Single Technology Appraisal

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Boehringer Ingelheim:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Psoriasis and Psoriatic Arthritis Alliance (PAPAA)
   b. Psoriasis Association
   c. British Association of Dermatologists

4. Expert personal perspectives from:
   a. Helen McAteer – patient expert, nominated by Psoriasis Association
   b. Donna Larmour – patient expert, nominated by Psoriasis Association

5. **External Assessment Report** prepared by Southampton Health Technology Assessment Centre (SHTAC)

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Document B

Company evidence submission

August 2024

File name	Version	Contains confidential information	Date
ID3963_Spesolimab_Document B	1.0	Yes	14 August 2024

Contents

Tables and figures

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication, addressing the clinical and cost-effectiveness of spesolimab intravenous (IV) infusion for the treatment of adult patients with generalised pustular psoriasis (GPP) presenting with flares.

The decision problem, as specified in the final NICE scope, is presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adult patients with generalised pustular psoriasis presenting with flares	Adult patients with generalised pustular psoriasis presenting with flares	Not applicable
Intervention	Spesolimab	Spesolimab	Not applicable
Comparator(s)	Established clinical management without spesolimab which may include: • Systemic non-biological therapies such as ciclosporin • Biological therapies (such as TNF-alpha inhibitors, IL-17 and IL-23 family inhibitors)	Established clinical management without spesolimab	Not applicable
Outcomes	The outcome measures to be considered include: • Symptoms specific to GPP including pain • Severity of flares • Mortality • Response rate • Duration of response • Relapse rate • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Symptoms specific to GPP including pain • Severity of flares • Mortality • Response rate • Duration of response • Relapse rate • Adverse effects of treatment • Health-related quality of life	Not applicable
Key: GPP, generalised pustular psoriasis; IL, interleukin; TNF, tumour necrosis factor.			

B.1.2. Description of the technology being evaluated

Spesolimab (Spevigo®) is a first in class humanised antagonistic immunoglobulin (IgG) 1 monoclonal antibody (mAb) against human interleukin-36 receptor (IL-36R); details are provided in Table 2. Appendix C includes the summary of medicinal product characteristics (SmPC) and UK public assessment report.

Table 2: Technology being evaluated

UK approved name and brand name	Spesolimab (Spevigo®)
Mechanism of action	Spesolimab is a humanised antagonistic monoclonal IgG1 antibody which blocks human IL-36R signalling. The IL-36 pathway is central to GPP pathogenesis. Binding of spesolimab to IL-36R prevents the subsequent activation of IL-36R by cognate ligands (IL-36 α, β and γ) and downstream activation of pro-inflammatory pathways.
Marketing authorisation	Spesolimab received a conditional marketing authorisation (CMA) from the MHRA in July 2023 via the EC Decision Reliance Procedure. CMAs are intended for medical products that address an unmet medical need but where comprehensive clinical data is not yet complete. In the case of spesolimab, data on treatment of subsequent flares was not considered comprehensive. An additional open-label, single-arm post-authorisation study on the treatment of repeated flares with spesolimab is ongoing to comply with the CMA. Final results of this study (Effisayil™ REP; study 1368-0120; NCT06013969) must be submitted to the EMA by January 2028 and the MHRA by August 2028.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Spesolimab is indicated for the treatment of flares in adult patients with GPP as monotherapy.
Method of administration and dosage	Treatment should be initiated and supervised by physicians experienced in the management of patients with inflammatory skin diseases. The recommended dose is a single dose of 900 mg (two vials of 450 mg) administered as an intravenous infusion. If flare symptoms persist, an additional 900 mg dose may be administered 1 week after the initial dose.
Additional tests or investigations	Not applicable.

List price and average cost of a course of treatment	List price: £15,000 Average cost of a course of treatment: £20,265
Patient access scheme (if applicable)	Simple discount of [redacted] PAS price: [redacted] Average cost of a course of treatment: [redacted]
Key: CMA, conditional marketing authorisation; EC, European Commission; EPAR, European Public Assessment Report; GPP, generalised pustular psoriasis; IL, interleukin; IL-36R, interleukin 36 receptor; MHRA, Medicines and Healthcare products Regulatory Agency; PAR, Public Assessment Report; SmPC, Summary of Product Characteristics. **Source:** Spevigo EPAR[1]; Spevigo PAR[2]; Spevigo SmPC.[3]	

B.1.3. Health condition and position of the technology in the treatment pathway

- Generalised pustular psoriasis (GPP) is a rare chronic, severe, systemic autoinflammatory disease that is potentially life-threatening
- GPP is characterised by widespread eruption of pustules, known as GPP flares that can affect large and varied areas of the body
- GPP clinical course is highly variable, generally unstable and prolonged without treatment. The severity and frequency of flares varies widely between patients and within the same patient
- If left untreated, GPP flares can result in extensive complications and potential death; thus, flares are typically treated as a medical emergency
- UK real-world data suggest GPP patients experience up to 1 flare per year which can require around 11-13 days of hospital care on average.
- The IL-36 pathway is central to the pathogenesis of GPP, which alongside its clinical features, distinguishes GPP from plaque psoriasis
- Patients living with GPP experience a substantial negative impact on their daily activities, social interactions and mental wellbeing, which extends to their loved ones
- There is no current standard of care for treatment of GPP flares
- Best available care (BAC) typically defaults to off-label systemic therapies ± topical steroids developed to treat other conditions.
- BAC treatments are slow to elicit response and often do not fully resolve symptoms; experts in England predict ~70% of moderate-to-severe flares require an inpatient hospital stay with current BAC
- BAC treatments can also be associated with unwelcome side effects
- There is a clear unmet medical need for treatments specifically targeted for GPP that provide rapid control and fast resolution of flares with tolerable side effects

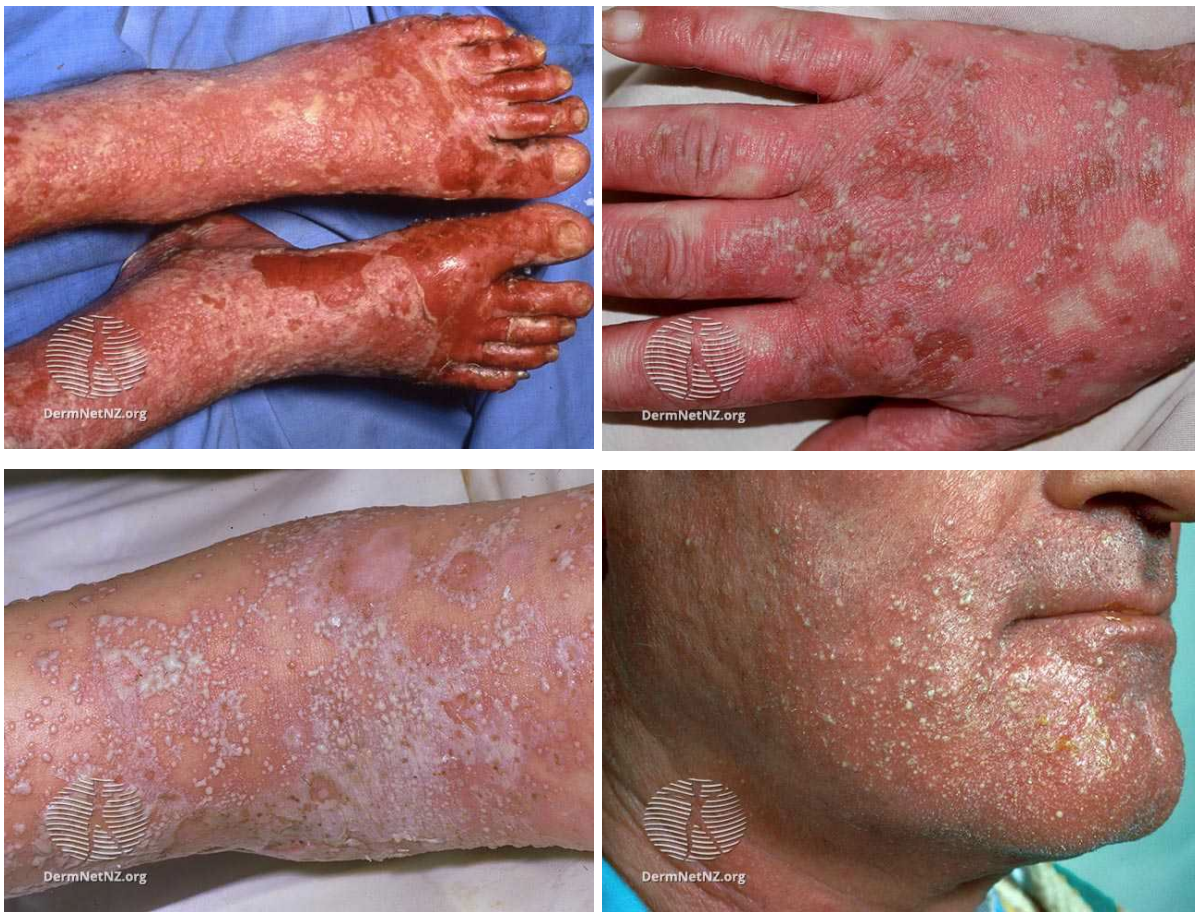
B.1.3.1. Disease overview

GPP is a rare, chronic, severe, systemic autoinflammatory disease that is potentially life-threatening, if left untreated.[4, 5]

GPP is characterised by episodes of widespread eruption of pustules (pus-filled blisters), known as GPP flares.[4] Flares can affect large and varied areas of the body with pustules merging and forming 'lakes of pus', accompanied by erythema (redness), severe itchiness and dry, cracked or scaly skin (Figure 1). Skin eruptions are usually also accompanied by fever, malaise, fatigue, swelling, pain and biological markers of inflammation and infection (Table 3).[4, 6-8]

GPP is a heterogeneous disease with a variable clinical course; patients may experience recurrent GPP flares with periods of clear skin or persistent disease with flares of increased severity.[4, 5]

Figure 1: Generalised pustular psoriasis images



Source: DermNet™.[9]

Table 3: Features associated with GPP flares

Skin features	Systemic features
Pustules	Fever
Pain	Swelling (oedema)
Itching	Malaise
Scaling	Joint pain
Redness (erythema)	Fatigue
Dryness	Headache
Burning	Biological markers of inflammation and infection: Leukocytosis, neutrophilia and increased CRP

Key: CRP, C-reactive protein; GPP, generalised pustular psoriasis.
Source: Choon et al., 2022; Hoegler et al., 2018; Rivera-Díaz et al., 2023; Zema et al., 2022.[4, 6-8]

The exact cause of GPP is not yet known, but the IL-36 pathway is central to its pathogenesis.[10] Overactivation of IL-36 signalling results in overexpression of IL-36 cytokines and/or loss-of-function mutations of the IL-36 receptor antagonist (IL-36Ra) protein, which in turn leads to induction of the downstream inflammatory cascade and recruitment of neutrophils.[10] Neutrophil accumulation in the epidermis (outer layer of skin) causes the formation of pustules. In 2019, a study that included UK data reported mutations in the gene encoding for the IL-36 receptor antagonist (*IL36RN*) in 24% of patients with GPP.[11] Additionally, triggers such as stress, certain medications or hormonal changes can contribute to the onset of GPP.[4, 5]

Despite GPP being first described over 100 years ago, there is still no international consensus on the definition of a GPP flare or GPP phenotypes. In 2017, the European Rare And Severe Psoriasis Expert Network (ERASPEN) published their consensus definition of pustular psoriasis[10], which defined GPP as:

- Primary sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques);
- With or without systemic inflammation;
- With or without plaque psoriasis;
- Either relapsing (more than one episode) or persistent (> 3 months).

