Abstract FRI0214 – Table 1. Key Endpoints at Wk 52

Endpoints	Sirukumab 50 mg q4w			Sirukumab 100 mg q2w		
	Placebo to 50 mg q4w (n=124)	50 mg q4w (n=235)	Combined 50 mg q4w (n=359)	Placebo to 100 mg q2w (n=123)	100 mg q2w (n=241)	Combined 100 mg q2w (n=364)
ACR20 response, n (%)	68 (54.8)	127 (54.0)	195 (54.3)	71 (57.7)	145 (60.2)	216 (59.3)
ACR50 response, n (%)	41 (33.1)	74 (31.5)	115 (32.0)	38 (30.9)	77 (32.0)	115 (31.6)
HAQ-DI change from baseline, mean (SD)	-0.30 (0.55)	-0.39 (0.58)	-0.36 (0.57)	-0.43 (0.51)	-0.43 (0.60)	-0.43 (0.57)
DAS28 (CRP) <2.6, n (%)	36 (29.0)	63 (26.8)	99 (27.6)	42 (34.1)	71 (29.5)	113 (31.0)
SF-36 summary scores						
PCS change from baseline, mean (SD)	4.47 (7.70)	6.33 (7.23)	5.69 (7.44)	5.45 (7.22)	5.98 (7.25)	5.80 (7.24)
MCS change from baseline, mean (SD)	3.64 (8.48)	5.19 (10.84)	4.65 (10.10)	5.60 (10.62)	4.46 (10.45)	4.85 (10.51)

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FRI0215 COMPARATIVE EFFICACY AND RETENTION RATE OF TOCILIZUMAB AND TNF INHIBITORS USED IN COMBINATION WITH METHOTREXATE AS FIRST-LINE BIOLOGIC THERAPY IN RHEUMATOID ARTHRITIS: DATA FROM A MULTICENTRE OBSERVATIONAL REGISTRY

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Background: Despite a demonstrated superiority of interleukin-6 over tumour necrosis factor (TNF) blockade when used as monotherapy, the choice of the first biologic agent (bDMARD) for treating rheumatoid arthritis (RA) in combination with methotrexate (MTX) is still a challenge for rheumatologist.
Objectives: To retrospectively evaluate in a multicentre observational cohort of Northern Italy (the LORHEN registry) the 6- and 12-month comparative drug survival and remission rate of tocilizumab (TCZ) and TNF inhibitors (TNFis) used as first bDMARD in combination with MTX.
Methods: All RA patients treated with TCZ or a TNFi as first-line bDMARD with at least 12-month follow-up were selected from the LORHEN registry. The analysis was limited to the period from January 2009 to May 2016 and to patients receiving either TCZ or TNFi in combination with MTX, excluding bDMARD monotherapy. Six- and 12-month clinical remission rate was defined as achievement of disease activity score 28 calculated by using erythrosedimentation rate (DAS28-ESR) <2.6. Drug persistence was calculated by Kaplan-Meier method. The comparison between treatment subgroups was performed by a chi-square test for remission data and by a log-rank test for drug survival. Moreover, DAS28-ESR remission rate has been corrected for drug discontinuation by using the LUNDEX formula [(1)].
Results: The overall study population included 591 patients (female 77.3%, mean age [± standard deviation, SD] 54.2±13.2 years, mean disease duration [±SD] 7.4±7.7 years, positive rheumatoid factor 67.5%, positive anti-citrullinated peptide antibodies 77.6%, mean baseline DAS28-ESR 5.1±1.2) treated with TCZ (n=61) or TNFis (n=530; infliximab 43, adalimumab 163, etanercept 195, golimumab 60, certolizumab pegol 69). Baseline characteristics were similar in the two groups, with the exception of mean age (TCZ 58.2 vs TNFis 53.7 years; p=0.021). No significant differences (p=0.361) emerged in the 6- (TCZ 88% vs TNFis 84.3%; p=0.752) and 12-month (TCZ 76.4% vs TNFis 71.5%;) retention rate. Clinical remission was achieved in overall 35.7% patients at 6 months (TCZ 59% vs TNFis 33%; p<0.001) and in 36.8% patients at 12 months (TCZ 58.8% vs TNFis 34.5%; p<0.001). Similar trends were observed after correction by LUNDEX formula at 6 (TCZ 51.9% vs TNFis 27.8%) and 12 months (TCZ 44.9% vs TNFis 24.6%).
Conclusions: Despite a similar 1-year retention rate, the proportion of patients achieving DAS28-ESR remission was significantly higher in TCZ+MTX treated group compared with TNFis+MTX, suggesting a deeper clinical response in patients receiving IL6 blockade.
References:
[1] Kristensen LE, et al. Arthritis Rheum 2006;54:600–6.
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FRI0216 RESULTS OF A LONGITUDINAL REVIEW OF PULMONARY FUNCTION AND SAFETY DATA IN A PHASE IIB CLINICAL PROGRAMME TESTING GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR (GM–CSF) RECEPTOR ANTAGONIST MAVRILIMUMAB FOR TREATMENT OF RHEUMATOID ARTHRITIS (RA)

