Patient-Reported Outcome Response and Safety Profile in Patients with Moderately to Severely Active Rheumatoid Arthritis Treated With Baricitinib 2-mg

Dalton Sholter[1], Jianmin Wu[2], Bochao Jia[2], Hong Zhang[3], Kirstin Griffing[2], Amanda K. Quebe[2], Julie Birt[2], Paulo Jorge Simoes Reis[2], Huaxiang Liu[4], Clifton O. Bingham III[5]

[1]Division of Rheumatology in the Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada; [2]Eli Lilly and Company, Indianapolis, IN, USA; [3]TechData Service, King of Prussia, PA, USA; [4]Qilu Hospital of Shandong University, Jinan, China; [5]Johns Hopkins Arthritis Center, Baltimore, MD, USA

BACKGROUND

- Baricitinib, an oral, selective Janus kinase (JAK)1/JAK2 inhibitor, is approved in more than 70 countries for the treatment of moderately to severely active rheumatoid arthritis (RA) in adults
- In the Phase 3 RA-BUILD (NCT01721057) and RA-BEACON (NCT01721044) trials, baricitinib was associated with improved patient-reported outcomes (PROs) compared to placebo in patients who were inadequate responders (IRs) to:
  - Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs)[1,2]
  - ≥1 tumor necrosis factor inhibitor or other biologic DMARDs (bDMARDs)[3,4]

OBJECTIVES

- To describe the PRO response of baricitinib 2-mg vs. placebo at Week 24 among patients who achieved minimally clinically important difference (MCID) improvement in PROs at Week 4 and Week 12
- To describe the long-term safety of baricitinib 2-mg vs. placebo

KEY RESULTS

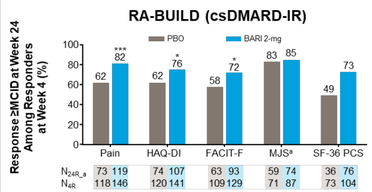
Observed Proportions of Patients Reported Improvement ≥MCID at Weeks 4, 12, and 24

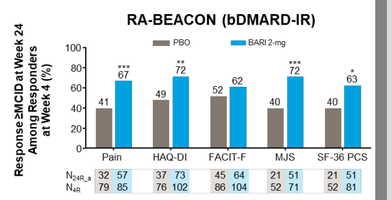
	RA-BUILD (csDMARD-IR)					
	Week 4		Week 12		Week 24	
%	PBO	BARI 2-mg	PBO	BARI 2-mg	PBO	BARI 2-mg
Pain	56.5	64.9	60.9	76.5	72.8	80.9
HAQ-DI	57.4	63.2	62.6	74.9	69.9	81.2
FACIT-F	50.7	57.1	65.7	67.4	69.3	73.8
MJS[a]	44.4	50.0	54.6	59.9	-	-
SF-36 PCS	33.8	45.8	45.1	59.6	55.0	69.4

	RA-BEACON (bDMARD-IR)					
	Week 4		Week 12		Week 24	
%	PBO	BARI 2-mg	PBO	BARI 2-mg	PBO	BARI 2-mg
Pain	47.6	51.5	46.3	60.9	63.2	71.4
HAQ-DI	45.5	61.1	50.0	64.6	59.8	76.3
FACIT-F	52.1	61.9	56.7	69.8	75.9	76.3
MJS	38.2	48.0	40.8	57.4	55.1	66.0
SF-36 PCS	31.5	48.2	37.3	54.1	42.5	59.6

[a] MJS duration in RA-BUILD was measured up to Week 12

Patients Maintaining Improvement ≥MCID From Week 4 to Week 24



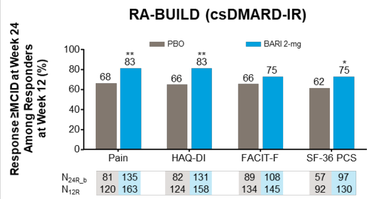


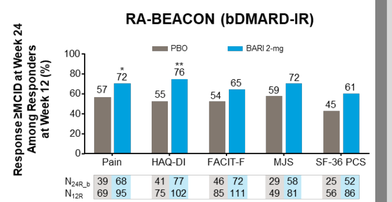
* p≤0.05, ** p≤0.01, *** p≤0.001 vs. PBO

[a] MJS duration in RA-BUILD was measured up to Week 12

N_{4R}=number of MCID responders at Week 4; N_{24R_a}=number of continued MCID responders from Week 4 to Week 24

Patients Maintaining Improvement ≥MCID From Week 12 to Week 24





* p≤0.05, ** p≤0.01 vs. PBO

N_{12R}=number of MCID responders at Week 12; N_{24R_b}=number of continued MCID responders from Week 12 to Week 24

Safety Summary[5]

