Changes in the molecular profile of lesional skin and blood of patients with generalized pustular psoriasis treated with spesolimab are associated with clinical response

Ahmed Farag[1], Sudha Visvanathan[2], Hervé Bachelez[3], Akimichi Morita[4], Mark Lebwohl[5], Jonathan N. Barker[6], Siew Eng Choon[7], A. David Burden[8], Germán Leparc[1], Denis Delic[1], Sebastian Bossert[1], Christian Thoma[1], James G. Krueger[9]

[1]Boehringer Ingelheim International GmbH, Biberach, Germany; [2]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA; [3]UMR INSERM U1163, Institut Imagine, Université de Paris, and Department of Dermatology, AP-HP Hôpital Saint-Louis, Paris, France; [4]Department of Geriatric and Environmental Dermatology, Nagoya City, University Graduate School of Medical Sciences, Nagoya, Japan; [5]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [6]St John's Institute of Dermatology, King's College London, London, UK; [7]Department of Dermatology, Hospital Sultanah Aminah, Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia; [8]Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK; [9]Laboratory for Investigative Dermatology, The Rockefeller University, New York, NY, USA

Spesolimab treatment reversed the lesional skin molecular profile associated with GPP, shown by the suppression of genes involved in GPP pathogenesis and IL-36 signalling, and sustained reduction in neutrophil infiltrates and IL-36γ protein level until Week 8

PURPOSE

To investigate gene and protein expression in lesional versus non-lesional skin biopsies and serum in patients with generalized pustular psoriasis (GPP) enrolled in the Effisayil™ 1 study as well as the treatment effect of spesolimab

INTRODUCTION

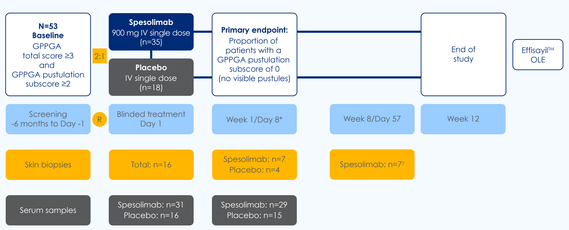
- GPP is a rare, neutrophilic skin disease characterised by sudden widespread eruptions of sterile pustules that may be associated with systemic inflammation[1,2]
- The natural clinical course of a GPP flare is highly variable and can lead to life-threatening complications if left untreated[2]
- Dysregulation of the IL-36 signalling pathway is involved in GPP pathogenesis[3–7]
- Spesolimab, a humanised anti-IL-36R monoclonal antibody, has demonstrated efficacy in controlling GPP flare skin symptoms within 1 week of treatment in the Effisayil™ 1 trial[8]

CONCLUSIONS

- In the Effisayil™ 1 trial, spesolimab treatment led to rapid improvements in skin and pustular clearance within 1 week in patients experiencing a GPP flare
- At baseline, lesional versus non-lesional skin gene expression analysis demonstrated an upregulation of genes related to IL-36 (e.g. *IL36A*, *IL36B*, *IL36G*) and those associated with neutrophil recruitment, pro-inflammatory cytokines and skin inflammation
- Spesolimab reversed the lesional skin gene expression pattern associated with GPP
- Spesolimab downregulated GPP- and IL-36 pathway-related gene expression
- Spesolimab led to a marked reduction in neutrophil infiltrates and IL-36γ protein level in lesional skin, which was sustained to Week 8
- Spesolimab led to a reduction in serum GPP biomarkers from Week 1 through Week 12, correlating with clinical improvement

METHODS

Effisayil™ 1 study design and biomarker analysis



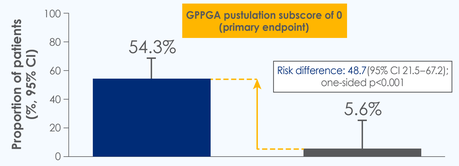
- Baseline samples were collected prior to drug administration on Day 1
- Lesional (and non-lesional at baseline) skin biopsies were 5 mm samples; half for RNA sequencing and half for immunohistochemistry
- Serum samples to assess soluble protein biomarkers were also collected on Days 2 and 3 and Weeks 2, 4 and 12

*Patients could receive open-label spesolimab on Week 1 (if their GPPGA total score was ≥2 and their GPPGA pustulation subscore was ≥2 on Week 1) and a single dose of rescue spesolimab after Week 1 (if they had a ≥2-point increase in both the GPPGA total score and GPPGA pustulation subscore after a previous clinical response to treatment);
†All patients have received spesolimab at this time point.

GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; IV, intravenous; OL, open-label; OLE, open-label extension; R, randomisation.

