Figure 1. Kaplan Meyer Survival Analyses. A, risk of immunogenicity according to the number of biosimilars infliximab received; B, risk of treatment interruption according to the presence of anti-drug antibodies (ADA); and C, treatment retention within the observation period

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OP0228

GSK3196165 AN INVESTIGATIONAL ANTI-GM-CSF MONOCLONAL ANTIBODY, IMPROVES PATIENT REPORTED OUTCOMES IN A PHASE IIB STUDY OF PATIENTS WITH RHEUMATOID ARTHRITIS (RA)

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Background: GSK3196165 is a human mAb that inhibits GM-CSF, a key driver in a broad range of immune-mediated conditions (Hamilton, 2016). In trials of patients with RA, inhibition of GM-CSF signaling has resulted in clinical benefit. GM-CSF is not only a key mediator of inflammation, but emerging science suggests it is also an important regulator of pain.

Objectives: To evaluate the treatment effect of GSK3196165 on pain, fatigue, physical functioning, mental functioning and global assessment of disease, in patients with moderate-to-severely active RA.

Methods: 222 adult patients with active, moderate-severe RA (ACR 2010 criteria), ≥ 4 each of swollen and tender joints, DAS28(CRP) ≥ 3.2 and CRP ≥ 5.0 mg/L, were randomized equally to placebo or GSK3196165 22.5mg, 45mg, 90mg, 135mg or 180mg SC weekly for 5 injections, then every other week until Week 50. The Patient Reported Outcomes (PROs) measured throughout the study included, pain Visual Analogue Scale (VAS), Patient's Global Assessment of Arthritis (PtGA), Health Assessment Questionnaire - Disability Index (HAQ-DI), Brief Fatigue Inventory (BFI) Question 3, the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F), and the 36-item short form health survey (SF-36). The primary outcome was the proportion of patients who achieved remission (DAS28(CRP) < 2.6) at Week 24 and the data has been previously reported (Buckley, 2018).

Results: 37 patients were randomised to each treatment group. The observed GSK3196165 pharmacokinetic exposures were lower than anticipated but despite this, there was a rapid and substantial improvement in RA symptoms in patients treated with GSK3196165 compared with placebo.

The table below summarizes the change from baseline data for the GSK3196165 180 mg dose and placebo at Week 12. An increase in the FACIT-F and SF-36

scores and a decrease in all other scores indicate an improvement in RA symptoms.

PRO endpoint at Week 12	Placebo (N=37)	GSK3196165 180mg (N=37)	
	Least squares mean change from baseline (SE)	Difference from placebo (95% CI, p Value)	
Pain VAS	-7.07 (3.705)	-25.01 (3.650)	-17.94 (-28.18, -7.70, p<0.001)
PtGA	-6.72 (3.660)	-23.90 (3.606)	-17.18 (-27.27, -7.10, p<0.001)
HAQ-DI	-0.26 (0.091)	-0.50 (0.090)	-0.24 (-0.49, 0.01, p=0.059)
BFI Question 3	-0.63 (0.346)	-2.20 (0.339)	-1.57 (-2.53, -0.62, p=0.001)
FACIT-F	3.37 (1.291)	8.70 (1.262)	5.33 (1.77, 8.89, p=0.004)
SF-36 Physical Component	3.42 (1.203)	6.97 (1.182)	3.55 (0.22, 6.88, p=0.037)
SF-36 Mental Component	3.54 (1.558)	6.79 (1.521)	3.25 (-1.05, 7.54, p=0.138)

Conclusion: The results of this Phase IIB study showed that GSK3196165 substantially improved the scores of a range of PRO measures among RA patients. In particular, there was a highly significant improvement in pain; a key symptom of RA. These effects were observed despite achieving much lower drug exposure than predicted. Further studies are required to confirm the additional patient relevant benefits that are expected to arise from increased exposure to GSK3196165.

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OP0229

PHASE II CLINICAL TRIALS SYSTEMATICALLY OVERESTIMATE TREATMENT EFFECTS OF SUBSEQUENT PHASE III TRIALS IN RHEUMATOID ARTHRITIS

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Background: Phase 3 (P3) clinical trials are the mainstay of drug development in all areas of medicine, including rheumatology, allowing to determine safety and efficacy of new drugs on their way to approval. Historically, efficacy results of P3 trials have often been disappointing with respect to the expectations set by phase 2 (P2) trials. It is unclear whether these observations are reflection of a true bias or merely a play of chance.

Objectives: To systematically compare efficacy results of P2 versus P3 trials in RA and investigate potential determinants of efficacy differences.

Methods: We performed a systematic review of disease modifying anti-rheumatic drugs (DMARDs) tested in P2 trials in rheumatoid arthritis (RA) over the last 20 years for which also P3 trials exist. We searched Medline, EMBASE, and the

Cochrane Library to identify all randomized controlled double-blind trials investigating biological (b) and targeted synthetic DMARDs in RA. The criteria for inclusion in the analyses were defined as follows: (i) treatment arms in P2 and P3 used the same treatment regimen; (ii) the same RA population was studied (DMARD naïve; conventional DMARD insufficient responders (IR); bDMARD IR). The treatment regimen was regarded the same when a DMARD was used at the same dose, interval and route in P2 and P3. Multilevel mixed model logistic regression was used to determine a summary estimate for comparison of P2 versus P3 results on the outcomes of American College of Rheumatology (ACR)20, ACR50, and ACR70 responses (in separate models). Results are expressed as Odds Ratio (OR) and 95% confidence intervals (95% CI). Possible determinants of systematic overestimation were explored using the same statistical technique, investigating study and baseline characteristics of the individual trials and study arms, respectively.

