Title

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ORIGINAL RESEARCH

Tapinarof Improved Outcomes and Sleep for Patients and Families in Two Phase 3 Atopic Dermatitis Trials in Adults and Children

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ABSTRACT

***Introduction*:** Tapinarof is a topical aryl hydrocarbon receptor (AhR) agonist in development for the treatment of atopic dermatitis (AD). In two phase 3 trials (ADORING 1 and 2), tapinarof cream 1% once daily (QD) demonstrated significant efficacy and was well tolerated in patients down to age 2 years with AD. Here, we evaluate patient-reported outcomes (PROs), including family impact, with tapinarof in ADORING 1 and 2.

***Methods*:** In ADORING 1 and 2, 813 patients were randomized to tapinarof or vehicle QD for 8 weeks. PROs were assessed using the Dermatology Life Quality Index (DLQI), Children's Dermatology Life Quality Index (CDLQI), Infants' Dermatitis Quality of Life Index (IDQOL), Dermatitis Family Impact Questionnaire (DFI), and Patient Oriented Eczema Measure (POEM).

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***Results*:** Mean baseline DLQI, CDLQI, IDQOL, and DFI scores indicated that the impact on families and patients' quality of life (QoL) of AD was moderate to very large. Mean POEM scores indicated moderate to severe AD symptoms at baseline. Tapinarof improved QoL versus vehicle across all endpoints at week 8: DLQI, −6.2 vs −3.5 ($P=0.0031$) and −5.5 vs −3.5 ($P=0.0028$); DFI, −5.6 vs −2.9 ($P<0.0001$) and −5.6 vs −3.8 ($P=0.0037$), in ADORING 1 and 2, respectively. Similar improvements in CDLQI and IDQOL were reported with tapinarof versus vehicle. Tapinarof also significantly improved CDLQI, DFI, and POEM sleep subdomain scores versus vehicle. POEM scores also improved with tapinarof versus vehicle: ≥ 12 years, −9.4 vs −5.3 and −10.6 vs −3.6 (both $P<0.0001$); < 12 years, −11.4 vs −5.7 ($P<0.0001$), and −10.8 vs −7.3 ($P=0.0005$).
***Conclusions*:** Tapinarof significantly improved QoL across PROs, including sleep and family impact, regardless of age, from week 1 (the earliest evaluation) through week 8. Tapinarof is a once-daily, non-steroidal cream that rapidly improves AD symptoms, sleep, and QoL in patients down to age 2 years with AD.
***Trial Registration*:** Clinical Trials.gov identifier: NCT05014568; NCT05032859.

Keywords: Atopic dermatitis; Family impact; Patient-reported outcomes; Quality of life; Sleep improvement; Tapinarof cream 1% once daily; Topical aryl hydrocarbon receptor agonist

Key Summary Points

Why carry out this study?

Patients with atopic dermatitis (AD) report lower quality of life (QoL) and greater psychological distress than the general population. AD also impacts the QoL and sleep of family members.

Few AD studies evaluate how non-steroidal topical monotherapy impacts QoL and the family.

In ADORING 1 and 2, two phase 3 trials, tapinarof cream 1% once daily (QD) demonstrated significant efficacy and was well tolerated in adults and children down to 2 years of age with AD; here, patient-reported outcomes, including QoL, sleep and family impact, are reported.

What was learned from the study?

Tapinarof cream 1% QD demonstrated significant improvements across patient-reported AD symptoms, sleep, and QoL, regardless of age, from week 1 (the first assessment) through week 8.

Tapinarof is a once-daily, non-steroidal cream that rapidly improves AD symptoms, sleep, and QoL in patients down to 2 years of age with AD.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by eczematous lesions and intense pruritus [1, 2]. Pruritus (itch) is the most burdensome symptom, often leading to excoriation, bleeding, or infection [3, 4]. AD negatively impacts the quality of life (QoL) of affected children and adults, including effects on physical activity, sleep, school attentiveness and learning, and psychological well-being (e.g., low self-esteem) [1, 5–8]. Sleep disturbance can impact function (at school/work and home), mood, and interpersonal relationships [9]. Insomnia can also lead to the development of

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anxiety and depression, and increase the risk for psychiatric conditions [10]. AD also has the potential to impact children's growth and psychological development through multiple mechanisms, including the effect of sleep disruption on secretion of growth hormone, and the effects of certain AD therapies, such as systemic corticosteroids [11–13].

AD can have far-reaching effects beyond affected children, with detrimental effects on caregivers and the family unit [3]. A child with AD can substantially affect family life, including through disturbed sleep, and can impact the mental and social well-being of other family members [3, 14]. In addition to parental sleep loss, AD may place a great financial burden on families, including healthcare provider visits, medications, transportation costs, and parental work productivity losses [3, 15, 16]. Family members of children with AD, particularly parents/caregivers, may also experience feelings of helplessness regarding their child's symptoms [14]. Understanding the burden of AD on the family may lead to improved medical, family, and psychosocial outcomes [17].

