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LB0002

BARICITINIB IN JUVENILE IDIOPATHIC ARTHRITIS: A PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED, WITHDRAWAL, EFFICACY AND SAFETY STUDY

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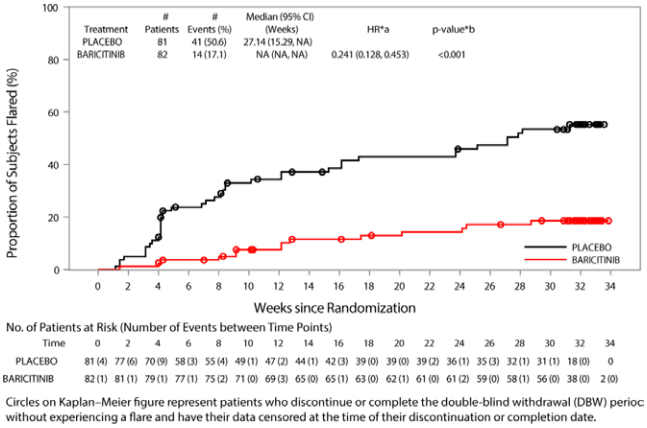
Background: Baricitinib is a JAK1/2 selective inhibitor approved for the treatment of rheumatoid arthritis. Juvenile idiopathic arthritis (JIA) is a group of diseases characterized by immune mediated chronic arthritis which often requires treatment with conventional synthetic or biologic disease-modifying antirheumatic drugs (cs or b-DMARDs).

Objectives: To investigate baricitinib efficacy and safety in pediatric patients with JIA and an inadequate response to cs or b-DMARDs.

Methods: This Phase 3 multicenter, double-blind, withdrawal, efficacy, and safety study, enrolled patients (pts) age 2 to <18 years with extended oligo- or poly-articular JIA, ERA, or JPsA, per ILAR criteria, and an inadequate response to ≥1 cs and/or b-DMARDs (NCT03773978). There were 3 periods: a 2-week (wk) pharmacokinetic/safety assessment (PKS), a 12-wk open-label lead-in (OLLI), and an up-to 32-wk double-blind withdrawal (DBW). Dosage and safety were confirmed in the PKS and then pts, including those from the PKS, enrolled in the OLLI, receiving age-based, oral, once daily doses of baricitinib. Pts with a JIA-ACR30 response at wk12, end of OLLI, entered the DBW to be randomized 1:1 to continued baricitinib or newly started placebo (PBO) and remained until flare or up to wk32. Primary endpoint was time to flare during the DBW. Secondary endpoints included JIA-ACR30/50/70/90 response rates at wk12, and proportion of pts with a flare during the DBW. Survival curves were estimated using the Kaplan-Meier method.

Results: Of 220 pts enrolled, 29 participated in the PKS, 219 entered the OLLI, and 163 entered the DBW. The JIA-ACR30/50/70/90 response at wk12 was 76.3%/63.5%/46.1%/20.1%, respectively. During the DBW, time of flare was significantly shorter with PBO vs baricitinib (hazard ratio 0.24 [95% CI 0.13,0.45], p<0.001; Figure 1). The proportion of pts with a flare during the DBW was significantly lower for baricitinib vs PBO (14 (17.1%) vs. 41 (50.6%), p<0.001). In the PKS and OLLI periods, 126 (57.3%) pts reported ≥1 treatment emergent adverse event (TEAE), while 6 (2.7%) reported ≥1 serious adverse event (SAE); Table 1. In the DBW, 38 (46.9%) and 54 (65.9%) pts reported ≥1 TEAE for PBO and baricitinib, respectively, whereas those with ≥1 SAE were 3 (3.7%) and 4 (4.9%). The mean wks of exposure was higher in the baricitinib vs PBO group during DBW (26.34 vs 18.91) due to study design. There were no deaths, cardiovascular events or uveitis and 1 case of herpes zoster.



Circles on Kaplan–Meier figure represent patients who discontinue or complete the double-blind withdrawal (DBW) perioc without experiencing a flare and have their data censored at the time of their discontinuation or completion date.

