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SAT0217 IDENTIFICATION OF DISTINCT DISEASE ACTIVITY TRAJECTORIES IN PATIENTS WITH RHEUMATOID ARTHRITIS RECEIVING TOFACITINIB OVER 12 MONTHS

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Background: Persistence of active disease in patients (pts) with rheumatoid arthritis (RA) is highly variable following treatment initiation. One possible explanation is the existence of distinct disease activity/response trajectories influenced by baseline variables, such as sociodemographics, disease characteristics and health status.¹

Objectives: To identify distinct disease activity trajectories over 12 months and distinguishing baseline factors using pooled data from 3 randomised, controlled Phase 3 (P3) studies of tofacitinib 5 mg twice daily (BID) in pts with active RA who were inadequate responders (IR) to conventional synthetic (cs)DMARDs, with or without prior biologic (b)DMARDs (NCT00847613, NCT00856544 and NCT00853385).

Methods: Disease Activity Score in 28 joints, erythrocyte sedimentation rate (DAS28-4[ESR]) data from 3 P3 studies were pooled. A group-based trajectory modelling strategy was applied to find unique longitudinal groups of pts with similar disease activity over time.² Trajectories were latent models, fit as polynomials. The number of groups and polynomial degree of each group were specified and fit for all combinations of up to 6 groups and up to a 4th degree polynomial; a best-fit model was chosen using Bayesian information criteria.

Results: csDMARD-IR/bDMARD-naïve pts (n=677) were separated into 5 unique disease activity trajectories (figure 1); csDMARD-IR pts who received prior bDMARDs (n=149) were separated into 4 trajectories (not shown). In the bDMARD-naïve pts, Group 5 (3.8%) had the highest predicted baseline DAS (7.3) with minimal improvement (6.4) at Month 12; Group 4 (26.7%) had baseline DAS 7.0, improving to DAS 5.0 at Month 12; Groups 2 (30.4%) and 3 (36.6%) had baseline DAS 5.9 and 6.2, respectively, leading to low DAS (2.9) and moderate DAS (3.9), respectively, at Month 12; Group 1 (2.4%) had the lowest baseline DAS of 4.3, improving to remission (DAS 2.1) at Month 12 (figure 1). The 4 trajectories in csDMARD-IR pts who received prior bDMARDs were similar to Groups 2–5 in bDMARD-naïve pts. While baseline demographics were generally similar between bDMARD-naïve groups, there were statistically significant differences in baseline disease activity measures and pt-relevant outcomes between groups.

n = sample size of trajectory; d = degree of polynomial of trajectory
 Solid lines represent predicted values, with 95% CI indicated by shading. Percentages reflect the proportion of subjects in each group
 csDMARD, conventional synthetic DMARD; BID, twice-daily; CI, confidence interval; csDMARD, conventional synthetic DMARD; DAS28-4[ESR], Disease Activity Score in 28 joints, erythrocyte sedimentation rate; DMARD, disease-modifying antirheumatic drug; HDA, high disease activity; IR, inadequate responder; LDA, low disease activity; RA, rheumatoid arthritis

Figure 1. Predicted group trajectories based on DAS28-4(ESR) with 95% CI identified using group-based trajectory modeling in patients with active RA who were csDMARD-IR and bDMARD-naïve and receiving tofacitinib 5 mg BID = sample size of trajectory; d = degree of polynomial of trajectory

Conclusions: It was possible to identify heterogeneous phenotypic subgroups as distinct disease activity trajectories in csDMARD-IR pts treated with tofacitinib.

The groups were characterised by differences in disease activity and pt-relevant outcomes, including baseline pain and physical function. Very high disease activity may limit pts' ability to achieve low disease activity. The identification of distinct trajectory groups could be used to develop personalised treatment optimisation algorithms incorporating clinical and molecular phenotypes.

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SAT0218 EFFICACY AND SAFETY OF BARICITINIB IN MTX-IR PATIENTS WITH RHEUMATOID ARTHRITIS: 52 WEEK RESULTS FROM A PHASE 3 STUDY (RA-BALANCE)

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Background: Baricitinib (BARI) is an oral selective inhibitor of Janus kinase 1 (JAK1) and JAK2. In the EU and some other countries, baricitinib has been approved for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients. This abstract reports efficacy and safety results from a phase 3, double-blinded, 52-week study (RA-BALANCE) that enrolled patients (pts) in China, Argentina and Brazil (NCT02265705).

