Tapinarof Cream 1% Once Daily for Plaque Psoriasis: Interim Analysis of a Long-Term Extension Trial of a Novel Therapeutic Aryl Hydrocarbon Receptor Modulating Agent

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BACKGROUND

- Tapinarof cream 1% once daily (QD) demonstrated highly statistically and clinically significant efficacy versus vehicle at 12 weeks and was well tolerated in adults with mild to severe plaque psoriasis in two identical pivotal phase 3 trials: PSOARING 1 (NCT03956355) and PSOARING 2 (NCT03983980), which enrolled 510 and 515 patients, respectively[1]
- Furthermore, a potential remittive effect warranting further investigation was observed in a 12-week phase 2b trial where efficacy with tapinarof cream 1% QD was maintained for 4 weeks after treatment cessation[2]

OBJECTIVE

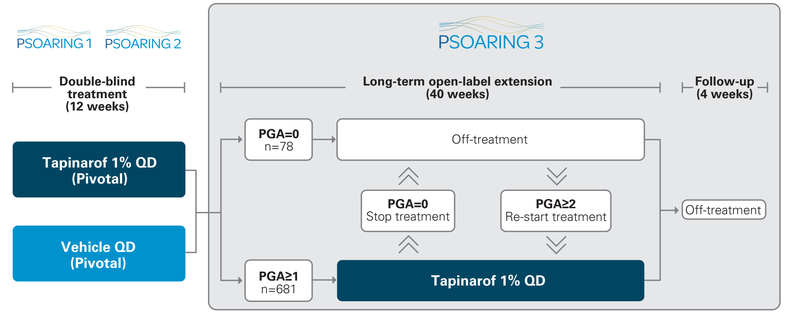
- To present a pre-specified interim analysis of PSOARING 3 (NCT04053387), the long-term, open-label, multicenter extension trial that assessed the safety, tolerability, efficacy, durability of response, and duration of remittive effect of tapinarof cream 1% QD in adults with mild to severe plaque psoriasis

METHODS

Study Design

- Eligible patients completing PSOARING 1 or PSOARING 2 could enroll in PSOARING 3 for up to 40 weeks of open-label treatment with tapinarof 1% QD, followed by a 4-week off-treatment follow-up period (**Figure 1**)
  - As such, patients randomized to receive tapinarof 1% QD during the 12-week phase 3 pivotal trials were eligible for up to 52 weeks of tapinarof 1% QD treatment on completing PSOARING 3
- In PSOARING 3, patients were treated based on their Physician Global Assessment (PGA) score:
  - Patients entering with, or achieving, a PGA score of 0 discontinued treatment and were monitored for remittive effect, defined as off-therapy maintenance of a PGA score of 0 (clear) or 1 (almost clear)
  - Patients entering with a PGA score ≥1 received tapinarof 1% QD until they achieved complete disease clearance, defined as a PGA score of 0 (clear)
  - If disease worsening occurred, defined as a PGA score ≥2, tapinarof 1% QD was started and continued until a PGA score of 0 (clear) was achieved

Figure 1. PSOARING 3 Study Design



PGA, Physician Global Assessment; QD, once daily.

Endpoints and Statistical Analysis

- Safety: Adverse events (AEs), patient- and investigator-rated local tolerability, laboratory, vital and physical exams
- Efficacy:
  - **Complete disease clearance**: Proportion of patients achieving PGA of 0 (clear)
  - **Remittive effect**: Duration of efficacy maintenance (PGA of 0 [clear] or 1 [almost clear]) while off therapy after achieving complete disease clearance (PGA of 0)
  - **Response**: Proportion of patients who entered the trial with a PGA ≥2 and achieved a PGA of 0 (clear) or almost clear (1) at least once during the trial
  - **Durability of response** (absence of tachyphylaxis on therapy): Maintenance of efficacy while on treatment, measured by proportion of patients who achieved a PGA score of 0 or 1 at least once during the trial and trends in Psoriasis Area and Severity Index (PASI) score and %BSA affected over time
- Efficacy analyses were based on the intent-to-treat (ITT) population using observed case (OC) analysis
- Data from all enrolled patients at the time of data cut (November 2020) are included in this pre-specified interim analysis; this includes 671 patients who completed assessments up to 14 weeks and 349 patients who completed assessments up to 40 weeks

