Patient-Reported Outcomes in Subjects with Atopic Dermatitis Treated with Tapinarof Cream: Results from a Phase 2b, Randomized Parallel-Group Study

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SYNOPSIS

- Atopic dermatitis (AD) is a chronic relapsing skin disease[1] characterized by pruritus, burning sensations, xerosis, erythematous papules and plaques, exudation, crusting, and lichenification[2]
- Patients with AD report an impact on sleep, quality of life, and psychosocial domains (social, academic, and occupational) due to persistent, intense pruritus, and the stigma associated with having visibly diseased skin[1,2]
- The primary goal in the treatment of AD is to stabilize the disease and reduce the number of flares[1]
- Tapinarof cream is a therapeutic aryl hydrocarbon receptor modulating agent (TAMA) under investigation for the treatment of AD and psoriasis
- This Phase 2b dose-finding study (ClinicalTrials.gov ID: NCT02564055) was designed to assess the efficacy and safety of tapinarof cream in adolescents and adults with AD
- The primary analysis showed that tapinarof cream was efficacious and well tolerated in adolescents and adults with AD[2]

OBJECTIVES

- To present patient-reported outcomes from the Phase 2b study in subjects with AD following treatment with topical tapinarof cream, including adolescent and adult impression of change in severity of AD symptoms and pruritus, changes in expanded Patient-Oriented Eczema Measure (POEM), and Daily Sign and Symptom Severity Diary scores

METHODS

Study Design

- In this multicenter (United States, Canada, and Japan), Phase 2b, double-blind, vehicle-controlled randomized study, subjects with AD were randomized 1:1:1:1:1:1 to receive tapinarof cream 0.5% or 1% once (QD) or twice daily (BID) or vehicle QD or BID for 12 weeks and followed up for 4 more weeks (**Figure 1**)

Figure 1. Study Design

*Excluding scalp. AD, atopic dermatitis; BID, twice daily; BSA, body surface area; IGA, Investigator Global Assessment; QD, once daily.

Study Outcomes and Statistical Analysis

- The primary endpoint was the proportion of subjects with an Investigator Global Assessment (IGA) score of clear or almost clear (0 or 1) and ≥2-grade improvement in IGA score from baseline to Week 12[2]
- Subject-reported outcomes assessed in this study included subject impression of severity of AD symptoms, overall change in severity of AD symptoms, overall change in severity of pruritus symptoms, the expanded POEM, and a Daily Sign and Symptom Severity Diary
  - Subjects were asked to rate the overall severity of their AD symptoms and overall severity of their pruritus symptoms at baseline on a scale ranging from 1 'mild' to 4 'very severe'
  - The change in overall severity of AD symptoms and pruritus symptoms from baseline to Week 12 was rated by subjects from 1 'very improved' to 7 'very worse'
  - The expanded POEM consisted of seven symptoms (skin that is itchy, bleeding, weeping or oozing, cracked, flaking, dry or rough, and disturbed sleep) measured using a 5-point scale of frequency of occurrence during the previous week plus three additional questions to assess sleep
  - The self-administered Daily Sign and Symptom Severity Diary assessed the severity of 11 disease-related signs and symptoms (skin that is itchy, discolored, bleeding, oozing, cracked, scaly, flaky, dry or rough, painful, burning, and stinging). Response options were on an 11-point numeric rating scale and ranged from 0 'absent' to 10 'worst imaginable'
- Incidence, frequency, and nature of adverse events (AEs) and serious AEs were collected from the start of study treatment until end of study visit at Week 16
- No formal hypothesis tests were planned

RESULTS

Subject Characteristics

- A total of 247 subjects (of 363 subjects originally screened) were randomized into the study at 32 sites in the United States, eight sites in Canada, and 13 sites in Japan (intent-to-treat analysis population)
- Of those randomized, 191 subjects (77%) completed the study including the Week 16 follow-up visit
- Overall, mean demographic and baseline characteristics were comparable across treatment groups (**Table 1**)
- Most subjects (91%) had a baseline IGA score of 3 (moderate) and a baseline mean Eczema Area and Severity Index (EASI) score of 11.3 (standard deviation 6.0)
- Primary endpoint: IGA response rates (defined as IGA score 0 or 1 and ≥2-grade improvement) at Week 12 were higher in the tapinarof cream groups than the vehicle groups (53% [1% BID], 46% [1% QD], 37% [0.5% BID], 34% [0.5% QD] vs 24% [vehicle BID] and 28% [vehicle QD]) and were maintained for 4 weeks after the end of study treatment (non-responder imputation method)[2]