An alternative definition is provided by the Japanese Dermatological Association (JDA) guidelines for the management and treatment of GPP[12] as:

- Systemic symptoms such as fever and fatigue;
- Systemic or extensive flush accompanied by multiple sterile pustules that sometimes merge to form lakes of pus;
- Neutrophilic subcorneal pustules histopathologically characterised by Kogoj's spongiform pustules;
- The above clinical and histological features recur repeatedly.

Most recently, a global Delphi panel study was conducted to gain advanced insights into the clinical course, diagnosis, treatment goals and management of GPP.[5] Expert consensus was reached for 157 statements including 61 on clinical course and flare definition and 24 on diagnosis. Those with 100% agreement included[5]:

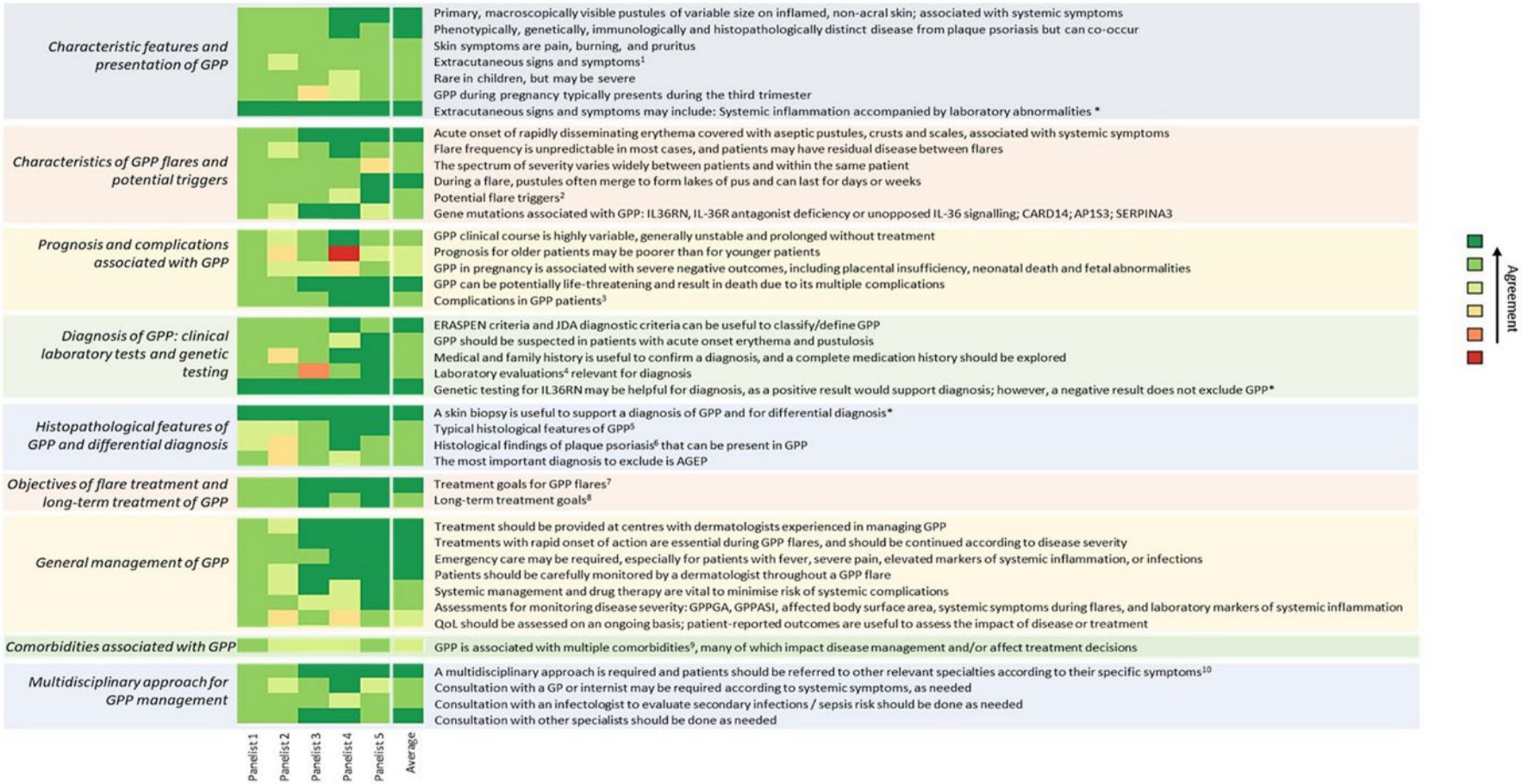
- GPP is historically considered a variant of psoriasis but is indeed phenotypically, genetically, immunologically and histopathologically distinct from plaque psoriasis
- A GPP flare consists of the acute onset of a rapidly disseminating erythema covered with aseptic pustules, crusts and scales and associated with systemic symptoms: fever, arthralgia and asthenia
- Flares may occur as often as several times per year or with long dormant periods between activity
- Flaring frequency is unpredictable in most cases of GPP
- The spectrum of severity of flares varies widely among patients and also varies across flare episodes in the same patient
- In the post flare phase/between flares, patients still may have residual disease, most commonly with symptoms such as minimal skin scaling and crusts, and minor erythema
- The diagnosis of GPP should be suspected in patients with acute onset erythema and pustulosis

There was a lack of UK representation in this global Delphi panel study, and thus a UK-focused extension study was conducted to assess the generalisability of the findings in the UK healthcare system.[13] This extension involved a panel of five UK-

based dermatologists experienced in GPP management. Their level of agreement with the conclusions reached in the global study was expressed on a Likert scale ranging from 1 (strong disagreement) to 7 (strong agreement); a visual summary of outcomes from this UK extension is provided in Figure 2.

Irrespective of the exact definition applied to GPP, the clinical, pathological and genetic features of GPP clearly distinguish it from other forms of psoriasis, including plaque psoriasis.[5, 10, 13] Patients can, however, have concomitant diagnoses of GPP and other forms of psoriasis.[5, 13, 14]

Figure 2: Statements on generalised pustular psoriasis with expert consensus and UK agreement ratings



Key: ERASPEN, European Rare And Severe Psoriasis Expert Network; GP, General Practitioner; GPPASI, generalised pustular psoriasis area and severity index; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; JDA, Japanese Dermatological Association; QoL, quality of life.
Notes: *These two statements reached consensus after being rephrased but were not assigned new scores. Their scores here are demonstrative and only represent the fact that they reached consensus.
Source: Barker et al. 2024.[13]

B.1.3.2. Disease burden

Disease burden data are available from multiple real-world evidence (RWE) studies and Structured Expert Elicitation (SEE) exercises; summary data are presented here with further details of each study provided in Appendix M.

B.1.3.2.1. Patient numbers and demographics

B.1.3.2.1.1. Prevalence and incidence

GPP is a rare disease, with an estimated global prevalence of 1–9 cases per million persons.[15]

Boehringer Ingelheim carried out a cohort study (POLARIS) involving analyses of longitudinal electronic health record data in the Clinical Practice Research Datalink (CPRD) Aurum database and linked hospital and mortality data between 2008 and 2019.[14] The age- and sex-adjusted incidence rate was stable, ranging from 0.14 to 0.34 per 100,000 person-years; the age- and sex-adjusted prevalence rates increased from 1.61 per 100,000 patients in 2008 to 3.00 per 100,000 patients in 2019.[14] Of the incident cases, 129 patients (63%) had one or more GPP flare between 2008 and 2019.[14]

B.1.3.2.1.2. Patient demographics

GPP can present at any age, although early onset is more likely in patients with the *IL36RN* mutation.[4] There is a female dominance with female–male ratios of up to 2:1 reported.[16, 17]

Demographic data from UK RWE studies are summarised in Table 4. The mean age of GPP patients is 53–58 years and 64-67% of patients are female.[14, 18, 19]

Table 4: GPP patient demographics based on RWE from the UK

Study ID (setting)	Mean age (SD)	Female, %
POLARIS (England) N = 373	55.9 (18.6) GPP flare patients (n = 129): 57.3 (19.0)	66%
HES data (England) N = 1,178	[redacted]	[redacted]

Study ID (setting)	Mean age (SD)	Female, %
SCRIPTOR (UK) N = 27	53.1 (19.7)	67%
Key: GPP, generalised pustular psoriasis; HES, hospital episodes statistics; ID, identification; RWE, real-world evidence; SD, standard deviation. **Source:** POLARIS - Frysz et al. 2024[14]; HES - data on file[18]; SCRIPTOR - data on file.[19]		

B.1.3.2.2. Clinical burden

B.1.3.2.2.1. Flare frequency and severity

The severity and frequency of GPP flares vary widely between patients and within the same patient; patients may have multiple flares per year or a flare every few years.[5, 6, 13]

Of incident patients with GPP in the POLARIS study (England; n = 206), 39-63% experienced at least one GPP flare during the study period (2008-2019), depending on the definition (retrospectively) applied.[14] The observed flare rate was 0.2 per person per year, with a flare definition of ≥ 3 consecutive days of hospitalisation associated with any GPP code.[14] Other RWE data similarly support an average flare frequency of up to 1 per year, as summarised in Table 5.

