Baricitinib Provides Better Pain Relief Across all Disease Activity Levels Compared With Placebo and Adalimumab in Rheumatoid Arthritis

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BACKGROUND

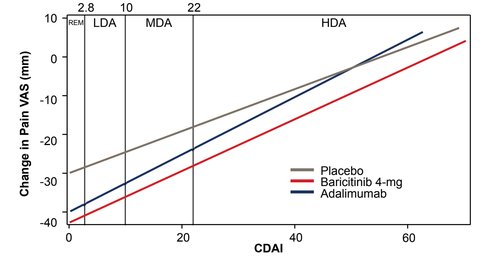
- Baricitinib, an oral selective Janus kinase (JAK 1/JAK 2) inhibitor, is approved in more than 60 countries for the treatment of moderately to severely active rheumatoid arthritis (RA) in adults
- In the Phase 3, RA-BEAM (NCT01710358) trial, baricitinib was associated with significant clinical improvements compared with placebo and adalimumab in patients with RA[1]
  - Baricitinib demonstrated greater efficacy than adalimumab with respect to the American College of Rheumatology 20% response rate and improvement in Disease Activity Score for 28 joints (DAS28) based on the C-reactive protein (CRP) level
  - Baricitinib and adalimumab had a similar level of improvement in swollen joint count (SJC); however, baricitinib demonstrated significantly greater improvement in pain
  - Although pain is a generic feature of inflammation, not all pain in RA is due to inflammation,[2,3] and the contribution of different pathways to pain is unclear

OBJECTIVE

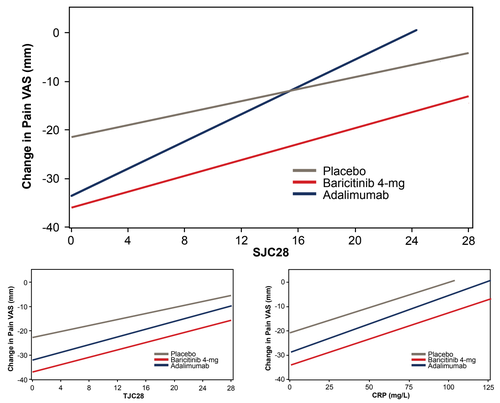
- To assess the relationship between pain improvement and disease activity, and evaluate whether baricitinib provides additional pain improvement compared with placebo and adalimumab at various levels of disease activity

KEY RESULTS

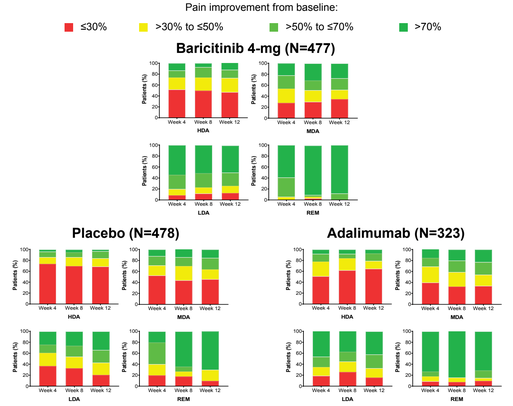
Estimated Change in Pain VAS by Disease Activity at Week 12



Estimated Change in Pain VAS by SJC28, TJC28, and CRP at Week 12



Distribution in Percentage Improvement From Baseline in Pain VAS by CDAI Disease Activity at Weeks 4, 8, and 12

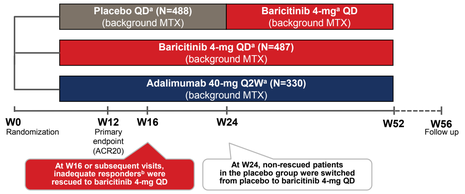


CONCLUSIONS

- Baricitinib provided additional pain improvement compared with placebo and adalimumab across all levels of disease activity, as measured by CDAI, SDAI, DAS28-CRP, or DAS28-ESR at Week 12
  - When the quantitative components of disease activity composites are examined relative to pain, the differences between baricitinib, placebo, and adalimumab are most apparent in SJC
    - This finding may indicate that the difference in pain relief between baricitinib and adalimumab cannot be attributed to differing effects on inflammation alone

