Health Technology Briefing
July 2024

Spesolimab for preventing generalised pustular psoriasis flares in adults and adolescents aged 12 years and over

Company/Developer	Boehringer Ingelheim Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30965	NICE ID: 11789	UKPS ID: 674890

Licensing and Market Availability Plans

Phase II clinical trial completed.

Summary

Spesolimab is in development for the prevention of flares in generalised pustular psoriasis in adults and adolescents aged 12 years and over. Generalised pustular psoriasis is a rare dermatological condition characterised by the sudden appearance of multiple small blisters filled with pus (called pustules) on large areas of the skin on the body, arms, and legs, that also become red and painful. These episodes are called flares. Generalised pustular psoriasis flares greatly affect a person's quality of life and can cause life-threatening complications such as heart failure, sepsis, potentially leading to hospitalisation or even death. There are currently no approved treatments for the prevention of generalised pustular psoriasis flares; the relapsing nature of generalised pustular psoriasis (recurrent flares or persistent disease with intermittent flares) highlights the need to develop treatments to prevent flares.

Spesolimab is a monoclonal antibody (a type of protein) that binds to and blocks the receptor (target) for a protein involved in inflammation called interleukin-36 (IL-36). By preventing IL-36 from attaching to its receptor, spesolimab reduces inflammation and improves the symptoms of generalised pustular psoriasis. Spesolimab is administered by subcutaneous injection. If licenced, spesolimab would provide an additional treatment option for the prevention of generalised pustular psoriasis flares.

Proposed Indication

Prevention of generalised pustular psoriasis (GPP) flares in adults and adolescents aged 12 years and over.[1]

Technology

Description

Spesolimab (Spevigo, BI 655130) is the first-in-class humanised monoclonal immunoglobulin G1 (IgG1) antibody that specifically binds to interleukin-36 (IL-36) receptors and antagonises IL-36 signalling. IL-36 is a family of cytokines that signal downstream pro-inflammatory and pro-fibrotic pathways that result in inflammatory skin conditions including generalised pustular psoriasis (GPP). Given its role in GPP pathogenesis, IL-36 has been identified as a potential drug target.[2]

Spesolimab is currently in development for the prevention of GPP flares. In phase II clinical trials (Effisayil™ 2; NCT04399837), participants received a 600-mg subcutaneous loading dose of spesolimab followed by a 300-mg maintenance dose administered every 4 or 12 weeks, or a 300-mg loading dose followed by a 150-mg maintenance dose administered every 12 weeks, for 48 weeks.[1-3]

Key Innovation

Treatments used for GPP flares are limited.[4,5] Conventional psoriasis treatments are generally used to treat GPP.[5] Hence, there is an unmet need for GPP-specific treatments that can act rapidly and improve clinical outcomes in patients, with favourable safety profiles.[5,6] The relapsing nature of GPP (recurrent flares or persistent disease with intermittent flares) highlights the need to develop treatments to prevent flares.[3] Spesolimab treatment in GPP leads to significant downregulation of inflammatory genes, T-cell activity, and clinical severity of symptoms. RNA sequence analysis in blood post treatment revealed sustained downregulation of immune response pathways, with markedly reduced serum biomarkers of inflammation.[2] Spesolimab also reduces the risk of GPP flare and the rate of flare occurrence over 48 weeks, strengthening its potential utility in chronic GPP management.[2]

In the UK, spesolimab has been approved for the treatment of GPP flares in adults.[7] If licensed, spesolimab would prevent GPP flares in adults and adolescents from 12 years of age.

Regulatory & Development Status

Spesolimab currently has Marketing Authorisation in the UK as a monotherapy for the treatment of flares in adult patients with GPP.[7]

Spesolimab has the following regulatory designations/awards:[8,9]

- a Breakthrough Therapy by the US FDA for the prevention of GPP flares in adolescents and adults in May 2023
- a Breakthrough Therapy by the US FDA for the treatment of GPP flares in adults in 2021
- an orphan drug in the USA in 2021 for the treatment of GPP flares in adults

Spesolimab is also currently in phase II/III development for the following indications:[10]

- Pyoderma Gangrenosum
- Palmoplantar pustulosis
- Hidradenitis Suppurativa
- Dermatitis
- Psoriasis
- Colitis
- Crohn Disease

- Netherton Syndrome

Patient Group

Disease Area and Clinical Need

Generalised pustular psoriasis (GPP) is an uncommon and potentially life-threatening subtype of pustular psoriasis characterised by relapsing flares of sterile pustules, accompanied by systemic symptoms of pyrexia, erythema, and fatigue. GPP patients may experience serious complications, such as sepsis, acute respiratory distress syndrome, renal failure, and heart failure, potentially leading to hospitalisation or even death.[2] Genetic mutation has been thought to be a primary driver of GPP.[11] Drug-related triggers are common, including steroid withdrawal, antimalarials, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and lithium. Pregnancy, menstruation, stress, upper respiratory tract infections and bacterial infections may also trigger GPP.[11]