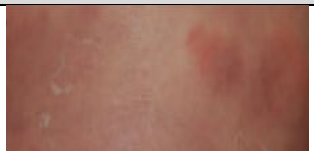
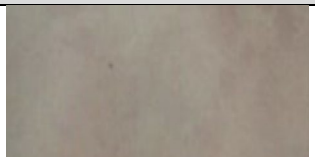
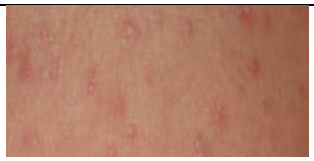
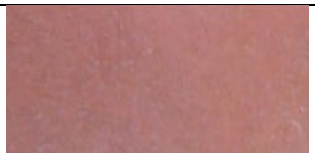
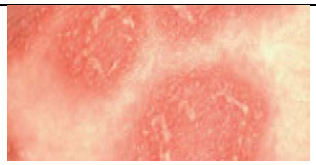
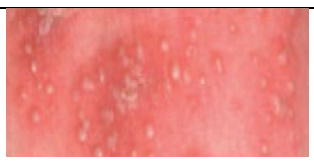
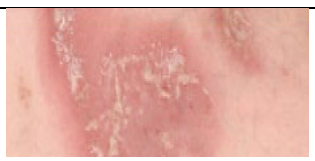
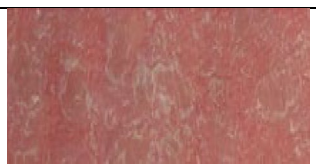
Table 5: GPP flare frequency based on RWE from Europe

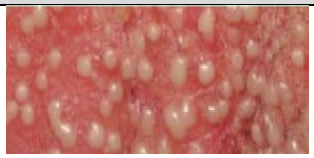
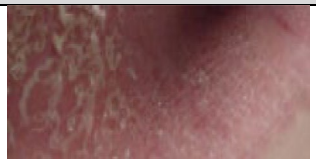
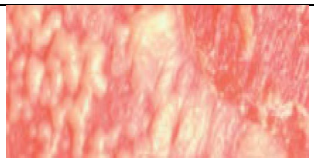
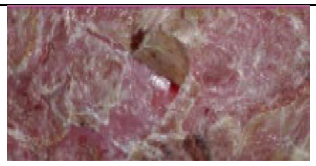
Study ID (setting)	Flare definition	Flare frequency – per person, per year
POLARIS (England) N = 206	GPP incident patients with ≥3 consecutive days of hospitalisation associated with any ICD-10 code indicative of GPP diagnosis	Annual rate: 0.18 Median: 0.15 (IQR: <0.01, 0.48)
SNDS data (France) N = 1,842	GPP incident patients with ≥3 consecutive days of hospitalisation associated with an ICD code indicative of primary GPP diagnosis (L40.1)	Of incident patients, observed: 0.1 Of patients hospitalised with GPP flare, observed: 0.4
SCRIPTOR (UK) N = 27	[redacted]	Mean (SD): 0.9 (0.6) Mean time between flare episodes: [redacted] months (SD: [redacted]
Key: GPP, generalised pustular psoriasis; ICD, International Classification of Diseases; ID, identification; RWE, real-world evidence; SNDS, French National Health System database; SD, standard deviation. **Source:** POLARIS - Frysz et al. 2024[14]; SCRIPTOR - data on file.[19]; SNDS - Viguier et al. 2024[20]		

The majority of flares present as a medical emergency, with 67% of non-elective admissions captured in HES data from England being via Accident & Emergency (A&E).[18] Of the 27 patients diagnosed with GPP and enrolled to the observational, non-interventional SCRIPTOR study, 74% were diagnosed in an inpatient hospital / A&E or outpatient A&E setting.[19] In the POLARIS study, the mean number of accident and emergency (A&E) visits was reported to be 2.98 per person per year.[14]

Multiple potential tools are available to assess the severity of flares on presentation, but historically there were no tools developed specific to GPP. The Generalised Pustular Psoriasis Physician Global Assessment (GPPGA) is a modification of the well-established Physician Global Assessment (PGA) used to assess psoriatic lesions, but adapted to assess the key clinical features of GPP (Table 6).[21] It was first used in a proof-of-concept study of spesolimab and clinical validation of the accuracy, responsiveness, reliability and reproducibility of the GPPGA has since been demonstrated.[21] Full details of the scoring approach for the GPPGA are provided in Appendix N but in summary each component is scored separately and the average calculated to give a GPPGA total score[21]; details on how the three components of the GPPGA (pustules, erythema and scaling / crusting) are scored is depicted in Table 6.

Table 6: Components of the GPP Physician Global Assessment (GPPGA)

GPPGA subscore	Pustules	Erythema	Scaling / crusting
0, clear			
1, almost clear			
2, mild			

GPPGA subscore	Pustules	Erythema	Scaling / crusting
3, moderate			
4, severe			

Key: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment.
Source: Burden et al. 2023[21]

In a retrospective observational study from 16 dermatology centres in Italy, severity of GPP flare at presentation was captured on a shared case report form.[22] The mean GPPGA total score of a GPP flare was 3.3 (SD : 0.8), representative of a moderate to severe flare.

B.1.3.2.2.2. Signs and symptoms

Of the GPP patients enrolled in the SCRIPTOR study who presented with at least one cutaneous sign and symptom (n = 22), almost all (96%) presented with pustules, most presented with erythema (91%) and scaling (68%), and just over half presented with pain (55%).[19] On average, patients presented with five cutaneous signs and symptoms. In addition to cutaneous signs and symptoms, 45% of patients also had extracutaneous signs and symptoms with an average of three extracutaneous signs and symptoms observed. The most common extracutaneous signs and symptoms, reported in at least 40% of patients were fever, fatigue, joint swelling pain and oedema.[19] Of patients for whom laboratory tests were available (n=[redacted]%), biological markers of inflammation and infection including elevated C-reactive protein (CRP), absolute neutrophil count (ANC) and high white blood cell (WBC) count were recorded in [redacted]%, [redacted]% and [redacted]% of patients, respectively.[19]

In a recent patient experience study that included primary data collection via a web-based survey, as well as qualitative telephone interviews with adult participants living with GPP across Canada, China, Japan, the UK, and the US, pustules were most

often reported among the three most bothersome symptoms (n = 10/21; 48%), and one of the most important symptoms to manage (n = 4/9; 44%).[23]

B.1.3.2.2.3. Comorbidities and mortality

GPP is associated with significant morbidity and can be life-threatening. If left untreated, microbial infections can occur in pustules, with the potential to develop sepsis.[8] Additionally, as a multisystemic inflammatory disease, GPP can have varied and extensive complications affecting the cardiovascular system, liver, respiratory system and nervous system, which can lead to a range of life-threatening conditions relating to renal, hepatic, respiratory and heart failure.[6, 8]

In the POLARIS study (England), 76% of patients with GPP (n = 285/373) had at least one comorbidity.[14] Similarly in the SCRIPTOR study (UK), [redacted]% of patients with GPP [redacted] had at least one comorbidity. [19] The most common comorbidities across these studies were psychiatric, pulmonary, hormonal/metabolic and renal.[14, 19] The majority (58–76%) also had concomitant plaque psoriasis.[14, 19]

Reported mortality rates associated with GPP are between 2% and 16%.[6, 20] During the full study period of the POLARIS study (England; 2008–2019), 18% of patients with GPP died, increasing to 24% of patients with a history of GPP flare.[14] The most common causes of death were due to diseases of the circulatory and respiratory systems. GPP survival rates were lower than for patients with other psoriasis types included in the study (plaque psoriasis and palmoplantar pustulosis).[14] In the SNDS study (France; 2010-2018) – a population-based study from the French National Health System database – the GPP-specific mortality was reported at 8-13%; the mortality rate within 4 weeks of a GPP flare was 3%.[20]

B.1.3.2.3. Health care burden

There is a marked burden on health care services relating to the management of GPP, with flares often resulting in lengthy stays in hospital. In a retrospective Central and Eastern European (CEE) GPP Expert Network study (n = 58), hospitalisation rates varied from 58% in patients whose last flare was not their most severe to 94% when the last flare was the most severe (Table 7).[24] Median duration of

hospitalisation was 4 weeks and 12% of patients with a severe flare were treated in the intensive care unit (ICU) (Table 7).

In the POLARIS study (England; n=297 for the HCRU analyses), hospitalisation was a pre-requisite for inclusion so hospitalisation rates are not reported but the mean hospitalisation length of stay (LOS) was 12.7 days[14]; this is in line with other RWE data from Western Europe that report mean hospitalisation LOS ranging from 11.1 to 12.3 days for GPP flares, as summarised in Table 7.[14, 18-20] In the SNDS study (France; n=1,842), 25% of patients needed a stay in the intensive care unit (ICU) with a mean LOS of 19.7 days (Table 7).[20]

As data describing HCRU for the treatment of GPP flares in England are limited, Boehringer Ingelheim carried out an SEE exercise in 2024 to identify HCRU for GPP flares in England to inform the economic model. As part of this exercise, experts agreed that [redacted]% of patients experiencing a moderate/severe GPP flare (defined as GPPGA pustulation sub score of 3 or 4) require inpatient care and the mean LOS is [redacted] days.[25] Of patients requiring inpatient care for a moderate/severe GPP flare, experts estimated [redacted]% would need critical care in an ICU for [redacted] days depending on mechanical ventilation needs. HCRU from this SEE exercise are also summarised in Table 7; more detail on this SEE exercise are presented in Section B.3.5.2.

Table 7: Health care resource use data based on RWE from Europe and SEE exercise in England

Study ID (setting)	Outpatient visits	Inpatient visits	ICU visits	Hospitalisation LOS	ICU LOS
POLARIS (England) N = 373	Mean (SD) per patient per year: 8.86 (8.92)	NR	NR	Mean (SD) days: 12.7 (50.0).*	NR
HES data (England) [redacted]	Calculated average: [redacted] per patient per year*	Calculated average: [redacted] per patient per year*	NR	Average days for GPP presenting via A&E: [redacted]	NR
SCRIPTOR (UK) N = 27	NR	NR	NR	Mean (SD) days: [redacted]	NR
SNDS (France) N = 1,842	NR	NR	25% of patients are admitted to the ICU	Mean (SD) days: 11.6 (10.4) Median (range) days: 8 (3–99)	Mean (SD) days: 19.7 (21.5) Median (range) days: 13 (3–176)
CEE GPP (Central and Eastern Europe) N = 58	NR	Last flare (n = 58): 78% required hospitalisation Most severe flare (n = 26): 93% required hospitalisation Last flare = most severe flare (n = 32): 94% required hospitalisation Last flare = other (n = 26): 58% required hospitalisation	Most severe flare (n = 26): 12% of patients required ICU care	Last flare (n = 58), median (range) weeks: 4.0 (1.0–48) Most severe flare (n = 26), median (range) weeks: 2.3 (0.4–28) Last flare = most severe flare (n = 32), median (range) weeks: 2.0 (0.1–4) Last flare = other (n = 26), median (range) weeks: 1.6 (0.1–9)	NR

Study ID (setting)	Outpatient visits	Inpatient visits	ICU visits	Hospitalisation LOS	ICU LOS
SEE – HCRU (England)	Mild flare: [redacted] visits per patient per week Moderate/severe flare: [redacted] [redacted]	Mild flare: [redacted]% treated as inpatients Moderate/severe flare: [redacted]% treated as inpatients	Moderate/severe flare: [redacted]% of inpatients treated in ICU without MV [redacted]% of inpatients treated in ICU with MV	Mild flare, median (95% CI) days: [redacted] Moderate/severe flare, median (95% CI) days: [redacted]	Moderate/severe flare, median (95% CI) days: ICU without MV: [redacted] ICU with MV: [redacted] Post-ICU stay: [redacted]

Key: A&E, accident and emergency; CI, confidence interval; HES, hospital episodes statistics; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; NR, not reported; RWE, real-world evidence; SEE, Structured Expert Elicitation; SNDS, French National Health System database; SD, standard deviation.
Notes: *data not specific to GPP flare.
Source: CEE GPP[24]; HES - data on file[18]; POLARIS - Frysz et al. 2024[14]; SCRIPTOR - data on file.[19]; SEE - HCRU[25]; SNDS - Viguier et al. 2024[20]

B.1.3.2.4. Patient burden

In addition to the clinical and health care impacts of their disease, patients experience a substantial negative impact on their daily activities, social interactions and mental wellbeing as a result of their GPP.[26-29] Patients living with GPP report not wanting to go out or be seen and hiding their skin if they do go out, and how GPP changes the way they feel about themselves due to the disfiguring nature of the disease and the fear and revulsion it invokes in others.[30] This is a disease that impacts every aspect of patient's lives and their relationships. Mothers report not being able to pick up their children because of the pain of their touch and partners report being unable to share a physical relationship. [30] Work can be challenging during severe episodes, and some career paths are closed off to GPP patients due to the unpredictable nature of the disease and its day-to-day impact. The constant worry of flares, the intensity of flares and peoples' reactions to GPP symptoms further add to the mental burden of disease.[30]

Testimonies from patients living with GPP in the UK (n = 3) are summarised in Figure 3. The gravity of the impact of this condition on patients' mental health and wellbeing is sadly prominent in these testimonies, alongside their despair around treatment options, or lack thereof.[31]

Figure 3: Testimonies from patients living with GPP in the UK

Source: Boehringer Ingelheim data on file.[31]

In a recent patient experience study that included primary data collection via a web-based survey, as well as qualitative telephone interviews with adult participants living with GPP across Canada, China, Japan, the UK, and the US, participants described the ways in which GPP flares specifically impacted their lives. All participants (n=9/9; 100.0%) reported an impact to their emotional function and physical function, while

nearly all participants (n=8/9; 88.9%) reported impacts to their sleep.[23] More than three-quarters reported impacts to dressing/clothing choices, finances, social life, and work (each reported by n=7/9; 77.8%).