METHODS

Study Design, RA-BEAM



[a] Concomitant treatment with stable doses of conventional synthetic DMARDs, NSAIDs, analgesics, and/or glucocorticoids (≤10 mg of prednisone or the equivalent per day) was permitted
[b] Inadequate responder was defined as <20% change in SJC and TJC

Key Eligibility Criteria

- Inclusion criteria
  - Inadequate response to methotrexate (MTX)
  - ≥ 3 erosions (or 1 erosion and seropositive for rheumatoid factor or anti-citrullinated peptide antibodies)
  - Stable background MTX (mean 15 mg/week)
  - ≥ 6/68 tender joint count (TJC), ≥6/66 SJC
  - High-sensitivity CRP ≥6 mg/L
- Exclusion criteria
  - Prior biologic disease-modifying antirheumatic drug use

Assessments

Pain

Pain VAS (0-100 mm)
Grouped by % improvement from baseline at Week 12:
- ≤30%
- >30% to ≤50%
- >50% to ≤70%
- >70%

30% improvement[4,5]:
- "Much improved, meaningful difference"

50% improvement[4,5]:
- "Very much improved, substantial improvement"

70% improvement[4]:
- Analogous to ACR response endpoint

Disease Activity

SDAI[a]
Thresholds:
- REM = 3.3
- LDA = 11
- MDA = 22

CDAI[b]
Thresholds:
- REM = 2.8
- LDA = 10
- MDA = 22

DAS28-CRP[c]
Thresholds:
- REM = 2.6
- LDA = 3.2
- MDA = 5.1

DAS28-ESR[d]
Thresholds:
- REM = 2.6
- LDA = 3.2
- MDA = 5.1

[a] Calculated as TJC28 + SJC28 + hsCRP + Patient's Global Assessment + Physician's Global Assessment
[b] Calculated as TJC28 + SJC28 + Patient's Global Assessment + Physician's Global Assessment
[c] Calculated as a composite numeric score including TJC28, SJC28, Patient's Global Assessment, and hsCRP
[d] Calculated as a composite numeric score including: TJC28, SJC28, Patient's Global Assessment, and hsESR

Statistical Analysis

- All analyses were post hoc
- To evaluate change in pain with disease activity, regression was used with continuous composite disease activity measure (Clinical Disease Activity Index [CDAI], Simplified Disease Activity Index [SDAI], DAS28-CRP, and DAS28 based on erythrocyte sedimentation rate [ESR]) values as primary explanatory variables and continuous change in pain VAS score from baseline to Week 12 as the outcome
  - Other variables included treatment group and the interaction term between treatment and disease activity measure
  - Last observation carried forward was used to impute missing values
- Pain visual analog scale (VAS) change at Week 12 was also estimated from regression for the quantitative components of disease activity composites (SJC28, TJC28, CRP), to further explore the impact of those components on pain VAS change
  - Analyses were not adjusted for multiplicity
- Data visualization with the percentage of pain VAS improvement versus disease activity (CDAI) was created to examine pain improvement with treatment over time
  - CDAI was selected as this was the most commonly used disease activity measure among rheumatologists in the USA assessed in the RA-BEAM study[6]