Approximately 22.0% to 36.3% of patients with GPP require hospitalisation, with an average stay in the hospital lasting 10 to 16 days and 25% of patients requiring intensive care during their hospital stay.[2,12] Also, GPP flares led to patient hospitalisation in 35.1%, 74.2%, and 64.3% of patients for their typical, most severe, and longest flares, respectively.[13] In England (2022-23) there were 304 finished consultant episodes (FCEs) and 172 admissions for GPP (ICD-10 code L40.1), which resulted in 73 day cases and 1094 FCE bed days.[14] An English cohort study of 373 patients with GPP, which involved analyses of longitudinal data from electronic health records in the Clinical Practice Research Datalink Aurum database and linked hospital and mortality data between 2008 and 2019, reported a prevalence rate of 1.61 to 3.0 per 100,000 for GPP.[15]

Recommended Treatment Options

There are currently no NICE recommended treatment options for preventing flares in GPP.

Clinical Trial Information

Trial	**Effisayil™ 2;** NCT04399837, EudraCT 2018-003081-14; Multi-center, Randomized, Parallel Group, Double-Blind, Placebo-Controlled, Phase IIb Dose-finding Study to Evaluate Efficacy and Safety of BI 655130 (Spesolimab) Compared to Placebo in Preventing Generalised Pustular Psoriasis (GPP) Flares in Patients With History of GPP. **Phase II** – Completed **Location (s):** Seven EU countries, US, and other countries **Study completion date:** November 2022
Trial Design	Randomised, parallel assignment, quadruple masking, and placebo-controlled
Population	N = 123 (actual); patients aged 12 to 75 years, with history of moderate to severe Generalised Pustular Psoriasis (GPP) flares
Intervention(s)	• Subcutaneous (SC) 600-mg loading dose of spesolimab followed by a 300-mg maintenance dose administered every 4 weeks or every 12 weeks for 48 weeks.[3] • SC 300-mg loading dose of spesolimab followed by a 150-mg maintenance dose administered every 12 weeks for 48 weeks.[3]

Comparator(s)	Matched placebo.
Outcome(s)	Primary outcome measure: Time to first GPP flare [Time Frame: Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) was regularly assessed at baseline (Week 1) and up to Week 48 (at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48).] See trial record for a full list of other outcomes.
Results (efficacy)	Spesolimab showed significant prevention of generalised pustular psoriasis (GPP) flares for up to 48 weeks in adolescents and adults.[3,16]
Results (safety)	Safety data were in line with previously conducted clinical trials with spesolimab.[3,16]

Estimated Cost

Spesolimab is already marketed in the UK; a vial (60 mg per 1 ml) costs £15,000.[17]

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Psoriasis: assessment and management. October 2012 (Last updated September 2017)
- NICE quality standard. Psoriasis (QS40). August 2013

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Specialised Dermatology Services (All ages). A12/S/a.

Other Guidance

- Barker JN, Becher G, Burden DA, Pink AE, Zacharioudaki M, Warren RB. Clinical course, treatment and management of generalised pustular psoriasis from a United Kingdom extension of a global Delphi panel. 2024.[18]
- Puig L., Choon S.E., Gottlieb A.B., Marrakchi S., Prinz J.C., Romiti R., et al. Generalised pustular psoriasis: A global Delphi consensus on clinical course, diagnosis, treatment goals and disease management. 2023.[19]
- Takeichi T., Akiyama M. Generalised pustular psoriasis: Clinical management and update on autoinflammatory aspects. 2020.[20]
- Smith CH, Jabbar-Lopez ZK, Yiu ZZ, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. British Journal of Dermatology. 2017.[21]

Additional Information

References

1 ClinicalTrials.gov. *A Study to Test Whether BI 655130 (Spesolimab) Prevents Flare-ups in Patients With Generalized Pustular Psoriasis*. *Trial ID: NCT04399837*. 2020. Status: Completed. Available from: https://clinicaltrials.gov/study/NCT04399837 [Accessed May 10, 2024].

2 Pathak GN, Wang E, Dhillon J, Parikh PN, Esseghir R, Rao BK, Feldman SR. Spesolimab: A Review of the First IL-36 Blocker Approved for Generalized Pustular Psoriasis. *Annals of Pharmacotherapy*. 2024;0(0):10600280241252688. Available from: https://doi.org/10.1177/10600280241252688.

3 Morita A, Choon SE, Bachelez H, Anadkat MJ, Marrakchi S, Zheng M, et al. Design of Effisayil™ 2: A Randomized, Double-Blind, Placebo-Controlled Study of Spesolimab in Preventing Flares in Patients with Generalized Pustular Psoriasis. *Dermatol Ther (Heidelb)*. 2023;13(1):347-59. Available from: https://doi.org/10.1007/s13555-022-00835-6.

4 Krueger J, Puig L, Thaçi D. Treatment Options and Goals for Patients with Generalized Pustular Psoriasis. *American Journal of Clinical Dermatology*. 2022;23(Suppl 1):51-64. Available from: https://doi.org/10.1007/s40257-021-00658-9.