Management of AD includes reducing symptoms and improving QoL for patients and caregivers. Topical therapy forms the mainstay of treatment for patients with AD; however, topical corticosteroids (TCSs), although efficacious, are associated with adverse events that limit their use [18, 19]. The use of TCSs is often limited, particularly in sensitive skin areas, and among infants and children who are at increased risk of systemic absorption and adverse events [20–22]. Topical calcineurin inhibitors may be used to treat sensitive skin areas but are associated with application-site irritation, burning, and stinging [19, 23, 24]. Patients are often instructed to apply multiple topical therapies from different therapeutic classes, leading to difficulties in adherence to complex regimens [25, 26]. There is an unmet need for efficacious and well-tolerated topical monotherapies that are suitable for all patients, including very young children, without limitations on duration of use, application sites, and disease severity [27, 28].

Tapinarof (VTAMA®, Dermavant Sciences, an Organon Company) is a first-in-class, non-steroidal, topical aryl hydrocarbon receptor (AhR) agonist approved by the US Food and Drug Administration for the treatment of AD in adults and children down to 2 years of age and for the treatment of plaque psoriasis in adults, and under investigation for the treatment of plaque psoriasis in children down to 2 years of age [29]. Tapinarof binds to and activates AhR to restore the skin barrier through upregulation of skin barrier components (filaggrin, loricrin, hornerin, involucrin, and ceramide lipids), downregulate pro-inflammatory cytokines interleukin (IL)-4, IL-5, IL-13, and IL-31 that are implicated in AD and itch, and to reduce oxidative stress, both via direct free radical scavenging and through the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway (Supplementary Fig. S1) [27].

In ADORING 1 and ADORING 2, two pivotal phase 3, randomized, double-blind, vehicle-controlled trials, tapinarof cream 1% once daily (QD) monotherapy demonstrated statistically significant efficacy and was well tolerated in a diverse population of adults and children down to 2 years of age with AD [30]. Tapinarof cream also demonstrated rapid, statistically significant, and clinically meaningful reductions in pruritus in this patient population [31]. We report patient-reported outcomes, including family impact and sleep improvement, from the phase 3 ADORING 1 and 2 trials.

METHODS

Trial Design

In ADORING 1 and 2, two identically designed phase 3, double-blind, randomized, vehicle-controlled trials, patients with moderate to severe AD were randomized 2:1 to tapinarof cream 1% or vehicle QD for 8 weeks (Supplementary Fig. S2). Following the double-blind period, eligible patients could enroll in an open-label, long-term extension trial (ADORING 3, NCT05142774) for an additional 48 weeks of treatment or complete a follow-up visit, 1 week after the end of treatment (week 9).

Trials were conducted according to Good Clinical Practice and the Declaration of Helsinki. Approval was obtained from all local ethics

committees or institutional review boards. All patients (or parents/legal guardians) provided written informed consent.

Trial Participants

Key inclusion and exclusion criteria for ADORING 1 and 2 were previously reported [30]. Patients were adults and children down to 2 years of age with a diagnosis of AD by Hanifin and Rajka criteria [32], with a Validated Investigator Global Assessment for Atopic Dermatitis™ (vIGA-AD™) score of ≥ 3 (moderate or severe), an Eczema Area and Severity Index (EASI) score of ≥ 6, and body surface area (BSA) involvement of 5–35% at screening and baseline.

Outcome Measures

DLQI, CDLQI, and IDQOL

Impact on QoL was reported using the Dermatology Life Quality Index (DLQI) in patients aged ≥ 16 years; the Children's Dermatology Life Quality Index (CDLQI) in patients aged 4–15 years; and the Infants' Dermatitis Quality of Life Index (IDQOL) in patients aged 2–3 years. These validated, dermatology-specific questionnaires assess the impact of the disease on QoL for adults, children, and infants, respectively.

The DLQI and CDLQI are 10-item questionnaires; each question rates impact on QoL on a 4-point scale from 0 (not at all) to 3 (very much). DLQI questions are grouped into six domains: symptoms and feelings; daily activities; leisure; work and school performance; personal relationships; and treatment. Total scores for DLQI range from 0 to 30, with 0–1 = no effect on a patient's life; 2–5 = small effect; 6–10 = moderate effect; 11–20 = very large effect; and 21–30 = extremely large effect [33]. CDLQI questions are also grouped into six domains: symptoms and feelings; leisure; school/holidays; personal relationships; sleep; and treatment. CDLQI total scores range from 0 to 30, with 0–1 = no effect; 2–6 = small effect; 7–12 = moderate effect; 13–18 = very large effect; and 19–30 = extremely large effect [34]. The IDQOL is a 10-item questionnaire; each question rates the impact on QoL on a 4-point scale. The sum of IDQOL item scores gives a total from 0 to 30, with lower scores indicating better QoL.

A minimal clinically important difference (MCID) of four points from baseline has been established for DLQI in adults with AD [35]. For adolescents with AD, a change of 6–8 points can be considered clinically meaningful for CDLQI scores [36].