RESULTS

Patient Disposition and Baseline Characteristics

- Overall, 763 (91.6%) of eligible patients in PSOARING 1 and PSOARING 2 elected to enroll into PSOARING 3
- There were no apparent differences in baseline demographics between groups (**Table 1**)
- Lower baseline disease scores in patients previously randomized to tapinarof 1% QD (tapinarof 1% QD pivotal) compared with vehicle QD (vehicle QD pivotal) are reflective of the significant efficacy of tapinarof in the pivotal trials
  - 14.4% (73/508) versus 2.0% (5/255) of patients had complete disease clearance, defined as a PGA of 0, and 65.4% (332/508) versus 30.2% (77/255) of patients had a PGA score of 1 or 2 in the tapinarof QD pivotal group versus the vehicle QD pivotal group, respectively

Table 1. PSOARING 3 Baseline Patient Demographics and Disease Characteristics

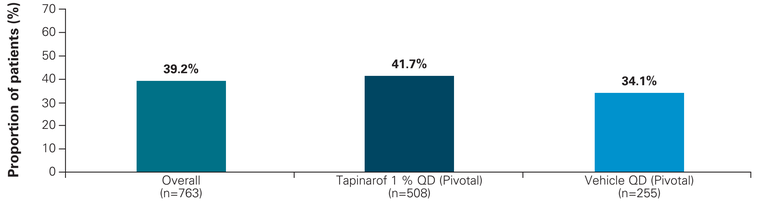
	Overall (n=763)	Tapinarof 1% QD (Pivotal) (n=508)	Vehicle QD (Pivotal) (n=255)
Age, years, mean (SD)	50.7 (12.88)	50.5 (12.87)	51.0 (12.93)
Male, n (%)	448 (58.7)	304 (59.8)	144 (56.5)
Weight, kg, mean (SD)	92.4 (23.90)	92.6 (25.13)	92.1 (21.28)
BMI, kg/m², mean (SD)	31.7 (7.71)	31.6 (8.07)	31.8 (6.97)
PGA, n (%)*			
0 – Clear	78 (10.2)	73 (14.4)	5 (2.0)
1 – Almost clear	161 (21.1)	144 (28.3)	17 (6.7)
2 – Mild	248 (32.5)	188 (37.0)	60 (23.5)
3 – Moderate	249 (32.6)	93 (18.3)	156 (61.2)
4 – Severe	23 (3.0)	7 (1.4)	16 (6.3)
PASI, mean (SD)	4.8 (4.72)	3.3 (3.53)	7.7 (5.39)
BSA affected, %, mean (SD)	4.7 (5.60)	3.3 (4.74)	7.3 (6.21)

*Four patients (three tapinarof, one vehicle) did not have a baseline PGA, PASI, and BSA value and are listed as missing. ITT population.
BMI, body mass index; BSA, body surface area; ITT, intent-to-treat; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment, QD, once daily; SD, standard deviation.

Complete Disease Clearance (PGA of 0)

- Complete disease clearance was achieved by 39.2% (299/763) of patients; this included 78 patients entering the trial with a PGA of 0, and 221 patients entering with a PGA ≥1 (**Figure 2**)

Figure 2. Patients Who Achieved Complete Disease Clearance (PGA of 0) at Least Once During the Trial

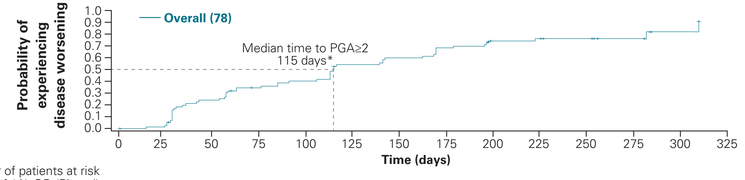


ITT, OC. ITT, intent-to-treat; OC, observed cases, QD, once daily

Remittive Effect (Time To First Worsening Among Patients Entering With a PGA of 0, n=78)

- The duration of remittive effect (Kaplan-Meier estimated median, 95% confidence interval) for patients entering the trial with PGA of 0 was 115 days (85.0; 162.0) (**Figure 3**); a likely underestimate as trial end, not disease worsening, truncated the duration for some patients

Figure 3. Duration of Remittive Effect Among Patients Entering With a PGA of 0: Maintenance of a PGA of 0 (Clear) or 1 (Almost Clear) While Off Therapy



Number of patients at risk

Tapinarof 1% QD (Pivotal)	73	70	53	44	40	29	25	19	13	12	10	6	3	0
Vehicle QD (Pivotal)	5	5	4	3	3	3	3	3	3	3	3	3	1	0
Overall	78	75	57	47	43	32	28	22	16	15	13	9	4	0

ITT, OC. *Kaplan-Meier estimate.
ITT, intent-to-treat; OC, observed cases, PGA, Physician Global Assessment; QD, once daily.