	PBO-Controlled (to Week 24)		RA-BEYOND (LTE)
	PBO (N=551) PYE=188.9	BARI 2-mg (N=479) PYE=185.8	BARI 2-mg Extended[a] (N=479) PYE=675.6
≥1 AE, n (EAIR)[b]			
TEAE	348 (184.2)	316 (170.1)	378 (55.9)
SAE including death	28 (14.8)	18 (9.7)	62 (9.2)
Temporary interruption due to an AE	42 (22.2)	50 (26.9)	108 (16.0)
Permanent discontinuation due to an AE	21 (11.1)	20 (10.8)	30 (4.4)
Death	2 (1.0)	0	1 (0.2)[c]
Malignancy, n (incidence rates)[d]			
Malignancy excluding NMSC	0	1 (0.5)	3 (0.4)
			12 (0.8)[RAN]
Lymphoma	0	0	0
NMSC	0	0	2 (0.3)
Infection, n (incidence rates)[d]			
Serious infection	10 (5.1)	8 (4.2)	21 (3.1)
Herpes zoster infection	2 (1.0)	6 (3.1)	18 (2.7)
Tuberculosis	0	0	0
OI excluding tuberculosis	1 (0.6)	0	2 (0.3)
MACE, n (incidence rates)[d,e]	2 (1.2)	0	2 (0.3)
DVT/PE, n (incidence rates)[d]	0	0	4 (0.6)
DVT	0	0	4 (0.6)
PE	0	0	1 (0.2)
GI perforation, n (incidence rates)[b]	0	0	0

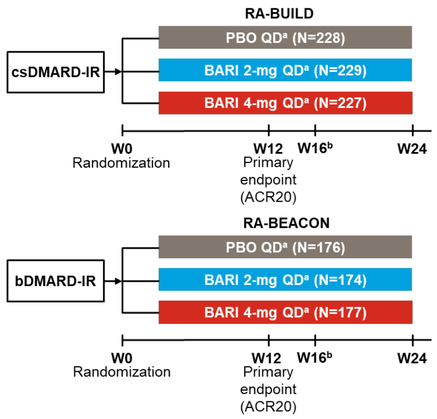
[a] Patients with active RA randomized to BARI 2-mg in 2 Phase 2 and 2 Phase 3 trials (RA-BUILD and RA-BEACON), including those who responded inadequately to csDMARDs and bDMARDs, entered RA-BEYOND with a follow-up time up to 6.9 years[5]; [b] EAIR were calculated as the number of unique patients with an event per 100 PYE (exposure time not censored at event); [c] AEs leading to death: natural causes; [d] Incidence rates were calculated as the number of unique patients with an event per 100 PYE (exposure time up to the event for patients with the event and exposure time up to the end of observation for patients without the event, up to dose change); [e] Potential cardiovascular AEs from the Phase 3 trials and LTE, identified by investigators or according to a predefined list of event terms, were adjudicated by an independent, external Clinical Endpoint Committee who remained blinded to treatment assignments

CONCLUSIONS

- Early clinically meaningful improvements in pain, physical function, fatigue, MJS duration, and quality of life (physical component) continued to Week 24 with baricitinib 2-mg vs. placebo in patients with active RA
- A higher proportion of patients on baricitinib 2-mg who showed MCID response at Weeks 4 or 12 continued clinically meaningful responses in PROs at Week 24 than the control group in csDMARD-IR and bDMARD-IR patients
- After 6.9 years of exposure, the safety profile of baricitinib 2-mg was consistent with that determined in earlier analyses,[5] and no new safety signals were identified

METHODS

Study Design



[a] Concomitant treatment with stable doses of csDMARDs, NSAIDs, analgesics, and/or glucocorticoids (≤10 mg of prednisone or the equivalent per day) was permitted; [b] At W16, IRs (TJC and SJC not improved by ≥20% from baseline at W14 and W16) were rescued to BARI 4-mg QD

ABBREVIATIONS

ACR20=American College of Rheumatology ≥20% response; AE=adverse event; BARI=baricitinib; bDMARD=biologic disease-modifying anti-rheumatic drug; CRP=C-reactive protein; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; DVT/PE=deep vein thrombosis and/or pulmonary embolism; EAIR=exposure-adjusted incidence rates per 100 patient-years; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; GI=gastrointestinal; HAQ-DI=Health Assessment Questionnaire-Disability Index; IR=inadequate responder; LTE=Long-term Extension; MACE=major adverse cardiovascular event; MCID=minimally clinically important difference; MJS=morning joint stiffness; N=number of patients in modified Intent-to-Treat population; N_{4R}=number of MCID responders at Week 4; N_{12R}=number of MCID responders at Week 12; N_{24R_a}=number of continued MCID responders from Week 4 to Week 24; N_{24R_b}=number of continued MCID responders from Week 12 to Week 24; NA=not applicable; NMSC=non-melanoma skin cancer; NSAID=non-steroidal anti-inflammatory drug; OI=opportunistic infection; PBO=placebo; PYE=patient-years of exposure; QD=once daily; RA=rheumatoid arthritis; RAN=as-randomized; SF-36 PCS=Short Form-36 Physical Component Score; SAE=serious adverse event; SJC=swollen joint count; TEAE=treatment-emergent adverse event; TJC=tender joint count; TNFi=tumor necrosis factor inhibitor; VAS=visual analog scale; W=Week

