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HEALTH TECHNOLOGY BRIEFING
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Spesolimab for the treatment of acute flares of generalised pustular psoriasis

NIHRIO ID	27208	**NICE ID**	10497
Developer/Company	Boehringer Ingelheim Ltd	**UKPS ID**	657793

Licensing and market availability plans	Currently in phase II clinical trial.

SUMMARY

Spesolimab is currently in clinical development for the treatment of acute flares of generalised pustular psoriasis (GPP). Individuals with GPP experience repeated episodes where large surface areas of the skin become inflamed and red, and develop small pus-filled blisters known as pustules. It is a disease that spreads and affects a large surface area of the body. The main cause of GPP is not yet known but it is thought that environmental factors such as stress and genetic susceptibility can trigger disease onset. GPP can be a life-threatening disease if left untreated as it can lead to organ failure. Spesolimab is administered intravenously for the treatment of flares of GGP . It blocks the interaction of interleukin 36 receptor (IL-36R) and IL-36 which also blocks downstream inflammatory responses. Many patients with moderate to severe GPP struggle with insufficient disease control. There is currently no biologic treatment for GPP. If licensed spesolimab will offer a new treatment option for patients with flares of GPP.

PROPOSED INDICATION

For the treatment of adult patients with acute flares of generalised pustular psoriasis (GPP).[1,2]

TECHNOLOGY

DESCRIPTION

Spesolimab (BI 655130) is a humanised monoclonal antibody that inhibits the action of the receptor IL-36R.[2,3] IL-36 is a member of the pro-inflammatory cytokines family and is expressed in various types of cells including keratinocytes. The IL-36R potentiates the production of type-1 interferon through stimulation of leucocyte recruitment and innate immune inflammation.[4] This signalling pathway may play a role in many inflammatory diseases.[5]

Spesolimab is currently in phase II clinical development for the treatment of GPP flares. In the phase II clinical trial (NCT03886246), there are two parts to the clinical development. Firstly, participants will receive an intravenous injection of spesolimab with the option for additional open-label administration at day 8, investigated for the treatment of flares in patients with GPP. The second part of this clinical development includes a subcutaneous injections participant will receive for the prevention of GPP flares.[1]

INFORMATION PROVIDED BY BOEHRINGER-INGELHEIM

INNOVATION AND/OR ADVANTAGES

Currently, there is no biologic treatment available specifically for the treatment of GPP. To date, the management approach used to treat patients with GPP is largely based on interleukin 1 (IL-1) inhibitor trials and/or treatment guidelines of plaque psoriasis. The volatile efficacy of current treatment options and the increased risk of systemic complications in patients with GPP call for a novel targeted drug development.[4]

The National Institute for Health and Care Excellence (NICE) do not currently have specific guidance for the management of GPP.[6] Spesolimab would provide the first specific biologic treatment for patients experiencing acute GPP.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Spesolimab does not currently have Marketing Authorisation in the EU/UK for any indication.

Spesolimab is currently in phase II and phase III clinical development for the treatment of patients with hidradenitis suppurativa, palmoplantar pustulosis, atopic dermatitis and complicated Crohn's disease (fistulizing and fibrostenosing).[7]

INFORMATION PROVIDED BY BOEHRINGER-INGELHEIM

PATIENT GROUP

DISEASE BACKGROUND

Psoriasis is an immune disease whereby activated T-cells migrate to the skin and release cytokines that cause the skin cells to reproduce and mature at an accelerated rate.[8] A normal skin cell goes through several phases of development before maturing and falling off (shedding) from the body's surface as dead skin cells in 28 to 30 days. However, skin affected by psoriasis takes only three to four days to mature and move to the surface. This results in dead skin cells not being shed quickly enough to keep up with the new skin cells being produced so the cells pile up and form thick, flaky lesions resulting in plaque psoriasis.[9]

