Four-weekly dosing intervals with subcutaneous spesolimab appear to be required for optimal prevention of generalized pustular psoriasis flares:

Data from the EFFISAYIL® 2 and EFFISAYIL® ON trials

Diamant Thaçi,[1] Akimichi Morita,[2] Bruce E. Strober,[3] Tiago Torres,[4] Andreas Pinter,[5] Angelo V. Marzano,[6,7] James G. Krueger,[8] Ming Tang,[9] Patrick Hofmann,[10] Christian Thoma,[10] Mark G. Lebwohl[11]

[1]Institute and Comprehensive Center for Inflammation Medicine, University of Lübeck, Lübeck, Germany; [2]Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [3]Department of Dermatology, Yale University School of Medicine, New Haven, and Central Connecticut Dermatology Research, Cromwell, CT, USA; [4]Department of Dermatology, Centro Hospitalar Universitário de Santo António, University of Porto, Porto, Portugal; [5]Department of Dermatology, Venereology and Allergology, University Hospital Frankfurt am Main, Frankfurt am Main, Germany; [6]Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [7]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy; [8]Laboratory for Investigative Dermatology, The Rockefeller University, New York, NY, USA; [9]Boehringer Ingelheim (China) Investment Co., Ltd, Shanghai, China; [10]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [11]The Kimberly and Eric J. Waldman Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Objective

- To present data from the EFFISAYIL® 2 and EFFISAYIL® ON OLE trials, comparing the relative efficacy of a q4w vs q12w dosing schedule of spesolimab SC for preventing GPP flares

Conclusions

- EFFISAYIL® 2 and EFFISAYIL® ON results suggest that spesolimab 300 mg SC q4w* is the optimal dosing regimen for prevention of GPP flares
- Further research is needed to understand the mechanisms underlying superior flare prevention with q4w dosing

*Following a 600 mg SC loading dose

Scan QR code or visit URL for a webpage featuring all Boehringer Ingelheim-supported publications at Fall Clinical Dermatology Conference 2024 https://go.boehringer.com/QMa

Scan QR code or visit URL to view the e-poster https://bit.ly/3vCv2ql

Introduction

- GPP is a chronic, heterogeneous, unpredictable, and potentially life-threatening neutrophilic inflammatory skin disease that exerts a considerable burden on patients and healthcare systems[1]
- Spesolimab is a first-in-class anti-interleukin-36 receptor monoclonal antibody approved in 48 countries as an IV dosage in adults to treat GPP flares, and in the US and China in adults and pediatric patients aged ≥12 years and weighing at least 40 kg, as an IV dosage to treat GPP flares, and as a SC dosage to treat GPP when not experiencing a flare[2]
- EFFISAYIL® 2, a randomized, placebo-controlled, phase IIb trial (NCT04399837),[3] provided dose-ranging data for 3 SC dose regimens, and evaluated the efficacy, safety, and tolerability of spesolimab for the prevention of GPP flares compared with placebo
- EFFISAYIL® ON (NCT03886246)[4] is a non-randomized, long-term extension study to assess the efficacy and safety of spesolimab in preventing reoccurrence of flares

Methods

EFFISAYIL® 2 (Table 1, Figure 2)

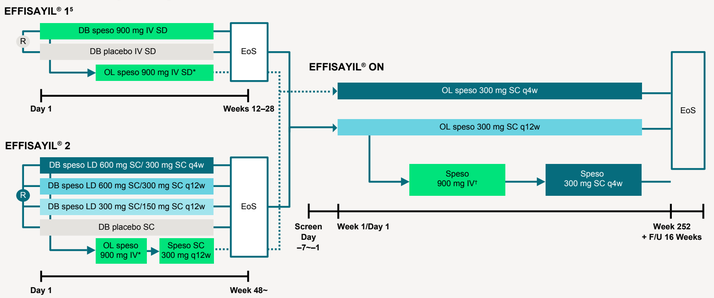
- Participants:
  - History of GPP and GPPGA score of 0 or 1* at screening/randomization
  - ≥2 past GPP flares with fresh pustulation†
- Spesolimab dosing regimens were LD 300 mg SC/150 mg SC q12w, LD 600 mg SC/300 mg SC q12w, or LD 600 mg SC/300 mg SC q4w
- Primary endpoint was time to GPP flare‡ and key secondary endpoint was the occurrence of ≥1 GPP flare, both up to Week 48