B.1.3.3. Clinical pathway of care

Patients experiencing a GPP flare typically present at Accident & Emergency and are often misdiagnosed, with many seeing multiple specialists before receiving an accurate diagnosis.[18, 23]

The aim of treatment of GPP flares is to achieve rapid and sustained clearance of pustules and other skin features of disease, rapidly alleviate systemic symptoms and reduce pain, while maintaining a favourable safety profile.[5] However, there has been limited development of treatments for GPP. There are no established clinical guidelines for the treatment of GPP flares in the UK, and prior to spesolimab, there were no licensed treatments available in the UK. Best available care (BAC) therefore defaults to systemic therapies used to treat other types of psoriasis, including systemic non-biological treatments such as ciclosporin and methotrexate or biological treatments.[16] Topical treatments such as corticosteroids may also be used in combination with systemic therapy. Evidence supporting the use of these treatments for GPP flares are restricted to small, low quality, uncontrolled studies.[32]

Data describing the current pathway of care for the treatment of GPP flares in the UK are limited. Boehringer Ingelheim therefore consulted clinical experts to determine the treatment options for patients with GPP experiencing flares in the UK. Dermatologists in the UK and Ireland, with experience treating GPP patients at specialist centres, participated in a structured expert elicitation (SEE) exercise.[33] A visual overview of their estimated composition of BAC is provided in Figure 4. This is a necessary simplification of an undefined clinical pathway due to a lack of standard of care. Further detail on this SEE exercise is presented in more detail in Section B.2.9.2.

Figure 4: Clinical pathway of care for GPP flares in the UK

Key: 1L, first-line; 2L, second-line; 3L+, third- or later-line; GPP, generalised pustular psoriasis.
Source: Data on file.[33]

B.1.3.4. Unmet need

Despite GPP being a chronic, severe disease with higher clinical, humanistic and economic burden than other psoriasis types, it is poorly studied. A systematic review of available treatments for GPP found that all included studies were of low or very low quality, with evidence typically based on small, open-label, uncontrolled studies.[32]

In the absence of a standard of care in current practice, best available care (BAC) defaults to systemic therapies used to treat other types of psoriasis.[33] These therapies do not target the bespoke pathophysiology of GPP and can be ineffective and/or slow to take effect, increasing the risk of complications and potential threat to life from a GPP flare. A survey of dermatologists who manage GPP found that 72% of respondents considered existing treatments too slow to control flares, and that it was at least 'somewhat common' for a flare to require hospitalisation.[34] Patient testimonies further talk to the lack of effective treatment options (Figure 3), and of BAC options, treatments can be associated with toxicities that make them

inappropriate for long-term use.[12] With the current pathway of care, an estimated 69–94% of GPP patients experiencing a moderate-to-severe flare are hospitalised with an average hospital stay of 11–13 days; this can include a stay in intensive care for the most severe flares.[14, 18-20, 24, 25]

There is a clear and substantial unmet medical need for treatments specifically targeted for GPP that provide rapid control and fast resolution of flares with tolerable side effects.

B.1.4. Equality considerations

No equality issues are anticipated.

B.2. Clinical effectiveness

- Spesolimab is a first in class monoclonal antibody, developed to target the IL-36 signalling pathway that plays a key role in the pathophysiology of GPP
- Effisayil™ 1 provides clinical trial data supporting the use of spesolimab IV infusion for the treatment of GPP flares in adults
- Spesolimab IV infusion demonstrated superior efficacy to placebo for all tested endpoints:
  - 54% vs 6% of patients achieved a GPPGA pustulation sub score of 0 at Week 1, indicating complete pustular clearance ($p<0.001$)
  - 43% vs 11% of patients achieved a GPPGA total score of 0 or 1 at Week 1, indicating clear or almost clear skin ($p=0.02$)
- Onset of response was rapid with pustular clearance observed as early as Day 2 and sustained through Week 12 end of trial in the spesolimab group
- Improvements in skin manifestations were accompanied by clinically meaningful benefits in patient-reported outcomes and biological markers of inflammation and infection:
  - The adjusted mean change from baseline in pain VAS was -30.5 in patients randomised to spesolimab by Week 1 and -58.1 by Week 4
  - The adjusted mean change from baseline in PSS score was -3.6 in patients randomised to spesolimab by Week 1 and -5.9 by Week 4
  - The adjusted mean change from baseline in FACIT-Fatigue score was 13.0 in patients randomised to spesolimab by Week 1 and 24.1 by Week 4
  - The adjusted mean change from baseline in DLQI score was -4.3 in patients randomised to spesolimab by Week 1 and -12.2 by Week 4
  - Neutrophil and CRP levels dropped below ULN within 1-2 weeks of spesolimab treatment and stayed there through the Week 12 end of trial timepoint
- Spesolimab IV infusion demonstrated an acceptable safety profile in the Effisayil™ 1 trial with tolerable side effects
  - Infections were the most common side effect in the spesolimab arm (reported in 17% of patients) but they were generally mild to moderate with no distinct pattern regarding pathogen or type of infection

B.2.1. Identification and selection of relevant studies

See Appendix D for full details of the systematic literature review (SLR) used to identify and select the relevant clinical evidence.

B.2.2. List of relevant clinical effectiveness evidence

The SLR identified 81 unique trials reported in 98 publications; 15 trials reported some data specific to GPP flares. These included pivotal trials of spesolimab for the treatment of adults with GPP:

- Proof of concept (NCT02978690): a phase I proof-of-concept Phase I study assessing the viability of spesolimab intravenous (IV) infusion for treatment of GPP flares[35]
- Effisayil™ 1 (NCT03782792): a global, multicentre, randomised, double-blind, placebo-controlled Phase II study assessing the efficacy and safety of spesolimab IV infusion for treatment of GPP flares[36]
- Effisayil™ 2 (NCT04399837): a randomised, placebo-controlled Phase IIb study assessing the efficacy and safety of subcutaneous (SC) spesolimab for prevention of GPP flares[37]
- Effisayil™ ON study (NCT03886246): an open-label extension study of patients enrolled to Effisayil™ 1 and Effisayil™ 2 that will provide long-term safety and efficacy data on spesolimab SC maintenance treatment[38]

Of these trials, the Effisayil™ 1 trial provides evidence specific to spesolimab 900mg IV infusion for treatment of flares in adults with GPP and is therefore the pivotal trial providing relevant evidence to this submission, as summarised in Table 4.

Table 8: Clinical effectiveness evidence

Study	**Effisayil™ 1** (NCT03782792)
Study design	Multicentre, randomised, double-blind, placebo-controlled study
Population	Adult patients with GPP presenting with flares of moderate-to-severe intensity
Intervention(s)	Spesolimab 900 mg IV infusion (n = 35)
Comparator(s)	Placebo (n = 18)

Supports application for marketing authorisation	Yes
Study used in the economic model	Yes
Rationale if study not used in the model	Not applicable
Reported outcomes specified in the decision problem	• Symptoms specific to GPP including pain, severity of flares and response outcomes: – **GPPGA pustulation sub score** – GPPGA total score – GPPASI – Pain VAS – PSS – FACIT-Fatigue – *JDA GPP severity score* – *CGI-Improvement* • Mortality • Adverse effects of treatment – **The occurrence of TEAEs** • Health-related quality of life: – *DLQI* – ***EQ-5D®***
All other reported outcomes	Please see a full list of outcomes in Appendix D

Key: CGI, Clinical Global Impressions; DLQI, Dermatology Life Quality Index; FACIT, Functional Assessment of Chronic Illness Therapy; GPP, generalised pustular psoriasis; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; GPPASI, Psoriasis Area and Severity Index for Generalised Pustular Psoriasis; IV, intravenous; JDA, Japanese Dermatological Association; PSS, Psoriasis Symptom Scale; TEAE, treatment-emergent adverse event; VAS, Visual Analogue Scale.
Notes: Outcomes in **bold** are incorporated into the model; outcomes in *italics* were defined as further endpoints rather than primary or secondary endpoints in the trial.
Source: Bachelez et al. 2021.[36]

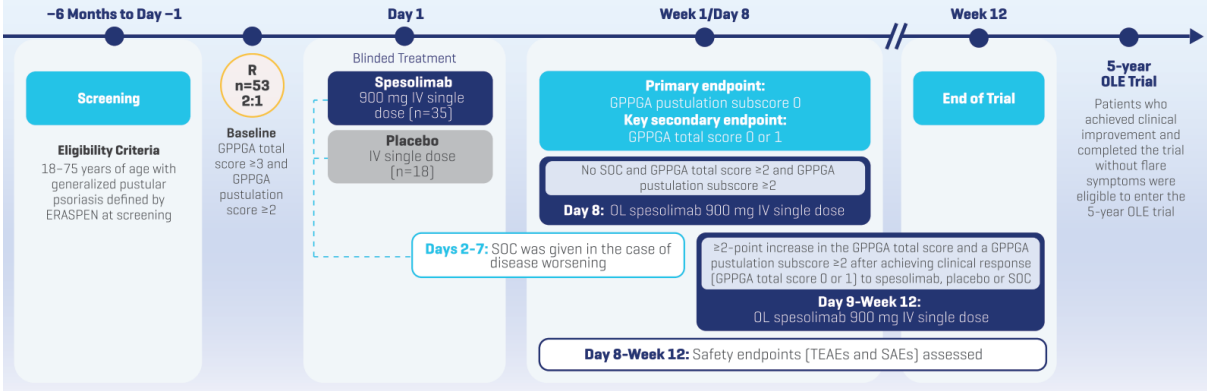
Early results for GPP flare treatment with spesolimab IV infusion from the Effisayil™ 2 and Effisayil™ ON trials are presented as supportive evidence. They are not included in the economic model as they provide less robust (single-arm) data compared with Effisayil™ 1, and represent a spesolimab SC exposed population, which is not reflective of GPP patients being addressed in the decision problem for this submission. Results from the proof-of-concept trial are provided in Appendix F.

