Effect of subcutaneous spesolimab on the prevention of generalized pustular psoriasis flares over 48 weeks: Subgroup analyses from the Effisayil 2 trial

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High-dose spesolimab showed consistent efficacy in preventing GPP flares in patients, over 48 weeks, irrespective of *IL36RN* mutation status, the presence or absence of plaque PsO at baseline, or BMI category

AIM

To analyze the effect of high-dose spesolimab vs placebo on the prevention of GPP flares, over 48 weeks, in prespecified subgroups from the Effisayil 2 trial

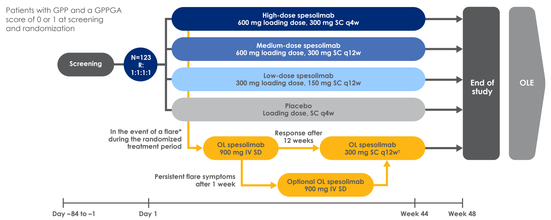
INTRODUCTION

- GPP is a rare, chronic inflammatory skin disease characterized by episodic flares of widespread pustular eruption and erythema, and can be life-threatening without effective management[1–3]
- Dysregulation of the IL-36 signalling pathway plays a central role in GPP pathogenesis[2]
- Spesolimab is an anti-IL-36 receptor monoclonal antibody; based on its efficacy and safety in the Effisayil 1 trial,[4] it has been approved for the treatment of GPP flares[5]
- Spesolimab has also been evaluated for the prevention of GPP flares in multiple patient types in Effisayil 2, a pivotal, randomized, placebo-controlled trial (NCT04399837)[6]

METHODS

- The primary endpoint, **time to GPP flare**, up to Week 48, and key secondary endpoint, **proportion of patients with ≥1 GPP flare** by Week 48, were analyzed for high-dose spesolimab (n=30) vs placebo (n=31) in the following prespecified subgroups:
  - ***IL36RN* mutation status** (no/yes)
  - **Baseline comorbid plaque PsO status** (no/yes)
  - **BMI category** (<25, 25 to <30, ≥30 kg/m²)
- Patients were classified as having a **GPP flare** if they had an **increase in GPPGA total score of ≥2** and an **increase in GPPGA pustulation subscore of ≥2** from baseline[6]
- Subsequent use of OL IV spesolimab also indicated a GPP flare

Figure 1. Study design



*Increase in GPPGA total score of ≥2 from baseline and GPPGA pustulation subscore ≥2. †Patients receiving OL SC spesolimab 300 mg q12w had the option to escalate to SC 300 mg q4w if there was an increase in the pustular component of GPPGA score of ≥1 from any of the previous OL visit(s).

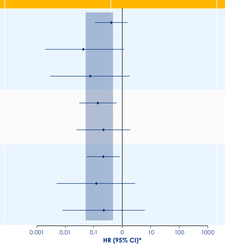
CONCLUSIONS

- In Effisayil 2, high-dose spesolimab showed superiority vs placebo in preventing GPP flares over 48 weeks
- In this subgroup analysis, spesolimab showed consistent efficacy in preventing GPP flares, over 48 weeks, regardless of *IL36RN* mutation status, the presence or absence of plaque PsO at baseline, or BMI category
- The main limitation of this analysis is the low patient number within each subgroup
- The findings were generally consistent across most prespecified subgroups for the primary and key secondary endpoints

RESULTS

Table 1. Primary endpoint: Time to GPP flare, up to Week 48, by prespecified subgroups

Subgroup		Number of patients with a flare, n/N		High-dose spesolimab	Placebo	HR (95% CI)*
		High-dose spesolimab (n=30)	Placebo (n=31)			
***IL36RN* mutation**	No	3/19	9/22			0.408 (0.109, 1.537)
	Yes	0/7	3/4			0.043 (0.002, 1.152)
	Unknown	0/4	4/5			0.075 (0.003, 1.829)
Baseline comorbid plaque PsO	No	2/23	11/21			0.139 (0.031, 0.629)
	Yes	1/7	5/10			0.218 (0.025, 1.883)
BMI category (kg/m²)	<25	3/19	9/14			0.215 (0.057, 0.816)
	25 to <30	0/5	5/9			0.122 (0.005, 2.817)
	≥30	0/6	2/8			0.225 (0.008, 6.033)

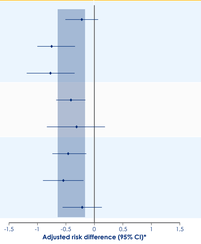


*HR and 95% CI are calculated from a Cox regression model stratified by use of systemic GPP medication at randomization. The interaction term, subgroup treatment, is included in the Cox regression model. If zero events occur in one/some of the arms by stratum, the model is conducted using Firth's penalization.