Objectives: To assess the efficacy and safety of BARI vs placebo (PBO) in the treatment of RA.

Methods: Patients with moderately to severely active RA (tender joint counts ≥ 6 & swollen joint counts ≥ 6 & hsCRP ≥ 6 mg/L) despite stable background methotrexate (MTX), were randomized 1:1 to PBO (n=145) or BARI 4-mg (n=145) once daily (QD), stratified by country and baseline joint erosion status. Background MTX was continued. Non-responders were rescued from Week 16. At Week 24, pts receiving PBO were switched to BARI 4-mg QD. ACR20 at Week 12 was the primary endpoint and there were multiple secondary endpoints e.g., assessing physical function, low disease activity and pain.

Results: The primary ACR20 response was significantly greater for BARI than PBO (58.6% vs 28.3%, $p \leq 0.001$, Table). At Weeks 12 and 24, significant improvements were seen in pts receiving BARI vs PBO for ACR20/50/70, DAS28-hsCRP, CDAI low disease activity and SDAI low disease activity, many as early as by Week 1. At Week 16, significantly less radiographic progression was seen in pts receiving BARI vs PBO and numerical improvement was observed at Week 24. At Week 12, significant improvement in HAQ-DI minimum clinically important difference ≥ 0.3 (physical function), duration of morning joint stiffness, severity of morning joint stiffness numeric rating scale (NRS), worst tiredness NRS and reduced pain (0–100 mm VAS) were seen in pts receiving BARI vs PBO.

During Weeks 0–24, treatment emergent adverse events and infections were reported in 74.5% and 42.1% of BARI pts and 62.1% and 28.3% of PBO pts, respectively. Serious adverse events were reported in 2.8% of pts in both groups. There was 1 nonserious esophageal candidiasis in the BARI group for Week 0–24. Four herpes zoster events (1 PBO, 3 BARI) were reported for Week 0–24. No major cardiovascular events, deaths, tuberculosis, venous thromboembolic

events or malignancies were reported in the study through Week 24 for PBO and through Week 52 for BARI group. No unexpected safety signals were observed.

Table 1. Study RA-BALANCE efficacy measures

	Week 12		Week 24		Week 52 [†]
	PBO (N=145)	BARI (N=145)	PBO (N=145)	BARI (N=145)	BARI (N=145)
ACR20, n (%)	41 (28.3)	85 (58.6)***	47 (32.4)	93 (64.1)***	91 (62.8)
ACR50, n (%)	12 (8.3)	44 (30.3)***	17 (11.7)	56 (38.6)***	68 (46.9)
ACR70, n (%)	2 (1.4)	14 (9.7)***	6 (4.1)	27 (18.6)***	36 (24.8)
DAS28-hsCRP ≤3.2, n (%)	13 (9.0)	36 (24.8)***	15 (10.3)	51 (35.2)***	67 (46.2)
DAS28-hsCRP <2.6, n (%)	4 (2.8)	17 (11.7)***	10 (6.9)	21 (14.5)***	48 (33.1)
CDAI ≤10, n (%)	13 (9.0)	26 (17.9)***	13 (9.0)	39 (26.9)***	67 (46.2)
SDAI ≤11, n (%)	12 (8.3)	30 (20.7)***	14 (9.7)	40 (27.6)***	67 (46.2)
HAQ-DI MCID ≥0.22, n (%)	89 (61.4)	102 (70.3)	51 (35.2)	94 (64.8)***	89 (61.4)
HAQ-DI MCID ≥0.3, n (%)	67 (46.2)	90 (62.1)***	45 (31.0)	85 (58.6)***	83 (57.2)
LS mean Δ Patient's Assessment of Pain (0-100 mm VAS) [‡]	-17.7	-31***	-20.1	-34.8***	-40.2
LS mean Δ Patient's Global Assessment of Disease Activity (0-100 mm VAS) [‡]	-20.0	-31.3***	-18.5	-33.4***	-37.8

PBO, placebo; BARI, baricitinib; MCID, minimum clinically important difference; VAS, visual analogue scale.
[†]Patients received stable background MTX throughout the study. Data are % patients (NRI), unless otherwise stated.
[‡]Data are least squares (LS) mean change from baseline; [†]initially randomized to baricitinib.
^{*}p<0.05, ^{**}p<0.01, ^{***}p<0.001 vs PBO.

