Safety Profile of Baricitinib for the Treatment of Rheumatoid Arthritis up to 8.4 Years: An Updated Integrated Safety Analysis

FRI0123

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BACKGROUND

- Baricitinib, an oral, selective inhibitor of Janus kinase (JAK) 1 and JAK2, is approved for the treatment of active rheumatoid arthritis (RA) in adults[1]
- The safety profile of baricitinib in RA has remained consistent over time and is considered acceptable in the context of demonstrated efficacy[2,3]
- An updated report on the safety of baricitinib in 3770 patients with exposure for up to 7 years has been recently published[4]

OBJECTIVE

- To summarize the safety profile of baricitinib through up to 8.4 years of treatment

REFERENCES

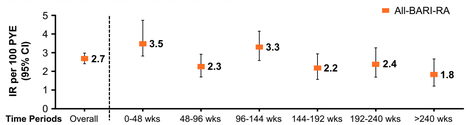
1. Fridman JS, et al. *J Immunol.* 2010;184:5298-5307.
2. Smolen JS, et al. *J Rheumatol.* 2019;46:7-18.
3. Genovese MC, et al. *Arthritis Rheumatol.* 2018;70(Suppl 10).
4. Genovese MC, et al. *Ann Rheum Dis.* 2019;78(Suppl 2):A308.

ABBREVIATIONS

AE=adverse event; BARI=baricitinib; CI=confidence interval; DC=discontinuation; DVT=deep vein thrombosis; DVT/PE=deep vein thrombosis and/or pulmonary embolism; EAIR=exposure-adjusted incidence rates per 100 patient-years (exposure time not censored at event); GI=gastrointestinal; IR=incidence rates per 100 patient-years (exposure time censored at event); MACE=major adverse cardiovascular event; MD HZ=multidermatomal herpes zoster; NMSC=non-melanoma skin cancer; n/N=number of patients with events/total number of patients; Nx=number of patients on treatment; nx/N=adjusted number of patients with events/total number of patients/total number of patients; OI=opportunistic infection; PBO=placebo; PE=pulmonary embolism; PYE=patient-years of exposure; RA=rheumatoid arthritis; SAE=serious adverse event; TEAE=treatment-emergent adverse event; WHO=World Health Organization; wks=weeks

KEY RESULTS

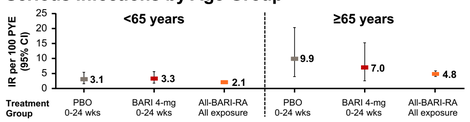
Serious Infections Over Time



Time Periods	Overall	0-48 wks	48-96 wks	96-144 wks	144-192 wks	192-240 wks	>240 wks
n/N	344/3770	108/3770	56/3007	72/2514	42/2228	39/1977	27/1520
(%)	(9.1)	(2.9)	(1.9)	(2.9)	(1.9)	(2.0)	(1.8)
PYE	12,820.1	3100.1	2491.8	2184.7	1930.5	1637.5	1475.5

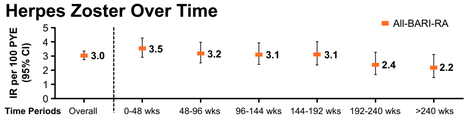
- The incidence of serious infections remained stable over time

Serious Infections by Age Group



Treatment Group	PBO 0-24 wks	BARI 4-mg 0-24 wks	All-BARI-RA All exposure	PBO 0-24 wks	BARI 4-mg 0-24 wks	All-BARI-RA All exposure
n/N	12/1027	13/937	215/3138	7/188	6/205	129/1016
(%)	(1.2)	(1.4)	(6.9)	(3.7)	(2.9)	(12.7)
PYE	389.3	394.0	10119.9	70.8	85.8	2700.1

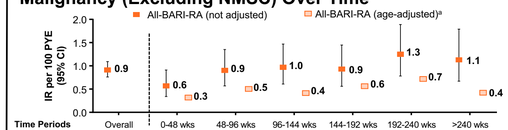
Herpes Zoster Over Time



Time Periods	Overall	0-48 wks	48-96 wks	96-144 wks	144-192 wks	192-240 wks	>240 wks
n/N	384/3770	110/3770	79/3020	67/2481	59/2191	38/1929	31/1468
(%)	(10.2)	(2.9)	(2.6)	(2.7)	(2.7)	(2.0)	(2.1)
PYE	12,659.5	3107.4	2482.9	2157.9	1895.6	1595.3	1420.5

