confounding by indication will make the non-TNFi drugs appear less safe than the TNFi. A simple adjustment for age and sex will reduce this confounding dramatically, but residual confounding is still expected to give higher rates of AEs, and comparisons should be adjusted for medical history and comorbidities when possible.

Acknowledgements: The ARTIS registry has been, or is, supported by agreements with Abbvie, BMS, MSD, Pfizer, Roche, Samsung Bioepis, and UCB.

Disclosure of Interest: T. Frisell: None declared, E. Baecklund: None declared, K. Bengtsson: None declared, D. Di Giuseppe: None declared, H. Forsblad-d'Elia: None declared, J. Askling Grant/research support from: Abbvie, UCB, Pfizer, Merck, Samsung, Roche, Lilly

DOI: 10.1136/annrheumdis-2017-eular.1319

THURSDAY, 15 JUNE 2017

PsA: an integrated perspective

OP0201 A PHASE 3 STUDY OF THE EFFICACY AND SAFETY OF IXEKIZUMAB IN PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS AND INADEQUATE RESPONSE TO TUMOUR NECROSIS FACTOR INHIBITOR(S)

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Background: Tumour necrosis factor inhibitors (TNF-i) have revolutionised the management of psoriatic arthritis (PsA) yet some patients (pts) have an inadequate response (IR) or intolerance. Ixekizumab (IXE), a monoclonal high affinity antibody that selectively targets IL-17, has shown efficacy in TNF-naïve PsA pts.[1]

Objectives: To compare efficacy and safety of IXE with placebo in pts with active PsA who are TNFi-IR.

Methods: In the 24 week (wk), double-blind, placebo-controlled period of a Phase 3 PsA study (SPIRIT-P2; NCT02349295), pts with prior IR or intolerance to 1 or 2 TNF-i were randomised to SC placebo or IXE 80 mg every 2 (Q2W) or 4 wks (Q4W), following a 160 mg initial dose at Wk 0. Pts with IR to treatment (protocol defined) received rescue therapy at Wk 16. Primary endpoint was ACR20 at Wk 24. Continuous data were analyzed using mixed-effects model for repeated measures; categorical data, using a logistic regression model with missing values imputed by non-responder imputation, which treats IR as non-responders.

Results: 363 pts were randomized: ~52 yrs old on average, female (53%), white (~92%), and IR to 1 or 2 TNF-i (204 [56.2%], 128 [35.3%], respectively) or TNF-intolerant (31 [8.5%]). Most pts had current psoriasis (93.4%) and BSA≥3 (62.5%). The majority (87%) completed the 24-wk, double-blind period. A significantly higher proportion of IXE- vs placebo-treated pts at Wk 24 achieved ACR20 (65 [53.3%], 59 [48%] vs. 23 [19.5%]; Q4W, Q2W, placebo, respectively), ACR50 (43 [35.2%], 41 [33.3%] vs 6 [5.1%]; Q4W, Q2W, placebo, respectively), ACR70 (27 [22.1%], 15 [12.2%] vs 0; Q4W, Q2W, placebo, respectively), MDA (34 [27.9%], 29 [23.6%] vs 4 [3.4%]; Q4W, Q2W, placebo, respectively), DAS28-CRP, and reductions in functional disability (HAQ-DI) (Table). A significantly higher proportion of IXE-Q4W- vs placebo-treated pts reached complete resolution of dactylitis (LDI-B=0). Although enthesitis improved from baseline with both IXE doses, rates of complete resolution (LEI=0) were not significantly different compared to placebo. At Wk 24, significantly greater proportions of IXE-treated pts with ≥3% BSA achieved PASI 75 than placebo-treated patients. The incidence of treatment-emergent adverse events (TEAE) was similar across groups (83 [68%], 90 [73.2%] vs 76 [64.4%]; Q4W, Q2W, placebo, respectively). A numerically higher proportion of IXE-treated pts reported infection and a significantly higher proportion reported injection site reactions (the majority were mild) (Table). Serious infection (0, 3 [2.4%], 0; Q4W, Q2W, placebo respectively), serious AE, and oral candidiasis were numerically higher with Q2W vs placebo. No deaths or cases of inflammatory bowel disease, uveitis, TB reactivation, or grade ≥3 neutropenia were reported.