Conclusions: Compared to PBO, BARI provided significant improvements in control of signs and symptoms, including pain and physical function with an acceptable safety profile.

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SAT0219

UPADACITINIB IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS AND INADEQUATE RESPONSE OR INTOLERANCE TO BIOLOGICAL DMARDS: A PHASE 3 RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY OF A SELECTIVE JAK1 INHIBITOR

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Background: Upadacitinib (UPA), an oral, selective JAK1 inhibitor was effective in ph 2 trials in rheumatoid arthritis (RA) pts with inadequate response (IR)/intolerance to csDMARDs and bDMARDs.

Objectives: To evaluate safety and efficacy of UPA in bDMARD-IR pts on stable background csDMARDs.

Methods: Pts with active RA (TJC≥6, SJC≥6; hsCRP≥3 mg/L) were randomized 2:2:1:1 to receive UPA 15 mg or 30 mg once daily (QD) or PBO for 12 wks followed by UPA 15 mg or 30 mg QD starting at Wk 12. The primary endpoints were the proportion of pts achieving ACR20 (for FDA) and the proportion achieving DAS28CRP≤3.2 (for EMA) at Wk 12 (NRI).

Results: Of 499 randomized pts, 498 received study drug; 451 (90.6%) and 419 (84.1%) completed Wks 12 and 24 respectively. BL disease characteristics

indicated long-standing severe, refractory disease: (means) duration since diagnosis 13 yrs; DAS28CRP, 5.8; TJC68, 27.9; SJC66, 16.8; 53% experienced ≥2 prior bDMARDs. At Wk 12, more pts (p<0.001) on UPA 15 and 30 vs PBO achieved the primary endpoints (ACR20: 64.6% and 56.4% vs 28.4%; DAS28CRP≤3.2: 43.3% and 42.4% vs 14.2%) and other secondary endpoints (Table). Among pts with IR to multiple bDMARDs/MOAs, and pts with lack of efficacy for α-IL-6, the proportions achieving ACR20 on UPA vs PBO were comparable to the overall treated population. By Wk 1, more pts achieved ACR20 on UPA 15 and 30 vs PBO (27.4% and 24.8% vs 10.7%, p<0.001). At Wk 12, significant improvements were observed on UPA 15 and 30 vs PBO for HAQ-DI (LSM change -0.39 and -0.42 vs -0.17, p<0.001). At Wk 24, responses were similar or greater for pts originally on UPA and comparable for pts who switched to UPA after 12 wks of PBO.

Up to wk 12, the frequency of AEs was comparable for PBO and UPA 15, but higher for UPA 30 (table 1). Overall AE rates (E/100 PY) through Wk 24 for UPA 30 were similar or slightly higher vs UPA 15; more AEs led to study drug discontinuation in UPA 30. Occurrence of infections was similar in all arms, but there were more serious infections and herpes zoster cases in UPA 30. Malignancies were reported in 3 pts over 12 wks with 1 additional case through Wk 24. Through Wk 12, pulmonary embolism (PE) was reported in 2 pts (1 each on UPA 15 and 30), none with DVT; through Wk 24, PE were reported in 4 more pts (UPA 15: 3, 1 of whom also had a DVT; UPA 30:1). All had risk factors for DVT/PE. 2 deaths were reported (UPA30: 1 before Wk 12; UPA 15:1 after Wk12).

