Safety data for patients through 52 weeks. 2 events of IBD were reported in the ixekizumab treatment arm but only 1 case met the adjudication criteria of confirmed inflammatory bowel disease.

Abbreviations: ADA, adalimumab; csDMARD, conventional synthetic DMARD; IBD, inflammatory bowel disease; IXE, ixekizumab; MTX, methotrexate; TEAE, treatment emergent adverse event.

Disclosure of Interests: Josef S. Smolen Grant/research support from: AbbVie, AstraZeneca, Celgene, Celltrion, Chugai, Eli Lilly, Gilead, ILTOO, Janssen, Novartis-Sandoz, Pfizer Inc, Samsung, Sanofi, Consultant of: AbbVie, AstraZeneca, Celgene, Celltrion, Chugai, Eli Lilly, Gilead, ILTOO, Janssen, Novartis-Sandoz, Pfizer Inc, Samsung, Sanofi, Anthony Sebba Consultant of: Genentech, Gilead, Lilly, Regeneron Pharmaceuticals Inc., Sanofi, Speakers bureau: Lilly, Roche, Sanofi, Eric Ruderman Consultant of: Pfizer, Amanda Gellett Shareholder of: Eli Lilly and Company, Employee of: Eli Lilly and Company, Christophe Sapin Shareholder of: Eli Lilly and Company, Employee of: Eli Lilly and Company, Aubrey Trevelin Sprabery Shareholder of: Eli Lilly and Company, Employee of: Eli Lilly and Company, Soyi Liu Leage Shareholder of: Eli Lilly and Company, Employee of: Eli Lilly and Company, Sreekumar Pillai Shareholder of: Eli Lilly and Company, Employee of: Eli Lilly and Company, Paulo Reis Shareholder of: Eli Lilly and Company, Employee of: Eli Lilly and Company, Peter Nash

Grant/research support from: AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly and Company, Gilead, Janssen, MSD, Novartis, Pfizer Inc, Roche, Sanofi, UCB, Consultant of: AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly, Gilead, Janssen, MSD, Novartis, Pfizer Inc, Roche, Sanofi, UCB, Speakers bureau: AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly, Gilead, Janssen, MSD, Novartis, Pfizer Inc, Roche, Sanofi, UCB

DOI: 10.1136/annrheumdis-2020-eular.4615

OP0229

GUSELKUMAB INDUCES SUSTAINED REDUCTION IN ACUTE PHASE PROTEINS AND TH17 EFFECTOR CYTOKINES IN ACTIVE PSORIATIC ARTHRITIS IN TWO PHASE-3 CLINICAL TRIALS (DISCOVER-1 AND DISCOVER-2)

S. Siebert¹, I. McInnes¹, M. J. Loza², K. MA², K. Leander², V. Lakshminarayanan², C. Franks², P. Cooper², K. Sweet². ¹Univ Glasgow, Glasgow, United Kingdom; ²Janssen Research & Development, LLC, Spring House, United States of America

Background: Guselkumab (GUS), an IL-23 inhibitor monoclonal antibody (Mab) that specifically binds to the IL-23p19 subunit, demonstrated efficacy compared to placebo (PBO) in reducing skin and musculoskeletal signs and symptoms in patients (pts) with active psoriatic arthritis (PsA) in two phase-3 studies, DISCOVER 1 & 2.^{1,2} Previous results from a GUS PsA Phase-2 trial³ and Ustekinumab (UST, anti-IL12/23p40 Mab) PsA Phase-3 trials (PSUMMIT 1 & 2)⁴ showed associations of baseline IL-17A, IL-17F, and CRP with baseline disease characteristics, and associations of GUS-induced cytokine reductions with clinical responses.

Objectives: To investigate plausible cytokine expression in PsA and alterations after exposure to GUS therapy.