HRs consistently favored high-dose spesolimab vs placebo for reducing the risk of GPP flares in all prespecified subgroups

Table 2. Key secondary endpoint: Proportion of patients with ≥1 GPP flare, by Week 48, by prespecified subgroups

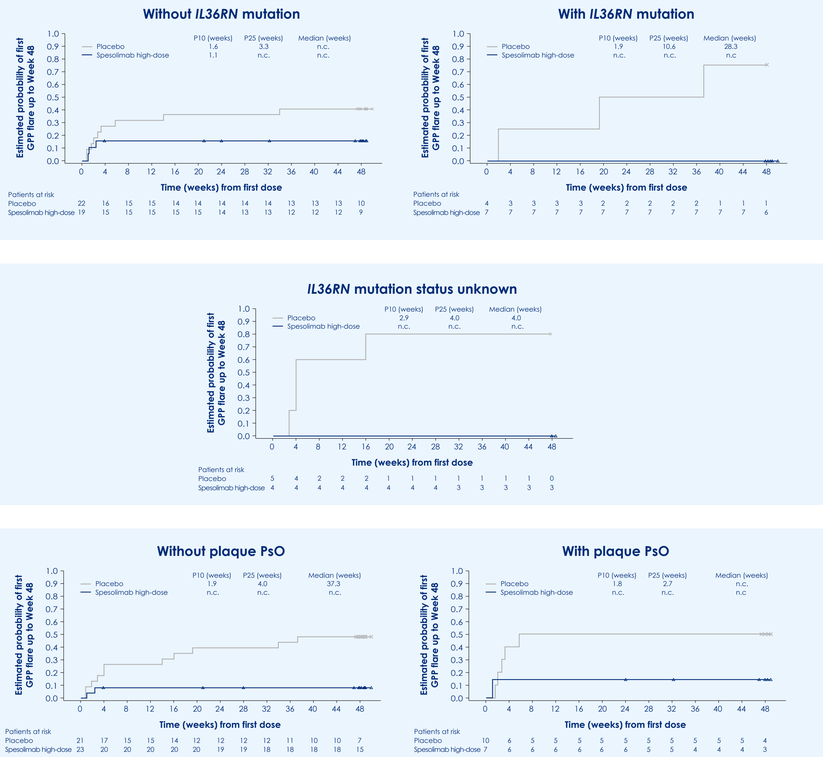
Subgroup		Number of patients with a flare, %		High-dose spesolimab	Placebo	Adjusted risk difference (95% CI)*
		High-dose spesolimab (n=30)	Placebo (n=31)			
***IL36RN* mutation**	No	19.4	40.9			−0.215 (−0.504, 0.074)
	Yes	0	75.0			−0.750 (−1.000, −0.326)
	Unknown	3.5	80.0			−0.765 (−1.187, −0.343)
Baseline comorbid plaque PsO	No	11.0	52.4			−0.413 (−0.672, −0.154)
	Yes	18.4	50.0			−0.319 (−0.830, 0.191)
BMI category (kg/m²)	<25	18.5	64.3			−0.457 (−0.771, −0.142)
	25 to <30	2.8	55.6			−0.544 (−0.903, −0.186)
	≥30	2.7	25.0			−0.212 (−0.557, 0.134)



*Adjusted risk difference is calculated by the Mantel-Haenszel type weighted average of risk difference introduced by Greenland and Robins, and 95% CI is calculated based on the variance estimator introduced by Sato.

The risk difference consistently favored high-dose spesolimab vs placebo for reducing the occurrence of ≥1 GPP flare in all prespecified subgroups

Figure 2. Primary endpoint: Time to GPP flare, up to Week 48, by prespecified subgroups



Probability of an event is estimated by the Kaplan–Meier approach.