DFI

AD has been shown to disrupt normal life and affect the social and psychological development of the affected child and other family members [37]. The Dermatitis Family Impact Questionnaire (DFI) for patients aged 15 years or younger evaluates how having a child with AD may affect the QoL and sleep of family members. The DFI is a 10-item questionnaire that is completed for pediatric patients < 16 years of age by a parent/caregiver aged ≥ 16 years of age; each question rates the impact on QoL of family members on a 4-point scale from 0 (not at all) to 3 (very much) [37, 38]. Total scores range from 0 to 30, with lower scores indicating less impact. Aspects of family life that are evaluated include emotional distress, sleep, expenditure, relationships, and daily activities [37]. The DFI sleep question was assessed post hoc and pooled for ADORING 1 and 2.

POEM

The Patient Oriented Eczema Measure (POEM) is used for monitoring AD severity, as experienced by patients. The POEM is endorsed by the Harmonizing Outcome Measures for Eczema (HOME) initiative as the most appropriate instrument for patients to measure symptoms in clinical trials [39]. The POEM comprises seven questions, including one evaluating sleep disturbance; total scores range from 0–28, with 0–2 = clear or almost clear; 3–7 = mild AD; 8–16 = moderate AD; 17–24 = severe AD; and 25–28 = very severe AD.

Patients aged ≥ 12 years self-completed the POEM, and parents/caregivers proxy-completed for children aged < 12 years. Increased severity of AD correlates with a greater reduction in QoL of family members [3]. A change of 6–8 points can be considered clinically meaningful for POEM score overall [36, 40]. The POEM sleep question was assessed post hoc and pooled for age groups and trials (ADORING 1 and 2).

Safety

Safety assessments included incidence and frequency of treatment-emergent adverse events (TEAEs).

Statistical Analysis

Continuous variables were analyzed using an analysis of covariance model with treatment as a main effect and the baseline value of the endpoint as a continuous covariate.

RESULTS

Baseline Patient Demographics and Disease Characteristics

Baseline demographics and disease severity, including patient-reported outcomes, including family impact, were similar across groups in ADORING 1 and 2 (Table 1). Overall, 80% of patients were children (aged 2–17 years). At baseline, 83.7–90.4% of patients had a vIGA-AD™ score of 3 (moderate), mean EASI scores were 12.2–13.5, and mean BSA affected was 15.8–17.7% across groups and trials. Mean baseline DLQI, CDLQI, IDQOL, and DFI scores were similar among the treatment groups and trials: 8.6–10.1, 8.6–9.7, 10.0–11.6, and 7.7–9.1, respectively. Baseline patient-reported measures, including family impact, indicated a significant burden of AD on patients and family members, with a moderate to large effect on QoL. Mean baseline POEM scores (ages ≥ 12 and < 12 years) were 16.4–17.4. Patients/caregivers reported moderate to severe AD symptoms, as assessed by the POEM.

Patient-Reported Outcomes

DLQI, CDLQI, IDQOL, and DFI

Greater improvements (reductions) in mean DLQI scores (patients aged ≥ 16 years) from baseline were demonstrated with tapinarof cream compared with vehicle at week 1, the earliest assessment. Improvements in DLQI reached statistical significance and exceeded the MCID of a 4-point reduction at week 2 in both ADORING 1 and 2: − 5.2 vs − 3.3 ($P = 0.0229$) and − 4.5 vs − 2.8 ($P = 0.0040$), respectively (Fig. 1). Significant improvements in DLQI continued through week 8: − 6.2 vs − 3.5 ($P = 0.0031$) and − 5.5 vs − 3.5 ($P = 0.0028$) in ADORING 1 and 2, respectively.

Tapinarof cream demonstrated significant improvements in mean CDLQI scores (aged 4–15 years) versus vehicle at week 1: − 3.4 vs − 1.8 ($P = 0.0039$) and − 3.9 vs − 1.6 ($P = 0.0001$) in ADORING 1 and 2, respectively (Fig. 2). Improvement in CDLQI with tapinarof compared with vehicle exceeded the MCID of six points at week 4 in ADORING 2: − 6.4 vs − 4.1 ($P < 0.0001$). Mean improvements from baseline with tapinarof cream versus vehicle continued through week 8: − 5.2 vs − 3.8 ($P = 0.0043$) and − 6.8 vs − 4.1 ($P < 0.0001$) in ADORING 1 and 2, respectively. Mean CDLQI sleep subdomain scores significantly improved with tapinarof versus vehicle at week 8: − 0.9 vs − 0.6 ($P = 0.0148$) and − 1.0 vs − 0.5 ($P < 0.0001$) in ADORING 1 and 2. Similar early improvements in IDQOL (aged 2–3 years) were demonstrated with tapinarof cream versus vehicle at week 1, continuing through week 8 in both trials. The IDQOL patient groups were too few in number to make meaningful interpretations.

