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Efficacy and safety of apremilast in patients with mild-to-moderate psoriasis up to 32 weeks: Results from the extension phase of the randomized, phase 3 ADVANCE trial

Linda F. Stein Gold
Henry Ford Health, lstein1@hfhs.org

Kim Papp

David Pariser

Neal Bhatia

Howard Sofen

See next page for additional authors

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Authors

Linda F. Stein Gold, Kim Papp, David Pariser, Neal Bhatia, Howard Sofen, Lorne Albrecht, Melinda Gooderham, Kristina Callis Duffin, Mindy Chen, Maria Paris, Sue Cheng, Hernan Picard, Yao Wang, and Lawrence Green

James G. Krueger, MD, PhD, Laboratory for Investigative Dermatology, The Rockefeller University, 1230 York Avenue, New York, NY 10065

E-mail: jgk@rockefeller.edu

Conflicts of interest

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REFERENCES

1. Strober B, Ryan C, van de Kerkhof P, et al. Recategorization of psoriasis severity: Delphi consensus from the International Psoriasis Council. *J Am Acad Dermatol*. 2020;82(1):117-122.
2. Kim J, Bissonnette R, Lee J, et al. The spectrum of mild to severe psoriasis vulgaris is defined by a common activation of IL-17 pathway genes, but with key differences in immune regulatory genes. *J Invest Dermatol*. 2016;136(11):2173-2182.
3. Lelios I, Cansever D, Utz SG, Mildenberger W, Stifter SA, Greter M. Emerging roles of IL-34 in health and disease. *J Exp Med*. 2020;217(3):e20190290.
4. Rønholt K, Nielsen AL-L, Johansen C, et al. IL-37 Expression is downregulated in lesional psoriasis skin. *Immunohorizons*. 2020;4(11):754-761.
5. Gold LS, Papp K, Pariser D, et al. Efficacy and safety of apremilast in patients with mild-to-moderate plaque psoriasis: results of a phase 3, multicenter, randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol*. 2022;86(1):77-85.

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Efficacy and safety of apremilast in patients with mild-to-moderate psoriasis up to 32 weeks: Results from the extension phase of the randomized, phase 3 ADVANCE trial

To the Editor: Mild-to-moderate psoriasis often involves special areas such as the scalp.[1] Patients can experience substantial quality-of-life impairment despite limited overall skin involvement.[1] In the phase 3 ADVANCE study (NCT03721172), apremilast demonstrated efficacy and tolerability in adults with mild-to-moderate psoriasis (static Physician's Global Assessment [sPGA] 2-3, psoriasis-involved body surface area [BSA] 2%-15%, and Psoriasis Area and Severity Index 2-15) inadequately controlled with/intolerant to ≥1 topical therapy.[2] Patients were randomized 1:1 to apremilast 30 mg BID or placebo for 16 weeks, followed by a 16-week extension phase. We present efficacy and safety of apremilast during the extension phase. Of 595 randomized patients (apremilast: 297; placebo: 298), 84.5% entered (apremilast: 257; placebo: 246) and 73.4% ($n = 437$) completed the extension phase, including 221 patients continuing apremilast treatment. Of 503 patients, 66 (13.1%) discontinued. The primary endpoint was met: 21.6% of apremilast-treated patients achieved an sPGA score of 0 (clear) or 1 (almost clear) and a ≥2-point reduction from baseline at week 16 vs 4.1% with placebo ($P < .0001$).[2] At week 32, the sPGA response was maintained by 30.2% (64 of 212) of patients continuing apremilast (apremilast/apremilast) and 34.3% (72 of 210) of patients initially randomized to placebo (placebo/apremilast) using data as observed (DAO); apremilast/apremilast: 24.9% (64 of 257) and placebo/apremilast: 29.3% (72 of 246) using nonresponder imputation.