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. Effisayil™ 1 study design

Effisayil™ 1 was a multicentre, randomised, double-blind, placebo-controlled Phase II trial that assessed the efficacy, safety, and tolerability of a single IV infusion dose of spesolimab in adults with GPP presenting with a flare of moderate-to-severe intensity.[36] The study design is presented in Figure 5.

Figure 5: Effisayil 1™ study design



Key: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; IV, intravenous infusion; OL, open-label; OLE, open-label extension; SD, single dose; SoC, standard of care.
Source: Adapted from Bachelez et al. 2021.[36]

The study was conducted between February 2019 and January 2021, and enrolled 85 patients at 37 sites in 12 countries across Europe, North America, North Africa, and Asia.[36] Patients aged 18–75 years were enrolled (screened) into the trial, if they met at least one of the following eligibility criteria:

- Have a Generalised Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1 and 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 upper limit of normal [ULN]), or
- Are experiencing a GPP 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), or

- Are experiencing their first episode of GPP flare of moderate-to-severe intensity with evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leucocytosis with peripheral blood neutrophilia (above ULN). For these patients, diagnosis was confirmed retrospectively by a central external expert/committee.

The GPPGA score is an adaptation from the Physician Global Assessment (commonly used in psoriasis), whereby induration has been replaced by pustulation.[21]

Patients with an immediate life-threatening flare of GPP or requiring intensive care treatment, according to the investigator's judgement, were not to be screened or treated.[36] Patients receiving biological therapies had to stop biologic treatment at least 2 months prior to randomisation; patients could not start or dose escalate systemic non-biological therapies after 2 weeks prior to randomisation, and these therapies had to be discontinued prior to randomised treatment receipt.

The full list of eligibility criteria for trial enrolment are provided in Appendix N.

Patients who satisfied the eligibility criteria were allowed to enrol into the study regardless of their current flare status.[36] For subsequent randomisation to treatment, patients had to experience a GPP flare of moderate-to-severe intensity, defined by the emergence of:

- A GPPGA score of at least 3 (moderate), and
- Presence of fresh pustules (new appearance or worsening of existing pustules), and
- A GPPGA pustulation sub score of at least 2 (mild), and
- At least 5% of body surface area covered with erythema (abnormal redness of the skin or mucous membranes) and the presence of pustules

Patients were randomised to receive spesolimab 900 mg or placebo in a ratio of 2:1 using interactive response technology (IRT) and stratification for Japanese vs non-

Japanese ethnic group.[36] Randomised treatment was initiated at Day 1, and primary and key secondary endpoint analyses were conducted at Day 8. During this period, escape treatment of the physician's choice was permitted to treat disease worsening, defined as worsening of clinical status or GPP skin and/or systemic symptoms as defined by the investigator.

At Day 8, patients who had both a GPPGA score and a GPPGA pustulation sub score of at least 2, and who had not received escape treatment during Week 1 were eligible for open-label spesolimab 900 mg (regardless of randomisation treatment group).[36] After Day 8 and through Week 12, patients who had a recurrence of GPP flare, defined as at least a 2-point increase in GPPGA score and GPPGA pustular sub score after achieving a clinical response to initial treatment (randomised treatment, escape treatment or open-label spesolimab), could receive a rescue dose of spesolimab 900 mg. Only one rescue dose was permitted per patient. Patients who had clinical improvement and completed the trial up to Week 12 without flare symptoms were eligible to enter Effisayil™ ON, the open-label extension study.

The primary endpoint in Effisayil™ 1 was a GPPGA pustulation sub score of 0 indicating no visible pustules at Week 1.[36] The key secondary endpoint was a GPPGA score of 0 or 1 indicating clear or almost clear skin at Week 1. Secondary endpoints included in the protocol and statistical analysis plan were:

- Psoriasis Area and Severity Index for GPP (GPPASI) 75 at Week 4
- Change from baseline in pain Visual Analogue Scale (VAS) score at Week 4
- Change from baseline in Psoriasis Symptom Scale (PSS) score at Week 4
- Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue score at Week 4

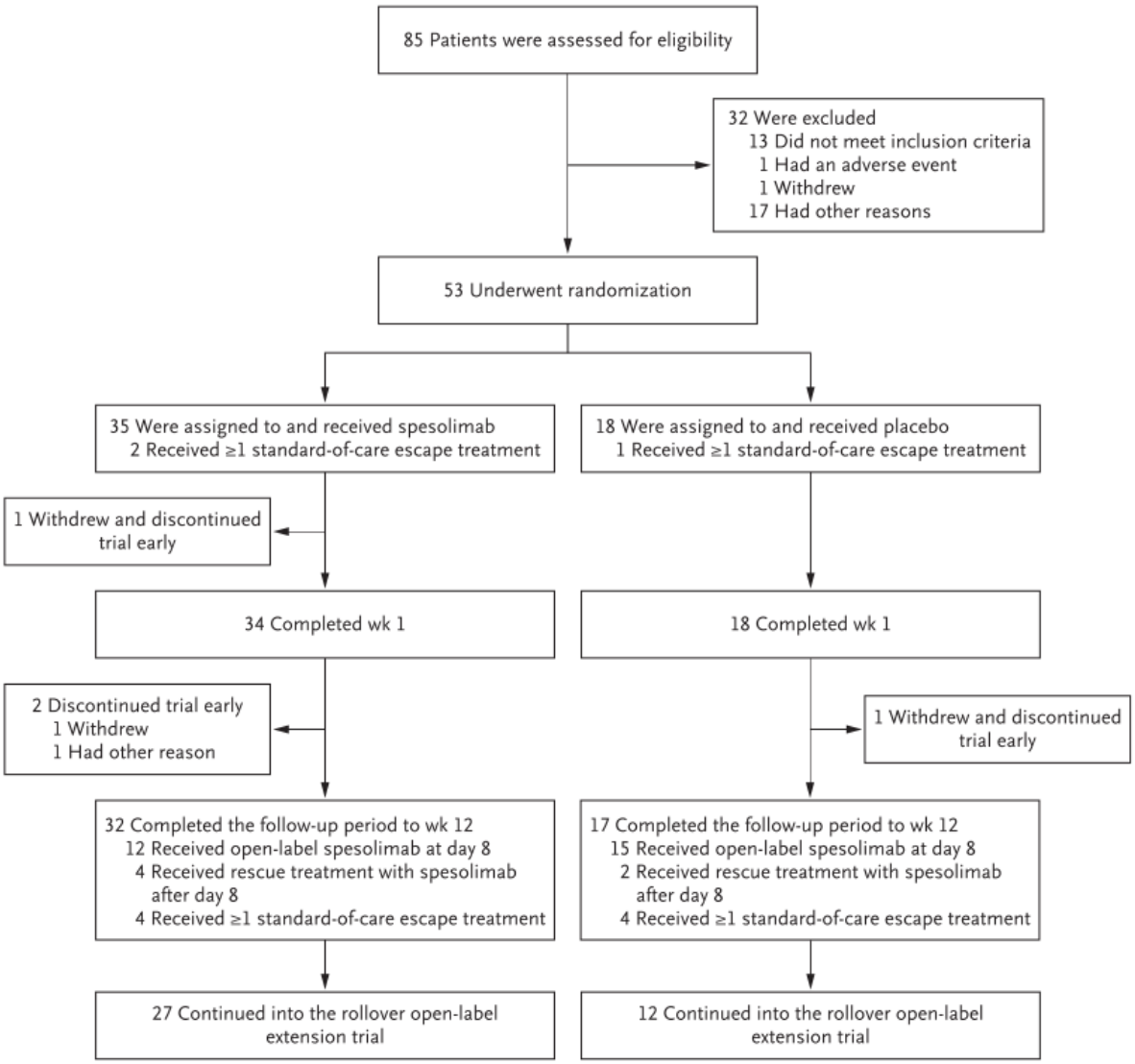
Details of additional secondary and further endpoints assessed at Week 1, Week 4 or both are provided in Appendix N, along with an endpoint overview table providing insight on scoring of endpoints. Safety was assessed at Week 1 and through Week 12. Adverse events (AEs) that began or worsened following treatment with spesolimab or placebo were captured, and the intensity of the AE graded by the investigators according to the Rheumatology Common Toxicity Criteria.[36]

B.2.3.2. Effisayil™ 1 patient flow

Patient flow from eligibility (screening) through to open-label extension study enrolment is shown in Figure 6. Of 85 patients assessed for eligibility, 53 underwent randomisation, and of these, 52 (98%) completed the first week of the trial.[36]

Prior to Day 8, a total of two patients (6%) in the spesolimab group and one patient (6%) in the placebo group received escape treatment. At Day 8, a total of 12 patients (34%) in the spesolimab group and 15 patients (83%) in the placebo group received an open-label dose of spesolimab.[36] After Day 8, a total of 32 patients (91%) originally randomised to the spesolimab group and a total of 17 patients (94%) originally randomised to the placebo group completed the 12-week follow-up period, during which four and two patients, respectively, received a rescue dose of spesolimab. After completing 12 weeks of treatment, 39 patients (77% Spesolimab, 67% placebo) were enrolled in the Effisayil™ ON study.

Figure 6: Patient flow in the Effisayil™ 1 trial



Key: wk, week.
Source: Bachelez et al. 2021.[36]

B.2.3.3. Effisayil™ 1 baseline characteristics

Of 85 patients assessed for eligibility, 53 underwent randomisation: 35 were randomised to receive spesolimab 900 mg and 18 were randomised to receive placebo (Figure 6).[36] Baseline characteristics (demographic and clinical) of the randomised patients are provided in Table 9.

At the time of randomisation, the majority of patients (81%) had a GPPGA total score of 3, indicating a moderate GPP flare; the remaining patients (19%) had a GPPGA

total score of 4, indicating a severe GPP flare.[36] Most patients (79%) also had a GPPGA pustulation sub score of 3 or 4, indicating high or very high density of pustules. Patients also reported impaired quality of life and clinical burden, as indicated by scores on the Dermatology Life Quality Index (DLQI), pain VAS, PSS and FACIT-Fatigue.