Improvements in mean DFI scores were significantly greater with tapinarof cream compared with vehicle at week 1, the first assessment, in ADORING 1: − 3.4 vs − 1.6 ($P < 0.0001$) and at week 2 in ADORING 2: − 4.0 vs − 2.8 ($P = 0.0461$) (Fig. 3). Statistically significant

Table 1 Baseline patient demographics and clinical characteristics

Characteristic	ADORING 1		ADORING 2	
	Tapinarof 1% QD (*n* = 270)	Vehicle QD (*n* = 137)	Tapinarof 1% QD (*n* = 271)	Vehicle QD (*n* = 135)
Age, years, mean (SD)	15.6 (16.6)	15.6 (16.5)	16.4 (16.2)	16.7 (16.1)
Age group, *n* (%)				
2–6 years	76 (28.1)	39 (28.5)	65 (24.0)	32 (23.7)
7–11 years	75 (27.8)	37 (27.0)	64 (23.6)	32 (23.7)
12–17 years	67 (24.8)	34 (24.8)	89 (32.8)	44 (32.6)
≥ 18 years	52 (19.3)	27 (19.7)	53 (19.6)	27 (20.0)
Male, *n* (%)	130 (48.1)	66 (48.2)	117 (43.2)	58 (43.0)
Race*, *n* (%)				
White	152 (56.3)	79 (57.7)	124 (45.8)	58 (43.0)
Black or African American	70 (25.9)	38 (27.7)	95 (35.1)	47 (34.8)
Asian	26 (9.6)	10 (7.3)	39 (14.4)	23 (17.0)
Other groups†	16 (5.9)	5 (3.6)	7 (2.6)	4 (3.0)
Not reported	6 (2.2)	5 (3.6)	6 (2.2)	3 (2.2)
Fitzpatrick skin type, *n* (%)				
I–III	135 (50.0)	60 (43.8)	113 (41.7)	65 (48.1)
IV–VI	135 (50.0)	77 (56.2)	158 (58.3)	70 (51.9)
vIGA-AD™ score, *n* (%)				
3 (Moderate)	244 (90.4)	122 (89.1)	228 (84.1)	113 (83.7)
4 (Severe)	26 (9.6)	15 (10.9)	43 (15.9)	22 (16.3)
EASI score, mean (SD)	12.2 (5.0)	12.9 (5.6)	13.5 (5.6)	13.1 (4.7)
BSA affected, mean (SD)	16.5 (8.7)	17.7 (9.5)	17.1 (8.7)	15.8 (7.9)
DLQI (≥ 16 years), mean (SD)	9.2 (5.8)	10.1 (5.6)	9.3 (6.6)	8.6 (5.5)
CDLQI (4–15 years), mean (SD)	8.6 (5.7)	9.6 (6.6)	9.7 (6.8)	9.5 (6.0)
IDQOL (2–3 years), mean (SD)	11.0 (5.8)	10.4 (5.3)	11.6 (7.0)	10.0 (7.0)
POEM (≥ 12 years), mean (SD)	16.7 (6.6)	17.4 (6.8)	16.4 (7.3)	17.3 (6.0)
POEM (< 12 years), mean (SD)	17.4 (6.2)	16.4 (6.7)	17.1 (6.1)	17.0 (6.3)
DFI (≤ 15 years), mean (SD)	8.2 (6.7)	7.7 (6.8)	7.8 (6.9)	9.1 (7.4)

BSA body surface area, *CDLQI* Children's Dermatology Life Quality Index, *DFI* Dermatology Family Impact, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *IDQOL* Infants' Dermatitis Quality of Life Index, *QD* once daily, *POEM* Patient Oriented Eczema Measure, *SD* standard deviation, *vIGA-AD™* Validated Investigator Global Assessment for Atopic Dermatitis™

*Race was patient reported

†"Other groups" comprised American Indian or Alaska Native, Native Hawaiian or Pacific Islander, or multiple races

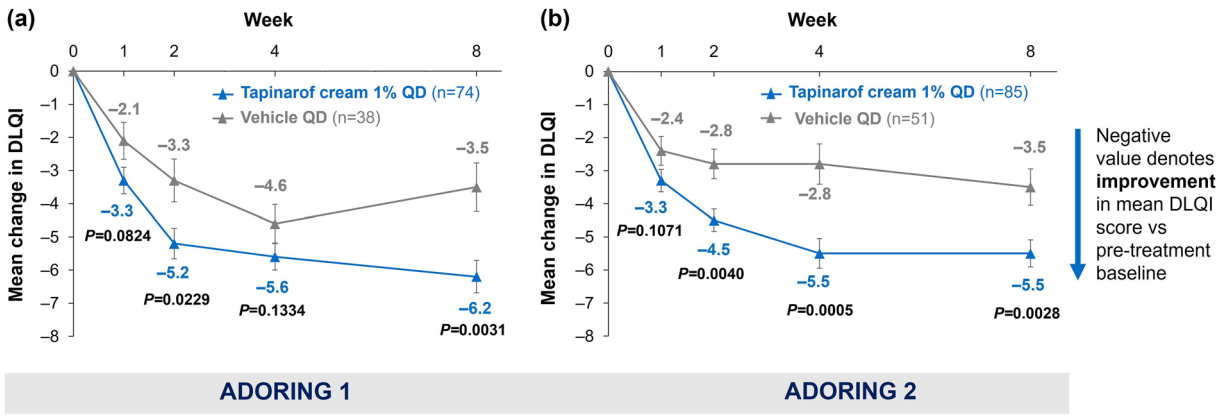

Fig. 1 Improvement in DLQI total score as early as week 1 (patients aged ≥ 16 years) in **a** ADORING 1 and **b** ADORING 2. Intention-to-treat, observed cases. Least squares mean, standard error. *DLQI* Dermatology Life Quality Index, *QD* once daily