Efficacy Measures [†] ; Percentage of Patients with a Response	Week 12			Week 24			
	PBO N=169	UPA 15 N=164	UPA 30 N=165	PBO→ UPA 15 N=85	PBO→ UPA 30 N=84	UPA 15 N=164	UPA 30 N=165
ACR20	28.4	64.6***	56.4***	61.2	60.1	61.6	59.4
DAS28-CRP≤3.2	14.2	43.3***	42.4***	38.8	36.0	52.4	51.5
ACR50	11.8	34.1***	35.8***	35.3	38.1	42.7	43.0
ACR70	6.5	11.6	23.0***	22.4	21.4	22.0	24.2
CDAI ≤10	14.2	31.7***	33.9***	34.1	30.6	47.0	43.6
CDAI ≤8	4.7	7.9	11.5*	12.9	14.3	10.4	15.2
DAS28-CRP <2.6	9.5	28.7***	23.6***	28.2	34.5	32.3	34.5
ACR20 in pts who failed ≥2 bDMARDs and/or ≥3 MOA	23.1	70.8	50.0	-	-	-	-
ACR20 in pts with LoE for anti-IL6	20.0	55.6	58.1	-	-	-	-
Summary of AEs, n (%)							
	Week 0-12			Week 12-24			
	PBO N=169	UPA 15 N=164	UPA 30 N=165	PBO→ UPA 15 N=72	PBO→ UPA 30 N=75	UPA 15 N=156	UPA 30 N=168
AEs	95 (56.2)	91 (55.5)	111 (67.3)	30 (41.7)	50 (66.7)	82 (52.6)	83 (56.1)
AE Leading To D/C	9 (5.3)	4 (2.4)	15 (9.1)	2 (2.8)	3 (4.0)	5 (3.2)	5 (3.4)
Serious AEs	0	8 (4.9)	12 (7.3)	5 (6.9)	5 (6.7)	5 (3.2)	5 (3.4)
Patients with Adverse Events of Special Interest, n (%)							
Infection	51 (30.2)	54 (32.9)	55 (33.3)	16 (22.2)	31 (41.3)	43 (27.6)	47 (31.8)
- Serious Infection	0	1 (0.6)	4 (2.4)	2 (2.8)	1 (1.3)	1 (0.6)	2 (1.4)
- Opportunistic Infection [‡]	0	1 (0.6)	2 (1.2)	0	0	0	1 (0.7)
- Herpes Zoster [‡]	1 (0.6)	1 (0.6)	4 (2.4)	0	1 (1.3)	2 (1.3)	2 (1.4)
- Tuberculosis	0	0	0	0	0	0	0
Malignancy (exc NMSC) [‡]	0	1 (0.6)	2 (1.2)	0	0	1 (0.6)	0
NMSC	0	0	0	0	0	0	0
Lymphoma	0	0	0	0	0	0	0
Hepatic Disorder	2 (1.2)	2 (1.2)	3 (1.8)	0	2 (2.7)	4 (2.6)	4 (2.7)
GI Perforation	0	0	0	0	0	0	1 (0.7)
PE	0	1 (0.6)	1 (0.6)	2 (2.8) [§]	1 (1.3)	1 (0.6)	0
CV Events adjudicated [§]	0	1 (0.6)	0	0	1 (1.3)	2 (1.3)	0
Deaths [‡]	0	0	1 (0.6)	0	0	1 (0.6)	0

D/C, discontinuation; LoE, lack of efficacy; NMSC, non-melanoma skin cancer; PE, pulmonary embolism; GI, gastrointestinal; CV, cardiovascular

[†]Opportunistic infections: oral candidiasis, one case of mucocutaneous candidiasis

[‡]Herpes Zoster: most were mild and all but one were single dermatome; 2 serious cases

[§]Malignancies through Wk 12-UPA 15: 1 malignant melanoma; UPA 30: 2 pts with prostate cancer. Wk 12-24, UPA 15: 1 pt with bladder cancer

[§]1 pt also had DVT; [§]Adjudicated CV events through Wk 12-UPA 15 mg: 1 pt with ischemic stroke. Wk 12-24, UPA 15: 1 pt with CV procedure, 1 pt with cardiac arrest adjudicated to undetermined/unknown cause of death; UPA 30: 1 pt with myocardial infarction; Deaths through Wk 12-UPA 30: 1 due to cardiac failure & PE. Wk12-24, UPA 15:1 unwitnessed death adjudicated as undetermined/unknown cause of death

Conclusions: In this treatment-refractory, bDMARD-IR RA population, rapid, significant improvements were observed with UPA at both doses vs PBO during 12 wks of treatment, and maintained through 24 wks. Overall safety was consistent with ph2 and other ph3 studies with UPA. The rates of PE and DVT observed in this study have not been reported for the other ph3 studies that have been unblinded to date. Overall data from the ph3 program will allow a comprehensive evaluation of the benefit:risk profile of UPA in RA.

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