There were some differences in baseline characteristics across treatment groups. The median GPPASI score in the spesolimab group was 27.4 compared with a median GPPASI score in the placebo group of 20.9, indicating more severe disease in the spesolimab group.[36] A similar indication is observed in the higher proportion of patients with GPPGA pustulation sub score of 2, indicating mild severity, in the placebo group (28% versus 17%). There were also a higher proportion of female patients randomised to the placebo group (83% versus 60%) and a higher proportion of Asian patients randomised to the placebo group (72% versus 46%). Fifteen patients (eight in the spesolimab group and six in the placebo group) had *IL36RN* mutations.[39]

Table 9: Characteristics of patients at baseline in Effisayil™ 1

Characteristic	Spesolimab (n = 35)	Placebo (n = 18)
Age, mean years (SD)	43.2 (12.1)	42.6 (8.4)
Weight, kg (SD)	73.7 (24.0)	68.8 (26.6)
Female, n (%)	21 (60)	15 (83)
Race, n (%)*		
Asian	16 (46)	13 (72)
White	19 (54)	5 (28)
GPPGA total score, n (%)†		
3 (moderate)	28 (80)	15 (83)
4 (severe)	7 (20)	3 (17)
GPPGA pustulation subscore — n (%)‡		
2 (mild)	6 (17)	5 (28)
3 (moderate)	16 (46)	7 (39)
4 (severe)	13 (37)	6 (33)
Median GPPASI total score (IQR) §	27.4 (15.5–36.8)	20.9 (12.0–32.0)
Median DLQI score (IQR)¥	19.5 (16–25)	19.5 (14–24)
Median pain VAS score (IQR)^	79.8 (70.5–87.8)	70.0 (50.0–89.4)

Characteristic	Spesolimab (n = 35)	Placebo (n = 18)
Median PSS score (IQR)**	11.0 (9–12)	10.5 (9–11)
Median FACIT-Fatigue score (IQR)ᵀ	14.0 (7–28)	18.0 (6–33)
***IL36RN* mutation, n (%)ǁ**		
***IL36RN* mutation, n (%)ǁ**	8 / 29 (28)	6 / 17 (35)

Key: DLQI, Dermatology Life Quality Index; FACIT, Functional Assessment of Chronic Illness Therapy; GPPASI, Psoriasis Area and Severity Index for Generalised Pustular Psoriasis; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; IQR, interquartile range; n, number; PSS, Psoriasis Symptom Scale; SD, standard deviation; VAS, Visual Analogue Scale.
Notes: * Race was reported by the patient; † Scores on the GPPGA range from 0 (clear skin) to 4 (severe disease); ‡ GPPGA pustulation sub scores range from 0 (no visible pustules) to 4 (severe pustulation); § Scores on the GPPASI range from 0 (least severe) to 72 (most severe); ^ Scores on the pain VAS range from 0 (no pain) to 100 (very severe pain); ** Scores on the PSS range from 0-16, with higher scores indicating more severe symptoms; ¥ Scores on the DLQI range from 0 (no effect) to 30 (extremely large effect) – spesolimab n = 34; ᵀ Scores on the FACIT-Fatigue range from 0-52, with lower scores indicating greater impact of fatigue on daily activities;
ǁ Samples from seven patients were missing.
Source: Bachelez et al. 2021[36] ; Burden et al. 2022.[39]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

An estimated 51 patients were to be enrolled to the Effisayil™ 1 trial to provide a 90% or greater power to detect any difference between spesolimab and placebo with an assumed response of 0.6 and 0.1, respectively, for both the primary and key secondary endpoints and a one-sided type I error rate of < 0.025 (equivalent to a two-sided type I error rate of < 0.05).[36] The primary endpoint and key secondary endpoint were analysed in the randomised intention-to-treat (ITT) population.

The protocol and statistical analysis plan called for hierarchical testing of four subsequent secondary end points, all at Week 4; however, randomisation to trial groups no longer pertained after Week 1 due to 15/18 patients who were assigned to receive placebo receiving open-label spesolimab on Day 8 (Figure 6).[36] These patients' data were imputed with non-response or the worst possible outcome. Comparisons according to randomised treatment as originally planned were therefore noninformative, and changes at Week 4 for secondary endpoints and further endpoints were instead reported descriptively for the following groups:

- Patients randomised to receive spesolimab (patients who received one dose [Day 1] or two doses [Day 1 and Day 8])
- Patients randomised to receive spesolimab and only received one dose (Day 1)
- Patients randomised to receive spesolimab and received two doses (Day 1 and Day 8)
- Patients randomised to placebo who received spesolimab (Day 8)

Further details of the statistical analysis are provided in Table 10.

Table 10: Summary of statistical analyses in Effisayil™ 1

Hypothesis objective	Spesolimab given as a single IV infusion dose of 900 mg may increase the proportion of patients achieving a GPPGA pustulation subscore of 0 at Week 1 compared with placebo.
Statistical analysis plan	• The primary endpoint and key secondary endpoint were analysed with an exact Suissa–Shuster z-pooled test. Suissa, 1985 #22} • Formal statistical testing was performed at an overall 1-sided alpha level of 0.025 (P value < 0.025); the two-sided P value was reported by doubling the one-sided P value (P value < 0.05). • Confidence intervals around the risk difference were calculated with the use of the Chan and Zhang method for the primary endpoint and all binary secondary endpoints.[40] • To control familywise type I error, the primary endpoint and key secondary endpoint (both assessed at Day 8 [end of Week 1]) were tested in a hierarchical manner at a two-sided P value of less than 0.05.[41] • If the between-group difference in the primary endpoint was not significant, the key secondary endpoints would not be tested.
Post-hoc analysis	• Secondary endpoint analyses planned for Week 4 were noninformative due to high levels of crossover, and thus data analyses were replaced with descriptive analyses • Sensitivity analyses of the primary and key secondary endpoints were performed using linear regression with adjustment for the imbalanced covariates at baseline, including sex, race, and GPPASI score; no conclusions can be drawn from these analyses.
Sample size, power calculation	It was estimated that a sample of 51 patients would provide 90% or greater power to detect any difference between spesolimab and placebo with an assumed response of 0.6 and 0.1, respectively, for both the primary and key secondary endpoints and a type I error rate of less than 0.025 (one-sided), which can be considered to be a type I error rate of less than 0.05 with a two-sided test.
Data management, patient	Death or use of any escape medication prior to Week 1 will be captured as a non-response at the Week 1 timepoint.

withdrawals	Death or use of any escape medication prior to Week 1/4, or open-label spesolimab use at Day 8, or an rescue medication with spesolimab prior to Week 4 will be captured as a non-response at the Week 4 timepoint. For binary endpoints, patients with missing data are considered not to have had the respective endpoint event. For continuous endpoints, the last-observation-carried forward method was used for data imputation.
Key: GPPASI, Psoriasis Area and Severity Index for Generalised Pustular Psoriasis; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment. **Source:** Bachelez et al. 2021.[36]	

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

A complete quality assessment for all studies identified in the SLR is provided in Appendix D. Appraisal of the Effisayil™ 1 trial is summarised in Table 11.

Table 11: Critical appraisal of the Effisayil™ 1 trial

Question	Conclusion	Comments
Was randomisation carried out appropriately?	Yes	Patients were randomised to receive spesolimab or placebo in a ratio of 2:1 with stratification for Japanese vs non-Japanese ethnic group
Was the concealment of treatment allocation adequate?	Yes	Interactive response technology was used to perform treatment allocation and manage ordering of drug supplies. Clinicians were provided with a solution for infusion which could be spesolimab or a placebo solution.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	There were some differences observed in some demographic and clinical characteristics at baseline, namely gender, race, GPPASI score, and GPPGA pustulation sub score. Clinical characteristics representative of more sever disease were observed in the spesolimab arm so any resulting bias would be in favour of the placebo arm.
Were the care providers, participants and outcome assessors blinded to treatment allocation?	Yes	Patients and clinicians were blinded to randomised treatment allocation until after the database lock for final analysis.

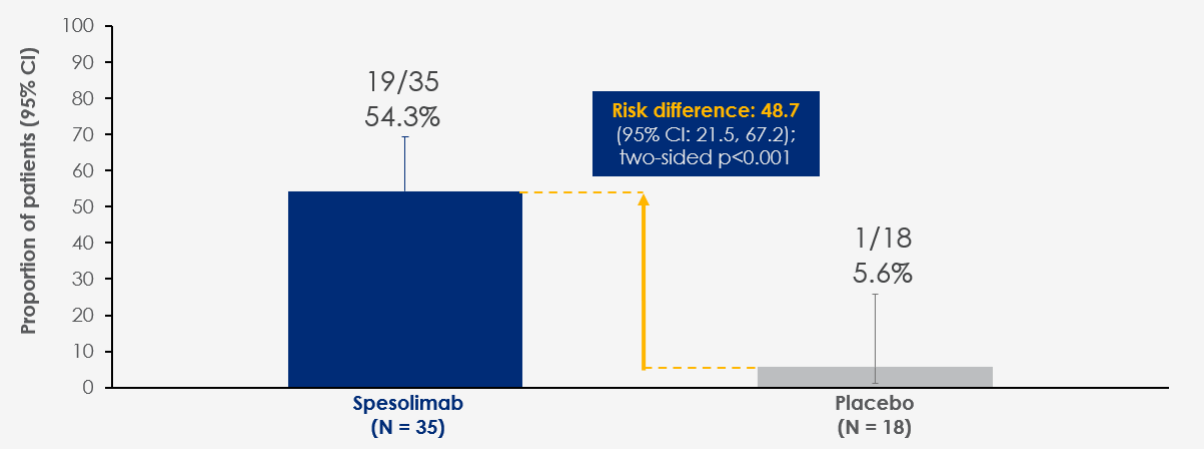
Were there any unexpected imbalances in drop-outs between groups?	No	91% of patients to the spesolimab arm and 94% of patients randomised to the placebo arm completed the 12-week trial period.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Primary endpoint and key secondary endpoint analysis at Week 1 was based on an ITT analysis with patients withdrawing or receiving escape medication assumed not to have responded. Due to high levels of open-label spesolimab use in the placebo arm after Week 1, changes at Week 4 for secondary endpoints and further endpoints were reported descriptively. The ITT principle was still adopted with appropriate methods used to account for missing data.
Does the study reflect routine clinical practice in England?	Yes	The study population, intervention, comparator and outcomes are applicable to routine clinical practice as discussed in Section B.2.12.3, despite not being directly reflective due to a lack of active treatment for the control arm and a high Asian cohort in the study population.
Key: GPPASI, Generalised Pustular Psoriasis Area and Severity Index; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; ITT, intention-to-treat.		