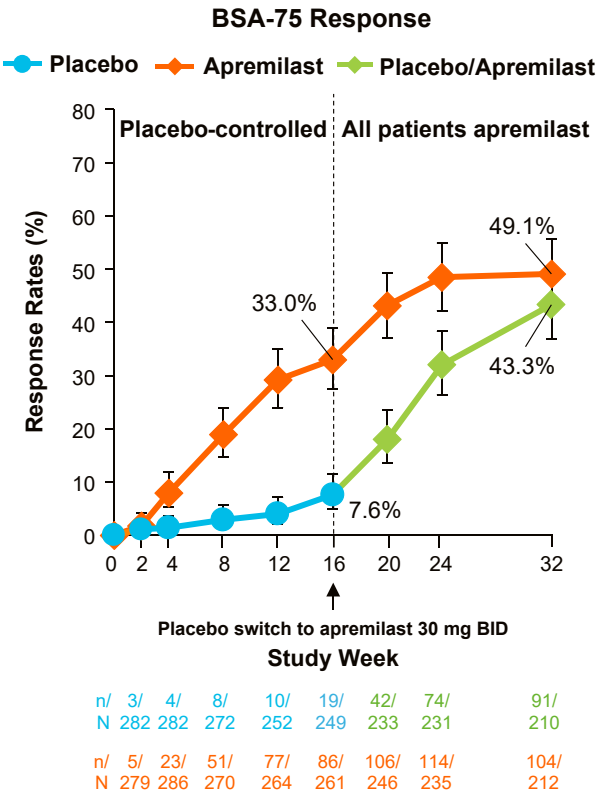

Fig 1. Proportions of patients with psoriasis achieving BSA-75 response. Bars represent two-sided 95% CIs. Data are presented as observed. *BSA-75*, ≥75% Improvement in psoriasis-involved body surface area.

Improvements in secondary endpoints observed at week 16 (Supplementary Material, available via Mendeley at https://data.mendeley.com/datasets/wf4g3yxvzz/1) were sustained up to week 32 in patients continuing apremilast (DAO: BSA-75: 49.1%

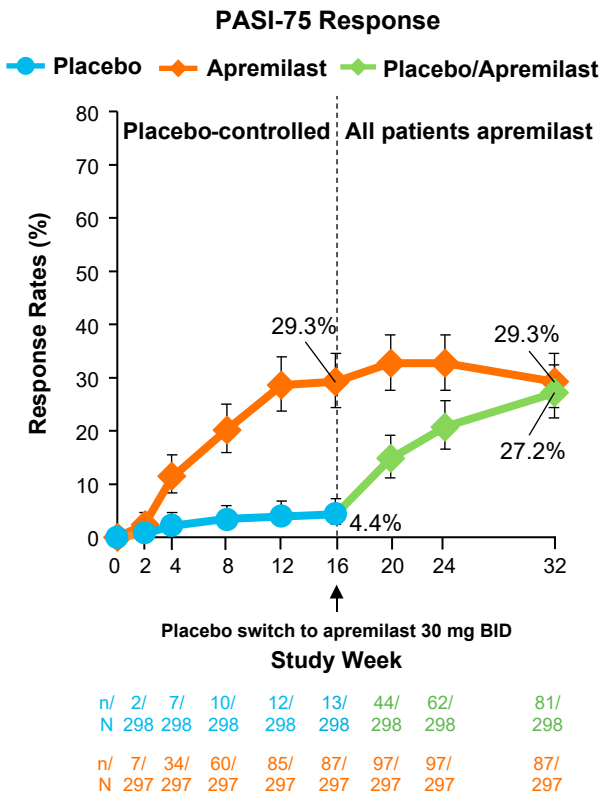

Fig 2. Proportions of patients with psoriasis achieving PASI-75 response based on NRI analysis. Bars represent two-sided 95% CIs. *NRI*, Nonresponder imputation; *PASI*, Psoriasis Area and Severity Index; *PASI-75*, ≥75% reduction from baseline in PASI score.

[104 of 212] [Fig 1]; Whole Body Itch Numeric Rating Scale response: 51.9% [95 of 183] and 62.1% [110 of 177] [Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/wf4g3yxvzz/1]; Scalp Physician's Global Assessment response: 49.7% [78 of 157] and 58.6% [78 of 133]; Dermatology Life Quality Index: −5.8 [n = 212] and −6.7 [n = 207] [Supplementary Fig 2, available via Mendeley at https://data.mendeley.com/datasets/wf4g3yxvzz/1]). At week 32, 29.3% of patients continuing apremilast achieved Psoriasis Area and Severity Index-75, comparable to the 27.2% of patients who switched from placebo to apremilast (nonresponder imputation; Fig 2). BSA-75, Whole Body Itch Numeric Rating Scale, and Scalp Physician's Global Assessment responses at week 32 analyzed with nonresponder imputation were consistent with DAO (Supplementary Fig 3, available via Mendeley at https://data.mendeley.com/datasets/wf4g3yxvzz/1).

