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

Bruce Strober,[1] Linda Stein Gold,[2] Robert Bissonnette,[3] April Armstrong,[4] Andrew Blauvelt,[5] Leon Kircik,[6,7] Philip M. Brown,[8] Anna M. Tallman,[8] Mark Lebwohl[7]

[1]Yale University, New Haven & Central Connecticut Dermatology Research, Cromwell, CT, USA, [2]Henry Ford Health System, Detroit, MI, USA, [3]Innovaderm Research Inc., Montreal, QC, Canada, [4]Keck School of Medicine at University of Southern California, Los Angeles, CA, USA, [5]Oregon Medical Research Center, Portland, OR, USA, [6]Skin Sciences PLLC, Louisville, KY, USA, [7]Icahn School of Medicine at Mount Sinai, New York, NY, USA, [8]Dermavant Sciences, Inc., Morrisville, NC, USA

SYNOPSIS

- In two 12-week pivotal phase 3 trials, PSOARING 1 (NCT03956355) and PSOARING 2 (NCT03983980), tapinarof cream 1% once daily (QD) demonstrated highly statistically and clinically significant efficacy versus vehicle and was well tolerated in adults with mild to severe plaque psoriasis[1]
- Tapinarof cream 1% QD also demonstrated maintenance of efficacy for 4 weeks after treatment discontinuation in a 12-week phase 2b trial, warranting further investigation of a potential remittive effect[2]

OBJECTIVE

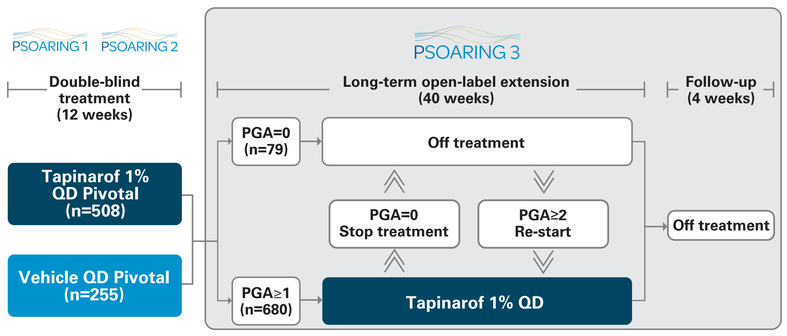
- To present the results of PSOARING 3 (NCT04053387), a long-term extension trial designed to assess the safety, efficacy, durability of response, tolerability, and duration of remittive effect of tapinarof during repeated intermittent treatment, based on patient Physician Global Assessment (PGA) score

METHODS

Study Design

- Patients completing PSOARING 1 and PSOARING 2 were eligible to enroll in PSOARING 3 for 40 weeks of open-label treatment with tapinarof cream 1% QD, followed by four weeks of follow-up (**Figure 1**)
- In PSOARING 3, patients were treated with tapinarof 1% QD based on individual patient PGA score:
  - Patients who entered with a PGA score of ≥1 received tapinarof 1% QD until complete disease clearance was achieved, defined as a PGA score of 0
  - Patients who entered with, or achieved, a PGA score of 0 discontinued treatment and were observed for remittive effect, defined as maintenance of a PGA score of 0 (clear) or 1 (almost clear), while off therapy
  - 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), laboratory values, vital signs and physical exams
- Efficacy:
  - Complete Disease Clearance: Proportion of patients achieving PGA of 0 (clear)
  - Remittive Effect: Duration of efficacy maintenance defined as PGA of 0 (clear) or 1 (almost clear) while off therapy after achieving complete disease clearance (PGA=0)
  - Response: Proportion of patients who entered the trial with a PGA≥2 and achieved a PGA of 0 (clear) or 1 (almost clear) at least once during the trial
  - Durability of Response (absence of tachyphylaxis): Maintenance of efficacy while on treatment, defined as the 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 percentage of body surface area (%BSA) affected over time
- Tolerability: Local tolerability using a patient-reported 5-point scale for burning/stinging and itching, and an investigator-assessed 5-point scale for dryness, erythema, and peeling
- Efficacy analyses used observed case (OC) or last observation carried forward (LOCF) analysis that were based on the intention-to-treat (ITT) population