	Week 12			Week 24		
Outcomes	Placebo (N=118)	IXEQ4W (N=122)	IXEQ2W (N=123)	Placebo (N=118)	IXEQ4W (N=122)	IXEQ2W (N=123)
ACR20 n (%)	26 (22.0)	61 (50.0)**	59 (48.0)**	23 (19.5)	65 (53.3)**	59 (48.0)**
ACR50 n (%)	4 (3.4)	38 (31.1)**	41 (33.3)**	6 (5.1)	43 (35.2)**	41 (33.3)**
ACR70 n (%)	2 (1.7)	18 (14.8)*	13 (10.6)*	0	27 (22.1)**	15 (12.2)**
HAQ-DI CFB LSM (SE)	-0.1 (0.06)	-0.4 (0.06)**	-0.4 (0.06)**	-0.2 (0.08)	-0.6 (0.07)**	-0.4 (0.07)**
DAS28-CRP CFB LSM (SE)	-0.6 (0.17)	-1.8 (0.17)**	-1.5 (0.16)**	-0.8 (0.20)	-2.1 (0.19)**	-1.8 (0.18) **
LEI (0)[a] n/N (%)	20/69 (29.0)	19/68 (27.9)	29/84 (34.5)	15/69 (21.7)	24/68 (35.3)	26/84 (31.0)
LDI-B (0)[b] n/N (%)	5/14 (35.7)	19/28 (67.9)	12/20 (60.0)	3/14 (21.4)	21/28 (75.0)*	10/20 (50.0)
PASI 75[c] n/N (%)	7/67 (10.4)	39/68 (57.4)**	42/68 (61.8)**	10/67 (14.9)	38/68 (55.9)**	41/68 (60.3)**
Minimal disease activity (MDA) n (%)	6 (5.1)	31 (25.4)**	21 (17.1)*	4 (3.4)	34 (27.9)**	29 (23.6)**
Safety, n (%)						
TEAE	--	--	--	76 (64.4)	83 (68.0)	90 (73.2)
SAE	--	--	--	4 (3.4)	3 (2.5)	8 (6.5)
Discontinued from AE	--	--	--	6 (5.1)	5 (4.1)	8 (6.5)
Infections	--	--	--	35 (29.7)	47 (38.5)	47 (38.2)
Serious	--	--	--	0	0	3 (2.4)
Oral candida	--	--	--	0	0	4 (3.3)
Injection site reactions[d]	--	--	--	5 (4.2)	14 (11.5)**	29 (23.6)**

Abbreviations: CFB=change from baseline; SAE=serious adverse event.
[a]Only pts with enthesitis at baseline (LEI >0) were included in the analysis.
[b]Only pts with dactylitis (LDI-B>0) at baseline were included.
[c]Only pts with psoriatic lesions ≥3% of BSA at baseline were included.
[d]Injection site reactions is a high-level term consisting of multiple lower-level terms.
*P<0.05,**P <0.001.

Conclusions: IXE improved arthritis[1], physical function, and psoriasis[2,3] vs placebo with no unexpected safety findings in patients with active PsA and prior IR or intolerance to TNF-inhibitor(s).

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Disclosure of Interest: P. Nash Grant/research support from: AbbVie, Amgen, BMG, Celgene, Eli Lilly and Company, Hospira, Janssen, MSD, Novartis, Pfizer, Roche, Sanofi, UCB, Consultant for: AbbVie, Amgen, BMS, Celgene, Eli Lilly and Company, Hospira, Janssen, MSD, Novartis, Pfizer, Roche, Sanofi, USB, Speakers bureau: AbbVie, Amgen, BMS, Celgene, Eli Lilly and Company, Hospira, Janssen, MSD, Novartis, Pfizer, UCB, Roche, Sanofi, B. Kirkham Grant/research support from: Arthritis Research UK, AbbVie, Eli Lilly and Company, Roche, UCB, Consultant for: AbbVie, Celgene, Eli Lilly and Company, Janssen, Pfizer, Novartis, M. Okada Consultant for: Eli Lilly and Company, P. Rahman Consultant for: AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly and Company, Janssen, Novartis, Pfizer, B. Combe Grant/research support from: Bristol-Myers Squibb, Celgene, Janssen, Eli Lilly and Company, Merck, Novartis, Pfizer, Roche-Chugai, UCB Pharma, Speakers bureau: Bristol-Myers Squibb, Janssen, Merck, Pfizer, Roche-Chugai, UCB PHarma, D. Adams Shareholder of: Eli Lilly and Company, Employee of: Eli Lilly and Company, L. Kerr Shareholder of: Eli Lilly and Company, Employee of: Eli Lilly and Company, C. Lee Shareholder of: Eli Lilly and, Employee of: E, C. Shuler Shareholder of: Eli Lilly and Company, Employee of: Eli Lilly and Company, M. Genovese Grant/research support from: AbbVie, Astellas, Eli Lilly and Company, Galapagos, Pfizer, Vertex, Consultant for: AbbVie, Astellas, Eli LIlly and Company, Galapagos, Pfizer, Vertex

DOI: 10.1136/annrheumdis-2017-eular.1576

OP0202 EFFICACY AND SAFETY OF TOFACITINIB, AN ORAL JANUS KINASE INHIBITOR, IN PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS AND AN INADEQUATE RESPONSE TO TUMOUR NECROSIS FACTOR INHIBITORS: OPAL BEYOND, A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 TRIAL

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Background: Tofacitinib is an oral Janus kinase inhibitor under investigation for treatment of PsA.