EFFISAYIL® ON (Figure 3)

- Participants completed the treatment period in prior spesolimab trials, including EFFISAYIL® 2, without premature discontinuation
- Dose selection based on treatment response in previous trials:
  - Patients who did not require OL spesolimab 900 mg IV in previous trial, or patients who received placebo, received OL spesolimab 300 mg SC q12w
  - Patients who required OL spesolimab 900 mg IV during the previous trial received an intensified treatment regimen with OL spesolimab 300 mg SC q4w
  - Dose regimen could be escalated or de-escalated based on specific criteria related to changes in GPPGA total score and pustulation subscore, and history of flares in previous trial
- Primary endpoint was TEAEs up to Week 252; secondary endpoints were reoccurrence of a GPP flare§ and time to achievement of a GPPGA score of 0 or 1¶

*GPPGA score of 0 or 1 is clear or almost clear skin. †Participants not on concurrent GPP treatment at randomization must have had ≥2 flares in the previous year; those on concurrent GPP treatment within 12 weeks prior to randomization must have a history of flaring during, or after dose reduction, or discontinuation of, concurrent treatment. ‡GPP flare defined as an increase in GPPGA total score of ≥2 and pustulation subscore of ≥2. §GPP flare defined as a ≥2-point increase in GPPGA total score with pustulation subscore of ≥2 (GPPGA score 0 or 1 at screening), or ≥1-point increase in GPPGA score and presence of fresh pustulation (GPPGA score 2 at screening); further reoccurrence of GPP flare was defined based on the participant's GPPGA score improvement after each rescue treatment. ¶Secondary endpoint was in participants who received 900 mg IV spesolimab for flare treatment.

Figure 1. Study designs



*900 mg IV dose given for GPP flare during DB treatment period. †900 mg IV dose given for GPP flare during treatment period.

Results

EFFISAYIL® 2 (Table 1, Figure 2)

- Spesolimab 300 mg SC q4w* vs 300 mg SC q12w* data indicate the need for q4w dosing
- Spesolimab 300 mg SC q4w* led to nearly two-thirds fewer participants experiencing GPP flares (10.0% [3/30] of participants [12.7% when exposure-adjusted] in the q4w arm vs 29.0% [9/31] in the q12w arm)
- EFFISAYIL® 2 demonstrated an 84% reduction in GPP flares for participants in the q4w arm compared with placebo

EFFISAYIL® ON (Figure 3)

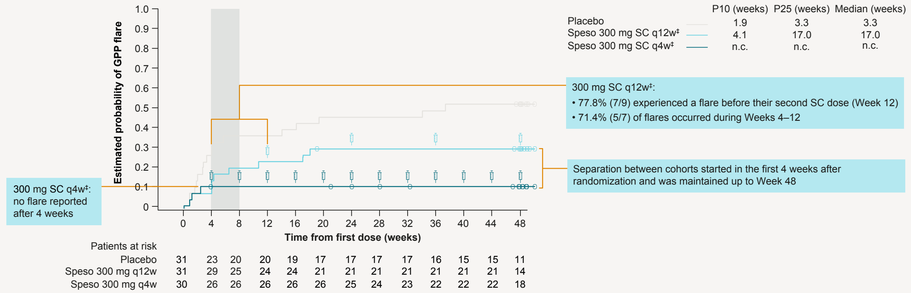
- OL spesolimab SC dosing (300 mg q12w) data from EFFISAYIL® ON further support the need for q4w dosing when initiating treatment for prevention of GPP flares