Table 1. Safety data

Events, N (%)		PKS and OLLI (N=220)	Events, N (%)	DBW Placebo (N=81)	DBW Baricitinib (N=82)
Discontinuations due to AEs		2 (0.9)		2 (2.5)	1 (1.2)
TEAEs		126 (57.3)		38 (46.9)	54 (65.9)
most common TEAEs	Nasopharyngitis	19 (8.6)	URTI	1 (1.2)	9 (11.0)
	Headache	14 (6.4)	Headache	3 (3.7)	9 (11.0)
	Arthralgia	12 (5.5)	Nasopharyngitis	3 (3.7)	6 (7.3)
	URTI	11 (5.0)	Arthralgia	3 (3.7)	6 (7.3)
	Nausea	11 (5.0)	Oropharyngeal pain	1 (1.2)	5 (6.1)
SAEs		6 (2.7)		3 (3.7)	4 (4.9)
All reported SAEs	Arthralgia	1 (0.5)	COVID-19	0	1 (1.2)
	Joint Destruction	1 (0.5)	Gastroenteritis	0	1 (1.2)
	Joint Effusion	1 (0.5)	Headache	0	1 (1.2)
	JIA	1 (0.5)	Pulmonary Embolism	0	1 (1.2)
	Musculoskeletal Chest Pain	1 (0.5)	Bronchospasm	1 (1.2)	0
	Decreased Appetite	1 (0.5)	JIA	1 (1.2)	0
			Suicide Attempt	1 (1.2)	0
Potential opportunistic infections		2 (0.9)		1 (1.2)	1 (1.2)
	Herpes virus	1 (0.5)	Herpes virus	1 (1.2)	0
	Herpes zoster	1 (0.5)	Candida	0	1 (1.2)

URTI= Upper Respiratory Tract Infection

Conclusion: Baricitinib significantly reduced time to and frequency of JIA flares in pts with JIA versus PBO, and improved JIA-ACR scores in the majority of pts within 12wks. Safety findings were consistent with the known safety profile in adult rheumatoid arthritis indications. These findings support baricitinib as a treatment for signs and symptoms of JIA with an inadequate response to cs or b-DMARDs.

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LB0003

WITHDRAWING METHOTREXATE AFTER BOTH VERSUS ONLY SECOND DOSE OF THE CHADOX1 NCOV-19 VACCINE IN PATIENTS WITH AUTOIMMUNE INFLAMMATORY ARTHRITIS: TWO INDEPENDENT RANDOMIZED CONTROLLED TRIALS (MIVAC I AND II)

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Background: Pausing methotrexate (MTX) for two to four weeks, improved immunogenicity of influenza vaccination in patients with rheumatoid arthritis (RA), albeit a risk of disease flare (1). This guided the framing of guidelines on MTX withdrawal for COVID-19 vaccination (2). However, evidence for MTX withdrawal for COVID-19 vaccination is limited to observational studies only.

Objectives: To compare the efficacy and safety of holding MTX after each (MIVAC 1) and only after the second dose (MIVAC II) of the ChAdOx1 vaccine versus continuation of MTX in two randomized controlled trials (RCTs).

Methods: Two single centre, investigator-blinded, RCTs were conducted in patients with RA or Psoriatic arthritis (PsA) on stable doses of MTX without prior COVID-19 (CTRI reg. no. MIVAC I: CTRI/2021/07/03463 & MIVAC II: CTRI/2021/07/035307). In MIVAC I, unvaccinated patients were randomised (1:1) to hold or continue MTX for two weeks after each dose of the vaccine. MIVAC II included patients who had continued MTX during the first dose of ChAdOx1 and were randomised (1:1) to hold or continue MTX for 2 weeks after the second vaccine dose. The primary outcome for both the trials was the anti-Receptor Binding Domain (RBD) antibody titres measured four weeks after the second vaccine dose (per protocol analysis). Secondary outcome was the flare rate, defined as an increase in disease activity scores (DAS28/cDAPSA) or physician intent to hike DMARDs.