Key Eligibility Criteria

	RA-BUILD (csDMARD-IR)	RA-BEACON (bDMARD-IR)
Inclusion		
Age ≥18 years	✓	✓
≥6/68 TJC, ≥6/66 SJC	✓	✓
High-sensitivity CRP	≥3.6 mg/L	≥3 mg/L
Inadequate response or intolerance to ≥1 prior csDMARD	✓	NA
Prior treatment with ≥1 TNFi, discontinued due to an insufficient response (≥3 months on therapy) or intolerance[a]	NA	✓
Stable background csDMARD[b]	✓	✓
Exclusion		
Prior bDMARD use	✓	NA

[a] Previous use of other bDMARDs was permitted (all must have been discontinued ≥4 weeks before randomization [≥6 months for rituximab]); [b] Patients without background csDMARDs could enroll if the last csDMARD dose was given >4 weeks before study entry

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2. Emery P, et al. *RMD Open.* 2017;3:e000410.
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Assessments: PRO Responses

- **Pain visual analog scale**
  - Scores range from 0-100 mm, with higher scores indicating more pain (MCID: defined as ≥10-mm reduction)[4]
- **Health Assessment Questionnaire-Disability Index (HAQ-DI)**
  - Scores range from 0-3, with lower scores indicating better physical function and, thus, less disability (MCID: defined as ≥0.22-unit reduction)
- **Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)**
  - Scores range from 0-52, with higher scores indicating less fatigue (MCID: defined as ≥3.56-point improvement)
- **Duration of Morning Joint Stiffness (MJS)**
  - In RA-BUILD, patients reported the duration of MJS in daily electronic diaries, and the average value across the 7 days preceding each visit was calculated
  - In RA-BEACON, the duration of MJS was reported by patients as the length of time (minutes) that MJS lasted on the day prior to the study visit
  - MCID: defined as ≥30-minute improvement
- **Short Form-36 Physical Component Score (SF-36 PCS)**
  - Scores range from 0-100, with higher scores indicating higher quality of life (MCID: defined as ≥5-unit improvement)

Statistical Analysis

- All analyses were post hoc, including patients in the placebo and baricitinib 2-mg Intent-to-Treat populations
- Responders were defined as patients who reported PRO score improvements ≥MCID
- For each PRO, the proportion of patients who maintained improvement ≥MCID at Week 24 (non-responder imputation method) was calculated among patients who reported improvement ≥MCID at Week 4 and Week 12 as observed
- MJS duration in RA-BUILD was measured up to Week 12 only, per protocol
- Observed proportion of patients who reported PRO improvement ≥MCID at Weeks 4, 12, and 24 was also presented
- Data from the baricitinib and placebo groups were compared by Chi-square test without multiplicity adjustment

Safety Analysis

Safety Outcomes

- Serious adverse events
- Adverse events of special interest
- Other adverse reactions

Safety Population

- **Placebo-Controlled Period (to 24 weeks):**
  - The placebo-controlled dataset includes data from 4 trials (including RA-BUILD and RA-BEACON) in which baricitinib 2-mg was one of the options during randomization with data up to 24 weeks
  - Data were censored at time of rescue treatment
- **RA-BEYOND (Long-term Extension [LTE] Trial) (to 6.9 Years)**
  - The baricitinib 2-mg extended dataset includes data from patients originally randomly assigned to baricitinib 2-mg from Phase 2 and Phase 3 trials (4 trials including RA-BUILD and RA-BEACON) with data from the LTE trial up to 6.9 years
  - Data were censored at time of rescue treatment or dose change or were followed up to the end of the trial if rescue treatment or dose change was not required (as-treated analysis)
  - Due to the latent period for malignancy, data for these events were analyzed without censoring (as-randomized analysis)

RESULTS

Baseline Characteristics

	RA-BUILD (csDMARD-IR)		RA-BEACON (bDMARD-IR)	
	PBO (N=228)	BARI 2-mg (N=229)	PBO (N=176)	BARI 2-mg (N=174)
Age, years	51 (13)	52 (12)	56 (11)	55 (11)
Female, n (%)	189 (83)	184 (80)	145 (82)	137 (79)
Duration of RA, years	7 (8)	8 (8)	14 (10)	14 (8)
SJC, of 66	13 (7)	14 (9)	17 (11)	19 (12)
High-sensitivity CRP	18 (20)	18 (22)	21 (25)	20 (22)
Pain (VAS)[a]	57 (23)	60 (21)	65 (19)	62 (22)
HAQ-DI	1.5 (0.6)	1.5 (0.6)	1.8 (0.6)	1.7 (0.6)
FACIT-F	27 (11)	27 (12)	22 (11)	23 (10)
Duration of MJS, min	142 (169)	144 (162)	132 (156)	149 (165)
SF-36 PCS	32 (9)	33 (8)	28 (8)	29 (8)

Data are mean (standard deviation) unless otherwise stated

[a] Values range from 0-100 mm, with higher values indicating greater levels of pain

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