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1. Primary endpoint: GPPGA pustulation sub score 0 at Week 1

The result of the primary endpoint (Figure 7) showed that the proportion of patients who achieved a GPPGA pustulation sub score of 0 (no visible pustules) at Week 1 was significantly higher for patients who received spesolimab (19/35 patients, 54.3%) compared with patients who received placebo (1/18 patients, 5.6%), leading to a risk difference of 48.7 percentage points (95% CI: 22, 67; p-value<0.001).[36, 42]

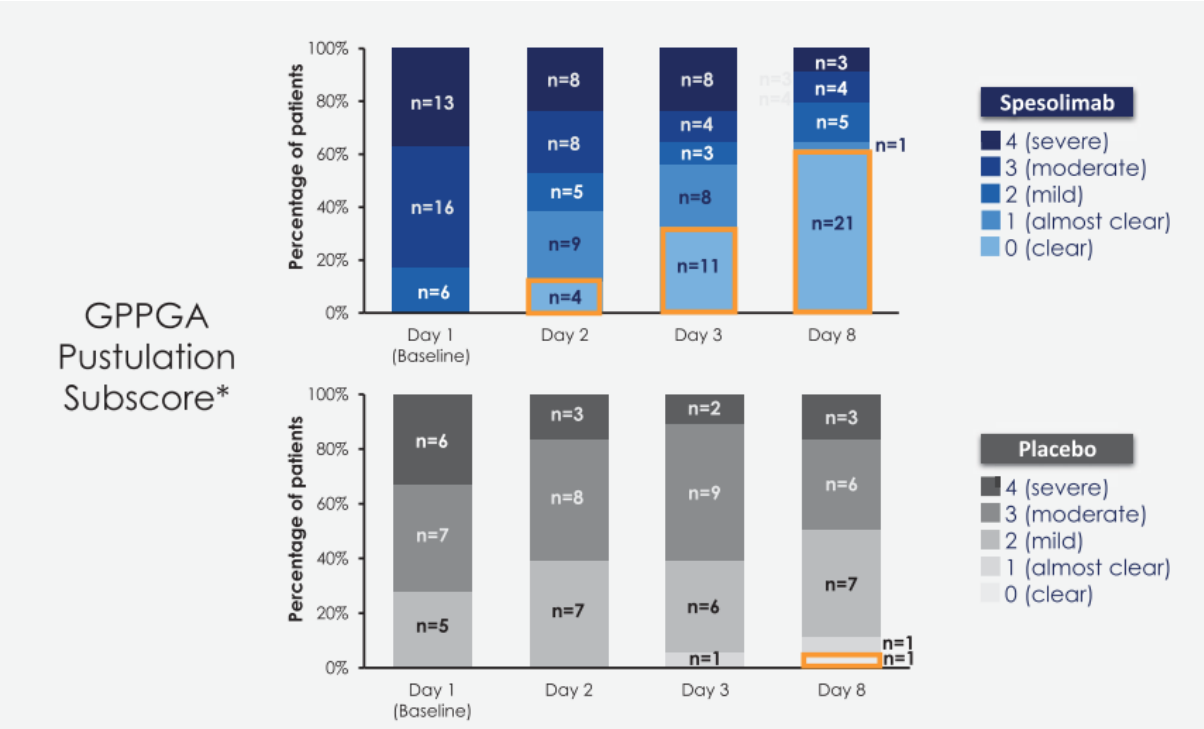
Figure 7: GPPGA pustulation sub score of 0 (no visible pustules) at Week 1



Key: CI, confidence interval; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; ITT, intention-to-treat.
Notes: primary endpoint analyses conducted on randomised ITT population with patients withdrawing or receiving escape medication assumed not to have responded.
One patient in the spesolimab arm discontinued before completing Week 1; two patients in the spesolimab arm received escape medication during Week 1. One patient in the placebo arm received escape medication during Week 1.
Source: adapted from Bachelez et al. 2021.[36]

Following spesolimab treatment, complete pustular clearance was observed as early as Day 2 in four patients, Day 3 in 11 patients and Day 8 in 21 patients (Figure 8; note that the data reported are observed cases without censoring for patients receiving escape medication).[42] All patients who reached GPPGA pustulation sub score of 0 (no visible pustules) with a single dose of randomised spesolimab (n = 19/35) achieved this by Week 1 (Day 8).[36]

Figure 8: Time to first achievement of GPPGA pustulation sub score 0 (no visible pustules)

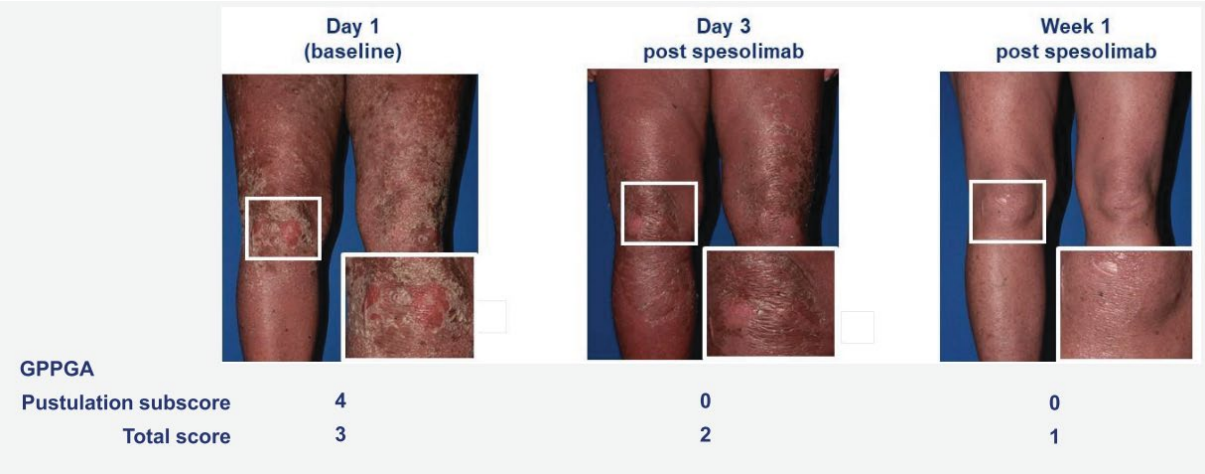


Key: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; ITT, intention-to-treat.
Notes: * data are all observed cases regardless of any other GPP medication (escape medication) used within the first week (ITT principle).
One patient in the spesolimab arm discontinued before completing Week 1; two patients in the spesolimab arm received escape medication during Week 1. One patient in the placebo arm received escape medication during Week 1.
Source: Bachelez et al. 2021.[42]

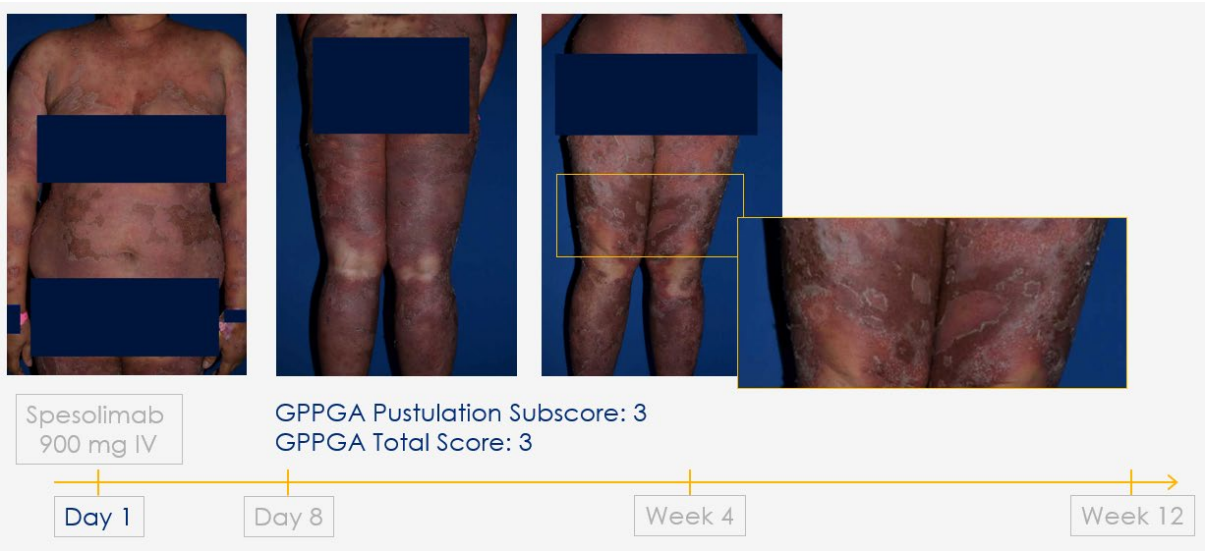
The improvement from Day 1 to Week 1 can clearly be seen in the patient case study pictures provided in Figure 9. Patient A presented with a moderate GPP flare (GPPGA total score of 3) with severe pustulation (GPPGA pustulation subscore of 4) at baseline (Day 1); one week after receiving a single dose of spesolimab, the patient had almost clear skin (GPPGA total score of 1) with no visible pustules (GPPGA pustulation subscore of 0).[42] Patient B presented with a moderate GPP flare (GPPGA total score of 3) with moderate pustulation (GPPGA pustulation subscore of 3) at baseline (Day 1); one week after receiving a single dose of spesolimab, the patient had almost clear skin (GPPGA total score of 1) with no visible pustules (GPPGA pustulation subscore of 0); this almost clear skin with no visible pustules was maintained through Week 12.[43]

Figure 9: Patient case study pictures to show skin before and after treatment with a single dose of spesolimab

Patient A



Patient B – Day 1 (baseline prior to spesolimab IV infusion)



Patient B – Day 8 (1 week after spesolimab IV infusion)

Patient B – Week 4 (4 weeks after spesolimab IV infusion)

Patient B – Week 12 (12 weeks after spesolimab IV infusion)

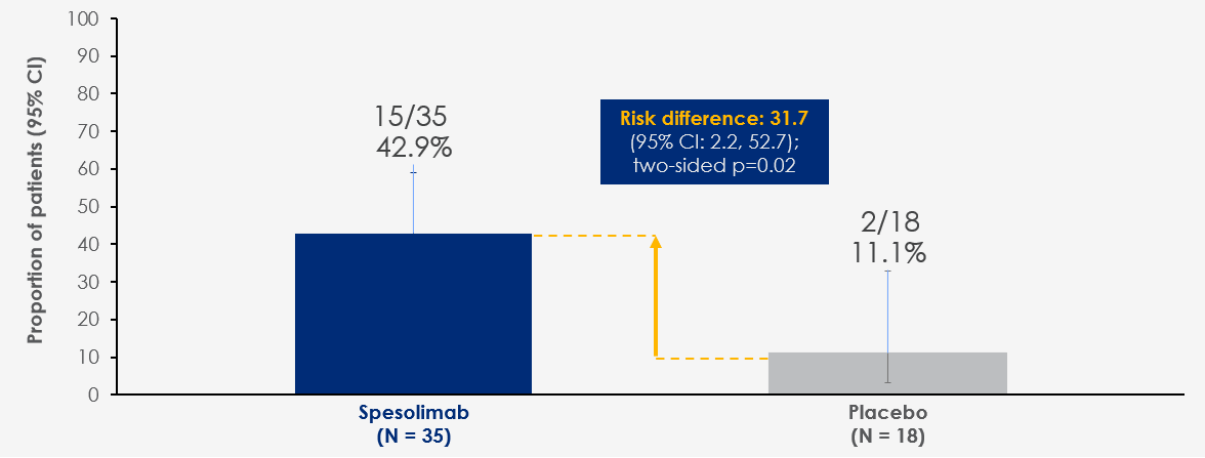
Key: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment.
Source: Bachelez et al. 2021[42]; GPP patient pictures – data on file.[43]

A post-hoc sensitivity analysis of the primary endpoint was performed using linear regression with adjustment for the imbalanced covariates at baseline, including sex, race, and GPPASI score.[36] Results are provided in Appendix E and support the conclusions of the ITT analyses.