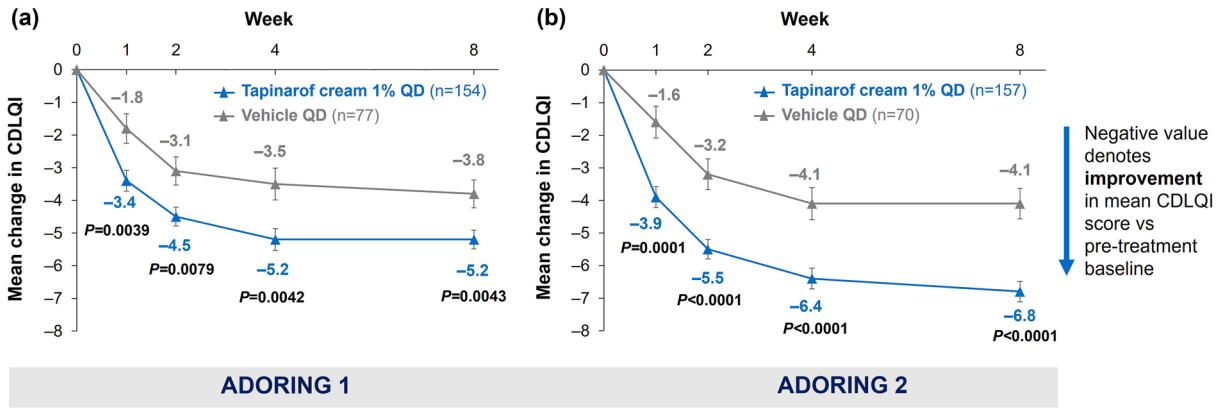

Fig. 2 Early, rapid, and continued improvement in CDLQI total score by visit (patients aged 4–15 years) in **a** ADORING 1 and **b** ADORING 2. Intention-to-treat, observed cases. Least squares mean, standard error. *CDLQI* Children's Dermatology Life Quality Index, *QD* once daily

improvements continued through week 8 in ADORING 1: −5.6 vs −2.9 ($P<0.0001$) and ADORING 2: −5.6 vs −3.8 ($P=0.0037$). Tapinarof demonstrated significant improvement in mean DFI sleep subdomain score versus vehicle as early as week 1: −0.4 vs −0.2 ($P=0.0112$) in a pooled analysis of ADORING 1 and 2. Sleep improvement continued through week 8: −0.7 vs −0.4 ($P<0.0001$).

POEM

Clinically meaningful improvements in POEM scores (AD severity) for patients aged < 12 years reached statistical significance and exceeded the MCID of six points with tapinarof compared with vehicle at week 1, the earliest assessment, in ADORING 1: −6.1 vs −3.4 ($P=0.0002$) and at week 2 in ADORING 2: −7.7 vs −5.1 ($P=0.0044$) (Fig. 4). Improvements continued through week 8: −11.4 vs −5.7 ($P<0.0001$) and −10.8 vs −7.3 ($P=0.0005$), in ADORING 1 and 2, respectively. For patients aged ≥ 12 years, significant improvements in mean POEM scores were reported with tapinarof cream at week 1: −4.6 vs −2.8 ($P=0.0282$) and −6.3 vs −2.5 ($P<0.0001$), through week 8: −9.4 vs −5.3 ($P<0.0001$) and

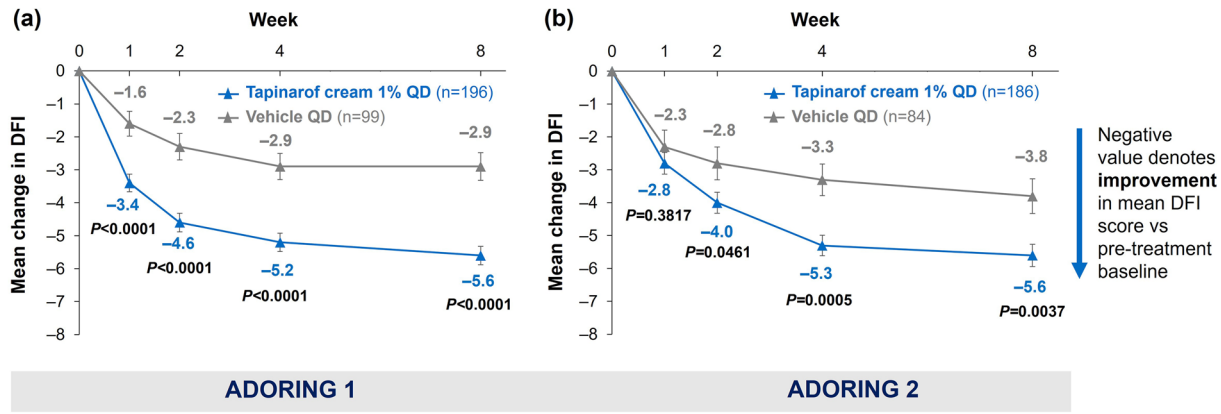

Fig. 3 Early and continued improvement in DFI total score by visit (patients aged < 116 years*) in **a** ADORING 1 and **b** ADORING 2. *The DFI questionnaire was completed for pediatric patients < 16 years of age by a parent/caregiver aged ≥ 16 years of age. Intention-to-treat, observed cases. Least squares mean, standard error. *DFI* Dermatitis Family Impact, *QD* once daily

