Table 1. Proportions and Rates of LDA/sustained LDA by Treatment Group

			csDMARD-IR pts[a]			bDMARD-IR pts[b]		
Pts achieving CDAI ≤10			PBO	Bari 2 mg	Bari 4 mg	PBO	Bari 2 mg	Bari 4 mg
Time	# of visits	Category	N=228	N=229	N=227	N=176	N=174	N=177
Original study (24 wks)	≥1	%	44.7	60.7	65.6	26.7	39.7	48.6
		i-rate	12.06	18.79	21.50	6.36	10.08	13.38
	≥2	%	32.0	48.5	52.9	15.9	28.7	35.6
		i-rate	7.32	12.11	13.95	3.50	6.42	8.29
Original study + LTE	≥1	%	56.6	70.7	71.4	39.8	47.7	53.1
		i-rate	4.93	8.14	9.40	2.85	3.81	4.85
	≥2	%	48.2	61.6	61.2	27.8	39.1	44.1
		i-rate	3.41	5.33	5.78	1.66	2.57	3.13

Pts were defined as responders if they met the response criterion within the stated time frame, prior to any rescue or discontinuation. % = percent of pts meeting response criteria; ≥2 = at least 2 consecutive visits with CDAI ≤10; i-rate = exposure-adjusted incidence rate (% pts/month); N = number of randomised and treated pts; PBO = placebo treated pts in original study, Bari 4 mg treated pts in LTE. [a]RA-BUILD, [b]RA-BEACON.

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FRI0090 ANALYSIS OF NEUTROPHILS, LYMPHOCYTES, AND PLATELETS IN POOLED PHASE 2 AND PHASE 3 STUDIES OF BARICITINIB FOR RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is associated with increased neutrophil levels[1] and platelet[2] counts and decreased lymphocyte levels.[1,3] Baricitinib (bari) is a selective and reversible Janus kinase (JAK)1/JAK2 inhibitor in development for patients (pts) with moderate to severe RA.[4]

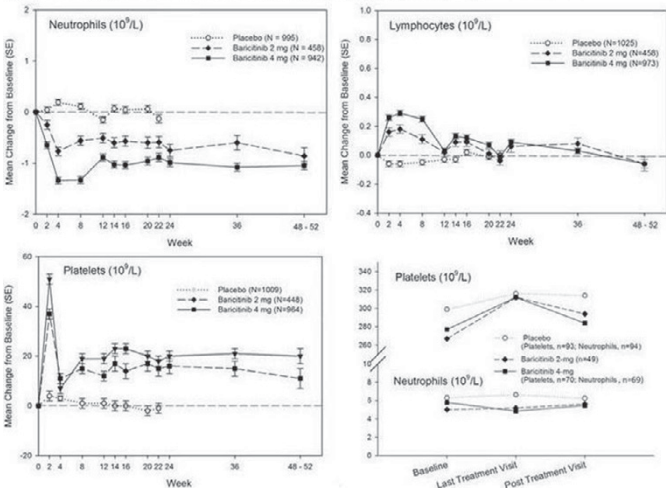
Objectives: To characterize changes in absolute neutrophil counts (ANC), absolute leukocyte counts (ALC), and platelet counts following once daily oral administration of bari.

Methods: Data were pooled from 6 placebo-controlled phase 2 and 3 studies of bari (2 and 4 mg). Changes in ANC, ALC, and platelets were evaluated for up to 52 weeks (wks) including data from a long-term extension study. Reversibility was evaluated in a subgroup of pts who discontinued treatment by wk 24.

Results: Mean ANC decreased within 1 month of administration of bari, followed by stabilization and an increase to baseline after treatment discontinuation (Figure 1). ANC <1000 cells/mm^3 were reported in <1% of pts, and 2 bari-treated pts (0.1%) reported permanent discontinuation of study drug due to neutropenia. Incidence of neutropenia was not associated with higher risk of overall or serious infections (Table 1).

Mean ALC increased within 1 month of bari administration and then decreased to baseline level in wks 12 to 24 (Figure 1). Lymphopenia appeared to be associated with slightly higher rate of overall infections (Table 1).

Figure 1: Longitudinal Profiles of Neutrophils, Lymphocytes, and Platelets



Mean platelet counts increased to peak at wk 2, returned towards baseline, stabilized over time, and returned to baseline after treatment discontinuation (Figure 1). Permanent study drug discontinuations from thrombocytosis occurred in 2 bari-treated pts (0.1%). No clear association between platelet increase and thromboembolic events was observed.