Methods: In DISCOVER 1 & 2, pts were treated with GUS 100mg at Wk 0, 4, then every 8Wks (q8w); GUS 100mg q4w; or matching PBO. 21 serum biomarkers were measured in a random subset of 300 PsA pts from the DISCOVER program at Weeks (Wks) 0, 4, & 24 and in 34 healthy controls matched for age, sex, and ethnicity. Serum proteins measured were acute phase reactants CRP & SAA (Meso Scale Discovery (MSD) Platform) and inflammatory cytokines/chemokines: Th17 effector cytokines IL-17A, IL-17F, & IL-22 (Single Molecule Counting Erenna® Immunoassay Platform) and soluble ICAM-1, soluble VCAM-1, IL-6, CXCL-8, IL-10, IL-13, IL-12p70, CCL22, IFN-γ, CCL2, CCL4, TNFα, IL-1β, IL-2, IL-4 (MSD), & YKL-40 (Quantikine Immunoassay). Serum IL-17A, IL-17B, & CRP measured in the Phase-3 PSUMMIT trials of UST for PsA⁴ were included for comparison with GUS.

Results: At baseline, serum levels of acute phase proteins CRP, SAA, & IL-6, and Th17-effector cytokines IL-17A & IL-17F were elevated in pts with PsA compared with healthy controls ($p < 0.05$, geometric mean $\geq 40\%$ higher, FIG 1). There was no significant dysregulation in the other cytokines measured in PsA pts compared to healthy controls. Baseline IL-17A, IL-17F, IL-22, & CCL22 were significantly associated with baseline psoriasis disease activity (Body Surface Area & Psoriatic Area and Severity Index, Spearman Signed Rank $p < 0.05$, $r > 0.25$). Baseline CRP, SAA, IL-6, & YKL40 were significantly associated with baseline joint disease (Disease Activity Score 28-CRP, Spearman $p < 0.05$, $r > 0.25$). Baseline SAA, IL-6, IL-17A, & IL-17F were higher in pts with prior TNF inhibitor exposure than without ($p < 0.05$, geometric mean $\geq 40\%$ higher), although pts with PsA both with and without prior TNF inhibitor had higher levels than the healthy control set.

GUS treatment resulted in decreases in serum CRP, SAA, IL-6, IL-17A, IL-17F, & IL-22 that were significantly greater than PBO as early as Week 4 (FIG 1). These protein levels continued to decrease through Wk 24 in GUS-treated pts with both dosing regimens ($p < 0.05$, geometric mean decrease from baseline $\geq 33\%$). Further, Wk 24 IL-17A & IL-17F levels for pts treated with either dose of GUS were not significantly different from healthy controls, suggesting a normalization of peripheral effector cytokines associated with the IL-23/Th17 axis following treatment with GUS. Effects on IL-17A/IL-17F were greater in GUS treated pts than UST treated pts, while CRP levels were similar in both programs (FIG 2).

Conclusion: Comprising a strong pharmacodynamic effect, GUS treatment reduced serum protein levels of acute phase and Th17-effector cytokines (whose elevations at baseline were associated with PsA disease characteristics) and achieved comparable levels to those in healthy controls. In pts with PsA, reductions of IL-17A and IL-17F by GUS were of greater magnitude than those by UST.

References:

- [1] Deodhar et al. ACR 2019, abs #807. Arth Rheumatol. 2019;71 S10: 1386
- [2] Mease et al. ACR 2019, abs #L13. Arth Rheumatol. 2019;71 S10:5247
- [3] Siebert et al. EULAR 2019, abs #479. Ann Rheum Dis. 2019;78 S2:293
- [4] Siebert et al. Arth Rheumatol. 2019;71:1660

FIGURE 1.

* P vs. baseline ≤ 0.05 , [fold difference] ≥ 1.4
 # P vs. placebo ≤ 0.05 , [fold difference] ≥ 1.4
 Error bars represent 2 standard errors of the mean ($\sim 95\%$ confidence interval)
 BL=Baseline, GUS=Guselkumab, PBO=Placebo, Wk=Week

FIGURE 2.