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Background: RA is associated with pulmonary comorbidity and lung function decline over time, but longitudinal assessment of pulmonary abnormalities in the context of RA treatment needs further characterisation. Mavrilimumab, an investigational human monoclonal antibody, inhibits GM-CSF by binding to the GM-CSF receptor α subunit.
Objectives: To investigate the pulmonary safety of mavrilimumab because of the theoretical risk of inhibiting alveolar macrophage function and causing pulmonary alveolar proteinosis (PAP).
Methods: Pulmonary monitoring included standardised serial pulmonary function testing (spirometry and diffusing capacity of lung carbon monoxide [DLCO]), chest X-rays, assessments of dyspnoea and pulmonary adverse events (AEs) in two randomised, double-blind studies (NCT01706926; NCT01715896) where patients (pts) with moderate to severe RA received mavrilimumab 30, 100 or 150 mg every other week (eow), or placebo and mavrilimumab 100 mg eow or golimumab 50 mg every 4 weeks, respectively. Eligible pts transferred to the open-label extension study (NCT01712399) and received mavrilimumab 100 mg eow. All studies excluded pts with clinically significant uncontrolled pulmonary disease. An Independent Pulmonary Evaluation Committee (IPEC), blinded to treatment, adjudicated pulmonary AEs and lung function abnormalities.
Results: Mavrilimumab was received by 442 pts with cumulative safety data exposure of approximately 900 pt-yrs and a median (range) exposure time of 2.5 (0.1–3.3) yrs. Baseline (BL) characteristics are shown (Table). Mean dyspnoea (Table), forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and DLCO were mostly maintained within 5% of BL values for pts treated with mavrilimumab during the clinical programme. Clinically relevant decreases in predicted FEV_1 and FVC (>20% from BL and <80% predicted) were demonstrated by ≤6.2% of pts at any visit (Table); decreases were mostly transient with no apparent trends. Overall, 83 pts (9.24/100 pt-yrs) reported ≥1 pulmonary AE; bronchitis was reported most frequently (34 pts [3.78/100 pt-yrs]); one AE was considered serious and treatment-related (acute bronchitis). The reported pulmonary AE rate was generally stable over time. No suspected or confirmed PAP cases were found by IPEC and no pulmonary-related deaths were reported.
Conclusions: We believe this is the most comprehensive longitudinal study of pulmonary function in a clinical RA programme. The BL pulmonary function profile indicates that this is not a normal population from a pulmonary health perspective. Mavrilimumab was not associated with substantial decline in pulmonary function or PAP in pts treated up to 3.3 years; its acceptable safety profile advocates initiation of Phase III studies with mavrilimumab. Further studies are now required to fully characterise pulmonary function over time in RA.
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	Mavrilimumab total[a] (n=442)
Demographics	
Age, years, median (min–max)	52 (19–79)
Sex, % female	85.1
BL disease characteristics	
Years since RA diagnosis, mean (SD)	7.91 (6.85)
MTX dose, mg/week, mean (SD)	15.00 (6.84)
DAS28-CRP, mean (SE)	5.77 (0.04)
Concomitant pulmonary disease, n (%)[b]	
Asthma COPD Other	17 (3.8) 8 (1.8) 21 (4.8)
Ever smoked, n (%)	134 (30.3)
Current smokers, n (%)	76 (17.2)
RF and ACPA positive, n (%)	359 (81.2)
BL pulmonary function	
% predicted FEV_1, mean (SD)	93.9 (14.7)
% predicted FVC, mean (SD)	94.0 (14.6)
% predicted DLCO, mean (SD) [n]	72.4 (9.3) [48]
Borg dyspnoea score, mean (SE)	0.4 (0.0)
Efficacy results	
Borg dyspnoea score, mean (SE) [N]	
Week 12[c,d]	NA
Week 74	0.3 (0.0) [279]
Week 134	0.3 (0.0) [58]
>20% reduction from BL to 80% predicted FEV_1, n/N (%)	
Week 12[c,d]	2/298 (0.7)
Week 74	8/231 (3.5)
Week 104	11/178 (6.2)
Week 130	1/29 (3.4)
>20% reduction from BL to 80% predicted FVC, n/N (%)	
Week 12[c,d]	2/298 (0.7)
Week 74	7/239 (2.9)
Week 104	3/177 (3.4)
Week 130	0/32 (0.0)

