Low occurrence of predefined safety events across six randomized clinical trials of spesolimab in dermatologic conditions

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Aim: To describe rates of predefined safety events, using available data from six randomized trials of spesolimab across GPP and other dermatologic conditions in this pooled analysis

Background

- The IL-36 pathway plays a central role in the pathogenesis of GPP and is a key regulator of pustule formation. IL-36 signaling has also been implicated in other chronic inflammatory skin diseases, such as PPP, HS, and AD[1–4]
- Spesolimab, a humanized mAb against the IL-36 receptor, is approved in 48 countries* as an IV dosage in adults to treat GPP flares, and in the US and China in both adults and pediatric patients aged 12 years or older 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[5]
- Spesolimab demonstrated a favorable safety profile when administered over 48 weeks for the prevention of GPP flares in the Effisayil® 2 trial[6–8]
- Given its novel mechanistic approach, it is important to characterize events potentially related to IL-36 receptor inhibition with spesolimab, as well as those of potential relevance to an intravenously/subcutaneously administered biologic

*Approved for the treatment of GPP flares in adults in the US, Canada, Brazil, India, Japan, China, Taiwan, and the EU.

Methods

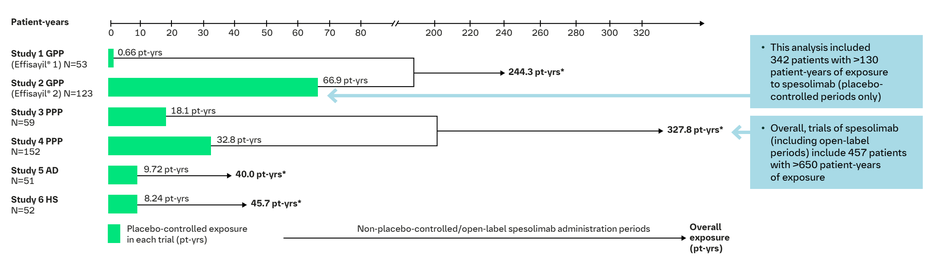
- Predefined events* included: infections,† malignant tumors, peripheral neuropathy, and potential hypersensitivity events

Table 1. Summary of included trials

Study details	Study 1 GPP (Effisayil® 1)	Study 2 GPP (Effisayil® 2)	Study 3 PPP	Study 4 PPP	Study 5 AD	Study 6 HS
Phase	II	IIb	IIa	IIb	IIa	II
Double-blind, randomized, placebo-controlled	Yes	Yes	Yes	Yes	Yes	Yes
Spesolimab dosage	Single 900 mg IV	LD: 600 mg or 300 mg SC q4w: 300 mg SC q12w: 300 mg or 150 mg SC	900 or 300 mg q4w IV	LD: 1500 or 3000 mg SC q4w: 300 or 600 mg SC	600 mg IV q4w	1200 mg IV qw, 1200 mg SC q2w
Patients (N)	53	123	59	152	51	52
Spesolimab (n)	35	92	38	109	33	35
Placebo (n)	18	31	21	43	18	17
Primary endpoint period	Week 1	Week 48	Week 16	Week 16	Week 16	Week 12
NCT number	NCT03782792	NCT04399837	NCT03135548	NCT04015518	NCT03822832	NCT04762277

*MedDRA hierarchy search terms: Infections all (severe infections: SOC "Infections and infestations" of at least severe RCTC grade; serious infections: SOC "Infections and infestations", all SAEs; opportunistic infections: narrow SMQ "Opportunistic infections"); malignant tumors (narrow sub-SMQ "Malignant tumors": narrow sub-SMQ "Hematological malignant tumors" and narrow sub-SMQ "Non-hematological malignant tumors)"; Peripheral neuropathy (narrow SMQ "Guillain-Bararé Syndrome; narrow SMQ "Peripheral neuropathy", narrow SMQ "Demyelination"); and hypersensitivity all (anaphylactic reactions: narrow SMQ "Anaphylactic reaction"; angioedema: narrow SMQ "Angioedema"; hypersensitivity: narrow SMQ "Hypersensitivity", and SMQ "Drug reaction with eosinophilia and systemic symptoms", using the respective broad or narrow algorithm). †Infections included serious, severe, and opportunistic infections.