Error bars represent standard error of the mean
 Wk=Week

Acknowledgments: None

Disclosure of Interests: Stefan Siebert Grant/research support from: BMS, Boehringer Ingelheim, Celgene, GlaxoSmithKline, Janssen, Novartis, Pfizer, UCB, Consultant of: AbbVie, Boehringer Ingelheim, Janssen, Novartis, Pfizer, UCB, Speakers bureau: AbbVie, Celgene, Janssen, Novartis, Iain McInnes Grant/research support from: Bristol-Myers Squibb, Celgene, Eli Lilly and Company, Janssen, and UCB, Consultant of: AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly and Company, Gilead, Janssen, Novartis, Pfizer, and UCB, Matthew J Loza Employee of: Janssen Research & Development, LLC, Keying Ma Employee of: Janssen Research & Development, LLC, Karen Leander, Employee of: Janssen Research & Development, LLC, Vani Lakshminarayanan Employee of: Janssen Research & Development, LLC, Carol Franks Employee of: Janssen Research & Development, LLC, Philip Cooper Employee of: Janssen Research & Development, LLC, Kristen Sweet Employee of: Janssen Research & Development, LLC
DOI: 10.1136/annrheumdis-2020-eular.1240

OP0230

EFFICACY AND SAFETY OF TILDRAKIZUMAB, A HIGH-AFFINITY ANTI-INTERLEUKIN-23P19 MONOCLONAL ANTIBODY, IN PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS IN A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE-DOSE, PHASE 2B STUDY

P.J. Mease¹, S. Chohan², F. J. García Fructuoso³, A. B. Gottlieb⁴, M. E. Luggen⁵, P. Rahman⁶, S. P. Raychaudhuri⁷, R. C. Chou⁸, A. M. Mendelsohn⁹, S. Rozzo⁹, A. M. Orbai¹⁰. ¹Swedish Medical Ctr/Providence St. Joseph Health and Univ of Washington, Seattle, United States of America; ²Arizona Arthritis and Rheumatology Research, PLLC, Phoenix, United States of America; ³Hospital CIMA Sanitas, Barcelona, Spain; ⁴Dept of Dermatology, Icahn School of Medicine at Mount Sinai, New York, United States of America; ⁵Cincinnati Rheumatic Disease Study Group, Inc, and Univ of Cincinnati College of Medicine, Cincinnati, United States of America; ⁶Craig L Dobbin Genetics Research Ctr, Memorial Univ, St. John's, Canada; ⁷Division of Rheumatology, Allergy & Clinical Immunology, Univ of California School of Medicine, Davis, and VA Medical Ctr Sacramento, Sacramento, United States of America; ⁸Division of Allergy, Immunology and Rheumatology, Univ at Buffalo School of Medicine and Biomedical Sciences, Buffalo, United States of America; ⁹Sun Pharmaceutical Industries, Inc, Princeton, United States of America; ¹⁰Johns Hopkins Arthritis Ctr, Johns Hopkins Bayview Medical Ctr, Baltimore, United States of America

Background: Tildrakizumab (TIL), a high-affinity anti-interleukin-23p19 monoclonal antibody, is approved to treat moderate to severe plaque psoriasis and is under investigation for treatment of psoriatic arthritis (PsA).¹

Objectives: To evaluate efficacy and safety of TIL up to week (W)52 in a randomised, double-blind, placebo-controlled, multiple-dose, phase 2b study in PsA (NCT02980692).