[a]Mavrilimumab total=all patientswho received mavrilimumab in either of the two randomised studies or in the OLE study. [b]Clinically significant uncontrolled pulmonary disease was an exclusion criterion for all three studies. [c]Between weeks 12 and 24, 3(3.8%), 8(9.4%), 12(14.8%) and 37 (45.7%) pts receiving mavrilimumab 150 mg, 100 mg, 30 mg eow, and placebo, respectively, transferred from NCT01706926 to the OLE study because of lack of efficacy. [d]Between Weeks 12 and 24, 2 (2.9%) and 0 (0.0%) pts receiving mavrilimumab 100 mg and golimumab 50 mg, respectively, transferred from NCT01715896 to the OLE study because of lack of efficacy.
ACPA, anti-citrullinated protein antibody; BL, baseline; COPD, chronic obstructive pulmonary disease; DAS28–CRP, disease activity score 28 C-reactive protein; DLCO, diffusing capacity of the lung for carbon monoxide; eow, every other week; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; MTX, methotrexate; NA, not available; OLE, open-label extension; pts, patients; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SE, standard error

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FRI0217 IMPACT OF RITUXIMAB IN COMBINATION WITH LEFLUNOMIDE AND RITUXIMAB RETREATMENT WITH TWO DIFFERENT DOSAGES ON PATIENT-REPORTED OUTCOMES: RESULTS FROM A MULTICENTER RANDOMIZED PLACEBO CONTROLLED INVESTIGATOR INITIATED CLINICAL TRIAL IN ACTIVE RHEUMATOID ARTHRITIS (AMARA-STUDY)

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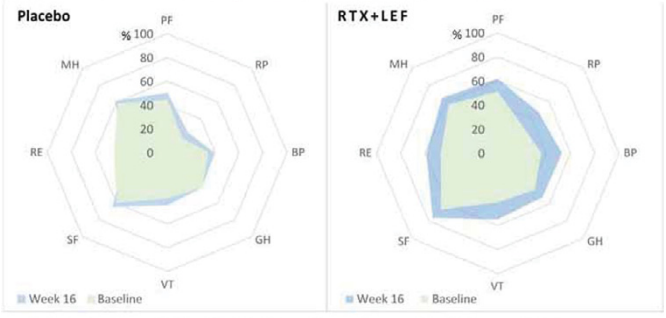
Background: Use of biologicals such as Rituximab (RTX) in Rheumatoid Arthritis (RA) is effective and often only licensed in combination with Methotrexate (MTX). In cases of contraindications to or intolerances of MTX other cDMARDs are frequently used without robust data from RCTs. In addition, different strategies of retreatment of RTX are available.

