Efficacy of baricitinib in patients with RA who failed 2 or more DMARDs

Efficacy measure, Week 24[¥]	RA-BEACON (N=527)			RA-BUILD (N=381)[§]			RA-BEAM (N=704) [§]		
	PBO N=176	Bari 2-mg N=174	Bari 4-mg N=177	PBO N=131	Bari 2-mg N=122	Bari 4-mg N=128	PBO N=283	Bari 4-mg N=244	ADA N=177
ACR20	27	45***	46***	45	58*	71***	33	73***	68***
ACR50	13	23*	29***	25	39*	49***	17	51***	49***
ACR70	3	13***	17***	10	25**	25**	6	30***‡	19***
ΔCDAI	-10.96	-15.42**	-19.41***	-14.74	-19.94***	-23.55***	-12.50	-23.98***	-21.96***
CDAI ≤10	15	23	31***	30	44*	56***	17	48***	47***
CDAI ≤2.8	3	5	9*	5	11	17**	2	14***	11***
ΔSDAI	-10.67	-15.89**	-20.20***	-14.92	-20.72***	-24.29***	-12.70	-25.56***	-23.09***
SDAI ≤11	14	22*	31***	31	48**	57***	17	50***	49***
SDAI ≤3.3	2	5	9**	4	13*	14**	2	14***	12***
DAS28-CRP≤3.2	11	20*	33***	24	46***	55***	16	53***	48***
DAS28-CRP≤2.6	6	11	22***	9	30***	37***	5	35***	31***
ΔHAQ-DI	-0.15	-0.38***	-0.43***	-0.39	-0.60**	-0.59**	-0.30	-0.71***‡	-0.61***
ΔmTSS[¶]	-	-	-	0.72	0.33	0.08**	0.77	0.35*	0.26**

[2] Braun J, et al. A&R 2008;58(1):73–81.
[3] Hazlewood GS,eta l. T. Ann Rheum Dis 2016;75(6):1003–08.

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LONG-TERM SAFETY AND EFFICACY OF UPADACITINIB (ABT-494), AN ORAL JAK-1 INHIBITOR IN PATIENTS WITH RHEUMATOID ARTHRITIS IN AN OPEN LABEL EXTENSION STUDY

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Background: Upadacitinib (UPA, ABT-494) is a selective, oral JAK-1 inhibitor studied in two phase 2 randomized controlled trials (RCTs) in patients (pts) with rheumatoid arthritis (RA).
Objectives: We assessed UPA safety and efficacy in BALANCE-EXTEND, an ongoing, combined open-label extension (OLE) of the phase 2 RCTs.
Methods: Pts completing the two 12-week RCTs (in TNF-IR and (MTX-IR pts)[1,2] could enter the OLE. Pts switched to 6 mg UPA from their RCT dose of UPA 3, 6, 12, 18 mg twice daily (BID), 24 mg once daily (QD) or Placebo. A dose increase to 12 mg BID was required for pts with <20% improvement in both SJC and TJC on 6 mg BID (at wk 6 or 12), and permitted for pts not meeting CDAI LDA. Pts without 20% improvement in SJC and TJC 6 wks after escalation, or at any 2 consecutive visits, were discontinued. The dose was decreased to 6 mg BID only in pts with a safety concern or intolerability. Pts are grouped as: Never-titrated (on 6 mg BID throughout); Titrated-up (from 6 to 12 mg BID); Titrated-up and back down (to 6 mg BID). After Jan 2017, the 6 and 12 mg BID doses were replaced by 15 and 30 mg QD extended-release equivalents currently being studied in phase 3. Data up to Jan 13 2017 are reported. Adverse events (AE) per 100 yrs of pt exposure (PY) are summarized starting from day 1 of OLE. Efficacy is assessed by ACR20/50/70 and LDA (by DAS28-CRP and CDAI), and observed data are presented up to Wk 72 of OLE due to sample size consideration.
Results: Out of 516 pts who completed the 2 RCTs, 494 entered the OLE, 493 were dosed, 328 (66.5 %) were never-titrated, 150 (30.4%) were titrated-up, and 15 (3%) were titrated-up and back down; 150 pts (30.4%) were discontinued [42 (8.5%) withdrew consent, 37 (7.5%) due to AE and 24 (4.9%) due to lack of efficacy]. Mean exposure to UPA was 525.4±221.4 days (range 1–961 days), and cumulative exposure was 725.1 PY **(Table)**. The E/100PY for any AE in the OLE (170.5) were lower than for the RCTs in the TNF-IR (697.9, 48 PY) and MTX-IR (408.4, 54.6 PY) study populations. The E/100PY were 2.3 for serious infection, 3.7 for herpes zoster, 0.8 for malignancies excluding non-melanoma skin cancer, and 0.7 for adjudicated cardiovascular events. There were 2 deaths: one sudden death (adjudicated as undetermined or unknown cause of death) and one death due to Hodgkin's lymphoma. Changes from baseline in laboratory parameters were consistent with observations from phase 2 RCTs. For those pts completing Wk 72, efficacy was maintained in pts on 6 mg BID UPA from day 1 of OLE (never-titrated); 55% pts met ACR70 and 83% were in LDA by DAS28-CRP and CDAI based on as observed data **(Table)**.