RESULTS

Baseline Demographics and Clinical Characteristics

	PBO (N=488)	BARI 4-mg (N=487)	ADA (N=330)
Age, years	53 (12)	54 (12)	53 (12)
Female, n (%)	382 (78)	375 (77)	251 (76)
SJC28	11 (6)	11 (5)	11 (6)
TJC28	14 (7)	14 (7)	14 (7)
Physician's Global Assessment	64 (17)	66 (17)	65 (17)
Patient's Global Assessment	61 (23)	63 (21)	64 (21)
Patient's assessment of pain	60 (23)	62 (22)	61 (23)
SDAI	40 (13)	40 (13)	40 (13)
CDAI	38 (13)	38 (12)	38 (13)
DAS28-CRP	5.7 (1.0)	5.8 (0.9)	5.8 (0.9)
DAS28-ESR	6.4 (1.0)	6.5 (0.9)	6.4 (1.0)

Data are mean (standard deviation) unless otherwise stated

Estimated Change in Pain VAS by Disease Activity at Week 12

Remission			Low Disease Activity			Moderate Disease Activity		
CDAI = 2.8			CDAI = 10			CDAI = 22		
PBO	ADA	BARI	PBO	ADA	BARI	PBO	ADA	BARI
-28.4	-37.9	-40.9	-24.5	-32.6	-36.1	-18.0	-23.7	-28.1
SDAI = 3.3			SDAI = 11			SDAI = 22		
PBO	ADA	BARI	PBO	ADA	BARI	PBO	ADA	BARI
-28.9	-37.7	-40.9	-24.8	-32.3	-35.8	-19.0	-24.5	-28.6
DAS28-CRP = 2.6			DAS28-CRP = 3.2			DAS28-CRP = 5.1		
PBO	ADA	BARI	PBO	ADA	BARI	PBO	ADA	BARI
-30.6	-35.1	-39.2	-26.6	-30.8	-34.6	-13.9	-17.4	-20.1
DAS28-ESR = 2.6			DAS28-ESR = 3.2			DAS28-ESR = 5.1		
PBO	ADA	BARI	PBO	ADA	BARI	PBO	ADA	BARI
-32.3	-37.8	-42.9	-28.9	-34.1	-39.1	-18.0	-22.5	-26.9

High disease activity values are those in excess of the threshold value for moderate disease activity and are not presented

DISCLOSURES

- **P. C. Taylor** has been a consultant and/or received research support from: AbbVie, Eli Lilly and Company, Galapagos, and Pfizer; **J. Pope** has been a consultant and/or has received grant/research support from: AbbVie, Amgen, Bayer, BMS, Eli Lilly and Company, Merck, Novartis, Pfizer, Roche, Sanofi, Sandoz, and UCB; **K. Ikeda** has been a consultant and/or received research support and/or honoraria from: AbbVie, Astellas Pharma, Bristol-Myers Squibb, Chugai Pharmaceutical, Eisai, Eli Lilly and Company, Kyowa Hakko Kirin, Pfizer, Takeda, Tanabe Mitsubishi Pharma, and UCB; **X. Zhang**, **B. Jia**, **A. Quebe**, **Y-F. Chen**, **C. Gaich**, **T. Holzkaemper**, and **A. Cardoso** are employees and shareholders of Eli Lilly and Company; **A. Sebba** has been a consultant and/or speaker for: Amgen, Eli Lilly and Company, Genentech, Gilead, Novartis, Sanofi, and Regeneron
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ABBREVIATIONS

ACR=American College of Rheumatology; ACR20=American College of Rheumatology 20% response rate; ADA=adalimumab; BARI=baricitinib; CDAI=Clinical Disease Activity Index; CRP=C-reactive protein; DAS28=Disease Activity Score for 28 joints; ESR=erythrocyte sedimentation rate; HDA=high disease activity; hs=high sensitivity; LDA=low disease activity; MDA=moderate disease activity; MTX=methotrexate; PBO=placebo; Q2W=every 2 weeks; QD=once daily; REM=remission; SDAI=Simplified Disease Activity Index; SJC=swollen joint count; SJC28=swollen joint count. of 28 joints examined; TJC=tender joint count. TJC28=tender joint count. of 28 joints examined; VAS=visual analog scale; W=week

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