Objectives: To demonstrate efficacy on patient-reported outcomes (PROs) of RTX in combination with leflunomide (LEF) in a multicenter investigator-initiated placebo (PLA)-controlled RCT in Germany.

Methods: A total of 189 patients with active RA (DAS28>3.2 and at least 3 SJC and 3 TJC) despite stable LEF treatment were screened for a 52-weeks double-blind placebo controlled RCT. Patients were randomized to receive either two-times 1000mg RTX i.v. followed by a retreatment at week 24 with two-times 1000 (RTX-RTXhigh) or 500mg (RTX-RTXlow) or two times PLA at baseline, followed by a retreatment of RTX of either two-times 1000 (PLA-RTXhigh) or 500mg (PLA-RTXlow) at week 24. Adult patients who had inadequate response to more than one antiTNF or failed more than three cDMARDs were excluded. PROs (HAQ, FACIT-F, SF36) were measured at each visit until week 52. Treatment effects on PROs were determined by differences from baseline to week 16, 24 and week52.

Results: Of 189 screened patients 148 were randomized (mean age 56 years; mean proportion of RF-and antiCCP-positivity 58.4% and 55.7% in the RTX-group; 74% female). DAS28 at baseline was 5.55 for RTX and 5.53 in the PLA-group. All baseline-characteristics were well balanced between treatment groups. An improvement in HAQ from baseline to week 16 was seen with a mean delta of -0.23 in the RTX-group (MCID) vs. -0.11 for PLA. In the RTX-group, retreatment until week 52 resulted in stable HAQ-values compared to week24 independent from its dosage. FACIT-F values increased in the RTX-group from baseline to weeks 16, 24 and 52 by 11.87, 12.3 and 14.25, respectively. All physical and mental domains of the SF36 showed a pronounced increase of levels at week 16 compared to baseline in the RTX-group (Figure 1). A total of 372 adverse events (AE) were observed during the one-year studyperiod, only 14 classified as severe (10 in RTX and 4 in PLA). 43 serious adverse events were reported, 28 of them in the RTX-group during the placebo-controlled period.

Figure 1: SF36 domains at baseline and week 16 after placebo or RTX+LEF treatment



PF: physical functioning; RP: physical role limitations; BP: pain; GH: general health; VT: energy/vitality; SF: social functioning; RE: emotional role limitations; MH: mental health

Conclusions: Efficacy of LEF plus RTX was demonstrated not only by measurements of disease activity (as presented previously) but also by measurements of PROs (HAQ, FACIT-F, SF36). This treatment regime showed equal effect sizes compared to the combinational therapy of MTX plus RTX. The treatment with LEF plus RTX illustrated an acceptable safety profile.

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FRI0218 SHARED EPITOPE POSITIVITY IS RELATED TO EFFICACY OF ABATACEPT IN RHEUMATOID ARTHRITIS

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Background: Abatacept, a soluble fusion protein composed of the extracellular domain of CTLA-4 molecule and the Fc portion of human IgG1, is approved therapy for RA by the mechanism of binding to CD80/86 (B7–1/B7–2) on antigen presenting cell (APC), and blocking the B7:CD28 interaction. Meanwhile, it is suggested that HLA-DRB1 shared epitope (SE) associates with the production of ACPA through MHC molecule-based antigen presentation. Moreover, the association between the efficacy of abatacept and the positivity for anti-cyclic citrullinated peptide antibody (ACPA) was reported. Thus, we speculated that there may be correlation between the efficacy of abatacept and patients' HLA-DRB1 SE positivity, so we investigated correlation between the clinical efficacy of abatacept in RA patients and their HLA-DRB1 genotype.

Objectives: To identify the relation between the efficacy of abatacept on patients with rheumatoid arthritis (RA) and their HLA-DRB1 phenotype including whether having shared epitope (SE).

Methods: HLA-DRB1 phenotype of 72 patients treated with abatacept was identified, and divided into 2 group, SE (HLA-DRB1 0101, 0401, 0404, 0405,