EDA) fused to the cytokine interleukin-10. Dekavil is currently in phase II clinical development for the treatment of rheumatoid arthritis (RA).
Objectives: In the phase Ib dose escalation study, the primary objective was to explore safety, tolerability and the maximum tolerated dose of Dekavil when administered in combination with methotrexate (MTX). The aim of the currently ongoing phase II study is to assess therapeutic activity of Dekavil plus MTX over MTX alone by measuring the mean change from baseline of DAS28-CRP. Immunogenicity of F8IL10 and its PK and PD profile will also be explored.
Methods: Patients with active RA despite MTX therapy and who failed anti-TNF treatment are the target population of both studies. In the phase Ib trial, cohorts of 3–6 patients were treated with escalating doses of Dekavil (6, 15, 30, 60, 110, 160, 210, 300, 450 and 600 μg/kg) in combination with a fixed dose of MTX (10–15 mg). In the multicenter, double-blind, placebo-controlled phase 2 study, patients are randomized into two treatment groups (Dekavil 30 or 160 μg/kg plus MTX) and one placebo group (placebo plus MTX). Dekavil is administered once weekly by *s.c.* injection for a maximum of 8 weeks in both studies.
Results: Dekavil has been shown to be well tolerated up to the highest investigated dose (600 μg/kg) and an MTD was not reached. In 33 out of 34 patients treated in the phase 1 study, no DLTs, no SAEs and no SUSARs have been reported. One patient in cohort 9 (450 μg/kg) experienced a DLT (G2 purpura) and a SAE (G2 dyspnea, not drug related). The patient received corticosteroids and fully recovered within one week. Mild injection site reactions were the most frequently observed adverse events and occurred in 62% of the patients. Furthermore, two cases of drug related anemia (G2 and G3) were reported in this study. All adverse reactions resolved completely. At the first efficacy assessment after 4 cycles of treatment, 48% of evaluable patients (16/33) revealed ACR and/or EULAR responses. The fraction of responding patients increased to 57.7% (15/26) after 8 cycles of treatment. Two patients benefited from ACR70 responses for more than 12 months after the last drug administration. As of January 2017, 22 out of 87 patients have been treated in the phase 2 clinical study and neither SUSAR nor treatment-related deaths were recorded.
Conclusions: The currently available data suggest that Dekavil is a safe and promising novel therapeutic for the treatments of RA.
Disclosure of Interest: M. Galeazzi: None declared, G. Sebastiani: None declared, R. Voll: None declared, J. Wollenhaupt: None declared, O. Viapiana: None declared, J. Dudler: None declared, E. Selvi: None declared, C. Baldi: None declared, M. Bardelli: None declared, B. Bannert: None declared, S. Finzel: None declared, C. Specker: None declared, P. Sarzi Puttini: None declared, F. Bootz Employee of: Philochem AG, D. Neri Shareholder of: Philogen SpA
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OP0100 OVERALL CANCER RISK IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH TNF INHIBITORS, TOCILIZUMAB, ABATACEPT, OR RITUXIMAB

H. Wadström, T. Frisell, J. Askling on behalf of The ARTIS study group.
Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden

Background: Immune incompetence may lower host surveillance against incipient tumours. Conversely, immune therapies have emerged as a promising therapeutic approach to cancer. Malignancies thus constitute an important aspect of the safety of biologics as used in Rheumatology, including agents targeting TNF, CD20 and IL6, and immunomodulation using CTLA4. Whereas previous reports concerning TNF inhibitors (TNFi) and risk of malignancies in rheumatoid arthritis (RA) have mostly been reassuring, risks with other biological disease modifying anti-rheumatic drugs (bDMARDs) are less studied.
Objectives: To assess the risk of malignancies in patients with RA treated with bDMARDs.
Methods: Through linkages of Swedish national and population-based registers we assembled cohorts of patients with RA initiating (Jan 2006 through Dec 2014) a first ever treatment of tocilizumab, abatacept, rituximab, or a TNFi, one cohort of patients initiating a second TNFi, one cohort of biologics-naïve csDMARD treated RA. Through linkage with the Swedish Cancer Register information on incident cancers was collected. Outcomes were defined as a first ever solid or hematologic malignancy excluding non-melanoma skin cancer (NMSC) during follow-up. Patients with a previous malignancy were excluded. Patients were followed from treatment start until death, emigration, outcome or end of follow up (Dec 2014). Hazard ratios were calculated using Cox-regression adjusted for age, sex, educational level, comorbidities, sero-positivity, number of hospitalizations and days spent in inpatient care, use of prednisolone at baseline, use of non-steroidal anti-inflammatory drugs (NSAIDs) at baseline, number of prescription drugs at baseline, and sick leave and disability (yes/no) the year before cohort entry.
Results: Adjusted for age, sex, disease- and treatment characteristics (see above), and educational level, there were no statistically significant differences in risk of a first solid or hematologic malignancy between initiators of tocilizumab, abatacept, rituximab, or a first- or second TNFi, and RA patients treated with csDMARDs.