Figure 1. Patient-years of exposure to spesolimab

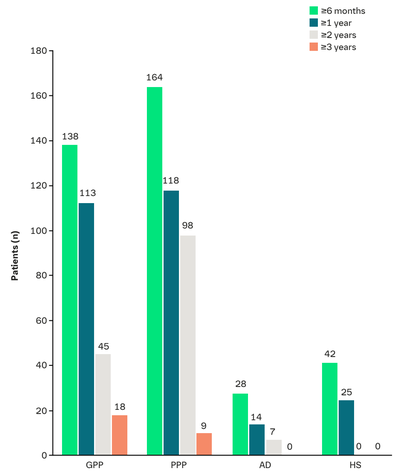


*Combined OLE period up to the cut-off date of December 1, 2022.

Results

Figure 2. Duration of exposure to spesolimab across dermatologic indications

Based on data from randomized, placebo-controlled periods plus OLE trials, a substantial number of patients have had long-term exposure to spesolimab*



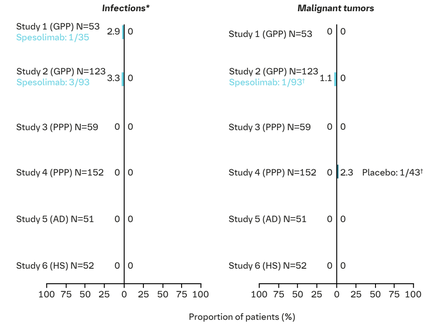
*A cumulative time at risk of ≥6 months.

Figure 3. Infections* and malignancies

Infections and malignancies were largely balanced between patients treated with spesolimab and those treated with placebo

- Severe, serious, opportunistic infections were identified only in GPP trials; no pattern regarding pathogen or affected organs was observed, and study drug was continued in all cases
- Underlying dermatologic conditions under investigation may account for some of the events

- Malignancies appeared infrequently across trials, and some patients had underlying risk factors



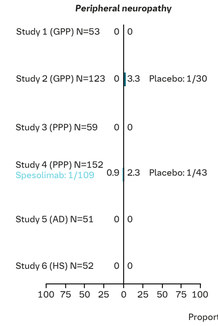
*Infections include serious, severe, and opportunistic infections. †Study drug was discontinued.

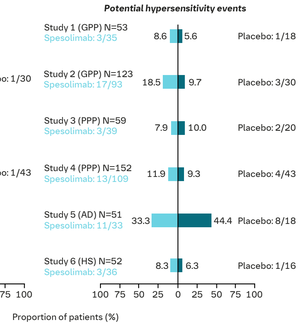
Figure 4. Peripheral neuropathy and potential hypersensitivity events

Peripheral neuropathy events appeared infrequently across trials. The incidences of potential hypersensitivity reactions were similar for spesolimab (7.7–33.3%) and placebo (5.6–44.4%) across trials

- Peripheral neuropathy events were infrequent in patients treated with spesolimab

- Potential hypersensitivity events were mostly non-serious, did not lead to premature discontinuation of trial medication, and did not indicate dose-dependency
- Many of the AEs were unspecific PTs, e.g. rash, eczema; underlying dermatologic conditions under investigation may account for some of the events
- Some AEs were clearly attributable to causes other than spesolimab





Spesolimab UDAEC ■ Placebo UDAEC

Conclusions

- Spesolimab has been studied across multiple dermatologic indications, with many patients having been treated ≥6 months to ≥1 year or longer
- With respect to infections, no pattern regarding pathogen or affected organ was identified
- Reported malignancies and peripheral neuropathy events were balanced between spesolimab and placebo
- Potential hypersensitivity events were numerically higher with spesolimab compared with placebo for study 2 (Effisayil® 2), and were mainly non-serious, non-severe, and not dose-dependent
- Underlying dermatologic conditions under investigation may account for some of the events of interest (particularly infections and potential hypersensitivity events)
- There were no consistent differences between spesolimab and placebo in the placebo-controlled trial periods
- Across all trials, spesolimab demonstrated a consistent and favorable safety profile

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Abbreviations

AD, atopic dermatitis; AE, adverse event; GPP, generalized pustular psoriasis; HS, hidradenitis suppurativa; IL, interleukin; IV, intravenous; LD, loading dose; mAb, monoclonal antibody; MedDRA, Medical Dictionary for Regulatory Authorities; NCT, National Clinical Trial; OLE, open-label extension; PPP, palmoplantar pustulosis; PT, preferred term; pt-yrs, patient-years; qw, every week; q2w, every 2 weeks; q4w, every 4 weeks; q12w, every 12 weeks; RCTC, Rheumatology Common Toxicity Criteria; SAE, serious adverse event; SC, subcutaneous; SMQ, standardized MedDRA query; SOC, MedDRA system organ class; UDAEC, user-defined adverse event category.

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