Results: 250 patients were randomized for MIVAC 1 and 178 for MIVAC II and after due exclusions, 158 and 157 were eligible for analysis respectively (Figure 1). In MIVAC I, median anti-RBD titres were significantly high in the MTX hold group [2484 (1050-4388) versus 1147(433-2360), p=0.001] but the flare rate was higher in the hold group [20 (25%) versus 6(8%) p=0.005] compared to continue group. In MIVAC II median anti-RBD titres were significantly high for the MTX hold group [2553 (1792-4823) versus 990 (356-2252), p=0.001] when compared to continue group but there was no difference in the flare rate between the groups [9(11.8%) and 4(7.9%), p=0.15] (Table 1). Since both were parallel studies in similar population, MTX hold arms across both the trials were compared for anti-RBD titres and flare. There was no difference in the anti-RBD titres [p=0.2] between the groups. In MIVAC I, 29(36.25%) patients had reported flare (19 in either first or second dose, 10 for both doses) when compared to MIVAC II where only 9(11.84%) patients had reported flare after the second dose (P <0.001).

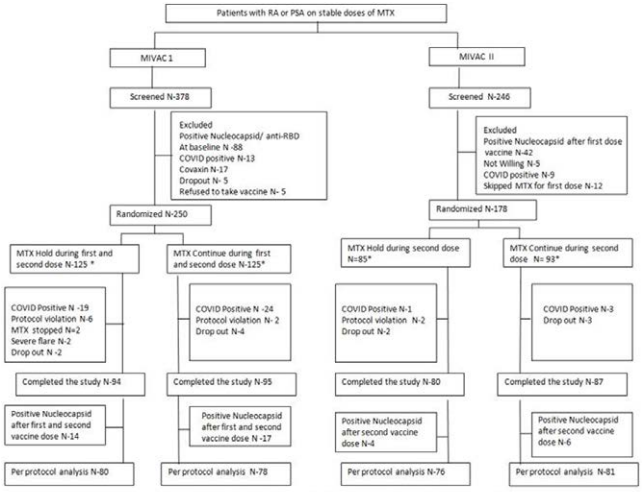

Figure 1 .Trial design *the interval between two ChadOx1 vaccines were 3 months

Conclusion: Holding MTX after both the doses or only after the second dose of ChAdOx1 yields higher anti-RBD antibody titres as compared to continuing MTX. Comparing across the trials, holding MTX only after the second dose appears to be non-inferior to holding MTX after both doses of the vaccine with a lesser risk of flare.

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Table 1. Baseline demographics and key results

	MIVAC I			MIVAC II		
	MTX Hold	MTX Continue	P	MTX Hold	MTX Continue	P value
Variable	N=80	N=78	value	N=76	N=81	
Age†	48 (38-53.3)	49 (39-59)	0.19	53 (42.3-59)	53(50-62)	0.14
Female (%) ‡	73 (91.3)	75 (96.2)	0.33	65 (85.5)	70 (86.4)	>0.99
RA (%) ‡	69(86.3)	69 (93.2)		70 (85.6)	80 (87.7)	
PsA (%) ‡	11(13.8)	6 (8.1)	0.31	6 (7.9)	1 (1.2)	0.057
DAS28†	2.7 (2.4-3.2)	2.6 (2-3.3)	0.6	2.7(2.3-3.4)	2.8 (2.1-3.5)	0.78
cDAPSA †	2(3-4.5)	2.5(1.3-3.8)	0.46	3(2.8-3)	3	0.15
Prednisolone (%) ‡	29 (36.3)	23(31.1)	0.4	24(31.6)	26 (32.1)	>0.99
MTX mg/week†	17.5 (10-25)	15 (10-20)	0.057	15 (9.4-25)	17.5(7.5-25)	0.92
Anti- RBD antibody titres post second dose (IU/mL) †	2484 (1050-4388.8)	1147.5 (433.5-2360.3)	**<0.001**	2553.5 (1792.5-4823.8)	990.5 (356.1-2252.5)	**<0.001**
Flare (N%) ‡						
Post first dose	20 (25)	6 (8)	**0.005**	NA	NA	
Post second dose	19 (23.8)	10(13.3)	0.1	9 (11.8)	4 (7.9)	0.15

All analysis as per protocol population. †Median (interquartile range): Mann Whitney U test. ‡ N (%): Fisher Exact test. Bolded if p<0.05.