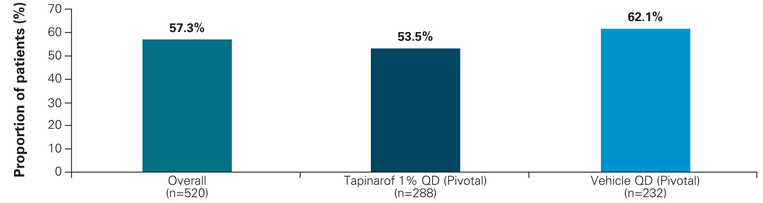
Total Duration of Remittive Effect (Among Patients Entering With, or Achieving, a PGA of 0, n=299)

- Overall, the total duration of remittive effect (mean, standard deviation [SD]) was 119.3 days (81.8); a likely underestimate as trial end, not disease worsening, truncated the duration for some patients

Response (Among Patients Entering With a PGA ≥2)

- Overall, 57.3% (298/520) of patients who entered the trial with a PGA ≥2 achieved a PGA of 0 or 1 at least once during the trial (**Figure 4**)

Figure 4. Patients Who Entered the Trial With a PGA ≥2 and Achieved a Response: PGA of 0 (Clear) or 1 (Almost Clear) at Least Once During the Trial



ITT, OC. ITT, intent-to-treat; OC, observed cases; PGA, Physician Global Assessment; QD, once daily.

Durability of Response

- Durability of response (absence of tachyphylaxis on therapy) was demonstrated for up to 52 weeks with intermittent use of tapinarof 1% QD, indicating no tachyphylaxis across groups based on proportion of patients achieving a PGA score of 0 or 1, and improvements in %BSA affected and PASI scores maintained over time

Safety

- AEs were consistent with previous studies,[1,2] with no new safety signals during this long-term trial (**Table 2**)
- The most common treatment-emergent AEs included folliculitis, contact dermatitis, and upper respiratory tract infection
- The incidence and severity of folliculitis and contact dermatitis neither increased nor worsened with long-term treatment compared with the 12-week pivotal trials[1]
- Study discontinuation due to folliculitis and contact dermatitis was low, 1.2% (9/763) and 1.4% (11/763) respectively, and similar to the rates observed in PSOARING 1 and PSOARING 2[1]

Table 2. Safety Overview

Patients, n (%)	Overall (n=763)	Tapinarof 1% QD (Pivotal) (n=508)	Vehicle QD (Pivotal) (n=255)
Study discontinuation due to TEAEs	40 (5.2)	26 (5.1)	14 (5.5)
Treatment-emergent AESI*			
Folliculitis	180 (23.6)	123 (24.2)	57 (22.4)
Study discontinuation due to folliculitis	9 (1.2)	6 (1.2)	3 (1.2)
Severity† of folliculitis, n (%) among subset of patients with AESI of folliculitis			
Mild	117 (65.0)	81 (65.9)	36 (63.2)
Moderate	63 (35.0)	42 (34.1)	21 (36.8)
Severe	0 (0.0)	0 (0.0)	0 (0.0)
Contact dermatitis	39 (5.1)	21 (4.1)	18 (7.1)
Study discontinuation due to contact dermatitis	11 (1.4)	7 (1.4)	4 (1.6)
Headache	12 (1.6)	7 (1.4)	5 (2.0)
Study discontinuation due to headache	0 (0.0)	0 (0.0)	0 (0.0)

*Investigator-specified grouped MedDRA-preferred terms. †Severity of AESIs was evaluated using CTCAE grading. ITT population. All AEs reported in study are considered as TEAE. A patient is counted once only for each MedDRA-preferred term.
AE, adverse event; AESI, adverse event of special interest; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Tapinarof cream 1% QD demonstrated continued and substantial improvement in efficacy endpoints beyond the 12 weeks of treatment observed in the pivotal trials[1]
- A high rate of complete disease clearance (39.2%) and a remittive effect of approximately 4 months off therapy was demonstrated with tapinarof 1% QD, with no tachyphylaxis observed over 52 weeks
- Tapinarof cream 1% QD was well tolerated with long-term use and had a safety profile consistent with previous studies[1,2]
- Tapinarof cream 1% QD may provide a novel non-steroidal topical therapeutic option for the care of patients with psoriasis that is highly effective and well tolerated

REFERENCES

1. Lebwohl M, et al. *Skin.* 2020;4(6):s75; 2. Robbins K, et al. *J Am Acad Dermatol.* 2019;80:714–721.

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