Table 1. Baseline Subject Demographics and Characteristics

	Tapinarof 1% cream		Tapinarof 0.5% cream		Vehicle	
	BID (n=40)	QD (n=41)	BID (n=43)	QD (n=41)	BID (n=42)	QD (n=40)
Mean age, years (SD)	28.5 (13.9)	31.6 (15.7)	29.0 (15.9)	29.3 (14.0)	27.9 (14.7)	29.4 (15.2)
Aged 12–17 years, n (%)	11 (28)	13 (32)	13 (30)	12 (29)	13 (31)	11 (28)
Aged 18–65 years, n (%)	29 (73)	28 (68)	30 (70)	29 (71)	29 (69)	29 (73)
Male sex, n (%)	22 (55)	17 (41)	26 (60)	19 (46)	19 (45)	23 (58)
IGA score, mean (SD)	3.1 (0.2)	3.1 (0.3)	3.1 (0.3)	3.1 (0.3)	3.1 (0.4)	3.1 (0.3)
EASI score, mean (SD)	9.8 (5.2)	10.9 (6.1)	13.1 (6.7)	11.4 (5.8)	11.1 (5.9)	11.1 (5.8)
% BSA affected, mean (SD)	14.8 (8.7)	18.7 (11.0)	19.7 (10.5)	17.6 (9.9)	14.5 (9.2)	16.0 (10.3)
Pruritus score, mean (SD)*	5.2 (2.3)	5.4 (1.9)	5.7 (2.5)	5.7 (2.0)	5.1 (2.0)	5.8 (1.9)

*Mean scores based on a numeric rating scale of 0 'absent' to 10 'worst imaginable'. Data provided for the safety analysis population (n=247).
BID, twice daily; BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; QD, once daily; SD, standard deviation.

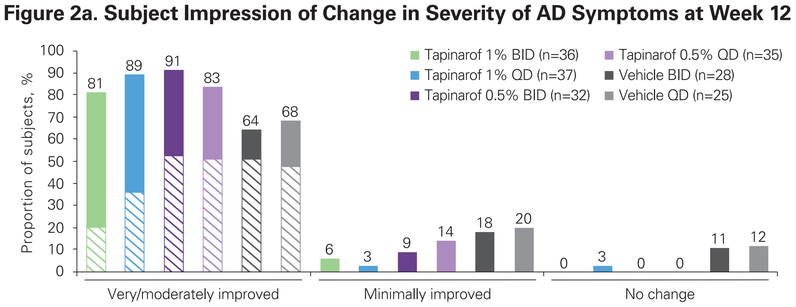
Subject Impressions

- At baseline, 86% of subjects rated their AD symptoms as moderate or severe across all treatment groups: 28–60% rated as moderate and 28–53% rated as severe
- At Week 12, a greater proportion of subjects in the tapinarof cream groups (81–89% in the 1% groups and 83–91% in the 0.5% groups) rated the overall severity of their AD symptoms as 'very/moderately improved' compared with 64–68% in the vehicle groups (**Figure 2a**)
- At Week 12, a greater proportion of subjects in the tapinarof cream groups (78–87% in the 1% groups and 80–81% in the 0.5% groups) rated the overall severity of their pruritus symptoms as 'very/moderately improved' compared with 47–64% in the vehicle groups (**Figure 2b**)

Expanded POEM

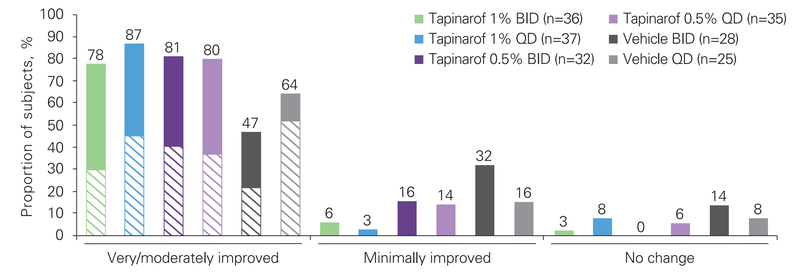
- At Week 12, improvements were observed in all tapinarof cream and vehicle-treated groups on all seven POEM items, except for the question relating to weeping or oozing for the 1% BID group
- The three additional items in the expanded POEM showed overall sleep quality improved across all treatment groups, with the largest improvements in the tapinarof cream groups
  - For item 8 related to how many nights subjects woke up at least once because of AD, the mean change reductions were largest in the tapinarof cream 0.5% groups (BID: –1.3 and QD: –1.2)
  - For items 9 and 10 related to how difficult it was it for subjects to fall asleep or fall back asleep after waking because of AD, the number of subjects finding it difficult or very difficult to fall (back) asleep were lower in all treatment groups at Week 12 compared with baseline, except for one subject in the vehicle BID group for item 10