- The incidence of herpes zoster remained stable over time

Malignancy (Excluding NMSC) Over Time

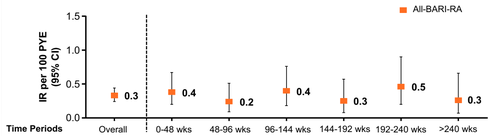


Time Periods		Overall	0-48 wks	48-96 wks	96-144 wks	144-192 wks	192-240 wks	>240 wks
Not adjusted	n/N	122/3770	18/3770	23/3066	22/2586	19/2339	22/2106	18/1645
	(%)	(3.2)	(0.5)	(0.8)	(0.9)	(0.8)	(1.0)	(1.0)
	PYE	13,361.7	3132.6	2553.6	2272.4	2050.3	1761.4	1591.3
Age-adjusted	n/N		10.1/3770	12.7/3066	9.5/2586	11.5/2339	12.6/2106	6.8/1645
	(%)		(0.3)	(0.4)	(0.4)	(0.5)	(0.6)	(0.4)
	PYE		3132.6	2553.6	2272.4	2050.3	1761.4	1591.3

- The incidence of malignancy (excluding non-melanoma skin cancer [NMSC]) remained stable over time
- There were no apparent increases in the incidence of malignancy after adjustment for aging of the cohort

[a]IRs were standardized to the WHO world population 2000-2025 using 5-year age increments within each reported 48-week time period to account for aging of the All-BARI-RA cohort over the 6 years of the reported data

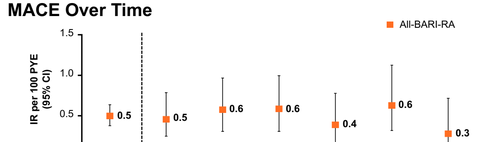
NMSC Over Time



Time Periods	Overall	0-48 wks	48-96 wks	96-144 wks	144-192 wks	192-240 wks	>240 wks
n/N	44/3770	12/3770	6/3061	9/2576	5/2328	8/2090	4/1622
(%)	(1.2)	(0.3)	(0.2)	(0.3)	(0.2)	(0.4)	(0.2)
PYE	13,279.5	3129.5	2546.9	2261.3	2035.2	1744.4	1562.4

- The incidence of NSMC remained stable over time

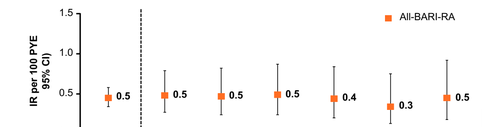
MACE Over Time



Time Periods	Overall	0-48 wks	48-96 wks	96-144 wks	144-192 wks	192-240 wks	>240 wks
n/N	63/3251	13/3251	14/2840	13/2514	8/2321	11/2089	4/1615
(%)	(1.9)	(0.4)	(0.5)	(0.5)	(0.3)	(0.5)	(0.2)
PYE	12,643.8	2803.2	2433.0	2218.6	2030.9	1740.6	1417.4

- The incidence of major adverse cardiovascular event (MACE) remained stable over time

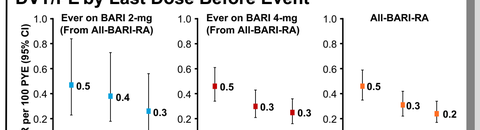
DVT/PE Over Time



Time Periods	Overall	0-48 wks	48-96 wks	96-144 wks	144-192 wks	192-240 wks	>240 wks
n/N	60/3770	15/3770	12/3061	11/2574	9/2329	6/2089	7/1628
(%)	(1.6)	(0.4)	(0.4)	(0.4)	(0.4)	(0.3)	(0.4)
PYE	13,286.9	3129.7	2546.3	2258.8	2033.5	1746.0	1572.6

- The incidence of deep vein thrombosis and/or pulmonary embolism (DVT/PE) remained stable over time

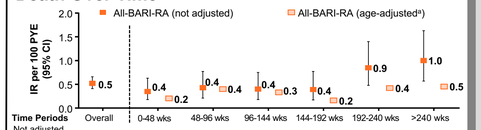
DVT/PE by Last Dose Before Event



		DVT/PE	DVT	PE
Ever on BARI 2-mg (From All-BARI-RA)	n/N	11/1077	9/1077	6/1077
	(%)	(1.0)	(0.8)	(0.6)
	PYE	2348.9	2348.9	2348.9
Ever on BARI 4-mg (From All-BARI-RA)	n/N	49/3400	32/3400	26/3400
	(%)	(1.4)	(0.9)	(0.8)
	PYE	10,605.1	10,605.1	10,605.1
All-BARI-RA	n/N	60/3770	41/3770	32/3770
	(%)	(1.6)	(1.1)	(0.8)
	PYE	13,148.0	13,148.0	13,148.0