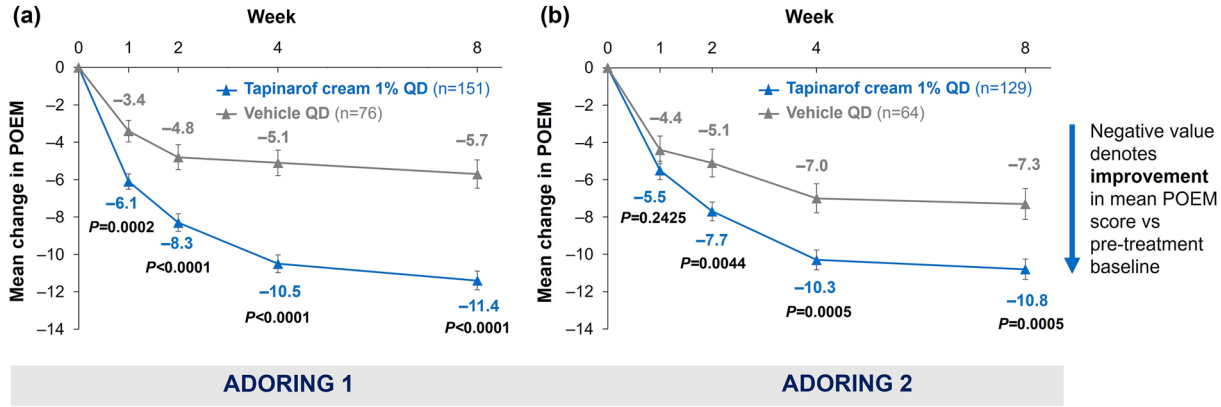

Fig. 4 Early, rapid, and continued improvement in AD symptoms measured by POEM total score (patients aged < 12 years) in **a** ADORING 1 and **b** ADORING 2. For patients aged < 12 years, the POEM was proxy-completed by parents/caregivers. Intention-to-treat, observed cases. Least squares mean, standard error. *AD* atopic dermatitis, *POEM* Patient Oriented Eczema Measure, *QD* once daily

−10.6 vs −3.6 ($P<0.0001$) in ADORING 1 and ADORING 2, respectively (Fig. 5).

Mean POEM sleep subdomain score (pooled ADORING 1 and 2; all patients) significantly improved as early as week 1, the first assessment, with tapinarof versus vehicle: −0.9 vs −0.5 ($P<0.0001$). Statistically significant improvement in sleep continued through week 8: −1.6 vs −0.9 ($P<0.0001$).

Case Photography

Case 1

The 7-year-old Black or African American patient in Fig. 6a had moderate AD (vIGA-AD™ = 3) at baseline. Prior to tapinarof treatment, this child experienced significant disease burden, impacting sleep and QoL. The baseline CDLQI score was 14 with a POEM score of 20 (indicating very large effect on QoL and

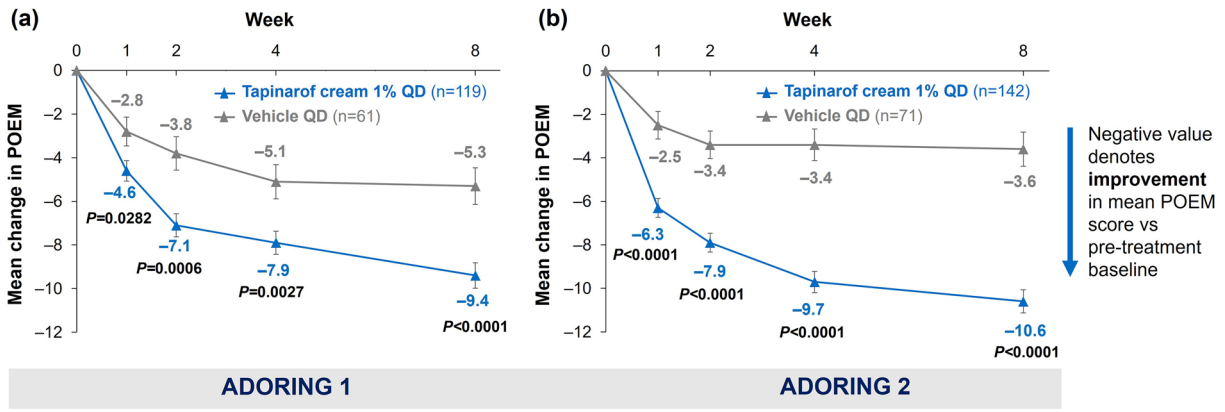

Fig. 5 Early, rapid, and continued improvement in AD symptoms measured by POEM total score by visit (patients aged ≥ 12 years) in **a** ADORING 1 and **b** ADORING 2. Patients aged ≥ 12 years self-completed the POEM. Intention-to-treat, observed cases. Least squares mean, standard error. *AD* atopic dermatitis, *POEM* Patient Oriented Eczema Measure, *QD* once daily