Conclusions: Treatment with bari was associated with a decrease in ANC and an increase in ALC and platelets, which stabilized over time and returned to baseline with prolonged treatment (ALC) or treatment discontinuation (ANC and platelets). No associations between ANC decrease and infections or between thrombocytosis and thromboembolic events were observed.

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FRI0091 PATIENT-PROVIDER DISCORDANCE MAY BE ASSOCIATED WITH INCREASED RISK OF SUBSEQUENT FLARES IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Patient-provider discordance in assessment of disease status has been linked to lower patient satisfaction with potential implications on patient compliance and outcomes of care. Global assessment (GA) of disease activity in rheumatoid arthritis (RA) is discordant between patient and provider in about one third of cases. Prospective studies evaluating the implications of patient-provider discordance on RA disease course are lacking.

Abstract FRI0090 – Table 1. Infection by Worst Neutropenia and Lymphopenia CTCAE Grade in Placebo-Controlled Period up to Week 24

	Placebo			Baricitinib 4-mg		
	Total Pts	Pts (%) with Overall Infection	Pts (%) with Serious Infection	Total Pts	Pts (%) with Overall Infection	Pts (%) with Serious Infection
Neutropenia CTCAE Grade						
0 (≥2x10^9 cells/L)	985	279 (28.3)	16 (1.6)	853	313 (36.7)	13 (1.5)
1 (<2 and ≥1.5x10^9 cells/L)	34	10 (29.4)	0	74	32 (43.2)	1 (1.4)
2 (<1.5 and ≥1.0x10^9 cells/L)	9	0	0	27	11 (40.7)	0
3 (<1.0 and ≥0.5x10^9 cells/L)	1	1 (100.0)[1]	0	3	1 (33.3)[2]	0
4 (<0.5x10^9 cells/L)	0	0	0	0	0	0
Lymphopenia CTCAE Grade						
0 (≥1.1x10^{9}cells/L)	710	201 (28.3)	12 (1.7)	704	246 (34.9)	8 (1.1)
1 (<1.1 and ≥0.8x10^9 cells/L)	233	65 (27.9)	2 (0.9)	205	81 (39.5)	2 (1.0)
2 (<0.8 and ≥0.5x10^9 cells/L)	103	30 (29.1)	1 (1.0)	71	31 (43.7)	3 (4.2)
3 (<0.5 and ≥0.2x10^9 cells/L)	13	3 (23.1)	1 (7.7)	8	4 (50.0)	1 (12.5)
4 (<0.2x10^9 cells/L)	0	0	0	0	0	0

CTCAE=common terminology criteria for adverse events; pts = patients. [1]Upper respiratory tract; [2]Pharyngitis.

Objectives: We aimed to assess the occurrence and severity of patient-reported flares of RA in patients who had discordant estimates of RA disease activity with their provider at baseline compared to those who had concordant estimates.
Methods: Patients with RA (age≥18 years; 2010 ACR criteria) participating in an ongoing prospective study underwent clinical evaluation by a rheumatology provider (MD/NP/PA) at baseline with assessment of tender (TJC28) and swollen joint counts (SJC28), C-reactive protein (CRP), patient and provider GA of RA disease activity, disease activity score (DAS28-CRP), clinical disease activity index (CDAI), completion of Health Assessment Questionnaire-II (HAQ-II), visual analogue scales (0–100 mm) for pain (VAS-pain) and the flare-assessment in RA (FLARE) questionnaire. Patient-provider discordance was defined as ≥25 mm difference in GA between the patient and provider. Occurrence of patient-reported RA flares was compared between patients with and without discordance in GA. Flare was defined based on patient report when answered "Yes" to the question "Are you having a flare of your RA at this time?" or a predefined cut-off ≥2.5 on FLARE questionnaire (1,2).
Results: The study included 55 patients with RA (mean age 60.7 years; 65% female), of whom 40 had GA concordant with their provider and 15 had higher GA than their provider. Table 1 summarizes patient characteristics depending on GA discordance at baseline. Patients with discordance were similar in age, sex, duration of follow-up, had similar TJC28 and SJC28, but had significantly higher HAQ-II, VAS-pain, CRP, DAS28, CDAI, provider GA and FLARE scores at baseline vs patients with concordant GA. During the follow up, patients with discordance had significantly higher numbers and rates of flares, and tended to have more visits with discordant GAs compared to patients who had concordant GA with their provider at baseline.