During the apremilast-exposure period (0-32 weeks), 544 patients received ≥1 apremilast dose (total apremilast exposure: 234.3 person-years). Most (93.2%) patients with treatment-emergent adverse events during this period had mild/moderate treatment-emergent adverse events. The most common treatment-emergent adverse events (≥5%) were diarrhea (14.3%, 78 of 544), headache (12.9%, 70 of 544), nausea (12.7%, 69 of 544), upper respiratory tract infection (8.5%, 46 of 544), and nasopharyngitis (6.8%, 37 of 544), consistent with the known apremilast safety profile.[3,4]

Although topical therapies are commonly prescribed for mild-to-moderate psoriasis, systemic treatment may benefit patients with intractable pruritus or special area involvement (eg, the scalp).[5] Bothersome symptoms and psoriasis locations can impair quality of life.[1] Per current guidelines, mild-to-moderate psoriasis may require systemic treatment in patients with high disease burden or psoriasis inadequately controlled with topicals. Efficacy results may be biased by lack of an active comparator and reporting DAO findings.

Improvements in sPGA, BSA, whole-body itch Numeric Rating Scale, Scalp Physician's Global Assessment, and Dermatology Life Quality Index were maintained through week 32 with apremilast treatment. These findings demonstrate that continued apremilast treatment results in sustained clinical improvements in overall disease severity, scalp psoriasis, itch, and quality of life for patients with mild-to-moderate psoriasis.

DATA SHARING

Qualified researchers may request data from Amgen clinical studies. Complete details are available at http://www.amgen.com/datasharing.

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Linda Stein Gold, MD,[a] Kim Papp, MD, PhD,[b,c] David Pariser, MD,[d] Neal Bhatia, MD,[e] Howard Sofen, MD,[f,g] Lorne Albrecht, MD,[b,h,i] Melinda Gooderham, MSc, MD,[b,j,k] Kristina Callis Duffin, MD, MS,[l] Mindy Chen, MS,[m] Maria Paris, MD,[m] Sue Cheng, MD, PhD,[m] Hernan Picard, MD, PhD,[m] Yao Wang, MD,[m] and Lawrence Green, MD[n]

From the Henry Ford Health System, West Bloomfield, Michigan[a]; Probity Medical Research, Inc, Waterloo, Ontario, Canada[b]; K Papp Clinical Research, Waterloo, Ontario, Canada[c] Eastern Virginia Medical School and Virginia Clinical Research, Inc, Norfolk, Virginia[d]; Therapeutics

Clinical Research, San Diego, California[e]; UCLA School of Medicine, Los Angeles, California[f]; Dermatology Research Associates, Los Angeles, California[g]; Enverus Medical, Surrey, British Columbia, Canada[b]; University of British Columbia, Vancouver, British Columbia, Canada[i]; SKiN Centre for Dermatology, Peterborough, Ontario, Canada[j]; Queen's University, Kingston, Ontario, Canada[k]; University of Utah, Salt Lake City, Utah[l]; Amgen Inc, Thousand Oaks, California[m]; and Department of Dermatology, George Washington University School of Medicine, Washington, District of Columbia.[n]

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Key words: ADVANCE; apremilast; clinical trial; long-term; mild-to-moderate psoriasis; pruritus; quality of life; scalp.