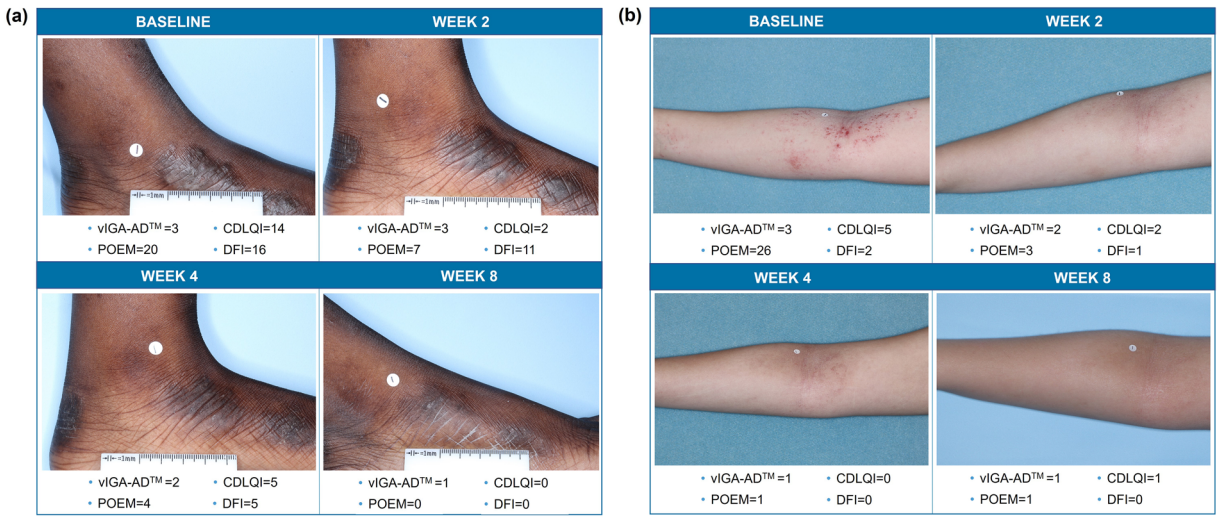

Fig. 6 **a** Rapid and continued improvement in PROs with tapinarof cream 1% QD in a 7-year-old Black or African American patient with AD. **b** Rapid improvement in PROs with tapinarof cream 1% QD in a 9-year-old white patient with AD. Examples of representative target lesions in tapinarof-treated patients from the ADORING 1 clinical trial. Individual results may vary. *AD* atopic dermatitis, *CDLQI* Children's Dermatology Life Quality Index, *DFI* Dermatitis Family Impact, *IDQOL* Infants' Dermatitis Quality of Life Index, *POEM* Patient Oriented Eczema Measure, *PRO* patient-reported outcome, *QD* once daily, *vIGA-AD*™ Validated Investigator Global Assessment for Atopic Dermatitis™

severe AD, assessed by the parent/caregiver). The parent/caregiver reported a DFI score of 16 at baseline. At week 8, the primary endpoint (vIGA-AD™ score of clear [0] or almost clear [1] and ≥ 2-grade improvement) was achieved. QoL rapidly improved to CDLQI = 2 (small effect on QoL) at week 2 and POEM = 4 (mild AD) at week 4. Improvements continued through week 8, with a CDLQI score of 0 indicating no impact of AD on the patient's QoL, a parent/caregiver-evaluated POEM score of 0 showing

clear AD, and a DFI score of 0 indicating no impact on the family.

Case 2

The 9-year-old white patient in Fig. 6b had moderate AD (vIGA-AD™ = 3) at baseline. At baseline, the parent/caregiver reported the patient's symptoms as very severe AD with a POEM score of 26 and CDLQI score of 5. The parent/caregiver reported a DFI score of 2 at baseline. At week 4, the patient achieved the primary endpoint (vIGA-AD™ score = 1), and her QoL rapidly improved to CDLQI = 0 (no effect on QoL) and POEM = 1 (almost clear AD). At week 4, the DFI score improved to 0 indicating no impact on the family. Improvements were sustained at week 8.

Safety

ADORING 1 and 2 safety data have been previously reported [30]. Most TEAEs were mild or moderate; the most common TEAEs (≥ 5% in any group) were folliculitis, headache, and nasopharyngitis. There were lower rates of trial discontinuations due to TEAEs with tapinarof compared with vehicle (ADORING 1: 1.9% vs 3.6%; ADORING 2: 1.5% vs 3.0%, respectively).