Table 1. Number of persons, events, crude incidence, and hazard ratios for a first invasive solid or hematologic malignancy excluding NMSC

Outcome definition Cohort	Number of persons at risk	Number of events	Crude incidence per 10,000 pys	HR*
First invasive solid or hematologic malignancy excluding NMSC				
Tocilizumab	1408	30	80	0.78 (0.54–1.12)
Abatacept	1565	45	104	0.95 (0.70–1.28)
Rituximab	2793	108	103	0.86 (0.70–1.04)
First TNFi	9355	369	93	0.91 (0.82–1.01)
Second TNFi	3610	129	87	0.88 (0.73–1.05)
csDMARD RA	40071	2797	131	1 (reference)

*Adjusted for age, sex, disease- and treatment characteristics, and educational level.

Conclusions: The overall risk of malignancies among RA patients initiating, tocilizumab, abatacept, rituximab, or a first- or second TNFi in clinical practice did not differ substantially from that of RA patients treated with csDMARDs. Increased risk of tumours at specific sites, or with longer latency, cannot be excluded.
Disclosure of Interest: None declared
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OP0101 RISK OF OPPORTUNISTIC INFECTIONS IN PATIENTS WITH RHEUMATOID ARTHRITIS INITIATING ABATACEPT: ANALYSIS OF ALL AVAILABLE CLINICAL TRIAL DATA

T. Simon[1], T. Gelarden[1], E. Nkhoma[1], M. Zhou[1], S. Banerjee[1], K. Winthrop[2].
[1]*Bristol-Myers Squibb, Princeton;* [2]*Oregon Health & Science University, Portland, United States*

Background: Opportunistic infections (OI) during treatment with abatacept (ABA) have been previously reported but are lacking a comprehensive analysis.
Objectives: To present the overall incidence rates of OI and herpes infections observed in patients (pts) receiving ABA using combined clinical trial data.
Methods: OI adverse events were summarized from 16 clinical trials (both placebo-controlled and cumulative abatacept exposure); all pts randomized to placebo were on a non-biologic DMARD. Incidence rates (per 100 person-years [p-y]) were calculated by the number of pts experiencing the first event divided by the total number of p-y of exposure. The p-y of exposure was censored at the time of the first event, death, discontinuation or end of study. Random effects meta-regression was performed across the trials to estimate the frequency of OI after adjusting for between-study heterogeneity. OI were identified using a pre-specified list in the setting of biologic therapy for patients with RA. Criteria for consideration were based on type, location of the infection and causing organism. Excluded from the list were non-specific infections caused by organisms considered to be opportunistic, but common in the general population.
Results: A total of 7044 pts with RA with ~21,330 p-y of ABA exposure were included in the cumulative randomized trial data (Table). The frequency of OI

