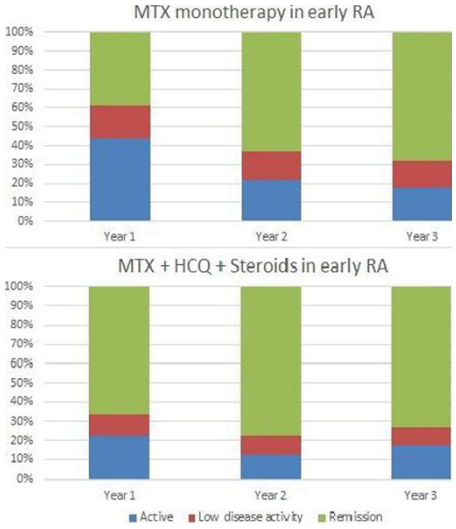

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Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.3892

OP0228

OP0229

EFFECT OF BASELINE SERUM CRP LEVELS ON CLINICAL EFFICACY IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH FILGOTINIB: POST-HOC ANALYSIS FROM TWO PHASE 2B STUDIES

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Background: Filgotinib (GLPG0634, GS-6034) is an oral, selective JAK1 inhibitor that has shown a favorable safety and efficacy profile both as add-on to methotrexate (MTX) and as monotherapy in two 24-week placebo-controlled phase 2B studies in active rheumatoid arthritis (RA) patients with inadequate response to MTX (MTX-IR)[1,2].

Objectives: To assess effect of baseline serum CRP levels on clinical efficacy in MTX-IR RA patients treated with filgotinib.

Methods: Patients were randomized in a double blind manner to placebo (PBO) or one of 3 daily doses of filgotinib (50mg, 100mg or 200mg) for 24 weeks. In the DARWIN 1 study, filgotinib on the background of MTX was evaluated as once (QD) or twice daily treatment. In the DARWIN 2 study once-daily filgotinib was assessed as monotherapy. The inclusion criterion for CRP was amended during the studies and decreased over time from 13.5 mg/L to 6.3 mg/L. This post hoc analysis included patients treated with the selected Phase 3 filgotinib doses, 100mg and 200mg QD, and PBO. Efficacy outcomes were analyzed by baseline CRP level (low: ≤9 mg/L and high: >9 mg/L, with 9mg/L as ULN).

Results: Baseline disease activity was high, with mean DAS28(CRP) scores of 5.6 and 5.7 in the low CRP subgroups for DARWIN 1 and DARWIN 2, respectively, and 6.3 in the high CRP subgroups for both studies. Mean CRP levels at baseline were elevated (16.3 - 35.3 mg/L). In both low and high CRP subgroups, patients on filgotinib 100mg or 200mg QD for 12 weeks showed efficacy over PBO, as measured by change from baseline in DAS28(CRP), CDAI and HAQ-DI, and ACR20 (Table 1). Despite slight numerical differences, baseline CRP level had no consistent effect on filgotinib efficacy, neither for endpoints including CRP (DAS28(CRP) or ACR20) nor for endpoints not including CRP (CDAI). Results were similar across both studies.

Table 1. Change from baseline in key efficacy parameters at Week 12 by CRP subgroup (mean (SE))

	DARWIN 1			DARWIN 2		
	PBO	Filgotinib 100mg QD	Filgotinib 200mg QD	PBO	Filgotinib 100mg QD	Filgotinib 200mg QD
Low CRP subgroup (≤9 mg/L)						
N	33	25	15	11	20	20
DAS28 (CRP)	-1.2 (0.30)	-2.2 (0.24)	-2.2 (0.32)	-0.9 (0.55)	-2.1 (0.33)	-2.3 (0.25)
CDAI	-18.3 (3.52)	-23.7 (2.66)	-25.1 (3.45)	-11.5 (6.19)	-25.8 (3.53)	-27.4 (3.05)
HAQ-DI	-0.21 (0.121)	-0.76 (0.133)	-0.64 (0.100)	-0.12 (0.163)	-0.74 (0.172)	-0.74 (0.158)
High CRP subgroup (>9 mg/L)						
N	53	60	71	61	50	49
DAS28	-1.2 (0.15)	-2.3 (0.19)	-2.5 (0.15)	-1.0 (0.17)	-2.0 (0.19)	-2.3 (0.19)
CDAI	-15.6 (2.04)	-23.8 (2.08)	-25.5 (1.67)	-11.7 (1.94)	-23.3 (2.38)	-24.1 (2.12)
HAQ-DI	-0.49 (0.080)	-0.61 (0.087)	-0.78 (0.076)	-0.25 (0.074)	0.65 (0.081)	-0.74 (0.086)
ACR20 by subgroup, n (%)						
Low CRP	15 (45%)	19 (76%)	10 (67%)	2 (18%)	13 (65%)	16 (80%)
High CRP	23 (43%)	35 (58%)	49 (69%)	19 (31%)	33 (66%)	34 (69%)

Conclusions: Post hoc analysis of two Phase 2B studies in MTX-IR RA patients suggests that filgotinib treatment once daily at 100mg and 200mg both on the background of MTX and as monotherapy is consistently associated with improved clinical outcomes compared to placebo, regardless of baseline CRP levels.