RESULTS

Baseline Patient Demographics and Disease Characteristics

- Overall, 763 (91.6%) of eligible patients completing PSOARING 1 and PSOARING 2 opted to enroll in PSOARING 3
- Patient demographics and disease characteristics are summarized in Table 1, including baseline values by prior treatment arm in the pivotal trials
- Patients previously randomized to tapinarof 1% QD (Tapinarof→Tapinarof) had lower baseline disease scores compared to the vehicle QD (Vehicle→Tapinarof) group, reflecting the significant efficacy of tapinarof in the pivotal studies
  - 14.6% (74/508) versus 2.0% (5/255) of patients had complete disease clearance (PGA of 0), and 65.2% (331/508) versus 30.2% (77/255) of patients had a PGA score of 1 (almost clear) or 2 (mild) in the tapinarof QD pivotal group (Tapinarof→Tapinarof) versus the vehicle QD pivotal group, (Vehicle→Tapinarof) respectively

Table 1. PSOARING 3 Baseline Patient Demographics and Disease Characteristics

	Overall (n=763)	Tapinarof → Tapinarof* (n=508)	Vehicle → Tapinarof* (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	79 (10.4)	74 (14.6)	5 (2.0)
1 – Almost Clear	161 (21.1)	144 (28.3)	17 (6.7)
2 – Mild	247 (32.4)	187 (36.8)	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)

*Tapinarof→Tapinarof: patients previously assigned to tapinarof in the pivotal trials who enrolled in PSOARING 3; Vehicle→Tapinarof: patients previously assigned to vehicle in the pivotal trials who enrolled in PSOARING 3.

†Four patients (3 previously assigned to tapinarof, 1 previously assigned to 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, intention-to-treat; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment, SD, standard deviation.

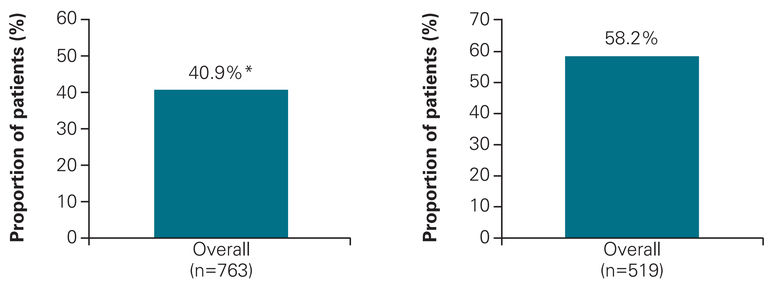
Complete Disease Clearance (PGA of 0)

- Overall, 40.9% (312/763) of patients achieved complete disease clearance at least once during the study; this included 233 patients who entered the study with a PGA of ≥1, and 79 patients who entered with a PGA of 0 (**Figure 2a**)

Response Among Patients Entering With a PGA of ≥2

- Overall, 58.2% (302/519) of patients entering the study with a PGA of ≥2 achieved a PGA of 0 (clear) or 1 (almost clear) at least once during the study (**Figure 2b**)

Figure 2. Complete Disease Clearance (PGA=0) and Response Rates (PGA=0 or 1)



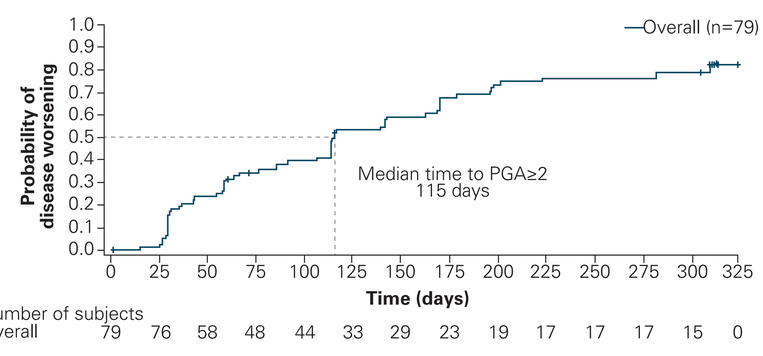
*Including patients who entered with PGA=0 (n=79) and patients entering with PGA ≥1 who achieved PGA=0 at least once during the study (n=233) ITT population, OC.

ITT, intention-to-treat; OC, observed cases; PGA, Physician Global Assessment.

Remittive Effect: Time To First Worsening Among Patients Entering with a PGA of 0 (n=79)

- The duration of remittive effect (Kaplan-Meier estimated median, 95% confidence interval [CI]) while off therapy for patients who entered the study with a PGA of 0 (clear) was 115.0 (95% CI; 85.0-168.0) days (**Figure 3**)

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



ITT population, OC.