Abstract OP0101 – Table 1

Infection Outcome	Abatacept (N=2653) p-y=2355		Placebo (N=1485) p-y=1253		Cumulative abatacept (N=7044) p-y=21,330	
	N (%)	IR/100 p-y (95% CI)	N (%)	IR/100 p-y (95% CI)	N (%)	IR/100 p-y (95% CI)
Opportunistic infections*	4 (0.2)	0.17 (0.05, 0.43)	7 (0.5)	0.56 (0.22, 1.15)	45 (0.6)†	0.21 (0.15, 0.28)†
Bronchopulmonary aspergillosis	1 (<0.1)	0.04 (0, 0.2)	0	0	2 (<0.1)	0.01 (0.00, 0.03)
Eye infection fungal	1 (<0.1)	0.04 (0, 0.2)	0	0	3 (<0.1)	0.01 (0.00, 0.04)
Gastrointestinal candidiasis	0	0	1 (<0.1)	0.08 (0, 0.4)	–	–
Fungal oesophagitis	0	0	1 (<0.1)	0.08 (0, 0.4)	1 (<0.1)	0.00 (0.00, 0.03)
Meningitis cryptococcal	0	0	1 (<0.1)	0.08 (0, 0.4)	–	–
Oesophageal candidiasis	0	0	1 (<0.1)	0.08 (0, 0.4)	7 (0.1)	0.03 (0.01, 0.07)
Pneumocystis jirovecii pneumonia	0	0	1 (<0.1)	0.08 (0, 0.4)	1 (<0.1)	0.00 (0.00, 0.03)
Pneumonia pseudomonal	1 (<0.1)	0.04 (0, 0.2)	0	0	1 (<0.1)	0.00 (0.00, 0.03)
Respiratory moniliasis	0	0	1 (<0.1)	0.08 (0, 0.4)	2 (<0.1)	0.01 (0.00, 0.03)
Tuberculosis	1 (<0.1)	0.04 (0, 0.2)	1 (0.1)	0.08 (0, 0.4)	17 (0.2)‡	0.08 (0.05, 0.13)‡
Herpes						
Herpes simplex	57 (2.1)	2.5 (1.9, 3.2)	22 (1.5)	1.8 (1.1, 2.7)	60 (0.9)	0.28 (0.22, 0.37)
Herpes zoster	44 (1.7)	1.9 (1.4, 2.5)	21 (1.4)	1.7 (1.1, 2.6)	284 (4)	1.38 (1.22, 1.55)
Herpes virus infection	5 (0.2)	0.2 (0.1, 0.5)	4 (0.3)	0.3 (0.1, 0.8)	–	–

*Except herpes; †n (%) for SAE was 19 and IR/100 p-y was 0.1 (95% CI 0.05, 0.14); ‡n (%) for SAE was 11 and IR/100 p-y was 0.05 (95% CI 0.03, 0.09); '–' indicates value is not available. SAE = serious AE.

was 64% lower among pts treated with ABA vs placebo. After adjusting for heterogeneity across studies, the frequency (95% CI) of OI remained lower for the ABA group (0.15% [0.06, 0.42] vs the placebo group (0.48% [0.22, 1.04]).

Conclusions: Abatacept-treated pts had a lower incidence rate of OI compared with placebo. The OI and herpes infection incidence rates in the cumulative data are similar or lower to those reported in the literature.[1–3]

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OP0102 PATIENT REPORTED BENEFITS OF SARILUMAB MONOTHERAPY VERSUS ADALIMUMAB MONOTHERAPY IN ADULT PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS

V. Strand[1], L. Gossec[2], C. Proudfoot[3], C. Chen[4], M. Reaney[3], S. Guillonneau[5], T. Kimura[4], J. van Adelsberg[4], Y. Lin[6], E. Mangan[4], H. van Hoogstraten[6], G.R. Burmester[7]. *[1]Stanford University, Palo Alto, United States; [2]Universite Pierre et Marie Curie and Hopital Pitie-Salpetriere, Paris, France; [3]Sanofi, Guildford, United Kingdom; [4]Regeneron Pharmaceuticals, Inc., Tarrytown, United States; [5]Sanofi, Paris, France; [6]Sanofi, Bridgewater, United States; [7]Charité - University Medicine, Berlin, Germany*

Background: The phase 3 MONARCH superiority study (NCT02332590) compared efficacy and safety of sarilumab (a human anti-IL-6Rα monoclonal antibody [mAb]) 200 mg administered subcutaneously every 2 weeks (q2w), with adalimumab (an anti-TNF-α mAb) 40 mg administered q2w, in patients with active rheumatoid arthritis (RA) who were either intolerant of, or inadequate responders to methotrexate treatment. Sarilumab monotherapy demonstrated superiority to adalimumab monotherapy in reduction of disease activity and improvements in physical function and signs and symptoms of RA, with safety and tolerability consistent with IL-6R or TNF blockade.

Objectives: To compare patient-reported outcomes (PROs) with sarilumab vs adalimumab from MONARCH.

Methods: PROs assessed at baseline, weeks 12 and 24 included ACR components (Patient Global Assessment of Disease Activity [PtGA], Pain visual analog scale [VAS], Health Assessment Questionnaire Disability Index [HAQ-DI]), Medical Outcomes Study Short Form-36 (SF-36), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Morning Stiffness VAS, RA Impact of Disease (RAID) and RA-specific Work Productivity Survey (WPS-RA). Least-squares mean (LSM) between-group differences were determined by mixed-model for repeated measures with treatment, visit, treatment-by-visit interaction and region as fixed effects, and the corresponding baseline PRO scores as continuous covariates. A *P*-value <0.05 was considered statistically significant for PROs in a predefined hierarchy (ACR components, SF-36 physical component summary [PCS], FACIT-F and SF-36 mental component summary [MCS] scores). For PROs not in the hierarchy, significance is not claimed. Changes from baseline were compared with published values for minimum clinically important differences (MCIDs).

