Safety and Efficacy of Upadacitinib Monotherapy in Adolescents and Adults with Moderate-to-severe Atopic Dermatitis: Results From 2 Pivotal, Phase 3, Randomized, Double-blinded, Monotherapy, Placebo-controlled Studies (Measure Up 1 and Measure Up 2)

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Introduction & Objective: There is a significant medical need for additional treatment options for patients with moderate-to-severe atopic dermatitis (AD). Upadacitinib (UPA) is an oral Janus kinase 1 (JAK1)–selective inhibitor with phase 2 data showing safety and efficacy in patients with moderate-to-severe AD. Here, efficacy and safety of UPA monotherapy vs placebo (PBO) was further assessed in 2 replicate phase 3, double-blinded, multicenter studies–Measure Up 1 (NCT03569293) and Measure Up 2 (NCT03607422).

Materials & Methods: Eligible adolescents (aged 12–17 years with body weight ≥40 kg) and adults (aged 18–75 years) with moderate-to-severe AD (≥10% of body surface area affected by AD, Eczema Area and Severity Index [EASI] ≥16, validated Investigator's Global Assessment for AD [vIGA-AD] ≥3, and Worst Pruritus Numerical Rating Scale [NRS] score ≥4) were randomized 1:1:1 to receive UPA 15 mg, UPA 30 mg, or PBO once daily for 16 weeks. Coprimary endpoints were the proportion of patients achieving ≥75% reduction in EASI (EASI 75) and the proportion of patients achieving vIGA-AD of clear (0) or almost clear (1) with ≥2 grades of reduction from baseline (vIGA-AD 0/1), both at week 16. Multiple secondary efficacy endpoints related to improvements in skin clearance, itch, and quality of life were also assessed. Safety was assessed by monitoring for adverse events (AEs).

Results: A total of 847 patients (281 UPA 15 mg, 285 UPA 30 mg, and 281 PBO) in Measure Up 1 and 836 patients (276 UPA 15 mg, 282 UPA 30 mg, 278 PBO) in Measure Up 2 were randomized and treated; among these, 124 (14.6%) and 104 (12.4%), respectively, were adolescents. Demographics and baseline characteristics were well balanced among UPA 15 mg, UPA 30 mg, and PBO groups, including mean (SD) EASI (Measure Up 1: 30.6 [12.8], 29.0 [11.1], and 28.8 [12.6], respectively; Measure Up 2: 28.6 [11.7], 29.6 [12.2], and 29.1 [12.1], respectively) and proportion of patients with severe vIGA-AD (Measure Up 1: 45.2%, 46.0%, and 44.5%, respectively; Measure Up 2: 54.3%, 55.3%, and 55.0%, respectively). Both studies met the coprimary and all secondary endpoints, demonstrating superiority of UPA 15 mg and UPA 30 mg vs PBO (**Table 1**). In both Measure Up 1 and Measure Up 2, the proportions of patients who achieved either EASI 75 or vIGA-AD 0/1 at week 16 were significantly greater ($P < .001$ for all comparisons) for both UPA 15 mg and UPA 30 mg vs PBO. At week 16, UPA 30

mg achieved numerically higher response rates than UPA 15 mg for both coprimary endpoints and key secondary endpoints, including improvements in skin clearance, itch, and quality of life. Both UPA 15 and UPA 30 mg were well tolerated in adolescents and adults. The incidences of serious AEs and AEs leading to discontinuation of study drug were low and similar among treatment groups (**Table 2**). The most commonly reported treatment-emergent AEs (≥ 5% in any treatment group, in either study) were acne, upper respiratory tract infection, nasopharyngitis, headache, increased blood creatine phosphokinase (Measure Up 1 only), and dermatitis atopic. No new safety signals were observed compared with the known safety profile of UPA, except for higher rates of acne.

Conclusions: In these replicate pivotal, phase 3 trials, both UPA monotherapy doses demonstrated high degrees of efficacy and improved quality of life in adolescents and adults with moderate-to-severe AD. UPA was also well tolerated, with no new safety issues reported.