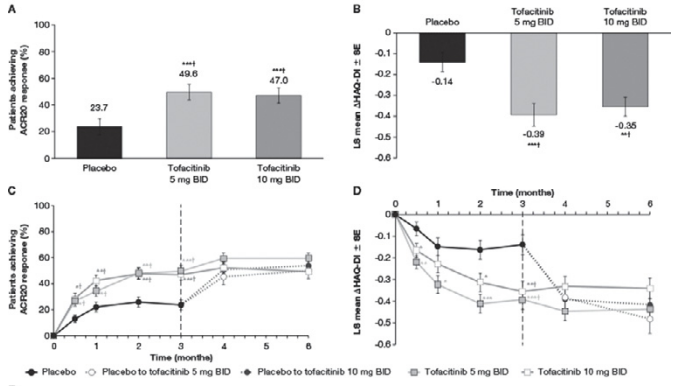
Objectives: Evaluation of efficacy and safety of tofacitinib vs placebo (PBO) in adult patients (pts) with active PsA and an inadequate response (IR) to TNF inhibitors (TNFi).

Methods: Eligible pts in this 6-month, randomised, PBO-controlled, double-blind, multicentre, Phase 3 study had ≥6 months' PsA diagnosis, met CASPAR criteria, had active arthritis (≥3 tender/painful and ≥3 swollen joints) at screening and baseline, active plaque psoriasis at screening and IR to ≥1 TNFi (discontinued due to inadequate efficacy or adverse event [AE]). Pts were randomised 2:2:1:1 to tofacitinib 5 mg twice daily (BID), tofacitinib 10 mg BID or PBO (advancing to tofacitinib 5 or 10 mg BID in a blinded manner at Month [M]3). Ongoing treatment with 1 conventional synthetic DMARD was required. Pts were followed through M6. Primary endpoints were ACR20 response rate and change (Δ) from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at M3.

Results: Pts were 92.1% white, 55.3% female and mean age was 50.0 years. At baseline, mean swollen and tender/painful joint counts were 22.0 and 11.8 respectively; mean HAQ-DI score was 1.3; 69.8% of pts had LEI >0; 49.2% had Dactylitis Severity Score (DSS) >0. Most patients (62.7%) had ≥3% BSA affected by psoriasis, for whom median PASI score was 7.9. Discontinuation rate at M3 was 7.6%, and 87.6% completed M6. ACR20 response and ΔHAQ-DI significantly improved with both tofacitinib doses vs PBO at M3 (Fig 1A,B) and were maintained to M6 (Fig 1C,D). Tofacitinib 5 mg and 10 mg BID demonstrated superior ACR20 response vs PBO as early as Week 2 (26.7% [p≤0.05] and

28.8% [p≤0.05] vs 13.0%). Secondary endpoints at M3 for tofacitinib 5 mg and 10 mg respectively were: ACR50 response, 29.8% (p≤0.05), 28.0% (p≤0.05); ACR70 response, 16.8% (not significant [NS]), 14.4% (NS); ≥75% improvement of PASI in pts with baseline BSA ≥3% and PASI >0, 21.3% (NS), 43.2% (p<0.0001); ΔLEI and ΔDSS in pts with baseline score >0: ΔLEI, -1.3 (p≤0.05) and -1.3 (p≤0.05) (least squares mean [LSM]); ΔDSS, -5.2 (p≤0.05) and -5.4 (p≤0.05) (LSM). Effects were maintained to M6. Frequency of serious AEs and discontinuations due to AEs was low and similar across treatment groups (Fig 1E). The most common AEs were upper respiratory tract infection (5.3–10.8%), nasopharyngitis (1.5–10.7%) and headache (4.5–9.1%).