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Disclosure of Interest: R. Westhovens Grant/research support from: Roche, Consultant for: Galapagos, Speakers bureau: BMS, A. Kavanaugh Consultant for: Galapagos, Pfizer, AbbVie, Amgen, Celgene, Janssen, Novartis, Eli Lilly, UCB, C. Jamoul Employee of: Galapagos NV, C. Tasset Employee of: Galapagos NV, P. Harrison Employee of: Galapagos NV, A. Van der Aa Employee of: Galapagos NV

DOI: 10.1136/annrheumdis-2017-eular.5428

OP0230

THE EFFECTIVENESS OF ZOSTER VACCINE IN RA PATIENTS SUBSEQUENTLY TREATED WITH TOFACITINIB

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Background: Rheumatoid arthritis (RA) patients (pts) are at increased risk of herpes zoster (HZ). The most recent ACR guidelines of 2015 recommend vaccination in pts aged ≥50 years prior to starting biologic DMARDs or tofacitinib,[1]

an oral Janus kinase inhibitor for the treatment of RA. Live zoster vaccine (LZV) has shown 70% efficacy in immunocompetent adults aged 50–59 years and 51% efficacy in those aged ≥60 years.[2] We previously reported that pts with RA on background methotrexate who started 3 months of treatment with tofacitinib after LZV had similar varicella zoster virus (VZV)-specific immunity to placebo (PBO) pts, and their VZV immunity at Week 6 post-vaccination was comparable with healthy individuals aged ≥50 years.[3]

Objectives: To evaluate the long-term effectiveness of LZV in pts with RA via the incidence of HZ after treatment with tofacitinib for up to 27 months.

Methods: Data were analysed from a prior cohort of pts (n=100) given LZV and then randomised 2–3 weeks later to tofacitinib 5 mg twice daily (BID) or PBO for 12 weeks (A3921237 [NCT02147587]). At 14 weeks post-vaccination, pts joining the long-term extension (LTE) study ORAL Sequel (NCT00413699; study ongoing; database not locked) initiated open-label treatment with tofacitinib 5 or 10 mg BID. The incidence of HZ post-vaccination after tofacitinib exposure up to 27 months (based on an extended follow-up beyond January 2016 data snapshot) was evaluated. Among HZ cases, we analysed measures of VZV-specific immunity with average immunity after LZV.

Results: 112 pts were randomised to PBO (n=57) or tofacitinib 5 mg BID (n=55). 100 pts continued to receive tofacitinib in ORAL Sequel. Five cases (not adjudicated) of HZ occurred (#1: 202 days [219 days post-LZV], #2: 267 days [281 days post-LZV], #3: 702 days [748 days post-LZV], #4: 699 days [741 days post-LZV], #5: 446 days [544 days post-LZV] after initiation of tofacitinib. Cases #1, #2, #3 and #4 were monodermatomal; #5 involved 5 dermatomes. All cases resolved with treatment. Cases #1, #4 and #5 had undetectable ELISPOT measures at baseline and Week 6 post-vaccination, indicating a lack of VZV-specific immunity. Cases #2 and #3 responded adequately to vaccination by both immunoglobulin G (IgG) and ELISPOT measures, but had lower than average VZV IgG levels, both at baseline and at Week 6. (Table).

Table. VZV ELISPOT and IgG levels

	Case #1 (HZ 219 days after zoster vaccine)	Case #2 (HZ 281 days after zoster vaccine)	Case #3 (HZ 748 days after zoster vaccine)	Case #4 (HZ 741 days after zoster vaccine)	Case #5 (HZ 544 days after zoster vaccine)	Study A3921237 Tofacitinib 5 mg BID (N=54)
VZV IFNγ ELISPOT at baseline (SFCs/10^6 PBMCs)	25 (LOD)	41	25 (LOD)	25 (LOD)	25 (LOD)	48
VZV IFNγ ELISPOT at Week 6 (SFCs/10^6 PBMCs)	25 (LOD)	76	51	25 (LOD)	25 (LOD)	70
Change from baseline in VZV ELISPOT at Week 6 (SFC fold-rise; SFCs/10^6 PBMCs)	1.00	1.85	2.04	1.00	1.00	1.50
VZV IgG titer at baseline (gpELISA units/mL)	224	37	97	237	208	201
VZV IgG titer at Week 6 (gpELISA units/mL)	444	71	187	232	223	403
Change from baseline in VZV IgG titer at Week 6 (fold-rise; gpELISA units/mL)	1.98	1.92	1.93	0.98	1.07	2.11

Individual values shown for Cases #1–#5, mean values shown for Study A3921237.