Table. Characteristics of patients with rheumatoid arthritis (RA) depending on the presence of discordance in general assessment of RA disease activity

Characteristics*	Patients with concordant baseline GA (n=40)	Patients with discordantly high baseline GA (n=15)	p-value
Age	59.5 (10.3)	64.0 (7.4)	0.22
Sex, female	26 (65%)	10 (67%)	0.91
Duration of follow up, months	6.5 (4.0)	8.2 (5.8)	0.37
TJC28, baseline	2.0 (4.2)	2.6 (6.2)	0.91
SJC28, baseline	0.6 (1.5)	1.1 (2.4)	0.92
HAQ-II, baseline	0.5 (0.5)	1.0 (0.5)	0.001
VAS pain, baseline	26 (27)	54 (14)	<0.001
CRP, mg/L	7.0 (12.8)	10.5 (10.6)	0.020
DAS-28 CRP, baseline	2.3 (1.2)	3.0 (1.0)	0.006
CDAI, baseline	6.2 (9.0)	10.9 (8.5)	0.002
Patient GA, baseline	20.7 (23.1)	56.5 (12.6)	<0.001
Provider GA, baseline	15.0 (22.5)	17.0 (11.3)	0.044
Patient-reported flare, baseline	6 (15%)	5 (33%)	0.13
Number of patient-reported flares during the follow up	0.6 (0.9)	2.0 (2.9)	0.010
Flare rate based on patient-reported flares (% of subsequent months with flare)	8.4 (15.1%)	25.4 (29.3%)	0.009
FLARE score, baseline			
- Overall FLARE	1.9 (2.6)	4.4 (2.6)	0.002
- Systemic subscale	1.6 (2.5)	4.3 (2.9)	0.001
- Joint subscale	2.3 (2.8)	4.5 (2.7)	0.006
Number of FLARE questionnaire reports scoring ≥2.5 during the follow up			
- Overall FLARE	0.7 (1.2)	3.2 (3.6)	0.001
- Systemic subscale	0.6 (1.0)	2.5 (3.3)	0.002
- Joint subscale	1.1 (1.5)	3.4 (3.5)	0.007
Number of visits with discordant GA during the follow up	0.1 (0.2)	0.3 (0.6)	0.076
Rate of discordance (% of subsequent months with discordance)	0.5 (2.5%)	2.9 (6.2%)	0.070

*All measures are shown as mean (standard deviation) or as number (%)

Conclusions: Patients with patient-provider discordance at baseline were more likely to report flares of RA during follow-up. Patient-provider discordance tended to persist at follow-up visits. Disease activity assessments with patient-reported component (i.e., HAQ-II, VAS-pain, DAS28, CDAI, FLARE score), as well as CRP and provider GA, but not joint counts, were higher at baseline in patients with discordance. Consideration of the results of clinical and laboratory assessment in combination with patient-reported measures of RA disease activity may be important to inform future risk of flares in patients with RA and help improve patient-provider communication and shared decision making.
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FRI0092 EFFECTS OF BARICITINIB ON HAEMOGLOBIN AND RELATED LABORATORY PARAMETERS IN RHEUMATOID ARTHRITIS PATIENTS