IR (95% CI) for patients while receiving BARI 2-mg (N=1077) were: DVT, 0.38 (0.18-0.73); PE, 0.26 (0.09-0.56); and DVT/PE, 0.47 (0.23-0.84)
IR (95% CI) for patients while receiving BARI 4-mg (N=3400) were: DVT, 0.30 (0.21-0.43); PE, 0.25 (0.16-0.36); and DVT/PE, 0.46 (0.34-0.61)

Death Over Time



Time Periods		Overall	0-48 wks	48-96 wks	96-144 wks	144-192 wks	192-240 wks	>240 wks
Not adjusted	n/N	70/3770	11/3770	11/3070	9/2590	8/2348	15/2113	16/1647
	(%)	(1.9)	(0.3)	(0.4)	(0.3)	(0.3)	(0.7)	(1.0)
	PYE	13,383.7	3134.1	2557.5	2276.5	2054.8	1766.3	1594.7
Age adjusted	n/N		6.5/3770	10.2/3070	7.4/2590	3.2/2348	7.4/2113	7.3/1647
	(%)		(0.2)	(0.3)	(0.3)	(0.1)	(0.3)	(0.4)
	PYE		3134.1	2557.5	2276.5	2054.8	1766.3	1594.7

- The incidence rate (IR) for death tended to increase in later time intervals before adjustment for aging of the cohort (beyond 192 weeks)
- No particular cause of death contributed to this increase
- There were no apparent increases in the incidence of death after adjustment for aging of the cohort

[a]IR were standardized to the WHO world population 2000-2025 using 5-year age increments within each reported 48-week time period to account for aging of the All-BARI-RA cohort over the 6 years of the reported data

CONCLUSIONS

- In the All-BARI-RA analysis set, based on 13,148 PYE, key safety parameters including IRs of serious infection, malignancy, MACE, and DVT/PE were similar to those previously reported[2-4]
- Age-standardized IRs of malignancy and death remained stable over time
- Rate of serious infections was comparable between the placebo and baricitinib 4-mg groups regardless of age, although patients ≥65 years had higher IRs than those <65 years

DISCLOSURES

- **M. C. Genovese** is a consultant for: AbbVie, Eli Lilly and Company, Galapagos NV, Gilead Sciences, and Pfizer; has received research funding from: AbbVie, Eli Lilly and Company, Galapagos NV, Gilead Sciences, and Pfizer; and is currently employed by and owns stock in: Gilead Sciences; **J. S. Smolen** has received grant/research support from: AbbVie, Eli Lilly and Company, Janssen, Merck Sharp & Dohme, Novartis, Pfizer, and Roche; and has received consultant fees from: AbbVie, Amgen, AstraZeneca, Astro Pharma, Bristol Myers Squibb, Celgene, Celltrion, Chugai, Eli Lilly and Company, Gilead Sciences, ILTOO Pharma, Janssen, MedImmune, Merck Sharp & Dohme, Novartis-Sandoz, Pfizer, Roche, Samsung, Sanofi-Aventis, and UCB Pharma; **T. Takeuchi** has received consultant and/or speakers fees from: AbbVie, Asahi Kasei Medical, Astellas, AstraZeneca, Bristol Myers Squibb, Chugai, Daiichi Sankyo, Eisai, Eli Lilly and Company, GlaxoSmithKline, Janssen, Mitsubishi Tanabe Pharma, Nippon Kayaku, Novartis, Pfizer Japan, Taiho Pharmaceutical, Taiho Toyama Pharmaceutical, Takeda, and UCB Japan; **G. Burmester** is a consultant for: Eli Lilly and Company, Janssen, Novartis, and Pfizer; and has received research funding from: Eli Lilly and Company; **W. Deberdt**, **D. E. Schlichting**, **D. Mo**, and **C. Walls** are current employees and shareholders of Eli Lilly and Company; **H. Song** is an employee of: Syneos Health; **K. L. Winthrop** has received grants/research support from: Bristol Myers Squibb and Pfizer; and has received consultant fees from: AbbVie, Amgen, Bristol Myers Squibb, Eli Lilly and Company, Pfizer, and UCB Pharma
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METHODS