Table 1. Time to the GPP flare, up to Week 48

	Placebo	Spesolimab 300 mg SC q12w*	Spesolimab 300 mg SC q4w*
Participants, N (%)	31 (100.0)	31 (100.0)	30 (100.0)
Participants with GPP flares, n (%)	16 (51.6)	9 (29.0)	3 (12.7¶)
Probability of GPP flare at Week 48, Kaplan–Meier estimate (95% CI)		**0.290 (0.163, 0.484)**	**0.100 (0.33, 0.279)**
HR for time to GPP flare vs placebo (98% CI)†		0.468 (0.206, 1.064)	0.157 (0.046, 0.541)
P-value‡		0.0269	0.0005
Risk difference for GPP flare occurrence vs placebo (95% CI)§		–0.225 (–0.462, 0.013)	–0.390 (–0.621, –0.159)
P-value			0.0013

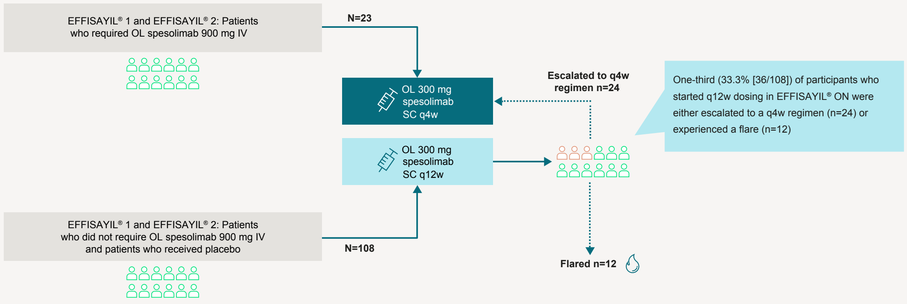
*Following a 600 mg SC loading dose. †Cox regression model stratified by the use of systemic GPP medications at randomization. ‡Log-rank test stratified by the use of systemic GPP medications at randomization. §Cochran–Mantel–Haenszel test after multiple imputations, stratified by the use of systemic GPP medications at randomization. ¶Exposure-adjusted.

Figure 2. Time to GPP flare, up to Week 48 (EM, PM) in EFFISAYIL® 2*,†



*EM, primary estimand for randomized treatment period, where any use of rescue medication with spesolimab IV or investigator-prescribed standard of care is considered as GPP flare; PM, primary method for censoring, which is made at the earliest date of end of study – Day 351 if no intercurrent event. †Probability of event is estimated by the Kaplan–Meier approach. ‡Following a 600 mg SC loading dose.

Figure 3. EFFISAYIL® ON



Poster presented at: Fall Clinical Dermatology Conference, Las Vegas, NV, USA; October 24–27, 2024

Originally presented at: American Academy of Dermatology Annual Meeting, San Diego, CA, USA; March 8–12, 2024

Abbreviations
DB, double-blind; EM, primary estimand for the randomized maintenance treatment period in EFFISAYIL® 2 with use of investigator prescribed standard of care for GPP or use of OL spesolimab IV for GPP flare treatment regarded as event or treatment failure; EoS, end of study; F/U, follow-up; GPP, generalized pustular psoriasis; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; HR, hazard ratio; IV, intravenous; LD, loading dose; n.c., not calculable; OL, open-label; OLE, open-label extension; PM, primary method for handling missing data for time-to-event endpoints; q4w, every 4 weeks; q12w, every 12 weeks; R, randomization; SC, subcutaneous; SD, single dose; speso, spesolimab; TEAE, treatment-emergent adverse event

References
1. Morita A, et al. *Lancet*. 2023;402:1541–51.
2. SPEVIGO® prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761244s003lbl.pdf (accessed May 24, 2024).
3. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04399837 (accessed Sept 11, 2024).
4. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03886246 (accessed Sept 11, 2024).
5. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03782792 (accessed Sept 11, 2024).

