A LOW DAS IN THE FIRST 4-MONTHS AFTER DIAGNOSIS IS IMPORTANT FOR THE LONG-TERM CHANCE OF ACHIEVING DMARD-FREE REMISSION

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Background: Sustained DMARD-free remission (SDFR) is increasingly achievable in RA. The pathogenesis underlying SDFR-development is unknown and patient-characteristics at diagnosis poorly explain whether SDFR will be achieved. This limits substantiated decisions to discontinue DMARD-treatment in clinical practice.

Objectives: To increase the understanding of SDFR, we studied the course of disease activity scores (DAS) over time in relation to SDFR-development. Subsequently, we explored whether DAS-time course could be helpful to identify patients likely to achieve SDFR.

Methods: 761 RA-patients consecutively included in the Leiden Early Arthritis Clinic, treated with initial methotrexate and treat-to-target treatment, were studied (median follow-up 7 years). The course of DAS was compared between patients achieving SDFR within 7 years and those who did not, using linear mixed models, stratified for ACPA. Subsequently, the relation between DAS at 4 months and the probability of achieving SDFR within 7 years was studied with logistic regression. Kaplan-Meier curves were constructed to illustrate cumulative incidence of SDFR for different DAS categories at 4 months, respectively <1.6, 1.6-2.4, 2.4-3.6, >3.6.

Results: Patients achieving SDFR were characterized by a remarkably different DAS response within 4 months after diagnosis. Compared to patients who did not achieve SDFR, the SDFR-group showed a prominently stronger decline in DAS between baseline and 4 months; 1.59 units decline (95%CI, 1.24-1.95) versus 0.96 units (95%CI, 0.85-1.07) decline ($p<0.001$) (figure 1). Stratification for ACPA yielded a similar and statistically significant effect in ACPA-negative RA. In ACPA-positive RA this effect was absent. Subsequently, the probability of achieving SDFR during 7 years was studied in ACPA-negative RA and it was observed to be lower for patients with higher DAS at 4 months. After 7 years of disease, the cumulative incidence for SDFR in ACPA-negative patients with DAS<1.6 at 4

months was high (71.0%), whilst SDFR was rare among those with DAS>3.6 at 4 months (7.1%) (figure 2).

Conclusion: In RA-patients treated according to current guidelines, SDFR is predominantly achieved in patients with a strong decline in DAS during the first four months after diagnosis. Especially in ACPA-negative RA, the DAS at 4-months can be useful for later decisions to stop DMARDs.

Course of DAS over time in relation to SDFR-achievement in ACPA-negative RA

Figure 1. Course of disease activity scores over time in relation to SDFR-achievement in 7 years of follow-up in ACPA-negative RA. Course of disease activity scores (DAS) over time between ACPA-negative patients achieving SDFR (SDFR group) and those not achieving SDFR (non-SDFR group). * Indicates significant stronger decline in DAS in SDFR-group. ACPA: anti-citrullinated protein antibodies, SDFR: sustained DMARD-free remission.

Disease activity score at 4 months and SDFR-achievement in ACPA-negative RA

Figure 2. Kaplan-Meier analysis demonstrating incidence of SDFR-achievement for DAS levels after 4 months in ACPA-negative RA. Cumulative incidence demonstrated using Kaplan-Meier curves to visualize differences in SDFR-achievement for patients achieving lower DAS 4 months after diagnosis. SDFR: sustained DMARD-free remission.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.1837

OP0236

RELEVANCE OF BIASED PAR2 INHIBITORS IN REDUCING INFLAMMATION AND CARTILAGE DEGRADATION IN IN VITRO AND IN VIVO MODELS OF RHEUMATOID ARTHRITIS

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Background: Protease-activated receptor-2 (PAR2) is a member of a family of G-protein-coupled receptors involved in multiple physiological mechanisms. Compelling evidences have unravelled the key roles of PAR2 in the pathology of both rheumatoid arthritis (RA) and osteoarthritis (OA)¹. Indeed, in vitro, in vivo and ex vivo experiments showed that this receptor promotes inflammation, cartilage erosion (and subsequent bone degradation), and pain. However, the signalling pathways involved in these functions are not well understood². This is of importance as some pathways can promote the pathogenesis³ while others prevent it⁴. We developed a new series of small molecules as novel biased PAR2 inhibitors to treat rheumatic diseases.

Objectives: To evaluate the efficacy and mechanism of action of new biased PAR2 inhibitors on cartilage erosion and inflammation.

Methods: The potency of compounds to inhibit human PAR2 signalling was evaluated in vitro by FLIPR calcium assay in HEK293 cells. The same assay was used to determine their selectivity over human PAR1 and PAR4 as well as murine versions of PAR2. The effect of several PAR2 inhibitors on 9 signalling pathways (Gi2, GoB, Gz, Gq, G13, G14, G15, B arrestin 2, EPAC) was evaluated by the BRET-based bioSens-All™ technology. In vitro anti-hypertrophic effect was determined by measuring the mRNA level of type II collagen, aggrecan