Table 1: Coprimary and Key Secondary Endpoints by Domain

		Measure Up 1			Measure Up 2		
		PBO	UPA 15 mg	UPA 30 mg	PBO	UPA 15 mg	UPA 30 mg
	Timeframe	N = 281	N = 281	N = 285	N = 278	N = 276	N = 282
Coprimary Efficacy Endpoints							
Patients achieving EASI 75, %	Week 16	16.3	69.6*	79.7*	13.3	60.1*	72.9*
Patients achieving vIGA-AD 0/1, %	Week 16	8.4	48.1*	62.0*	4.7	38.8*	52.0*
Key Secondary Efficacy Endpoints							
Skin Improvement							
Patients achieving EASI 90, %	Week 16	8.1	53.1*	65.8*	5.4	42.4*	58.5*
Itch							
Patients achieving Worst Pruritus NRS improvement ≥4,[a] %		N = 272	N = 274	N = 280	N = 274	N = 270	N = 280
	Week 16	11.8	52.2*	60.0*	9.1	41.9*	59.6*
	Week 4	4.4	51.5*	66.8*	3.6	48.9*	60.7*
Overall Symptom Frequency							
Patients achieving POEM total score improvement ≥ 4,[b] %		N = 276	N = 278	N = 280	N = 268	N = 268	N = 269
	Week 16	22.8	75.0*	81.4*	28.7	70.9*	83.5*
Quality of Life							
Patients achieving DLQI improvement ≥ 4,[c] %		N = 250	N = 254	N = 256	N = 250	N = 251	N = 251
	Week 16	29.0	75.4*	82.0*	28.4	71.7*	77.6*
Patients achieving DLQI 0/1,[d] %		N = 252	N = 258	N = 261	N = 257	N = 252	N = 256
	Week 16	4.4	30.3*	41.5*	4.7	23.8*	37.9*

*$P < .001$ for all UPA vs PBO.
[a]Among patients with Worst Pruritus NRS ≥4 at baseline, based on a rolling average calculated from the 7 consecutive days.
[b]Among patients with POEM total score ≥4 at baseline.
[c]Among patients ≥ 16 years with DLQI ≥4 at baseline.
[d]Among patients ≥ 16 years with DLQI >1 at baseline.
DLQI, Dermatology Life Quality Index; EASI 75/90, ≥ 75%/90% improvement in Eczema Area and Severity Index; NRS, numerical rating scale; PBO, placebo; POEM, Patient Oriented Eczema Measure; UPA, upadacitinib; vIGA-AD, validated Investigator's Global Assessment for Atopic Dermatitis.

Table 2. Treatment-emergent Adverse Events in the Double-blind Period

	PBO		UPA 15 mg		UPA 30 mg	
TEAEs, n (%)	**Measure Up 1 N = 281**	**Measure Up 2 N = 278**	**Measure Up 1 N = 281**	**Measure Up 2 N = 276**	**Measure Up 1 N = 285**	**Measure Up 2 N = 282**
Any TEAE	166 (59.1)	146 (52.5)	176 (62.6)	166 (60.1)	209 (73.3)	173 (61.3)
SAEs	8 (2.8)	8 (2.9)	6 (2.1)	5 (1.8)	8 (2.8)	7 (2.5)
AEs leading to discontinuation of study drug	12 (4.3)	12 (4.3)	4 (1.4)	11 (4.0)	11 (3.9)	7 (2.5)
Deaths	0	0	0	0	0	0
AESIs						
Serious infections	0	2 (0.7)	2 (0.7)	1 (0.4)	2 (0.7)	2 (0.7)
Opportunistic infection excluding TB, herpes zoster, and eczema herpeticum	0	0	0	0	0	0
Eczema herpeticum	4 (1.4)	0	0	3 (1.1)	3 (1.1)	0
Herpes zoster	0	2 (0.7)	5 (1.8)	6 (2.2)	6 (2.1)	3 (1.1)
Active TB	0	0	0	0	0	0
NMSC	0	0	1 (0.4)	2 (0.7)	0	1 (0.4)
Malignancy excluding NMSC	0	0	0	0	2 (0.7)	1 (0.4)
Hepatic disorder	2 (0.7)	4 (1.4)	5 (1.8)	2 (0.7)	8 (2.8)	4 (1.4)
Adjudicated GI perforations	0	0	0	0	0	0
Anemia	1 (0.4)	2 (0.7)	1 (0.4)	2 (0.7)	5 (1.8)	4 (1.4)
Neutropenia	2 (0.7)	1 (0.4)	4 (1.4)	2 (0.7)	15 (5.3)	6 (2.1)
Lymphopenia	2 (0.7)	0	1 (0.4)	0	2 (0.7)	1 (0.4)
Renal dysfunction	0	0	0	0	0	0
Adjudicated MACE	0	0	0	0	0	0
Adjudicated VTE	0	1 (0.4)	0	0	0	0

AE, adverse event; AESI, adverse event of special interest; GI, gastrointestinal; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; PBO, placebo; SAE, serious adverse event; TB, tuberculosis; TEAE, treatment-emergent adverse event; UPA, upadacitinib; VTE, venous thromboembolic event.