Disclosures
DT reports serving as a consultant, advisory board member, and/or investigator for AbbVie, Almirall, Amgen, Beiersdorf, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Eli Lilly, Galderma, Janssen, LEO Pharma, New Bridge, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharmaceuticals, and UCB. **AM** reports consultancy/advisory boards disease-relevant honoraria from AbbVie, Boehringer Ingelheim, Novartis, Pfizer, Janssen, Sanofi, and UCB. **BES** reports serving as a consultant (honoraria) for AbbVie, Alamar, Alumis, Almirall, Amgen, Arcutis, Arena Pharmaceuticals, Aristea, Asana, Boehringer Ingelheim, Bristol Myers Squibb, Capital One, Connect Biopharma, CorEvitas, Dermavant, DICE Therapeutics, Eli Lilly, Evelo Biosciences, GSK, Immunic Therapeutics, Janssen, Kangpu Pharmaceuticals, LEO Pharma, Maruho, Meiji Seika Pharma, Mindera Health, Monte Carlo, Novartis, Ortho Dermatologics, Pfizer, Protagonist, Regeneron, Sanofi-Genzyme, Sun Pharmaceuticals, TakedaNimbus, UCB, Union Therapeutics, Ventyx Biosciences, and vTv Therapeutics; has stock options in Connect Biopharma and Mindera Health; has served as a speaker for AbbVie, Arcutis, Dermavant, Eli Lilly, Incyte, Janssen, Regeneron, and Sanofi-Genzyme; has served as co-scientific director and investigator for and received consulting fees from the CorEvitas (Corrona) Psoriasis Registry; and is Editor-in-Chief (honorarium) of the *Journal of Psoriasis and Psoriatic Arthritis*. **TT** has received research grants and/or consulting fees from AbbVie, Almirall, Amgen, Arena Pharmaceuticals, Biocad, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, LEO Pharma, MSD, Novartis, Pfizer, Samsung Bioepis, Sandoz, and Sanofi. **AP** has served as an investigator, speaker, and/or advisor for AbbVie, Almirall Hermal, Amgen, Biogen Idec, BioNTech, Boehringer Ingelheim, Celgene, Eli Lilly, Eva Pharma, Galderma, GSK, Hexal, Janssen, LEO Pharma, MC2, Medac, Merck Serono, Mitsubishi Tanabe, MSD, Novartis, Pascoe, Pfizer, Regeneron, Roche, Sandoz, Sanofi-Genzyme, Schering-Plough, Tigercat Pharma, UCB, and Zuellig Pharma. **AVM** reports consultancy/advisory boards disease-relevant honoraria from AbbVie, Boehringer Ingelheim, Novartis, Pfizer, Sanofi, and UCB. **JGK** has received grants from and been an investigator for Boehringer Ingelheim; received personal fees from AbbVie, Baxter, Biogen Idec, Delenex Therapeutics, Kineta, Sanofi, Sensno, and XenoPort; and received grants from Amgen, Bristol Myers Squibb, Dermira, Eli Lilly, Innovaderm Research, Janssen, Kadmon, Kyowa Kirin, Merck, Novartis, Parexel, and Pfizer. **MT, PH**, and **CT** are employees of Boehringer Ingelheim. **MGL** has received research funds from AbbVie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Cara Therapeutics, Dermavant, Eli Lilly, Incyte, Inozyme, Janssen, Ortho Dermatologics, Sanofi-Regeneron, and UCB; and is a consultant for Almirall, Altrubio, Anaptysbio, Arcutis, AstraZeneca, Avotres, Brickell Biotech, Boehringer Ingelheim, Bristol Myers Squibb, Castle Biosciences, Celltrion, CorevitasDermavant, EPI, Evommune, Facilitation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Galderma, Genentech, Incyte, LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Seanergy, Strata, Trevi, and Verrica.

Acknowledgments
These studies were supported and funded by Boehringer Ingelheim. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors did not receive payment related to the development of this poster. Kristi Kistner of Nucleus Global provided writing, editorial, and formatting support, which was contracted and funded by Boehringer Ingelheim. Boehringer Ingelheim was given the opportunity to review the poster for medical and scientific accuracy, as well as intellectual property considerations.

Boehringer Ingelheim