Results: Baseline demographics, disease characteristics and PROs were generally balanced between treatment groups (n=184 sarilumab; n=185 adalimumab). Improvements from baseline to week 24 were greater with sarilumab vs adalimumab across PtGA, Pain VAS, HAQ-DI, SF-36 PCS, Morning Stiffness VAS, RAID and WPS-RA global scores (all $P<0.05$, statistical significance is claimed only for PROs in the hierarchy; see table). Between-group differences in FACIT-F and SF-36 MCS scores were not significant. Improvements ≥MCID were reported by a greater percentage of patients with sarilumab than adalimumab for HAQ-DI (≥0.22 units), RAID (≥3 units), SF-36 PCS (≥2.5), and Morning Stiffness VAS (≥10) (all nominal $P<0.05$).

Table. Mean change from baseline to week 24 with sarilumab 200 mg q2w or adalimumab 40 mg q2w

PRO	Mean (SD) Baseline score		LSM Changes (SE) from Baseline to Week 24		Least-Squares Mean Between-Group Difference (95% CI)	*P*-value*
	Sarilumab 200 mg q2w (n=184)	Adalimumab 40 mg q2w (n=185)	Sarilumab 200 mg q2w (n=184)	Adalimumab 40 mg q2w (n=185)		
ACR components						
HAQ-DI	1.64 (0.54)	1.62 (0.64)	-0.61 (0.05)	-0.43 (0.05)	-0.18 (-0.31, -0.06)	<0.005
Pain VAS	70.93 (18.77)	70.32 (19.31)	-36.19 (1.78)	-27.41 (1.80)	-8.78 (-13.66, -3.90)	<0.001
PtGA	68.22 (17.38)	67.51 (18.27)	-33.30 (1.73)	-24.82 (1.75)	-8.48 (-13.24, -3.72)	<0.001
SF-36						
PCS	30.77 (6.09)	31.53 (6.48)	8.74 (0.56)	6.09 (0.56)	2.65 (1.15, 4.15)	<0.001
MCS	36.43 (10.43)	36.93 (11.59)	7.86 (0.77)	6.83 (0.77)	1.04 (-1.06, 3.13)	0.332
Physical functioning	33.26 (19.68)	35.53 (22.01)	22.38 (1.64)	15.01 (1.65)	7.37 (2.91, 11.83)	<0.005
Role-physical	34.31 (18.03)	34.89 (20.51)	20.80 (1.61)	16.23 (1.63)	4.57 (0.18, 8.96)	<0.05
Bodily pain	36.77 (15.84)	39.15 (16.87)	25.69 (1.46)	19.40 (1.47)	6.28 (2.32, 10.25)	<0.005
General health	34.00 (16.03)	36.45 (15.85)	13.96 (1.18)	11.05 (1.19)	2.91 (-0.30, 6.12)	0.076
Vitality	33.29 (16.35)	35.51 (17.39)	17.95 (1.42)	14.39 (1.43)	3.56 (-0.31, 7.43)	0.071
Social functioning	46.27 (23.18)	47.55 (26.18)	21.41 (1.81)	15.04 (1.83)	6.37 (1.43, 11.30)	<0.05
Role emotional	47.15 (24.38)	47.57 (27.15)	18.04 (1.79)	14.10 (1.81)	3.94 (-0.94, 8.82)	0.113
Mental health	48.16 (18.01)	49.81 (19.44)	14.29 (1.31)	13.26 (1.32)	1.02 (-2.54, 4.58)	0.572
FACIT-F	23.59 (8.92)	24.43 (10.26)	10.18 (0.70)	8.41 (0.71)	1.77 (-0.14, 3.67)	0.069
Morning stiffness VAS	70.76 (18.93)	68.95 (21.42)	-36.08 (1.95)	-29.29 (1.97)	-6.80 (-11.10, -0.50)	<0.05
RAID	6.89 (1.69)	6.28 (2.06)	-3.08 (0.17)	-2.30 (0.17)	-0.78 (-1.23, -0.32)	<0.001
WPS-RA (global)†	N/A	N/A	N/A	N/A	N/A	<0.005

*Least-squares mean between-group differences (sarilumab vs adalimumab).
Items above the dotted line were part of the hierarchy and thus statistical significance may be claimed. Between-group differences were not significant for FACIT-F and SF-36 MCS. Items below the dotted line are outside of the hierarchy and thus statistical significance is not claimed and nominal *P*-values are provided.
†Global test for the chance from baseline in the eight WPS-RA scores.