Figure 1. A. ACR20 response rates with tofacitinib vs placebo at M3, B. ΔHAQ-DI with tofacitinib vs placebo at M3, C. ACR20 response rates up to M6, D. ΔHAQ-DI up to M6, E. Safety summary (safety analysis set;[a] all causality)



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	Up to M3	Up to M6			
	Placebo (N=131)	Placebo → tofacitinib 5 mg BID (N=66)	Placebo → tofacitinib 10 mg BID (N=65)	Tofacitinib 5 mg BID (N=131)	Tofacitinib 10 mg BID (N=132)
AEs, n (%)	58 (44.3)	40 (60.6)	38 (58.5)	93 (71.0)	96 (72.7)
SAEs, n (%)	3 (2.3)	2 (3.0)	1 (1.5)	5 (3.8)	8 (6.1)
Discontinuation due to AEs, n (%)	5 (3.8)	2 (3.0)	3 (4.6)	5 (3.8)	11 (8.3)
Deathe, n (%)	0	0	0	0	0
AEs of special interest, n (%) [day of onset]					
Serious infection	0	0	0	2 (1.5) [135, 166]	2 (1.5) [10, 69]
Herpes zoster (all non-serious)	0	0	0	1 (0.8) [77]	2 (1.5) [8, 156]
Malignancy[b]	0	0	0	0	0
MACE[c]	0	0	0	1 (0.8) [245]	1 (0.8) [94]

Nominal *p≤0.05, **p<0.001, ***p<0.0001 vs placebo; [a]Achieved statistical significance at p≤0.05 per the pre-specified step-down testing procedure; dashed line indicates the end of the placebo-controlled period; [b]All patients who received ≥1 dose of study medication; [c]Including non-melanoma skin cancer; [d]For this trial, MACE included one myocardial infarction and one cerebrovascular event (stroke)
ACR, American College of Rheumatology; AE, adverse event; BID, twice daily; HAQ-DI, Health Assessment Questionnaire-Disability Index; M, month; MACE, major adverse cardiovascular event; n, number of patients with event; SAE, serious adverse event; SE, standard error

Conclusions: In this study restricted to PsA pts with TNFi-IR, both tofacitinib doses appeared efficacious on musculoskeletal endpoints for treatment of PsA. No new safety risks were identified vs previous studies in other indications.

Acknowledgements: Previously presented at ACR 2016, to be presented at AAD 2017 and reproduced with permissions. This study was sponsored by Pfizer Inc. Editorial support was provided by AG McCluskey of CMC and was funded by Pfizer Inc.

Disclosure of Interest: D. Gladman Grant/research support from: Amgen, AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Eli Lilly, Pfizer Inc, Novartis, UCB, Consultant for: Amgen, AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Eli Lilly, Pfizer Inc, Novartis, UCB, Speakers bureau: Amgen, AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Eli Lilly, Pfizer Inc, Novartis, UCB, W. F. Rigby Grant/research support from: Amgen, Pfizer Inc, Roche, Consultant for: Bristol-Meyers Squibb, Eli Lilly, Pfizer Inc, Roche, V. Azevedo Grant/research support from: Bristol-Myers Squibb, GSK, Pfizer Inc, UCB, Consultant for: AbbVie, Bristol-Myers Squibb, Janssen, Merck Novartis, Pfizer Inc, Serono, F. Behrens Grant/research support from: Abbvie, Pfizer Inc, Roche, Chugai, Prophylix, Bioline, Novartis, Consultant for: Abbvie, Pfizer Inc, Roche, Chugai, UCB, BMS, Celgene, MSD, Novartis, Biotest, Janssen, Genzyme, Lilly, R. Blanco: None declared, A. Kaszuba Consultant for: Janssen, Eli Lilly, Novartis, E. Kudlacz Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, C. Wang Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, S. Menon Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, T. Hendrikx Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, K. Kanik Shareholder of: Pfizer Inc, Employee of: Pfizer Inc

DOI: 10.1136/annrheumdis-2017-eular.2443

THURSDAY, 15 JUNE 2017

Immunogenicity of biologics; myth or reality?

OP0203 IMPACT OF ADALIMUMAB SERUM CONCENTRATION ON EFFICACY AND ASSOCIATION BETWEEN ANTI-DRUG ANTIBODIES AND SERUM CONCENTRATION: 24 WEEK RESULTS FROM A PHASE III STUDY COMPARING SB5 (AN ADALIMUMAB BIOSIMILAR) WITH REFERENCE ADALIMUMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: SB5 has been developed as a biosimilar of reference adalimumab (ADL). The 24-week efficacy and safety results comparing SB5 and ADL were reported previously.[1] Here we report results of subgroup analyses of efficacy by adalimumab serum trough concentration (C_{trough}) and association between anti-drug antibodies (ADA) and C_{trough}.