Independent of *IL36RN* mutation status or baseline comorbid plaque PsO status, the probability of patients experiencing a GPP flare over 48 weeks was reduced with high-dose spesolimab vs placebo, with a greater effect observed in patients with an *IL36RN* mutation

Abbreviations

BMI, body mass index; CI, confidence interval; GPP, generalized pustular psoriasis; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; HR, hazard ratio; IL36RN, interleukin 36 receptor antagonist; IV, intravenous; n.c., non-calculable; OL, open label; OLE, open-label extension; P10, estimated probability of first GPP flare = 0.1; P25, estimated probability of first GPP flare = 0.25; PsO, psoriasis; q4w, every 4 weeks; q12w, every 12 weeks; R, randomization; SC, subcutaneous; SD, single dose.

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Disclosures & Acknowledgments

The study was supported and funded by Boehringer Ingelheim. **RBW** declares receiving research grants from AbbVie, Almirall, Amgen, Celgene, Janssen-Cilag, Eli Lilly, LEO Pharma, Medac, Novartis, Pfizer and UCB, and consultancy fees from AbbVie, Almirall, Amgen, Arena, Astellas, Avillion, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, DICE, GSK, Janssen-Cilag, Eli Lilly, LEO Pharma, Medac, Novartis, Pfizer, Sanofi, Sun Pharmaceutical Industries, UCB and UNION. **ADB** reports receiving consultancy fees from AbbVie, Almirall, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Janssen-Cilag, LEO Pharma, Novartis and UCB, and honoraria from Almirall, Boehringer Ingelheim, Eli Lilly and Janssen-Cilag. **SEC** declares paid activities as an advisor, speaker or consultant for AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen-Cilag, LEO Pharma, MSD, Novartis, Pfizer, Sanofi and UCB. **KBG** reports receiving grant support and consultancy fees from AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Janssen-Cilag, Novartis and UCB, and has received consultancy fees from Amgen, Almirall, Dermira, LEO Pharma, Pfizer and Sun Pharmaceutical Industries. **LP** has received consultancy/speakers' honoraria from and/or participated in clinical trials sponsored by AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Janssen-Cilag, LEO Pharma, Novartis, Pfizer, Sandoz, Sanofi and UCB. **AM** has received grant support and consultancy fees from AbbVie, Boehringer Ingelheim, Eli Lilly, LEO Pharma, Pfizer, Digital Diagnostics, Hims and Acorn Healthcare. **GK** has received travel grants or honoraria from, or has been a consultant member of advisory boards and speakers' bureaus or has served as an investigator for AbbVie, Actelion, Almirall, Amgen, Basilea, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Hexal-Sandoz, Janssen-Cilag, LEO Pharma, Eli Lilly, MSD, Novartis, Pfizer, Sanofi and UCB. **MJA** has served as a consultant and/or advisor for ImClone, Bristol Myers Squibb, AstraZeneca, Theraplex, Aspire Bariatrics, Biogen, Amgen, Veloce, Adgero, Eli Lilly, AbbVie, UCB, Innovaderm, Boehringer Ingelheim, OnQuality, Novocure, SpringWorks, Boiling and Protagonist, and has served as a Principal Investigator for Novartis, Boehringer Ingelheim, Lutris, OnQuality, UCB Biopharma, InflaRx, Eli Lilly, InCyte, AbbVie, MoonLake, AnaptysBio, Hana Biosciences, Xoma, Veloce, Biogen, XBiotech, ChemoCentryx, Mabeig, Regeneron and Phoenicis. **NH**, **PH** and **CT** are employees of 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. Boehringer Ingelheim was given the opportunity to review the poster for medical and scientific accuracy, as well as intellectual property considerations.
Clare Bellward, MRes, of Hyperion, OPEN Health Scientific Communications (London, UK), provided writing, editorial, and formatting support, which was contracted and funded by Boehringer Ingelheim.

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Presented at: Fall Clinical Dermatology Conference® 23, Las Vegas, NV, USA: October 19–22, 2023.
Previously presented at: European Academy of Dermatology and Venereology (EADV) Congress, Berlin, Germany: October 11–14, 2023.