Generalised pustular psoriasis is an autoinflammatory disease where the patho-immunology is not yet fully known but the IL-36 pathway is thought to play a pivotal role.[10] The IL-36 antagonist and receptors are expressed in keratinocytes amongst other cell types. The binding of the IL-36 antagonists to IL-36 receptors causes an inflammatory response that leads to the release of chemokines which activate the T-cells, macrophages, neutrophils and dendritic cells.[10] A mutation of the IL-36RN leads to a loss of function or functional impairment of IL-36Ra subsequently causing changes to the structure of the amino acid sequence and a growth of the downstream inflammatory cascade. This loss of function mutation leads to an excess in IL-36 signalling. This form of mutation can be found in both sporadic and familial cases of GPP.[10] GPP is a rare and severe form of psoriasis and is characterised by the presence of sterile pustules that can occur in various patterns.[11,12] GPP is clinically diverse in its severity, age at onset and precipitants. It is assumed that there is a relationship between GPP and plaque psoriasis as some patients may experience episodes of plaque psoriasis before or after the GPP, whilst in others GPP occurs as the only phenotype without the occurrence of plaque psoriasis.[12]

Individuals with GPP experience repeated episodes where large surface areas of the skin become inflamed and red, and develop pustules. Individuals may also experience muscle weakness, fatigue, fever, a higher number of white blood cells and systemic inflammation. These episodes that subside and reappear can be triggered by various factors.[13]

The specific trigger of GPP episode onset is often unknown but is thought to be a complex mix of genetic susceptibility and environmental factors such as withdrawal from or exposure to certain medications mainly corticosteroid treatment, infection, stress, pregnancy or menstruation.[13] In some cases, active disease triggered by hypocalcaemia caused by hypoparathyroidism have also been reported.[12] GPP can be life threatening if untreated, as it can lead to severe infection, heart failure or kidney failure.[13,14]

Psoriasis is commonly graded as mild, moderate or severe according to the surface area of the body affected or with the use of indices such as the Psoriasis Area Severity Index (PASI), which takes into accounts the size of the area covered with psoriasis as well as the redness, thickness and scaling. Severe psoriasis is defined by a total PASI score of >10.[15] The GPP-specific clinical efficacy endpoints (GPPGA, GPPASI) were created with minimal modification of the PGA and PASI (replacement of the induration component with pustulation), which are widely used and understood clinical instruments by dermatologists, and were created with the help of leading global experts in GPP and psoriasis vulgaris. For the GPPGA score, the investigator (or qualified site personnel) scores the erythema, pustules and scaling of all

psoriatic lesions from 0 to 4. Each component is graded separately, the average is calculated and the final GPPGA is determined from this composite score. A lower score indicates a lesser severity, with 0 being clear and 1 being almost clear. To receive a score of 0 or 1, the patient should be afebrile in addition to the skin presentation requirements.

INFORMATION PROVIDED BY BOEHRINGER-INGELHEIM

CLINICAL NEED AND BURDEN OF DISEASE

The estimated prevalence of psoriasis is around 1.3-2.2% within the UK.[6] GPP is a rare disease and there is currently no validated diagnostic criteria to diagnose psoriasis, so it is difficult to ascertain an accurate figure for its prevalence therefore, the precise prevalence of GPP in the UK is not yet known.[3,6]

In 2019-20 there were 243 finished consultant episodes (FCE) and 157 admissions for generalised pustular psoriasis (ICD-10 code L40.1) which resulted in 64 day cases and 1,058 FCE bed days.[16]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

In the case where GPP is suspected or confirmed, the individual should always be referred to a dermatologist. For the management of GPP, patients should see their dermatologist every 3 months or as needed.[14] The treatment option provided is usually dependent on the severity of the disease and the area of skin affected. There are currently no specific treatment guidelines for the treatment of GPP. Current treatment options for psoriasis, as noted in NICE guideline CG153 include:[17]

- Topical such as creams, ointments or lotions applied to the skin
- Systemic which consist of medications that work throughout the entire body such as oral and injected drugs.
- Phototherapy where the skin is exposed to different types of ultraviolet light

These treatments are often used in combination to treat patients. Regular review of treatment effective is advised and the use of a care plan made using the advice of a health professional and with the agreement of the patient can help in the management of GPP.[17]

CURRENT TREATMENT OPTIONS

There are two main types of systemic treatment for psoriasis. Biological treatments (mainly injections) which are usually used for severe psoriasis that has not responded well to other treatments and non-biological treatments (mainly orally by tablets or capsules). There is no specific NICE guidance or guideline for GPP. Current treatment options for psoriasis, as noted in NICE guideline include: [17,18]