5 Tsai T-F, Zheng M, Ding Y, Song Z, Liu Q, Chen Y, et al. Efficacy and Safety of Spesolimab in Patients with Generalized Pustular Psoriasis: A Subgroup Analysis of Chinese Patients in the Effisayil 1 Trial. *Dermatology and Therapy*. 2023;13(12):3097-110. Available from: https://doi.org/10.1007/s13555-023-01037-4.

6 Gooderham MJ, Van Voorhees AS, Lebwohl MG. An update on generalized pustular psoriasis. *Expert Review of Clinical Immunology*. 2019;15(9):907-19. Available from: https://doi.org/10.1080/1744666x.2019.1648209.

7 Electronic Medicines Compendium (EMC). *Spevigo 450 mg concentrate for solution for infusion*. 2023. Available from: https://www.medicines.org.uk/emc/product/15235 [Accessed 22 May, 2024].

8 PR Newswire. *Newly published results showed spesolimab significantly improved signs and symptoms of flares in rare, life-threatening skin disease, generalized pustular psoriasis*. 2021. Available from: https://www.prnewswire.com/news-releases/newly-published-results-showed-spesolimab-significantly-improved-signs-and-symptoms-of-flares-in-rare-life-threatening-skin-disease-generalized-pustular-psoriasis-301449928.html [Accessed 22 May, 2024].

9 Businesswire. *SPEVIGO® granted Breakthrough Therapy Designation in the U.S. for the prevention of generalized pustular psoriasis flares*. 2023. Available from: https://www.businesswire.com/news/home/20230502005731/en [Accessed 06 June, 2024].

10 ClinicalTrials.gov. *Spesolimab | Phase: 2, 3*. 2024. Available from: https://clinicaltrials.gov/search?term=Spesolimab&viewType=Table&aggFilters=phase:2%203&page=1 [Accessed 22 May, 2024].

11 Kodali N, Blanchard I, Kunamneni S, Lebwohl MG. Current management of generalized pustular psoriasis. *Experimental Dermatology*. 2023;32(8):1204-18. Available from: https://doi.org/10.1111/exd.14765.

12 Zimmermann TM, Hofmann P, Chiu GR. A narrative review of the socioeconomic burden associated with generalised pustular psoriasis. *Experimental Dermatology*. 2023;32(8):1219-26. Available from: https://doi.org/10.1111/exd.14841.

13 Choon SE, Lebwohl MG, Turki H, Zheng M, Burden AD, Li L, et al. Clinical Characteristics and Outcomes of Generalized Pustular Psoriasis Flares. *Dermatology*. 2023;239(3):345-54. Available from: https://doi.org/10.1159/000529274.

14 National Health Service (NHS) Digital. *Hospital Admitted Patient Care Activity, 2022-23*. 2023. Available from: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Ffiles.digital.nhs.uk%2F34%2FC4E943%2Fhosp-epis-stat-admi-diag-2022-23-tab.xlsx&wdOrigin=BROWSELINK [Accessed 22 May, 2024].

15 Frysz M, Patel S, Li MOY, Griffiths CEM, Warren RB, Ashcroft DM. Prevalence, incidence, mortality and healthcare resource use for generalized pustular psoriasis, palmoplantar pustulosis and plaque psoriasis in England: a population-based cohort study. *British Journal of Dermatology*. 2024. Available from: https://doi.org/10.1093/bjd/ljae217.

16 Boehringer Ingelheim. *Spesolimab meets primary and key secondary endpoint for prevention of generalized pustular psoriasis flares*. 2023. Available from: https://www.boehringer-ingelheim.com/human-health/skin-and-inflammatory-diseases/gpp/spesolimab-meets-key-endpoint-gpp-flare-prevention [Accessed 05 May, 2024].

17 National Institute for Health and Care Excellence (NICE): British National Formulary (BNF). *Spevigo 450mg/7.5ml concentrate for solution for infusion vials Boehringer Ingelheim Ltd*. 2024. Available from: https://bnf.nice.org.uk/drugs/spesolimab/medicinal-forms/ [Accessed 22 May, 2024].

18 Barker JN, Becher G, Burden DA, Pink AE, Zacharioudaki M, Warren RB. Clinical course, treatment and management of generalised pustular psoriasis from a United Kingdom extension of a global Delphi panel. *Skin Health Dis*. 2024;4(3):e359. Available from: https://doi.org/10.1002/ski2.359.

19 Puig L, Choon SE, Gottlieb AB, Marrakchi S, Prinz JC, Romiti R, et al. Generalized pustular psoriasis: A global Delphi consensus on clinical course, diagnosis, treatment goals and disease management. *Journal of the European Academy of Dermatology and Venereology*. 2023;37(4):737-52. Available from: https://doi.org/10.1111/jdv.18851.

20 Takeichi T, Akiyama M. Generalized Pustular Psoriasis: Clinical Management and Update on Autoinflammatory Aspects. *American Journal of Clinical Dermatology*. 2020;21(2):227-36. Available from: https://doi.org/10.1007/s40257-019-00492-0.

21 Smith CH, Jabbar-Lopez ZK, Yiu ZZ, Bale T, Burden AD, Coates LC, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. *British Journal of Dermatology*. 2017;177(3):628-36. Available from: https://doi.org/10.1111/bjd.15665.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.