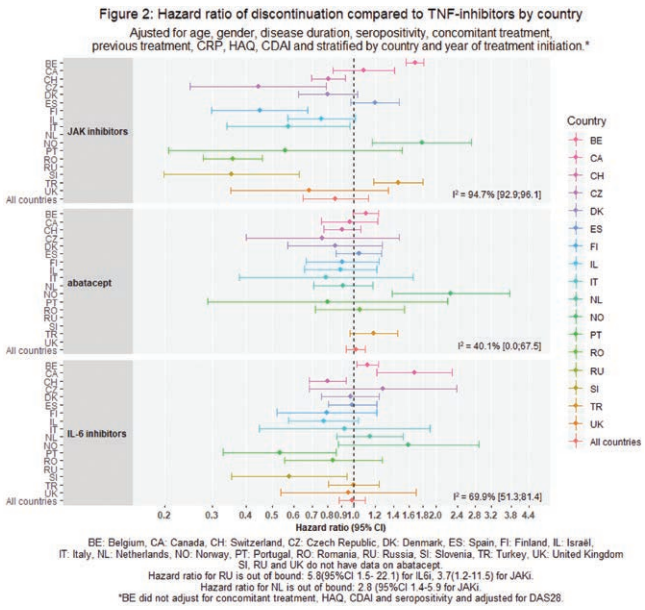

Conclusion: The adjusted overall drug retention of JAKi tended to be higher than for TNFi, with large variation between countries. Other measures of effectiveness, such as the evaluation of CDAI remission and low disease activity are planned to shape a more comprehensive picture of JAKi effectiveness in the real world.

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OP0232

TREATMENT WITH METHOTREXATE AND RISK OF LUNG DISEASE IN PATIENTS WITH RHEUMATOID ARTHRITIS: A NATIONWIDE POPULATION-BASED COHORT STUDY FROM DENMARK

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Background: Methotrexate (MTX) is the recommended first-line drug in EULAR and ACR treatment guidelines for rheumatoid arthritis (RA) and hence the most commonly prescribed DMARD in the treatment of this group of patients. However, lung disease is considered a potential adverse effect of MTX treatment.

Objectives: To investigate the risk of interstitial lung disease (ILD) and acute and chronic respiratory failure in RA patients treated with MTX and other medications.

Methods: From the Danish National Patient Register (DNPR) and the clinical DANBIO Register for rheumatic diseases, we retrieved data on RA patients registered between 1997 and 2015. Information on ILD and respiratory failure outcomes was obtained from DNPR, and information on redeemed prescriptions for MTX and other medications was obtained through linkage to the Danish Prescription Register. Associations between MTX and lung disease outcomes were analyzed in Cox regression models adjusted for age, calendar time, sex and use of other medications possessing the potential for pulmonary toxicity. Standardized Incidence Ratios (SIRs) of lung disease were calculated to compare RA patients to the general population.

Results: Of the 30,512 RA patients identified, 60% patients had redeemed at least one prescription for MTX, 35% had redeemed a prescription for sulphasalazine, 6% had redeemed a prescription of either amiodarone or

Table. Hazard ratios (HR) with 95% confidence intervals (95%CI) for the risk of interstitial lung disease (ILD) and acute or chronic respiratory failure in 30,512 patients with rheumatoid arthritis up to 5 years after diagnosis.

ILD (incl. drug-induced cases)	1 year of follow up		5 years of follow up	
	Events, N	HR (95% CI)	Events, N	HR (95% CI)
Methotrexate, ≥1 redeemed prescription(s) vs. none	62	1.03 (0.71 to 1.48)	166	1.00 (0.78 to 1.27)
Sulphasalazine, ≥1 redeemed prescription(s) vs. none	21	0.88 (0.54 to 1.43)	90	1.14 (0.89 to 1.48)
Amiodarone and/or nitrofurantoin, ≥1 redeemed prescription(s) vs. none	1	0.57 (0.08 to 4.10)	7	0.65 (0.31 to 1.38
Women	72	Ref.	155	Ref.
Men	55	1.51 (1.06 to 2.16)	130	1.74 (1.38 to 2.21)
Acute or chronic respiratory failure	**1-year of follow up**		**5-years of follow up**	
	Events, N	HR (95% CI)	Events, N	HR (95% CI)
Methotrexate, ≥1 redeemed prescription(s) vs. none	36	0.48 (0.32 to 0.73)	158	0.54 (0.43 to 0.67)
Sulphasalazine, ≥1 redeemed prescription(s) vs. none	14	0.70 (0.39 to 1.26)	99	1.09 (0.86 to 1.38)
Amiodarone and/or nitrofurantoin, ≥1 redeemed prescription(s) vs. none	6	3.01 (1.31 to 6.94)	22	1.33 (0.86 to 2.06)
Women	71	Ref.	239	Ref.
Men	38	1.07 (0.72 to 1.59)	120	1.04 (0.83 to 1.29)

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

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OP0233 EFFICACY, SAFETY, AND PHARMACODYNAMIC EFFECTS OF THE BRUTON'S TYROSINE KINASE INHIBITOR, FENEBRUTINIB (GDC-0853), IN MODERATE TO SEVERE SYSTEMIC LUPUS ERYTHEMATOSUS IN A PHASE 2 CONTROLLED STUDY

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

Table 2. Key Biomarker Results

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

#Patients 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

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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 TNFα inhibition in preclinical models[1].

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 120 mg qd or remained on 80 mg 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).