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Abstract THU0184 – Figure 1. The numbers of Th17, Tregs, and the ratio of Th17/Treg in healthy controls and RA patients. **A:** Healthy controls and RA patients before and after sirolimus treatment. **B:** Healthy controls and RA patients before and after conventional treatment.

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THU0185

THE FIRST REPORT OF SIGNIFICANTLY IMPROVEMENT OF NT-PROBNP LEVEL IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH TOFACITINIB DURING 12-MONTH FOLLOW-UP

Diana Novikova¹, Irina Kirillova¹, Eugenia Markelova¹, Helen Udachkina¹, Helen Gerasimova¹, Helen Luchihina², Dmitriy Karateev², Natalia Demidova¹, Anna Misiyuk¹, Maria Cherkasova¹, Tatiana Popkova¹. ¹V.A. Nasonova Research Institute of Rheumatology, Moscow, Russian Federation; ²Moscow Regional Research and Clinical Institute ("MONIKI"), Moscow, Russian Federation

Background: The amino-terminal fragment of the B-type natriuretic peptide prohormone (NT-proBNP) is a marker for functional cardiac impairment and is increased in heart disease with or without symptoms of congestive heart failure (CHF)¹.

Objectives: To prospectively investigate the effect of tofacitinib (TOFA) on the levels of NT-proBNP, as a predictor of CHF in patients (pt) with active rheumatoid arthritis (RA).

Methods: Twenty six RA pt (median age 54 [40;62] years, 81% female, disease duration 44[24;63.0] month (m), moderate to high activity (DAS28-5.1[4.6;6.1], SDAI-27(22;35)), positive for ACCP (73%)/RF (77%), who were non-responders to MTX at least 15 mg/week and/or other synthetic DMARDs and bDMARDs) free of clinical overt cardiovascular disease were treated with TOFA and followed for 12 m. TOFA therapy was started in all pt in dose 5 mg BID per os with dose escalation to 10 mg BID in 8 (31%) pt. TOFA used in combination with MTX in 24 (92%) pt, leflunomide in 1 (4%). Low-dose oral corticosteroids (<10 mg/day prednisone or equivalent) were received by 9 (35%) pt. Remission was achieved in 38,5% pt (DAS28), 38,5% (SDAI). Cardiovascular risk factors (CVRF) and the NT-proBNP levels were measured at baseline and after 12m. At baseline the most of pt had multiple CVRF and sub-clinical organ damage. Cardioprotective therapy received 16 (57%) pt (β-AB-7, ARA/ACE inhibitors-11, statins-11, dihydropyridine CCB-7). Twenty controls matched for CVRF were included for comparison of normal NT-proBNP levels with those of RA pt.

Results: The NT-proBNP level was significantly higher in RA pt than in the control group (median 62.2(26.9-101.7) pg/mL vs 44.0 (34.0-54.3) pg/mL, p<0.05). At baseline NT-proBNP level was higher in female than in male (p=0,019). Its concentration correlated with DAS28 (r=0,41,p=0,036). Three pt (11,5%) had NT-proBNP level over 125 pg/mL. All RA pt with a NT-proBNP level over 125 pg/mL were asymptomatic and exhibited normal echocardiography. Median DAS28 and SDAI were significantly

reduced following TOFA treatment (from 5.1 to 2.9, p < 0.001 and from 26.8 to 4.7, p < 0.001, respectively). During follow-up, no RA pt exhibited a cardiovascular event or CHF. NT-proBNP levels decreased by 63% over the 12-m of TOFA treatment (from 62.16 pg/mL to 14.8 pg/mL, p=0.011). The incidence rate of arterial hypertension (58%vs65%), overweight (62%vs62%), abdominal obesity (58%vs62%), smokers (27%vs27%), menopausal status (52%vs52%), DM type 2 (7%vs7%), mSCORE≥5% (23% vs27%), subclinical carotid atherosclerosis (58%vs58%) did not change significantly. An increase in body mass index (BMI) was observed from 26.5[22.9;29.0] to 26.9[24.0;30.1],p<0.001 and in HDL level from 1.37 [1.06;1.87] to 1.90[1.29;2.16],p<0.01. The percentage change in the NT-proBNP level significantly correlated with the percentage change in the BMI (r=0,6,p=0,007), DAS 28 (r = 0.41, p = 0.038) SDAI (r = 0.51, p = 0.009). Changes in NT-proBNP levels in RA pt with remission was greater than that observed in pt who didn't achieve remission (-87% vs -26%, p=0,005). The percentage change in the NT-proBNP level was not correlated with the percentage change in other CVRF.

Conclusion: TOFA decreased the NT-proBNP level in patients with RA without clinical overt cardiovascular disease and CHF. TOFA may have a cardioprotective effect in those with active RA.

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THU0186

SAFETY, TOLERABILITY AND PHARMACOKINETICS OF MBS2320, A SELECTIVE MODULATOR OF IMMUNE METABOLISM, IN HEALTHY VOLUNTEERS AND PATIENTS WITH RHEUMATOID ARTHRITIS

Lisa Patel¹, Paul Marcus¹, Jim Bush², Andy Gray¹, Richard Fitzgerald³, Sonya Abraham⁴, Martyn Foster¹, Hiep Huatan¹, Laurence Skillern¹, Anna Daroszewska⁵, Rob Van't Hof⁵, Sam Williams¹. ¹Istesso Ltd, London, United Kingdom; ²Covance Clinical Research Unit Ltd, Leeds, United Kingdom; ³The Royal Liverpool University Hospital, Liverpool, United Kingdom; ⁴Imperial College London, Faculty of Medicine, London, United Kingdom; ⁵University of Liverpool, Liverpool, United Kingdom

Background: Despite the availability of several treatment options some patients with Rheumatoid Arthritis (RA) fail to benefit and for those who do response rates are similar across therapeutic classes. Thus there remains a need for new therapies with novel mechanisms of action. MBS2320 is a selective modulator of immune metabolism that shows anatomically appropriate osteoid layering and a broader spectrum of osteoprotective efficacy compared to TNFα inhibition in preclinical models.

Objectives: To investigate the safety, tolerability and pharmacokinetics of MBS2320 in healthy volunteers and patients with Rheumatoid Arthritis (RA) receiving a stable dose of methotrexate (MTX).

Methods: Cohorts of healthy volunteers (randomised 6:2 drug:placebo) received single or multiple oral doses of MBS2320 for 14 days. Single Ascending Dose (SAD) cohorts comprised 2, 10, 25, 50, 75, 125, 250, 375 mg (PO) and Multiple Ascending Dose (MAD) cohorts 75, 100, 160 mg/d. Patients with RA received 75 mg/d for 14 days in addition to their existing weekly MTX treatment. Safety and tolerability were assessed throughout. Plasma MBS2320 (SAD, MAD and patients with RA) and MTX (patients with RA only) were measured using LC-MS/MS. In patients with RA, C-reactive protein (CRP) and biomarkers of bone turnover were assessed on Day 14.

Results: A total of 96 healthy subjects and 9 patients with RA entered the study and were randomised to the drug or matching placebo.

MBS2320 was well tolerated by healthy subjects at single oral doses of 2 to 375 mg. There were no serious adverse events (SAEs). Nausea was the most commonly reported adverse event (AE) and occurred most frequently at the high doses but was mild and resolved without treatment. Daily doses of 75 to 160 mg QD MBS2320 for 14 days were generally well tolerated by healthy subjects. The most common drug-related treatment emergent adverse events (TEAEs) were gastrointestinal disorders,