Methods: Patients (pts) ≥ 18 years with active PsA² were randomised 1:1:1:1 to TIL 200mg every 4 weeks (Q4W) to W52, TIL 200mg Q12W to W52, TIL 100mg Q12W to W52, TIL 20mg Q12W until W24 then TIL 200mg Q12W to W52, or placebo (PBO) Q4W until W24 then TIL 200mg Q12W to W52. Efficacy assessments included ACR20/50/70, 75%/90%/100% improvement in Psoriasis Area and Severity Index (PASI), proportion of pts with residual minimal disease activity (MDA) response; and mean change from baseline (BL) in HAQ-DI, Leeds Dactylitis Index (LDI, pts with BL LDI ≥ 1), and Leeds Enthesitis Index (LEI, pts with BL LEI ≥ 1) to W52. Treatment-emergent adverse events (TEAEs) were monitored.

Results: Of 500 pts screened, 391 were randomised and received ≥ 1 dose of drug. Proportions of ACR20/50/70 responders were superior with TIL vs PBO through W24; after W24 rates of responses further increased for TIL 20→200mg Q12W and PBO→200mg Q12W through W52 (Figure 1, 2). Other efficacy results are shown in Table. Overall from BL→W24/W25→W52, 50.4%/39.9% and 2.3%/1.0% of pts experienced a TEAE and serious AE, respectively. From BL→W24, 1 case of pyelonephritis and urinary tract infection was reported in the TIL 100mg Q12W arm and 1 case of chronic tonsillitis was reported in the TIL 20 mg→200mg Q12W arm. During W25→W52, 1 malignancy (intraductal proliferative breast lesion) was reported with TIL 20 mg→200mg Q12W. No deaths or major adverse cardiac events occurred.

Figure 1. ACR20/50/70 through W52

Missing data were not imputed.
 Q4W, every 4 weeks; Q12W, every 12 weeks; TIL, tildrakizumab.

Figure 2. ACR20/50/70 through W24

*P<0.05; **P<0.001; ***P<0.0001 vs PBO.
 Missing responses were imputed as nonresponses.
 Q4W, every 4 weeks; Q12W, every 12 weeks; TIL, tildrakizumab.

Table. W52 clinical efficacy

	TIL 200mg Q4W n=78	TIL 200mg Q12W n=79	TIL 100mg Q12W n=77	TIL 20→ 200mg Q12W n=78	PBO→ TIL 200mg Q12W n=79
HAQ-DI, BL ^a	1.0 ± 0.6	1.0 ± 0.6	1.0 ± 0.7	1.1 ± 0.6	1.2 ± 0.6
W52 ^b	-0.5 ± 0.5	-0.5 ± 0.6	-0.5 ± 0.6	-0.5 ± 0.5	-0.5 ± 0.5
LEI, BL ^{a,c}	1.9 ± 2.0	1.5 ± 1.9	2.2 ± 2.1	2.2 ± 2.0	1.5 ± 1.9
W52 ^b	-1.3 ± 1.9	-1.0 ± 1.6	-1.7 ± 2.1	-1.2 ± 1.8	-1.2 ± 1.8
LDI, BL ^{a,d}	32.8 ± 32.9	61.3 ± 73.5	93.8 ± 146.5	71.4 ± 118.5	99.6 ± 170.7
W52 ^{b,d}	-21.4 ± 37.1	-42.1 ± 76.7	-41.6 ± 89.3	-56.5 ± 123.4	-81.5 ± 173.0
BL, W52 median ^d	21.8, 7.4	28.3, 3.2	32.1, 20.0	28.6, 0	34.0, 5.6
MDA ^e	56.9	64.4	45.0	47.1	42.0
PASI 100 ^e	54.0	44.4	43.9	47.5	35.0
PASI 90 ^e	72.0	80.6	58.5	55.0	50.0
PASI 75 ^e	82.0	94.4	82.9	75.0	67.5

^aBL mean ± SD. ^bMean change from BL ± SD. ^cPts with BL LEI ≥ 1 will be presented at EULAR.

^dPts with BL LDI ≥ 1 (n = 27, 21, 21, 19, 25) using nonresponder imputation. ^e% at W52

Missing data not imputed.

SD, standard deviation.

Conclusion: TIL was well tolerated and improved joint and skin manifestations of PsA through W52.