ITT, intention-to-treat; OC, observed cases; PGA, Physician Global Assessment.

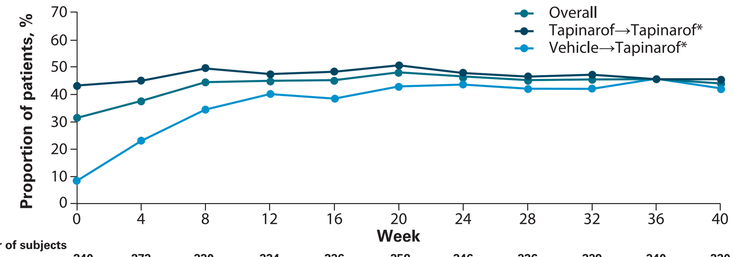
Total Duration of Remittive Effect Among Patients Entering With, or Achieving, a PGA of 0 (n=312)

- The total duration of remittive effect (mean, standard deviation [SD]) while off therapy was 130.1 (89.4) days, a possible underestimate as study end, not disease worsening, truncated the duration for some patients

Durability of Response

- Durability of response of up to 52 weeks was demonstrated with intermittent use of tapinarof 1% QD, indicating no observation of tachyphylaxis (defined as loss of response) while on therapy (**Figure 4**)
- Patients previously treated with vehicle in the 12-week pivotal trials achieved similar responses to patients previously treated with tapinarof (**Figure 4**)

Figure 4. Durability of Response (no tachyphylaxis while on therapy) Based on Proportion of Patients Achieving a PGA Score of 0 (Clear) or 1 (Almost Clear) at least Once During the Study



Number of subjects											
Overall	240	273	330	334	336	358	346	336	339	340	330
Tapinarof→Tapinarof*	218	216	243	233	239	250	236	230	233	225	224
Vehicle→Tapinarof*	22	57	87	101	97	108	110	106	106	115	106

*Tapinarof→Tapinarof: patients previously assigned to tapinarof in the pivotal trials who enrolled in PSOARING 3; Vehicle→Tapinarof: patients previously assigned to vehicle in the pivotal trials who enrolled in PSOARING 3.

ITT population, LOCF. ITT, intention-to-treat; LOCF, last observation carried forward; PGA, Physician Global Assessment.

Safety

- As previously reported, there were no new safety signals during the long-term safety trial[3] and AEs were consistent with previous studies[1,2]
- The most common treatment-emergent AEs included folliculitis, contact dermatitis, and upper respiratory tract infection
- 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]

CONCLUSIONS

- Tapinarof cream 1% QD provided sustained improvement in efficacy endpoints with long-term intermittent use
- A high rate of complete disease clearance (40.9%) and a remittive effect of approximately 4 months off therapy was demonstrated with tapinarof 1% QD, with no tachyphylaxis observed for up to 52 weeks
- Tapinarof cream 1% QD was well tolerated with long-term use and had a safety profile consistent with previous studies[1,2]

REFERENCES

1. Lebwohl M, et al. *Skin.* 2020;4(6):s75; 2. Robbins K et al. *J Am Acad Dermatol.* 2019;80:714–721; 3. Strober B, et al. Innovations in Dermatology Virtual Spring Conference 2021, Poster Presentation, March 16–20, 2021.