RESULTS

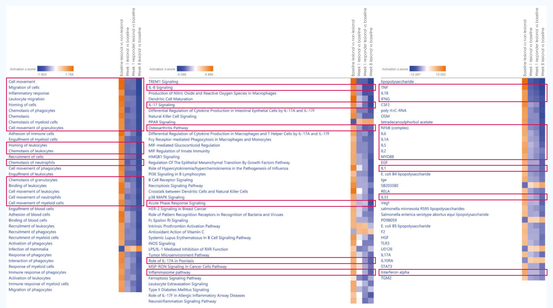
Spesolimab rapidly controlled symptoms of GPP flare skin within 1 week of treatment



CI, confidence interval; GPP, generalized pustular psoriasis; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment.

54% of patients with GPP receiving spesolimab had no visible pustules by Week 1

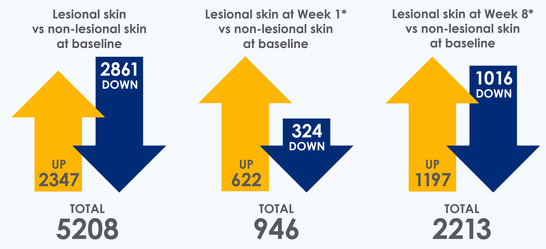
Spesolimab downregulates GPP-associated and IL-36 signalling pathways



GPP, generalized pustular psoriasis; GSVA, Gene Set Variation Analysis; IL, interleukin.

Targeting of the IL-36R with spesolimab downregulates GPP-associated and IL-36 signalling pathway genes in lesional skin confirming the central role of the IL-36 pathway in GPP

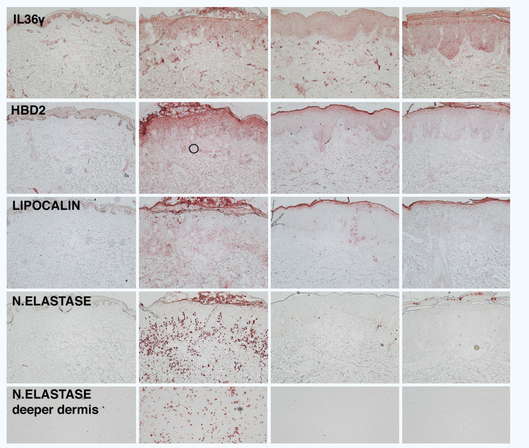
Overview of the number of differentially expressed genes for all comparisons



*for patients randomised to spesolimab.

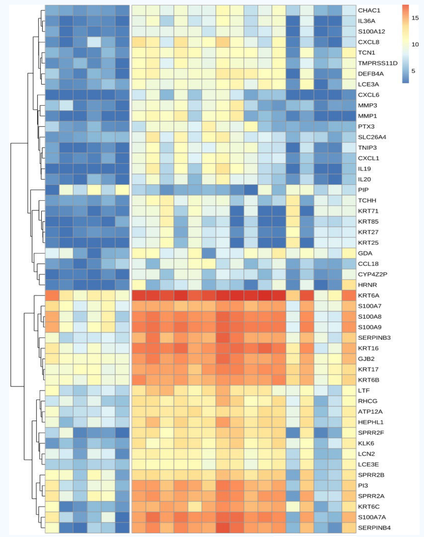
Spesolimab administration resulted in strong and sustained reductions in lesional skin biomarkers which started before Week 1 and were maintained until Week 8. Genes that were downregulated at Week 8 included those associated with proinflammatory mediators (e.g. *IL6*, *TNF*, *IL20*); neutrophil recruitment (e.g. *CXCL1*, *CXCL2*, *CXCL8*); Th1/Th17 mediated inflammation (e.g. *IL1B*, *IL17F*); and IL36 ligands (e.g. *IL36A*, *IL36B*, *IL36G*)

Histopathological changes in select biomarkers were observed in lesional versus non-lesional skin before and after treatment at Week 8



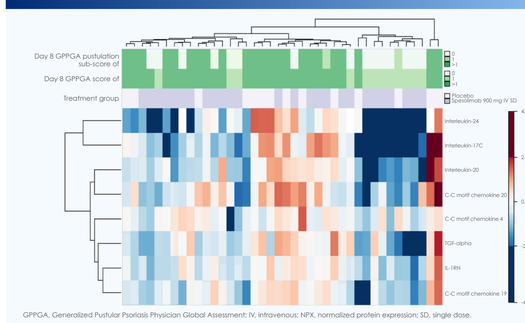
Spesolimab treatment led to a marked reduction in neutrophil infiltrates and IL-36γ in lesional skin that was sustained to Week 8

Spesolimab alters gene expression at Week 8



The decrease in lesional skin gene signature after treatment with spesolimab was sustained until Week 8 compared with non-lesional skin signature

Spesolimab treatment reduced key serum biomarkers associated with GPP



GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; IV, intravenous; NPX, normalized protein expression; SD, single dose.

Spesolimab treatment resulted in sustained reduction in serum biomarkers of GPP from Week 1 up to Week 12

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