Results: In total 1290 abstracts were screened of which 133 were regarded as potentially relevant, with 44 trials (19 agents, 48 regimens, 17476 patients) finally included in the analysis. Summary estimates revealed that outcomes of P2 trials were systematically overestimating the subsequent P3 results for ACR20 (OR: 1.40; 95% CI: 1.15-1.57; $p \leq 0.001$), ACR50 (OR: 1.36; 95% CI: 1.21-1.54; $p \leq 0.001$) and ACR70 (OR: 1.39; 95% CI: 1.02-1.90; $p = 0.037$).

Exploration of determinants of this systematic bias revealed that inclusion criteria for minimum number of required swollen (IC-SJC) and tender joints (IC-TJC) as well as the joint count used for inclusion (28 vs. 66/68 joint count) were significant determinants of P2/P3 efficacy differences. Figure 2 shows scatter plots of efficacy differences (shown as OR), revealing that higher IC-SJC and IC-TJC, as well as using the 66-JC instead of the 28-JC for study inclusion lead to a significantly lower chance of efficacy overestimation.

Conclusion: Our results reveal that Phase 2 clinical trials overestimate the treatment effects when compared with subsequent Phase 3 trials in RA. The identification of this systematic bias towards overestimation of efficacy by Phase 2 studies has implications for considerations of clinical investigators, sponsors, and regulatory agencies during the development and licencing process of new compounds, as well as potential ethical implications.

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OP0230

EFFECTIVENESS OF INFLUENZA VACCINE IN TNF INHIBITORS TREATED PATIENTS

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Background: Tumor Necrosis Factor- α inhibitors (TNFi) are immunosuppressive therapies that are known to increase infectious risk. Indeed, patients affected by TNFi requiring conditions are at higher risk of influenza compared with healthy controls. Furthermore, mildly reduced seroconversion rate after influenza vaccination had been reported in TNFi-treated patients. Nonetheless the immune response is considered large enough to recommend influenza vaccination in all patients affected by rheumatoid arthritis, regardless of treatment. However, there

are data showing that patients are not being vaccinated as recommended. In addition, given that subjects with autoimmune conditions treated with TNFi are at higher risk for influenza, the exact number needed to vaccinate (NNV) for this condition is still unknown.

Objectives: We sought to determine the NNV for influenza in TNFi treated patients and the cost for preventing one case of influenza compared with general population.

Methods: The present analysis included data from cohorts of healthy subjects [1] and TNFi treated patients [2]. We calculated NNV for preventing one case of influenza in each cohort. NNV is the required number of patients receiving vaccination to prevent one case of a given infectious disease. NNV is the inverse of the absolute risk reduction (ARR), which is calculated as following: Control Event Rate (CER) – Experimental Event Rate (EER). In addition, the NNV gives us the opportunity to calculate the cost for preventing one case of influenza, assuming a cost per vaccine from 20 to 40 \$.

Results: In 71,221 healthy individuals influenza vaccination reduced influenza rate from 2.3% in individuals without vaccination (CER = 0.023) to 0.9% in vaccinated individuals (EER = 0.009). The calculated NNV is 71 (NNV = 1/ARR, ARR = 0.023 – 0.009), namely 71 healthy adults need to be vaccinated to prevent one of them experiencing influenza. The costs to prevent a case of clinical influenza in healthy controls would range from 1,420 to 2,840 \$. On 15,132 patients exposed to adalimumab, influenza-related adverse events have been reported in 55 of 382 not-vaccinated patients (CER = 0.14) and in 8 of 179 vaccinated patients (EER = 0.04). In this population (mean age 53.5 years, predominantly white women) the NNV of influenza vaccines is 10 (NNV = 1/ARR, ARR = 0.144 – 0.045) and preventing a case of influenza would cost approximately from 200 to 400 \$, which is largely lower when compared to healthy controls' costs. The relative risk of influenza vaccination in healthy individuals (2.3% to 0.9%, RR 0.41, 95% confidence interval (CI) 0.36 to 0.47) and rheumatoid arthritis patients treated with TNFi (14.4% to 4.5%, RR 0.31, 95% CI 0.15 to 0.64) are similar, while there is a large difference between NNVs (71 vs 10) (Figure 1).

Conclusion: When estimating the effectiveness of vaccinations, clinicians should always include the calculation of the NNV and not only the calculation of relative risk, which might be misleading. The difference in NNV for influenza between healthy individuals and TNFi treated patients is due to a greater absolute risk for influenza in the latter group. The present analysis provides further evidences on the effectiveness of influenza vaccination in patients affected by rheumatoid arthritis receiving treatment with TNFi and should represent a call-to-action for all rheumatologists to consider vaccination in such patients.

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Figure 1. Number Needed to Vaccinate (NNT) for influenza in the general population and in patients treated with Tumor Necrosis Factor- α inhibitors (TNFi)

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