Figure 2a. Subject Impression of Change in Severity of AD Symptoms at Week 12



Results derived from the ITT analysis population. Hatched portion of bar corresponds to proportion of subjects with 'moderately improved' symptoms. AD, atopic dermatitis; BID, twice daily; ITT, intent-to-treat; QD, once daily.

Figure 2b. Subject Impression of Change in Severity of Pruritus Symptoms at Week 12



Results derived from the ITT analysis population. Hatched portion of bar corresponds to proportion of subjects with 'moderately improved' symptoms. BID, twice daily; ITT, intent-to-treat; QD, once daily.

Daily Sign and Symptom Severity Diary

- The highest mean baseline scores were seen for dry or rough, red or discolored, and flaky skin
  - Overall, there was an improvement in dry or rough, red or discolored, and flaky skin in all treatment groups as measured by the Daily Sign and Symptom Severity Diary scores, with the improvement being consistently smaller for the vehicle BID group vs the active tapinarof treatment groups for all items

Safety

- Overall, 51% (127/247) of subjects had treatment-emergent AEs (TEAEs): 56% in the tapinarof cream groups and 41% in the vehicle groups, and were mostly mild to moderate in severity
- The most frequently reported TEAE was nasopharyngitis (**Table 2**)

Table 2. Safety Overview and Most Common TEAEs (Occurring in ≥5% of Subjects in Any Group)

Preferred term, n (%)	Tapinarof 1% cream		Tapinarof 0.5% cream		Vehicle	
	BID (n=40)	QD (n=41)	BID (n=43)	QD (n=41)	BID (n=42)	QD (n=40)
Any TEAE	28 (70)	22 (54)	20 (47)	23 (56)	19 (45)	15 (38)
Treatment-related TEAEs	6 (15)	6 (15)	8 (19)	4 (10)	6 (14)	2 (5)
Serious TEAEs	1 (3)	0	0	0	0	0
Discontinuations due to TEAEs	1 (3)	0	5 (12)	1 (2)	4 (10)	2 (5)
TEAE by intensity						
Mild	14 (35)	14 (34)	11 (26)	14 (34)	12 (29)	7 (18)
Medium	14 (35)	8 (20)	6 (14)	8 (20)	4 (10)	8 (20)
Moderate	0	0	3 (7)	1 (2)	3 (7)	0
TEAEs occurring in ≥5% of subjects in any group						
Nasopharyngitis	3 (8)	5 (12)	4 (9)	1 (2)	4 (10)	3 (8)
Folliculitis	4 (10)	8 (20)	3 (7)	3 (7)	0	0
Dermatitis atopic	2 (5)	0	3 (7)	1 (2)	4 (10)	5 (13)
URTI	4 (10)	2 (5)	3 (7)	2 (5)	3 (7)	1 (3)
Headache	4 (10)	1 (2)	1 (2)	3 (7)	0	2 (5)
Acne	2 (5)	0	1 (2)	3 (7)	1 (2)	0
Impetigo	1 (3)	0	0	0	0	3 (8)

TEAE was defined as an AE that occurred on or after study treatment start date and on or before the last visit. AE, adverse event; BID, twice daily; QD, once daily; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

CONCLUSIONS

- In all tapinarof cream groups, a greater proportion of subjects (81–91%) reported AD signs and symptoms as 'very/moderately improved' after 12 weeks compared with the vehicle groups (64–68%)
- Similarly, a greater proportion of subjects in the tapinarof cream groups (78–87%) reported the overall severity of pruritus as 'very/moderately improved' after 12 weeks compared with the vehicle groups (47–64%)
- Overall, tapinarof cream was well tolerated and these results correspond to the previously reported clinical efficacy findings[2]
- Study findings demonstrated that tapinarof cream represents an important potential advance in topical medicine development, with beneficial effects on patient-reported outcomes in adolescents and adults with AD

REFERENCES

1. Drucker AM et al. *J Invest Dermatol.* 2017;137:26–30; 2. Peppers J et al. *J Am Acad Dermatol.* 2018; doi: 10.1016/j.jaad.2018.06.047

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