Analysis Set

All-BARI-RA

All-BARI-RA studies[a] (1 Phase 1, 3 Phase 2, and 5 Phase 3 studies + Long-term Extension study)

Phase 1
- JADB (I4V-MC-JADB)

Phase 2
- JADA (NCT01185353)
- JADC (NCT00902486)
- JADN (NCT01469013)

Phase 3
- RA-BEAM (JADV [NCT01710358])
- RA-BEACON (JADW [NCT01721044])
- RA-BUILD (JADX [NCT01721057])
- RA-BEGIN (JADZ [NCT01711359])
- RA-BALANCE (JAGS [NCT02265705])

Long-term extension
- RA-BEYOND (JADY [NCT01885078])[b]

[a] All patients treated with ≥1 dose of BARI; [b] The only study currently ongoing

Statistical Analyses

- IRs per 100 patient-years of exposure (PYE) were calculated for all patients treated with ≥1 dose of baricitinib through September 1, 2019 (All-BARI-RA analysis set)
  - IRs are 100 times the number of patients experiencing the adverse event divided by the event-specific exposure to treatment (exposure time up to the event for patients with the event and exposure time up to the end of the period for patients without the event, in years)
- IRs for DVT, PE, and DVT/PE were calculated for all patients treated with ≥1 dose of baricitinib (all doses) and by last dose before the event for patients who ever received baricitinib 2-mg or baricitinib 4-mg within All-BARI-RA
- MACEs were adjudicated in the 5 completed Phase 3 studies and are being adjudicated in the ongoing Long-term Extension
- In addition, to account for aging of the All-BARI-RA cohort, IRs were standardized to the World Health Organization world population 2000-2025 within each reported 48-week time period for malignancies (excluding NMSC) and death

RESULTS

Baricitinib Exposure

	All-BARI-RA[a] (N=3770) PYE=13148
Duration of exposure in years, n (%)	
≥0.5	3213 (85.2)
≥1	2961 (78.5)
≥2	2519 (66.8)
≥3	2264 (60.1)
Duration of exposure	
Minimum, days	2
Median, years	4.2
Maximum, years	8.4

[a] Data cut as of 01-Sep-2019

Safety Summary: All-BARI-RA Datasets

n (IR)	01-Sep-2016[2] All-BARI-RA[a] N=3492; PYE=6636.7	01-Apr-2017[3] All-BARI-RA[a] N=3492; PYE=7860.3	13-Feb-2018[4] All-BARI-RA N=3770; PYE=10,127	01-Sep-2019 All-BARI-RA N=3770; PYE=13,148
TEAE	2941 (44.3)	3023 (38.5)	3332 (32.9)	3391 (25.8)
SAE including death	611 (9.0)	655 (8.3)	786 (7.8)	940 (7.2)
Death	22 (0.3)	28 (0.4)	44 (0.4)	70 (0.5)
Malignancy				
Malignancy excluding NMSC	52 (0.8)	63 (0.8)	85 (0.8)	122 (0.9)
Lymphoma	6 (0.1)	6 (0.1)	8 (0.1)	8 (0.1)
NMSC	24 (0.4)	30 (0.4)	37 (0.4)	44 (0.3)
Infection				
Serious infection	194 (2.9)	231 (3.0)	283 (2.8)	344 (2.7)
Herpes zoster	212 (3.2)	258 (3.3)	323 (3.3)	384 (3.0)
Tuberculosis	10 (0.2)	11 (0.1)	15 (0.2)	20 (0.2)
OI including MD HZ	34 (0.5)	43 (0.5)	52 (0.5)	61 (0.5)
OI not including MD HZ	16 (0.2)	21 (0.3)	27 (0.3)	32 (0.2)
MACE	31 (0.5)	38 (0.5)	51 (0.5)	63 (0.5)
DVT/PE	34 (0.5)	42 (0.5)	49 (0.5)	60 (0.5)
DVT	23 (0.4)	30 (0.4)	35 (0.4)	41 (0.3)
PE	17 (0.3)	19 (0.2)	24 (0.2)	32 (0.2)
GI perforation	3 (0.1)	3 (0.0)	4 (0.0)	6 (0.0)
Permanent DC from treatment owing to AE, n (EAIR)	393 (6.0)	435 (5.5)	518 (5.1)	644 (4.8)

[a] Analyses did not include RA-BALANCE

- The IRs of safety measures of special interest were consistent with findings from previous analyses[2-4]

Study was sponsored by Eli Lilly and Company, under license from Incyte Corporation