Conclusions: Sarilumab monotherapy compared with adalimumab monotherapy resulted in greater and clinically meaningful improvements in many PROs, including patient-reported disease activity, pain, physical function, morning stiffness, productivity, health related quality of life and health status.

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OP0103 THE EFFECT OF SIRUKUMAB PLUS METHOTREXATE ON CIRCULATING BIOMARKERS OF JOINT DESTRUCTION IN MODERATE TO SEVERE RHEUMATOID ARTHRITIS PATIENTS FROM THE SIRROUND-D PHASE 3 STUDY

B. Dasgupta[1], K. Campbell[1], A.-C. Bay-Jensen[2], M. Karsdal[2], K. Sweet[1], M. Sims[3], M.J. Loza[1]. *[1]Janssen Research & Development, LLC, Spring House, PA, United States; [2]Nordic Bioscience, Herlev, Denmark; [3]GlaxoSmithKline, Stevenage, United Kingdom*

Background: Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation that can lead to progressive bone and joint damage. The cytokine interleukin-6 (IL-6) is implicated in inflammatory pathways associated with bone and cartilage degradation in RA. Inhibition of IL-6 signaling by sirukumab (SIR), an anti-IL6 cytokine monoclonal antibody, was shown to significantly reduce structural damage progression, relative to placebo (pbo), in disease-modifying antirheumatic drug inadequate responder (DMARD-IR) RA patients (pts) in the Phase 3 SIRROUND-D study.

Objectives: To investigate the mechanism of SIR on joint tissue remodeling, a panel of serum biomarkers associated with matrix metalloproteinase (MMP)-driven interstitial matrix and basement membrane degradation (C1M, C3M, C4M), bone turnover (β-isomerized C-terminal telopeptides of type I collagen, CTX-I), osteoblast formation (osteocalcin/NMID), synovial destruction (MMP-3), and tissue inflammation (MMP-mediated destruction of CRP/CRPM) were assessed in pts with moderate to severe RA from SIRROUND-D.

Methods: Serum samples from a sub-cohort of SIRROUND-D (for whom radiographic data were available) were analyzed ad hoc for the following biomarkers: C1M, C3M, C4M, CRPM, MMP-3, CTX, and osteocalcin. Samples from 100 pts treated with pbo and methotrexate (MTX) and 100 pts treated with SIR 50mg q4w + MTX were tested. Biomarkers were measured in all pts at baseline (BL) and Wk 4; samples from SIR and pbo-treated pts (50/group) were tested at Wk 52. Differences between groups were evaluated by comparing within-subject $\log_2$ ratio of Wk 4 or Wk 52 over BL values between treatment groups. Structural damage progressors versus non-progressors were defined based on changes from BL in Sharp/van der Heijde score (SHS) at Wk 52 (≥5 vs <5). Differences between groups were tested using General Linear Models.

Results: SIR significantly reduced serum levels of C1M (-48%), C3M (-30%), C4M2 (-42%), and CRPM (-22%) by Wk 4 vs pbo ($P<0.001$), with similar reductions observed at Wk 52; MMP-3 levels were more substantially decreased by SIR at Wk 52 (-39%) vs Wk 4 (-20%). In contrast, treatment with SIR resulted in increased levels of CTX-I (+20%) and osteocalcin (+12%) by Wk 4 ($P<0.001$; Figure 1). As 95% of the total study population included in this biomarker analysis did not progress (defined as ≥5 Wk 52 change in SHS), we were unable to demonstrate an association between changes in pharmacodynamic markers and radiographic progression. Nor were significant associations with pharmacodynamic changes with SIR treatment observed for comparisons among patients grouped by Wk 52 changes in SHS of ≥5 (n=5), <5 to ≥0.5 (n=41),

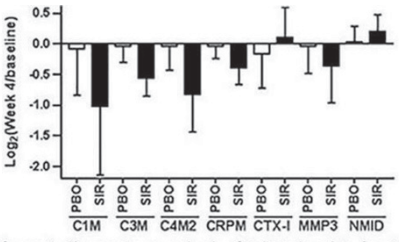

Figure 1. Changes in serum levels of indicated analyte (x-axis), displayed as mean ± SD of log2-transform of within-subject week 4/baseline ratios, stratified by treatment group (PBO, placebo; SIR, sirukumab 50mg q4w). P<0.05 for SIR vs. PBO for each analyte.