One patient who lacked pre-existing varicella immunity developed disseminated primary varicella from the vaccine strain 16 days post-vaccination (reported previously[2]). This case was excluded from calculations for HZ.

BID, twice daily; HZ, herpes zoster; IFNγ, interferon gamma; IgG, immunoglobulin G; LOD, limit of detection; PBMC, peripheral blood mononuclear cell; SFCs, spot-forming cells; VZV, varicella zoster virus

Conclusions: LZV prior to treatment with tofacitinib is effective at boosting IgG levels and cell-mediated immunity towards VZV. No pts who developed both strong cell-mediated and humoral immunity against VZV developed HZ. Of the 5 pts who developed HZ, 3 did not have any cell-mediated response and 2 had a low humoral response.

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Acknowledgements: This study was sponsored by Pfizer Inc. The authors would like to acknowledge Lisa McNeil. Editorial support was provided by K Haines and C Evans of CMC and was funded by Pfizer Inc.

Disclosure of Interest: K. Winthrop Grant/research support from: Bristol-Myers Squibb, Pfizer Inc, Consultant for: AbbVie, Amgen, Bristol-Myers Squibb, Eli Lilly, Galapagos, Pfizer Inc, UCB, A. Wouters Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, E. Choy Grant/research support from: Pfizer Inc, Consultant for: Pfizer Inc, Speakers bureau: Pfizer Inc, C. Nduaka Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, P. Biswas Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, L. Wang Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, J. Hodge Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, I. Lazariciu Consultant for: Pfizer Inc, Employee of: Quintiles, K. Soma Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, C. Mojcik Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, W. F. Rigby Grant/research support from: Amgen, Pfizer Inc, Roche, Consultant for: Bristol-Myers Squibb, Eli Lilly, Pfizer Inc, Roche

DOI: 10.1136/annrheumdis-2017-eular.2437

LB0003 TOFACITINIB WITH AND WITHOUT METHOTREXATE VERSUS ADALIMUMAB WITH METHOTREXATE FOR THE TREATMENT OF RHEUMATOID ARTHRITIS: RESULTS FROM ORAL STRATEGY, A PHASE 3B/4 RANDOMISED TRIAL

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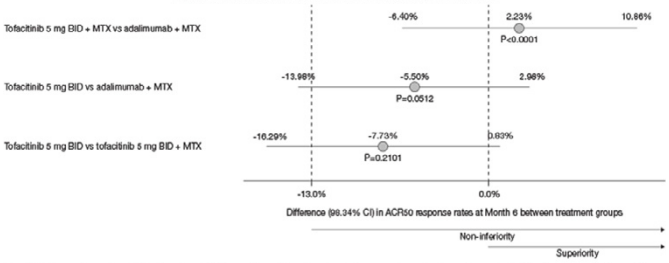
Background: Tofacitinib is an oral JAK inhibitor for the treatment of RA. There is no direct comparison of tofacitinib monotherapy vs tofacitinib +MTX in MTX inadequate responders (IR) and limited data comparing tofacitinib (±MTX) vs adalimumab (ADA) +MTX in patients (pts) with RA.

Objectives: To compare efficacy and safety of tofacitinib monotherapy, tofacitinib+MTX, and ADA+MTX in a head-to-head, non-inferiority trial in MTX-IR pts.

Methods: In this randomised, triple-dummy, active-controlled, 1-year, Phase 3b/4 trial (ORAL Strategy; NCT02187055), pts had active RA (≥4 tender/painful joints on motion and ≥4 swollen joints [28-joint count] at baseline [BL]) inadequately controlled with MTX. Pts were randomised 1:1:1 to receive tofacitinib 5 mg twice daily (5 mg mono BID), tofacitinib 5 mg BID +MTX (5 mg BID+MTX) or subcutaneous ADA 40 mg every other week +MTX (ADA+MTX); MTX dose: 15–25 mg/wk. The primary endpoint was ACR50 at Month (Mo) 6. Non-inferiority between treatments was declared if the lower bound of 98.34% two-sided confidence intervals of the difference of ACR50 response at Mo 6 was larger than -13% (based on meta analysis of ADA trials[1]), and superiority if it was larger than 0%. Other endpoints included: ACR20/50/70 and least-squares mean changes from BL in SDAI, DAS28-4(ESR) and HAQ-DI at Mos 6 and 12. Safety was assessed throughout the trial.