DISCUSSION

Tapinarof cream 1% QD demonstrated statistically significant and clinically meaningful improvements in patient-reported AD symptoms and QoL from week 1 (the earliest evaluation) through week 8, across measures and age groups. These patient-reported outcomes include impact of AD on the family/caregivers, as well as sleep and pruritus that are of major importance to patients with AD. Statistically significant and clinically meaningful improvements in CDLQI, DFI, and POEM sleep domains were also observed with tapinarof compared with vehicle. Tapinarof cream demonstrated rapid and significant reductions in pruritus, and a consistent safety profile across these and previously reported trials [31, 41, 42]. The most common TEAEs with tapinarof were folliculitis, headache, and nasopharyngitis.

Patients with AD have worse QoL and greater psychological distress than the general population [1, 5–7]. AD also impacts QoL and sleep of family members, including those involved in aspects of care and management of affected children [3]. AD management goals for patients and parents/caregivers involve reducing symptoms and improving QoL [19]. Patients or caregivers reported significant and clinically relevant improvements in QoL with tapinarof cream compared with vehicle, as assessed by CDLQI, DLQI, IDQOL, and DFI. These improvements were apparent as early as the first assessment at week 1 and continued through week 8. This is consistent with the improvements in patient-reported outcomes demonstrated with tapinarof cream in the pivotal and long-term extension trials for plaque psoriasis [41, 42].

Disrupted sleep is common in patients with AD, especially affecting children, resulting in impaired QoL for both patients and parents/caregivers. Lack of sleep and exhaustion may also impact education and employment [43], and can lead to the development of anxiety and depression [10]. Consequently, improvements in sleep may benefit the well-being of patients of all ages with AD and their families. In ADORING 1 and 2, tapinarof cream demonstrated significant and clinically meaningful improvements in CDLQI, DFI, and POEM sleep subdomain scores for adults and children down to 2 years of age.

Previous studies have shown that QoL correlates with AD disease activity and symptoms [4, 44]. Notably, in ADORING 1 and 2, patients or caregivers reported improvements in QoL and AD severity and symptoms (including pruritus) that were rapid, statistically significant, and clinically meaningful. The unfavorable impact of AD on sleep is well established and largely mediated through pruritus and scratching [20, 43]. Patients with baseline POEM scores indicating moderate to severe AD experienced significant improvement in AD symptoms (including pruritus) across all age groups after treatment with tapinarof cream. This may be due to the ability of tapinarof to decrease pro-inflammatory cytokines (particularly IL-4 and IL-31, which are key mediators of pruritus in AD) and promote

barrier repair through upregulation of skin barrier components [27, 45, 46].

A key strength of these trials was the large and diverse patient population, particularly with respect to the age and race of participants. A limitation included no assessment of long-term efficacy. In addition, the majority of patients entering these trials had a baseline vIGA-AD™ score of 3 (moderate disease), which may limit the generalizability of the findings to the full spectrum of AD severities.

CONCLUSION

Tapinarof cream 1% QD significantly improved AD symptoms and QoL, including sleep, compared with vehicle in patients with moderate to severe AD, irrespective of age. Tapinarof is a once-daily, non-steroidal cream that rapidly improves AD symptoms and QoL in patients down to 2 years of age with AD, and has the potential to be used without restrictions on duration of use, extent of BSA treated, or sites of application.

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Data Availability. Data from these trials are proprietary and not publicly available but may be made available, with conditions, upon reasonable request and with permission from the sponsor.

Declarations

Conflict of Interest. Eric L. Simpson reports grants and fees for participation as a consultant and principal investigator from Eli Lilly, LEO Pharma, Pfizer, and Regeneron; grants for participation as a principal investigator from Galderma and Merck & Co.; and fees for consultant services from AbbVie, Boehringer Ingelheim, Dermavant Sciences, Inc., Incyte, Forte Bio, Pierre Fabre Dermo, and Sanofi Genzyme. Adelaide A. Hebert has received research support paid to the medical school from AbbVie, Arcutis, Dermavant Sciences, Inc., and Pfizer; has received honoraria from Arcutis, Dermavant Sciences, Inc., Galderma, Incyte, LEO Pharma, Novan, Ortho Dermatologics, Sun Pharma, and Verrica; and has received honoraria as part of Data Safety Monitoring Boards for Alphyn, GSK, Ortho Dermatologics, and Sanofi Regeneron. John Browning has served as an investigator for AbbVie, Acelyrin, Amgen, Arcutis, Dermavant Sciences, Inc., Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron, Sanofi, UCB Pharma, and Vyne; and as a speaker for Krystal, Pfizer, and Regeneron. Rocco T. Serrao has served as a consultant and/or has received payment for the development of educational presentations, and/or has received grants from Abbott, AbbVie, Arcutis, Bristol Myers Squibb, Dermavant Sciences, Inc., Eli Lilly, Incyte, Janssen, Pfizer, Regeneron, and Sanofi-Genzyme. Howard Sofen has served as scientific adviser and/or clinical study investigator for AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant Sciences, Inc., Eli Lilly, Incyte, Janssen, LEO Pharma,

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