Summary of Adverse Events in Patients who Entered the OLE

	As of Jan 13 2017 N=493, PYs=725.1 Events (E/100PY)[a]
Any AE	1236 (170.5)
Serious AE	68 (9.4)
AE leading to discontinuation	42 (5.8)
AE leading to death[b]	2 (0.3)
Infections	427 (58.9)
-Serious infections	17 (2.3)
-Opportunistic infections[c]	3 (0.4)
-Herpes Zoster	27 (3.7)
Anemia	19 (2.6)
Neutropenia	10 (1.4)
Lymphopenia	17 (2.3)
GI perforation	0
NMSC[d]	5 (0.7)
Malignancy other than NMSC[e]	6 (0.8)
CPK elevation[f]	36 (5.0)
Hepatic disorders[g]	37 (5.1)
VTE	5 (0.7)
-Serious VTE[h]	4 (0.6)
Adjudicated cardiovascular events	5 (0.7)
-MACE	3 (0.4)
-Other cardiovascular events	2 (0.3)

PY, patient years; E/100 PY, events/100 PY; AE, adverse events; NMSC, non-melanoma skin cancer; CPK, creatine phosphokinase
[a] Multiple events occurring in the same patients are counted in the E/100PY calculation.
[b] includes patients from Never-titrated, titrated-up, and titrated-up and back down groups.
[c] 1 sudden death, likely due to cardiac disease (undetermined or unknown cause of death);1 death due to Hodgkin's lymphoma (non-cardiovascular death).
[d] 1 pt with coccidiomycosis (from an endemic area); 2 pts with oral candidiasis
[e] 3 pts with basal cell carcinoma; 1 pt with 2 events of squamous cell carcinoma of skin
[f] 2 pts with breast cancer (1 pt had bilateral cancer); 2 pts with lymphoma; 1 pt with prostate cancer
[g] Not symptomatic
[h] All isolated elevations of ALT/AST or bilirubin; no Hy's Law cases.
[i] Serious vs non-serious VTE as determined by investigator (typically based on hospitalization)

Efficacy Measures at Week 72 in Patients who Entered the OLE, n/N (%)

	Never-titrated	Titrated-up	Overall efficacy in OLE[a]
ACR20	208/231 (90)	78/99 (79)	297/342 (87)
ACR50	172/230 (75)	44/100 (44)	224/342 (65)
ACR70	127/232 (55)	22/101 (22)	153/345 (44)
DAS28-CRP LDA	194/233 (83)	46/104 (44)	250/349 (72)
CDAI LDA	191/230 (83)	42/104 (40)	242/346 (70)

Observed data presented for pts completing Week 72. Efficacy data reflect attrition in the OLE.
[a] Includes pts who were never-titrated, titrated-up, and titrated-up to and back down.
ACR20/50/70: 20/50/70% improvement in American College of Rheumatology criteria; DAS28-LDA, 28-joint count disease activity score using C-reactive protein; CDAI, clinical disease activity index; LDA, low disease activity

Conclusions: The safety profile of UPA remained consistent with that expected for an RA population treated with JAKi. Efficacy responses were maintained up to 72 wks in pts on 6 mg BID UPA in the OLE.

REFERENCES:

[1] Kremer, et al. Arth & Rheum 2016;68:2867
[2] Genovese, et al. Arth & Rheum 2016;68:2857.

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