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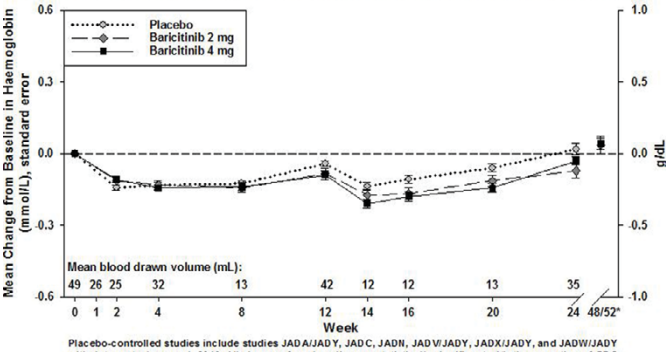
Background: Baricitinib (bari), a selective, transient and reversible inhibitor of Janus kinase (JAK)1 and JAK2, improved signs and symptoms of active rheumatoid arthritis (RA) in multiple phase 3 studies. Since erythropoietin (EPO) stimulates erythrocyte production via the JAK2 signaling pathway, haemoglobin (Hgb) and other haematologic parameters were thoroughly evaluated in the bari RA clinical development program.
Objectives: To evaluate baseline and subsequent changes in Hgb and related laboratory parameters in RA patients (pts) treated with bari (2 or 4 mg once daily), placebo (PBO), or active comparator (methotrexate [MTX] or adalimumab [ADA]).
Methods: Blood samples were analyzed at baseline and at each study visit for complete blood count, with more extensive phlebotomy at baseline (Wk 0) and Wks 12, 24, and 52 (Figure 1). Data were aggregated from completed Phase 2 and 3 RA studies and one ongoing long-term extension study. EPO and reticulocyte (RET) data were collected from a Phase 2 RA study in Japan.
Results: Hgb levels below the gender-adjusted lower limit of normal (LLN) were often observed at baseline (25%). Small declines in Hgb were observed at Wk 2 and again at Wk 14 in bari (2 and 4 mg) and PBO-treated RA pts consistent with the volume and frequency of phlebotomy (Figure 1). Initial decreases in Hgb were accompanied by declines in RET counts in bari-treated RA pts. Subsequent increases in Hgb were associated with increases in RET after Wk 8 and statistically significant dose-dependent increases vs. PBO in total iron (Fe), total iron binding capacity (TIBC) and EPO. Treatment-emergent (TE) shifts in Hgb from normal to <LLN were very common in all groups without differences across groups except for ADA, which was associated with a lower incidence of TE low Hgb. TE Common Terminology Criteria for Adverse Events (CTCAE) shifts in Hgb from <grade 3 to ≥grade 3 (<4.9 and ≥4.0 mmol/L; <8.0g/dL and ≥6.5g/dL) were uncommon and occurred in similar proportions of RA pts across groups (Table 1). Permanent discontinuation of study drug due to CTCAE ≥grade 3 Hgb shifts was uncommon (0.2%).

Figure 1. Mean Change from Baseline in Haemoglobin Over 52 Weeks in Placebo-Controlled Studies



Placebo-controlled studies include studies JADA/JADY, JADC, JADN, JADV/JADY, JADX/JADY, and JADW/JADY with data up to January 1, 2016. All changes from baseline are statistically significant with the exception of PBO and BARI 4-mg at Week 24 and BARI 2-mg and 4-mg at Week 52.
*Last blood draw prior to Week 48/52 data was up to 12 weeks prior.

Table 1. Summary of Treatment-Emergent Changes in Haemoglobin

	Treatment-emergent abnormally low, n/NAR (%)	Shift from <grade 3 to ≥grade 3[a], n/NAR (%)
RA bari PBO-controlled studies through Week 24[b]		
PBO (N=1070) [PYE=393.8]	193/747 (25.8)	2/1059 (0.2)
Bari 4 mg (N=997) [PYE=409.4]	204/696 (29.3)	1/988 (0.1)
RA bari studies containing 2- and 4-mg doses[c,d]		
Bari 2 mg (N=479) [PYE=434.8]	106/343 (30.9)	3/478 (0.6)
BARI 4 mg (N=479) [PYE=477.7]	126/360 (35.0)	1/474 (0.2)
All RA bari studies[d]		
N=3464 [PYE=4214.1]	829/2451 (33.8)	16/3407 (0.5)

Abbreviations Bari=baricitinib; NAR=number at risk; PYE=patient years of exposure; RA=rheumatoid arthritis.
[a]Grade 3 is <4.9 and ≥4 mmol/L (<8.0 and ≥6.5 g/dL).
[b]Includes Studies JADA, JADC, JADN, JADV, JADW and JADX.
[c]Includes Studies JADA/JADY, JADN, JADW/JADY and JADX/JADY.
[d]Includes data up to August 10, 2015.

Conclusions: The proportions of RA pts with TE abnormally low Hgb did not differ significantly between bari and PBO. Reductions in Hgb, including to ≥grade 3, were generally not associated with adverse outcomes. Despite concerns about the impact of JAK2 inhibition on EPO signaling, following initial declines incident to phlebotomy, dose-dependent increases in EPO, Fe, and TIBC with return to baseline in RET and Hgb were observed with bari. This suggests that homeostatic mechanisms counterbalance the pharmacologic effect of JAK inhibition on EPO signaling and that bari treatment enhances iron utilisation markers associated with anaemia of chronic disease.
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