Results: 1146 pts were randomised and treated (5 mg mono BID: n=384; 5 mg BID+MTX: n=376; ADA+MTX: n=386). Demographics and BL disease characteristics were similar across groups. Most pts were female (82.7–83.1%), white (75.9–77.1%), with a mean age of 49.7–50.7 years, median disease duration of 5.4–6.1 years and mean HAQ-DI score of 1.6. Across groups, 80.2–81.6% of pts completed the study. ACR50 response rate at Mo 6 was 38.3% for 5 mg mono BID, 46.0% for 5 mg BID+MTX and 43.8% for ADA+MTX. Non-inferiority was demonstrated for 5 mg BID+MTX vs ADA+MTX (P<0.0001) but not for 5 mg mono BID vs ADA+MTX (P=0.0512) or 5 mg mono BID vs 5 mg BID+MTX (P=0.2101) which, although numerically different, were not statistically different (Figure). Tofacitinib monotherapy achieved the efficacy expected of an effective immunomodulator in this pt population. Secondary efficacy analyses were generally consistent with the primary analysis (Table). Adverse event (AE), serious AE and discontinuation due to AE rates were generally clinically similar across groups, though numerically fewer pts had increased alanine aminotransferase with 5 mg mono BID vs 5 mg BID+MTX or ADA+MTX.

Figure. Difference in ACR50 response rates between treatment groups at Month 6



Non-inferiority was demonstrated if the lower bound of the confidence interval was larger than -13.0%; superiority was demonstrated if the lower bound of the confidence interval was larger than 0.0%. P-values presented are from non-inferiority hypothesis testing. P-values are multiplicity-adjusted and should be compared with 0.025.

Table. Efficacy analyses and summary of safety by treatment group

	Tofacitinib 5 mg BID monotherapy (N=384)		Tofacitinib 5 mg BID + MTX (N=376)		ADA 40 mg EOW + MTX (N=386)	
EFFICACY	**Mo 6**	**Mo 12**	**Mo 6**	**Mo 12**	**Mo 6**	**Mo 12**
ACR50, n (%) – primary endpoint at Mo 6	147 (38.3)	151 (39.3)	173 (46.0)	179 (47.6)	169 (43.8)	177 (45.9)
ACR20, n (%)	249 (64.8)	237 (61.7)	275 (73.1)	264 (70.2)	274 (71.0)	261 (67.6)
ACR70, n (%)	70 (18.2)	81 (21.1)	94 (25.0)	109 (29.0)	80 (20.7)	100 (25.9)
SDAI, LSM (SE) change from BL	-23.7 (0.6)	-25.1 (0.7)	-26.6 (0.6)	-28.7 (0.7)	-25.6 (0.6)	-28.1 (0.7)
DAS28-4(ESR), LSM (SE) change from BL	-2.1 (0.1)	-2.3 (0.1)	-2.4 (0.1)	-2.7 (0.1)	-2.4 (0.1)	-2.6 (0.1)
HAQ-DI, LSM (SE) change from BL	-0.5 (0.03)	-0.6 (0.03)	-0.6 (0.03)	-0.6 (0.03)	-0.5 (0.03)	-0.6 (0.03)
SAFETY						
AEs, n (%)	226 (58.9)		231 (61.4)		253 (65.5)	
SAEs, n (%)	35 (9.1)		27 (7.2)		24 (6.2)	
Discontinuations due to AEs, n (%)	23 (6.0)		26 (6.9)		37 (9.6)	
Herpes zoster, n (%)	4 (1.0)		8 (2.1)		5 (1.3)	
Nasopharyngitis, n (%)	22 (5.7)		16 (4.3)		18 (4.7)	
Upper respiratory tract infection, n (%)	25 (6.5)		37 (9.8)		29 (7.5)	
Alanine aminotransferase increased, n (%)	8 (2.1)		23 (6.1)		26 (6.7)	
Deaths, n (%)	2 (0.5)		0 (0.0)		0 (0.0)	

Efficacy data are for the full analysis set. ACR20/50/70 used component-wise LOCF before dropout and NRI after dropout; continuous endpoint data are from a Mixed-effect Model of Repeated Measurements
Safety analysis set was identical to the full analysis set
ACR, American College of Rheumatology; ADA, adalimumab; AE, adverse event; BID, twice daily; BL, baseline; DAS; Disease Activity Score; ESR, erythrocyte sedimentation rate; EOW, every other week; HAQ-DI, Health Assessment Questionnaire–Disability Index; LOCF, last observation carried forward; LSM, least-squares mean; Mo, month; MTX, methotrexate; NRI, non-responder imputation; SAE, serious AE; SDAI, Simplified Disease Activity Index; SE, standard error

Conclusions: Tofacitinib 5 mg BID+MTX was as effective as ADA+MTX in