NICE recommends the following first line therapies:[6]

- Topical therapies e.g. corticosteroids, vitamin D, vitamin D analogues, dithranol and tar preparations

NICE recommends the following second line therapies:[6]

- Systemic non-biological agents such as ciclosporin, methotrexate and acitretin

NICE recommends the following third line therapies:[6]

- Tumour necrosis factor (TNF) antagonists e.g. adalimumab, etanercept and infliximab
- Interleukin-12 and IL-23 monoclonal antibody, ustekinumab

PLACE OF TECHNOLOGY

If licensed, spesolimab will offer a novel treatment option for acute flares in patients with GPP.

CLINICAL TRIAL INFORMATION

Trial	NCT03886246, EudraCT 2018-003080-56; An Open-label, Long Term Extension Study to Assess the Safety and Efficacy of BI 655130 Treatment in Patients With Generalized Pustular Psoriasis (GPP) **Phase II** – Ongoing **Location(s):** EU (not incl UK), USA and other countries. **Primary completion date:** September, 2027
Trial design	Multicentre, open-label, single group assignment
Population	n=171 (planned); aged 12 to 75 years who have completed the treatment period without premature discontinuation in the previous spesolimab trials (NCT03782792) and EFFISAYIL-2 (NCT04399837) and are willing and able to continue treatment in the current trial
Intervention(s)	Participants will receive spesolimab intravenously every 4 weeks 6 weeks, and every 12 weeks
Comparator(s)	-
Outcome(s)	Occurrence of treatment emergent adverse events (TEAEs) up to week 252 of maintenance treatment [Time Frame: Up to 252 Weeks] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT03782792, EudraCT 2017-004231-37; Multi-center, Double-blind, Randomised, Placebo-controlled, Phase II Study to Evaluate Efficacy, Safety and Tolerability of a Single Intravenous Dose of BI 655130 in Patients With Generalized Pustular Psoriasis (GPP) Presenting With an Acute Flare of Moderate to Severe Intensity **Phase II** – Completed **Location(s):** EU (not incl UK), USA and other countries. **Primary completion date:** September 2020
Trial design	Multicentre, double-blind randomised, parallel assignment

Population	n=53 (actual); aged 18 to 75 years with GPPGA of 0 or 1 and a known and documented history of GPP per European Rare And Severe Psoriasis Expert Network (ERASPEN) criteria regardless of IL36RN mutation status, with previous evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leucocytosis with peripheral blood neutrophilia (above ULN) OR patients with an acute flare of moderate to severe intensity meeting the (ERASPEN) criteria of GPP with a known and documented history of GPP (per ERASPEN criteria) regardless of IL36RN mutation status, with previous evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leucocytosis with peripheral blood neutrophilia (above ULN)
Intervention(s)	Participants received a single 900mg dose of spesolimab intravenously
Comparator(s)	Participants received placebo intravenously
Outcome(s)	A GPPGA pustulation sub-score of 0 indicating no visible pustules at Week 1 [Time Frame: Up to Week 1] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of spesolimab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Ustekinumab for the treatment of adults with moderate to severe psoriasis (TA180) September 2009 (Last updated: March 2017).
- NICE technology appraisal. Adalimumab for the treatment of adults with psoriasis (TA146) June 2008.
- NICE technology appraisal. Infliximab for the treatment of adults with psoriasis (TA134) January 2008
- NICE technology appraisal. Etanercept and efalizumab for the treatment of adults with psoriasis (TA103) July 2006.
- NICE Clinical Guideline. Psoriasis: assessment and management (CG153). October 2012 (Last updated: September 2017).
- NICE interventional procedure guidance. Grenz rays therapy for inflammatory skin conditions (IPG236). November 2007.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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

OTHER GUIDANCE

- Lancashire Medicines Management Group. Guidelines for the Management of Psoriasis in Primary Care. May 2017.[19]
- British Association of Dermatologists. Guidelines for biologic therapy for psoriasis. April 2017.[20]

ADDITIONAL INFORMATION

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