Objectives: To investigate the impact of C_{trough} on efficacy and the association between ADA and C_{trough} in patients with rheumatoid arthritis (RA) treated with SB5 or ADL.

Methods: Patients with moderate to severe RA despite methotrexate treatment were randomly assigned to receive 40 mg of either SB5 or ADL administered subcutaneously every other week up to week 24. Blood samples were taken prior to study drug administration at weeks 0, 4, 8, 12, 16, and 24 to measure C_{trough}. The optimal C_{trough} cut-off point of adalimumab for good EULAR response at week 24 is reported to be 1.274 μg/mL.[2] Efficacy and immunogenicity were analysed in patients with C_{trough} <1.274 μg/mL and ≥1.274 μg/mL.

Results: C_{trough} was measured in 178 patients each from SB5 and ADL group. The post-dose mean C_{trough} was comparable up to week 24 for SB5 (range: 3.850 to 6.761 μg/mL) and ADL (range: 3.892 to 6.773 μg/mL). Generally, efficacy was higher in patients with C_{trough} ≥1.274 μg/mL for both SB5 and ADL but it was comparable between SB5 and ADL regardless of C_{trough} level. At week 24, the proportion of patients achieving good EULAR response, remission or low disease activity based on DAS28 was higher in patients with C_{trough} ≥1.274 μg/mL than in those with C_{trough} <1.274 μg/mL for both treatment groups (Figure). Other efficacy parameters, including ACR responses, DAS28, simplified disease activity index, and clinical disease activity index, showed similar results.

C_{trough} was higher for patients without detectable ADA, compared to those with ADA. Among patients with ADA, the proportion of patients with C_{trough} ≥1.274 μg/mL was 58.0% (29/50) for SB5 and 52.1% (25/48) for ADL. Among patients without detectable ADA, the proportion of patients with C_{trough} ≥1.274 μg/mL was 100.0% (121/121) for SB5 and 97.4% (114/117) for ADL.

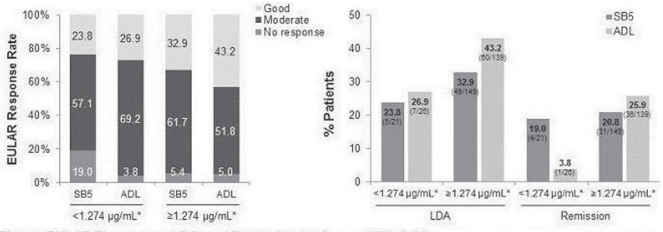

Figure. EULAR Responses, LDA, and Remission by C_{trough} at Week 24
*C_{trough} level; LDA, low disease activity
LDA defined as DAS28 ≤ 3.2 and remission defined as DAS28 < 2.6.

Conclusions: The presence of ADA reduces C_{trough} for both SB5 and ADL. In both treatment groups, almost all patients without detectable ADA, but only slightly more than half of patients with ADA, had C_{trough} ≥1.274 μg/mL at week 24. Efficacy and ADA incidence were generally comparable between SB5 and ADL regardless of C_{trough} level. However, patients with C_{trough} ≥1.274 μg/mL generally experienced greater efficacy of both SB5 and ADL than that in patients with C_{trough} <1.274 μg/mL.

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Disclosure of Interest: J. Kay Grant/research support from: Abbvie, Ardea Biosciences, Eli Lilly, Pfizer, Genentech, Roche, UCB, Consultant for: Alexion, Amgen, AbbVie, AstraZeneca, BI, BMS, Crescendo Bioscience, Eli Lilly, Epirus, Genentech, GSK, Hospira, Janssen, MSD, Novartis, Pfizer, Samsung Bioepis, Sandoz, Roche, UCB, M. Weinblatt Consultant for: Abbvie, Amgen, Samsung Bioepis, E. Keystone Grant/research support from: Abbott, Amgen, AstraZeneca, BMS, Janssen, Lilly, Novartis, Pfizer, Consultant for: Abbott, AstraZeneca, Biotest, BMS, Genentech, Janssen, Lilly, Merck, Pfizer, Samsung Bioepis, Speakers bureau: Abbott, AstraZeneca, BMS Canada, Janssen, M. Genovese Grant/research support from: Abbvie, Consultant for: Abbvie, Amgen, FkB, BI, Merck, Samsung Bioepis, J. Ghil Employee of: Samsung Bioepis Co., Ltd., S. Y. Cheong Employee of: Samsung Bioepis Co., Ltd., E. Hong Employee of: Samsung Bioepis Co., Ltd.

DOI: 10.1136/annrheumdis-2017-eular.3348