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Correspondence to: Linda Stein Gold, MD, Henry Ford Medical Center - Farmington Road, 6530 Farmington Rd, Ste 101, West Bloomfield, MI 48322

E-mail: LSTEIN1@hfhs.org

Conflicts of interest

Linda Stein Gold has received honoraria, grants, and/or research funding as a speaker, investigator, and/or advisory board member for AbbVie, Amgen Inc, Arcutis, Celgene Corporation, Dermira, Dermavant, Eli Lilly, Galderma, LEO Pharma, Novartis, Pfizer, Regeneron, Sanofi Genzyme, UCB, and Valeant. Kim Papp has received honoraria, grants, and/or research funding as a speaker, investigator, advisory board member, data safety monitoring board member, and/or consultant for AbbVie, Actelion, Amgen Inc, Astellas Pharma US, Boehringer Ingelheim, Bausch Health, Celgene Corporation, Dermira, Dow Pharmaceuticals, Eli Lilly, Frontier, Galderma, Janssen, Kyowa Hakko Kirin Pharma, LEO Pharma, MedImmune, Merck & Co, Inc, Novartis, Pfizer, Regeneron, Roche Laboratories, Sanofi Genzyme, Takeda Pharmaceuticals, UCB, and Valeant and is a steering committee member for PSLOAR, PURE. David Pariser is a honoraria, investigator, advisory board, or data monitoring board member for Amgen Inc, AO Biome, Asana, Brickel Biotech, Celgene Corporation, Dermavant, Dermira, Eli Lilly, Menlo Therapeutics, Merck, Novartis, Ortho, Regeneron, Atacama, Biofrontera, Bristol Myers Squibb, LEO Pharma, Pfizer, Sanofi, and Valeant. Neal Bhatia is an advisor, consultant, investigator, and/or speaker for AbbVie, Actavis, Allergan, Amgen Inc, Aqua, Bayer, Biofrontera, BioPharmX, Castle, Cipher, Dermira, Encore, Exeltis, Ferndale, Foamix, Galderma, Intraderm, ISDIN, LaRoche-Posay, LEO Pharma, Novan, Novartis, PharmaDerm, Pfizer, Promius, Regeneron, Sanofi, Sun Pharma, and Valeant. Howard Sofen has received honoraria, grants, and/or research funding as an investigator and/or advisory board member for AbbVie, Amgen Inc, Celgene Corporation, Dermira, Dermavant, Eli Lilly, Galderma, LEO Pharma, Novartis, Pfizer, and UCB. Lorne Albrecht has received honoraria, grants, and/or research funding as a speaker, investigator, advisory board member, and/or consultant for AbbVie, Amgen Inc, Arcutis, Boehringer Ingelheim, Bausch Health/Valeant, Celgene Corporation, Dermira, Dermavant, Eli Lilly, Galderma, Janssen, LEO Pharma, MedImmune, Merck & Co, Novartis, Pfizer, Regeneron, Roche Laboratories, Sanofi Genzyme, and UCB. Melinda Gooderham has received honoraria, grants, and/or research funding as a speaker, investigator, advisory board member, data safety monitoring board member, and/or consultant AbbVie, Amgen Inc, Akros, Arcutis, Bausch/Valeant, Boehringer Ingelheim, Celgene Corporation, Dermira, Dermavant, Eli Lilly, Galderma, Janssen, Kyowa Hakko Kirin Pharma, LEO Pharma, MedImmune, Merck & Co, Novartis, Pfizer, Regeneron, Roche Laboratories, Sanofi Genzyme, Takeda Pharmaceuticals USA Inc, and UCB. Mindy Chen, Maria Paris, Sue Cheng, and Hernan Picard are employees and stockholders for Amgen Inc. Yao Wang was employed at time of study. Kristina Callis Duffin has received honoraria, grants, and/or research funding as investigator, advisory board member, consultant, and nonpromotional speaker for Novartis and has received honoraria, grants, and/or research funding as an investigator, advisory board member, and/or consultant for AbbVie, Amgen Inc, Boehringer Ingelheim, Celgene Corporation, Eli Lilly, Janssen, Novartis, Pfizer, Regeneron, and UCB. Lawrence Green is an investigator, speaker, and/or consultant for AbbVie, Amgen Inc, Arcutis, Dermavant, MC2, Novartis, Lilly, OrthoDerm, Sun Pharma, and UCB.

REFERENCES

1. Lebwohl MG, Bachelez H, Barker J, et al. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *J Am Acad Dermatol*. 2014;70(5):871-881.
2. Stein Gold L, Papp K, Leonardi C, et al. Efficacy and safety of apremilast in patients with mild to moderate plaque psoriasis: results of a phase 3, multicenter, randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol*. 2022;86(1):77-85.
3. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM 1]). *J Am Acad Dermatol*. 2015;73(1):37-49.

4. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate to severe plaque psoriasis over 52 weeks: a phase III, randomized, controlled trial (ESTEEM 2). *Br J Dermatol*. 2015;173(6):1387-1399.
5. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80(4):1029-1072.

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Variation in second cancer risk by melanoma subtype among survivors

To the Editor: The incidence of melanoma in the United States is increasing, with 100,000 new cases projected in 2022.[1,2] Survivors of cutaneous melanoma (CM) are at an increased risk of developing second primary cancers (SPCs), including melanoma, breast cancer, prostate cancer, and non-Hodgkin lymphoma.[3,4] Variation in SPC risk according to CM subtype has not been systematically evaluated using population data.

The major CM subtypes were identified in the Surveillance, Epidemiology, and End Results 18 cancer registries using *International Classification of Diseases for Oncology, third edition* histology codes. We report the ratio of the observed to the expected number of cancers, the standardized incidence ratio (SIR), to compare the risk of cancer in survivors of CM with that in the general population. Analyses were restricted to individuals with a first primary cancer of CM.

There were 172,637 survivors of CM who developed 20,696 (12 %) SPCs during follow-up. Most SPCs occurred in non-Hispanic White individuals (19,893 [96%] cases), and risk varied according to subtype, with nodular melanoma (NM) (SIR, 2.11; 95% CI, 2.03-2.18) and lentigo maligna melanoma (LMM) (SIR, 1.55; 95% CI, 1.50-1.61) exhibiting the highest and lowest risk, respectively (Supplementary Tables 1 and 2, available via Mendeley at https://data.mendeley.com/datasets/7m379pybfh/1). The increased risk of SPCs was largely driven by subsequent melanoma diagnoses (SIR range excluding melanoma, 1.01 [LMM]-1.27 [NM]), which accounted for 41% ($n = 8455$ cases) of all second malignancies.

Survivors of NM were the most susceptible to internal cancers, with 3- to 4-fold increased risks of salivary gland cancer, sarcomas (excludes skin codes C44.0-C44.9), and thyroid cancer ($P < .05$). The risk of non-Hodgkin lymphoma was increased for most subtypes (SIR range, 1.38 [LMM]-2.19 [amelanotic melanoma]; $P < .05$ for all subtypes except acral lentiginous melanoma). The incidence of prostate cancer was elevated for superficial spreading melanoma (SIR, 1.24; 95% CI, 1.18-1.31), NM (SIR, 1.15; 95% CI, 1.02-1.29), and LMM (SIR, 1.21; 95% CI, 1.10-1.32). Contrastingly, the risk of breast cancer was only elevated for superficial spreading melanoma (SIR, 1.13; 95% CI, 1.06-1.20).

The risk of a second primary CM was highly elevated for male and female survivors across all CM subtypes (SIR range, 9.7 [LMM]-14.5 [NM] and 14.3 [desmoplastic melanoma]-26.3 [amelanotic melanoma] for male and female survivors, respectively) (Supplementary Tables 1 and 2). Male survivors of acral lentiginous melanoma and desmoplastic melanoma had an overall elevated risk of developing nonmelanoma SPCs that was not significant in females. Sex-based differences in risk were also suggested for specific cancer types, such as kidney cancer, where incidence was only significantly elevated for male survivors of superficial spreading melanoma.

Low case numbers, misclassification of CM subtype by pathologists,[5] and limited follow-up (2000-2018) may have resulted in our study being underpowered to detect elevations in the risk of certain cancers. We were also unable to evaluate the incidence of SPC for non-White survivors of melanoma because of a limited number of melanomas.

Despite these limitations, we observed variation in the risk of SPC according to melanoma subtype, which may be related to individual germline susceptibility and environmental risks. These findings highlight the importance of age-appropriate cancer screening for all patients with CM, particularly survivors of NM, who had a 27% increased risk of developing a nonmelanoma SPC. Furthermore, our results support intensive skin surveillance for all survivors of melanoma because of the highly elevated risk of a second primary melanoma associated with each CM subtype.

Yen T. Luu, BA,[a,b] Alisa M. Goldstein, PhD,[b] and Michael R. Sargen, MD[b]

From the University of Missouri–Kansas City School of Medicine, Kansas City, Missouri[a]; and Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, Maryland.[b]

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