ACKNOWLEDGMENTS

This study was funded by Dermavant Sciences, Inc. The authors thank the participating investigators, patients and their families, and colleagues involved in the conduct of the study. B.S. has served as an honorary consultant/speaker/scientific director/investigator for AbbVie, Almirall, Amgen, Arcutis, Arena, Aristea, Boehringer Ingelheim, Bristol-Myers-Squibb, Cara, Celgene, Corrona Psoriasis Registry, Dermavant Sciences Inc., Dermira, Equillium, Janssen, Leo, Eli Lilly, Meiji Seika Pharma, Mindera, Novartis, Pfizer, GlaxoSmithKline, UCB Pharma, Sun Pharma, Ortho Dermatologics, Regeneron, Sanofi-Genzyme. L.S.G has served as a consultant, and/or has received payment for the development of educational presentations, and/or has received grants from Arcutis, Amgen, Bristol Myers Squibb, Dermavant Sciences, Inc., Eli Lilly, LEO Pharma, Ortho Dermatologic and UCB Biopharma. R.B. has served as a consultant/advisory board member/speaker/investigator, and/or receives honoraria/grant from Almirall, Amgen, AnaptysBio, Arcutis, Arena Pharma, Aristea, Asana BioSciences, Bausch Health, Bellus Health, Bluefin Biomedicine, Boehringer-Ingelheim, Bristol-Myers Squibb, CARA, Dermavant Sciences Inc., Eli Lilly, EMD Serono, Escalier, Evidera, Galderma, GSK, Inmagene Bio, Incyte, Janssen, Kiniksa, Kyowa Kirin, LEO Pharma, Nimbus, Novan, Pfizer, Ralexar, RAPT, Regeneron, Respivant, Sanofi Genzyme, Sienna, Target RWE, UCB. R.B. is an employee and shareholder of Innovaderm Research. AM is a research investigator and/or scientific advisor to AbbVie, BI, BMS, EPI, Incyte, Leo, UCB, Janssen, Lilly, Novartis, Ortho Dermatologics, Sun, Dermavant Sciences Inc., Dermira, Sanofi, Regeneron, Pfizer, Modmed. AB has served as a scientific adviser and/or clinical study investigator for AbbVie, Abcentra, Aligos, Almirall, Amgen, Arcutis, Arena, Aslan, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, Eli Lilly and Company, Evommune, Forte, Galderma, Incyte, Janssen, Landos, Leo, Novartis, Pfizer, Rapt, Regeneron, Sanofi Genzyme, Sun Pharma, and UCB Pharma. L.K. has served as a consultant/speaker/investigator/advisory board member for Abbott Laboratories, Abbvie, Ablynx, Aclaris, Acambis, Allergan, Inc., Almirall, Amgen, Inc., Anacor Pharmaceuticals, Anaptys, Arcutis, Arena, Assos Pharma, Astellas Pharma US, Inc., Asubio, Bausch Health, Berlex Laboratories (Bayer HealthCare Pharmaceuticals), Biogen-Idec, Biolife, Biopelle, BMS, Boehringer-Ingleheim, Breckinridge Pharma, Cassiopea, Centocor, Inc., Cellceutix, Cipher, Coherus, Colbar, Combinatrix, Connetics Corporation, Coria, Dermavant Sciences Inc, Dermira, Dermik Laboratories, Dow Pharmaceutical Sciences, Inc., Dr. Reddy's Lab, Dusa , Embil Pharmaceuticals, Eli Lilly, EOS, Exeltis, Ferndale Laboratories, Inc., Foamix, Ferrer, Galderma, Genentech, Inc., GlaxoSmithKline, PLC, Glenmark, Health Point, LTD, Idera, Incyte, Intendis, Innocutis, Innovail, Isdin, Johnson & Johnson, Kyowakirin, Laboratory Skin Care Inc., Leo Pharma, L'Oreal, 3M, Maruho, Medical International Technologies, Merck, Medicis Pharmaceutical Corp., Merz, Nano Bio, Novartis AG, Noven Pharmaceuticals, Nucryst Pharmaceuticals Corp, Obagi, Onset, OrthoNeutrogena, PediaPharma, Pfizer, Promius, PuraCap, PharmaDerm, QLT, Inc, Quinnova, Quatrix, Regeneron, Sanofi, Serono (Merck Serono International SA), SkinMedica, Inc., Stiefel Laboratories, Inc., Sun Pharma, Taro, TolerRx, Triax, UCB, Valeant Pharmaceuticals Intl, Warner-Chilcott, XenoPort, ZAGE. P.M.B and A.N.T. are employees of Dermavant Sciences Inc., with stock options. M.L. has received grants, and/or is a consultant for Abbvie, Amgen, Aditum Bio, Almirall, AltruBio Inc., AnaptysBio, Arcutis, Aristea Therapeutics, Arrive Technologies, Avotres, BiomX, Boehringer Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Castle Biosciences, Corrona, Dermavant Sciences, Dr. Reddy's Laboratories, Eli Lilly, Evelo Biosciences, Evommune, Inc., Facilitation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Helsinn Therapeutics, Hexima Ltd., Incyte, Janssen Research & Development, LEO Pharma, LLC, Meiji Seika Pharma, Mindera, Ortho Dermatologics, Pfizer, Regeneron, Seanergy, UCB, Inc., Verrica. Editorial and medical writing support under the guidance of the authors was provided by Apothecom, UK, and was funded by Dermavant Sciences, Inc. in accordance with Good Publication Practice (GPP3) guidelines (*Ann Intern Med.* 2015;163:461–464).

Contact Dr Bruce Strober at brucestrober30@me.com with questions or comments.