B.2.6.2. Key secondary endpoint: GPPGA total score of 0 or 1 at Week 1

The result of the key secondary endpoint (Figure 10) showed that the proportion of patients who achieved a GPPGA total score of 0 or 1 (clear or almost clear skin) was significantly higher in the spesolimab arm (15/35 patients, 42.9%) compared with the placebo arm (2/18 patients, 11.1%), leading to a risk difference of 31.7 percentage points (95% CI: 2, 53; p-value=0.02).[36, 42]

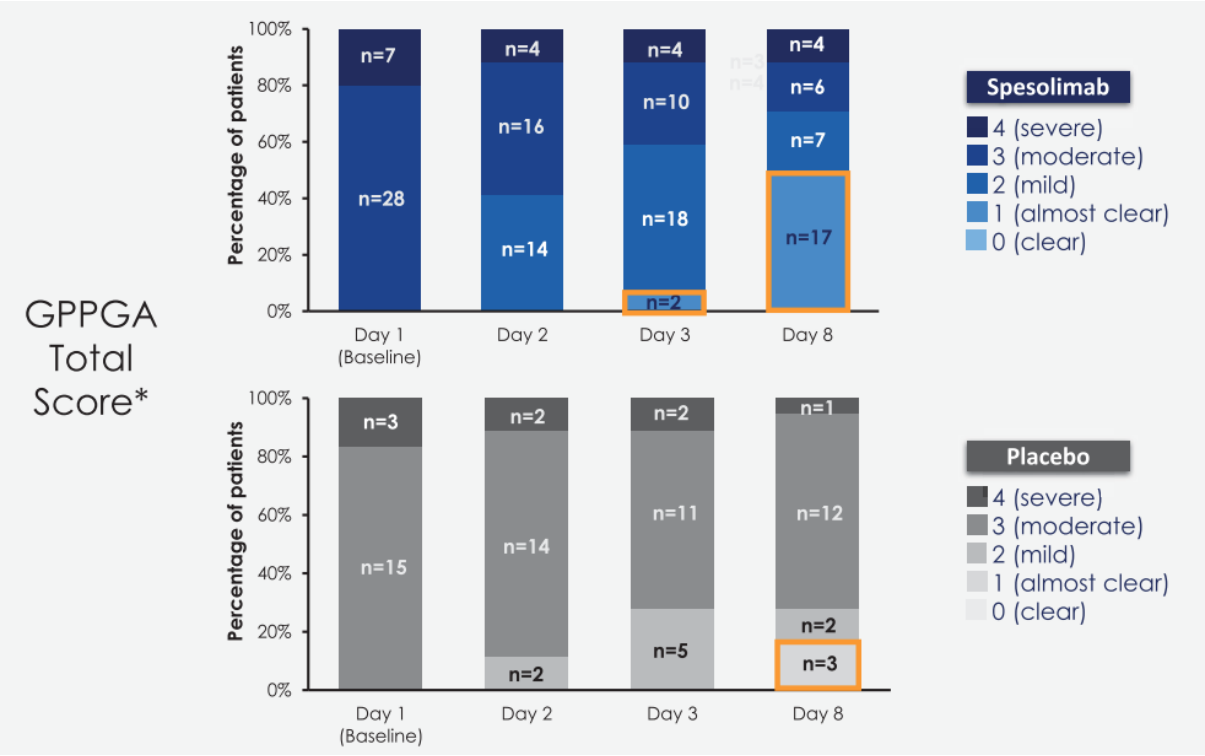
Figure 10: GPPGA total score of 0 or 1 (clear or almost clear skin) at Week 1



Key: CI, confidence interval; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; ITT, intention-to-treat.
Notes: key secondary endpoint analyses conducted on randomised ITT population with patients withdrawing or receiving escape medication assumed not to have responded.
One patient in the spesolimab arm discontinued before completing Week 1; two patients in the spesolimab arm received escape medication during Week 1. One patient in the placebo arm received escape medication during Week 1.
Source: adapted from Bachelez et al. 2021.[36]

The onset of skin clearance was rapid and started as early as Day 3 in 2 patients and Day 8 in 17 patients (Figure 11; note that the data reported are observed cases without censoring for patients receiving escape medication).[42] Nearly all patients (88%) who reached GPPGA total score of 0 to 1 (clear or almost clear skin) with a single dose of spesolimab achieved this by Week 1 (Day 8).[36]

Figure 11: Time to first achievement of a GPPGA total score of 0 or 1 (clear or almost clear skin)



Key: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; ITT, intention-to-treat.
Notes: * data are all observed cases regardless of any other GPP medication (escape medication) used within the first week (ITT principle).
One patient in the spesolimab arm discontinued before completing Week 1; two patients in the spesolimab arm received escape medication during Week 1. One patient in the placebo arm received escape medication during Week 1.
Source: Bachelez et al. 2021.[42]

A post-hoc sensitivity analysis of the key secondary endpoint was performed using linear regression with adjustment for the imbalanced covariates at baseline, including sex, race, and GPPASI score.[36] Results are provided in Appendix E and support the conclusions of the ITT analyses.

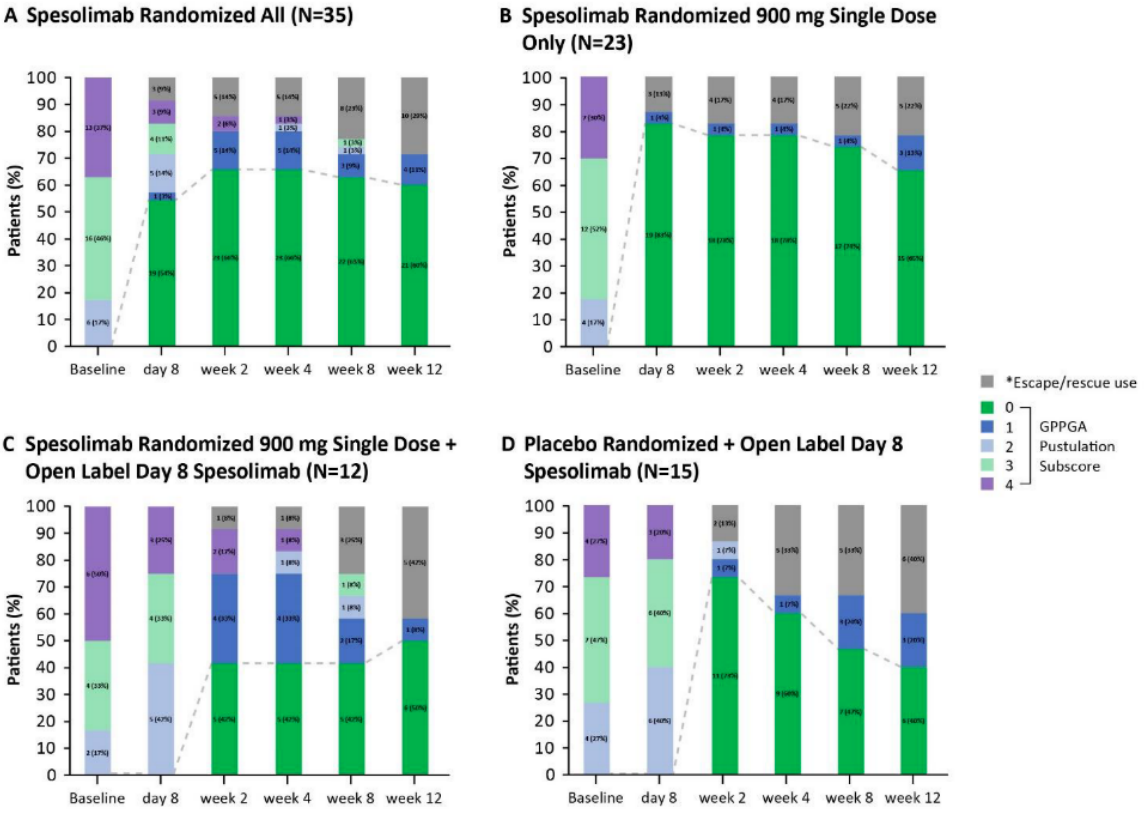
B.2.6.3. Exploratory endpoints after Week 1

Descriptive analyses of secondary endpoints at Week 4 originally included in the protocol and statistical analysis plan are provided for the treatment groups described post-hoc (see Section B.2.4) in Appendix E.

B.2.6.3.1.1. GPPGA pustular sub score and total score through Week 12

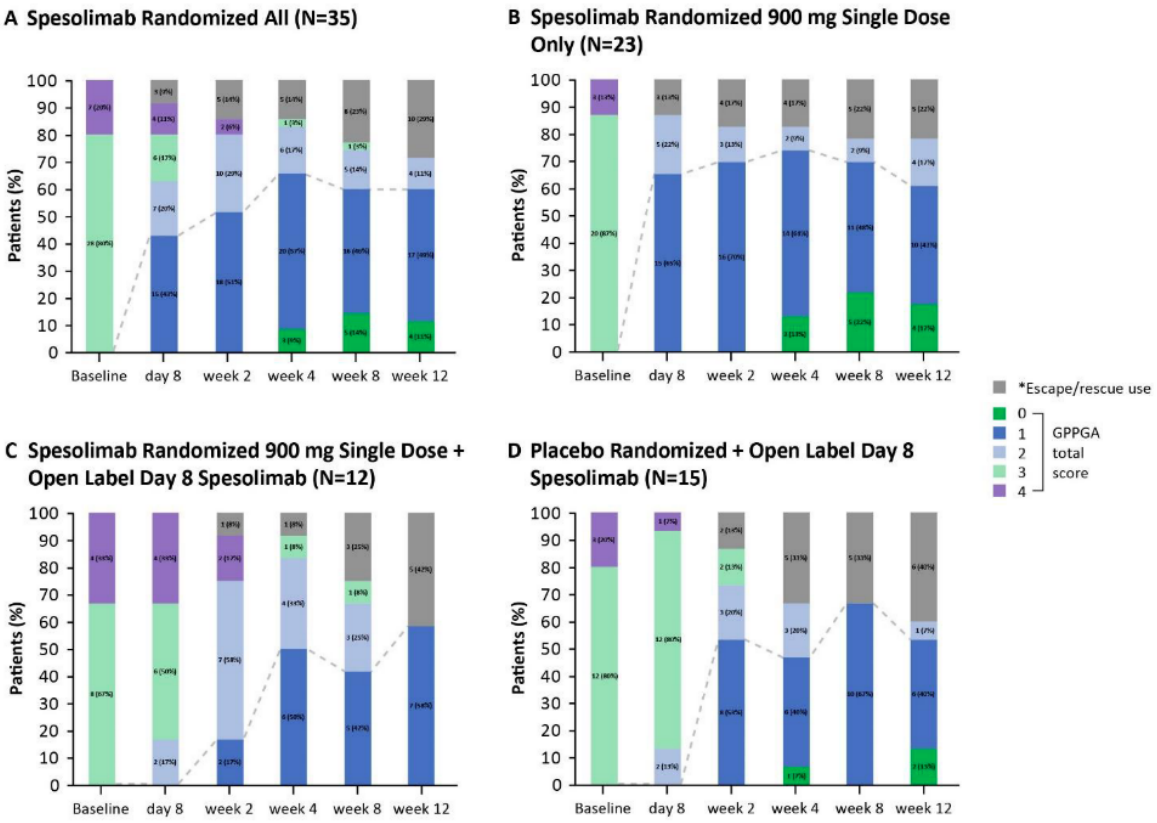
The benefits of spesolimab on the GPPGA pustular sub score and the GPPGA total score were reasonably sustained through Week 12, as shown in Figure 12 and Figure 13, respectively.[36] Of patients who received a single dose of randomised spesolimab (n = 23), 83% achieved GPPGA pustulation score of 0 by Week 1 and 65% maintained this over the 12 week study period.[36]

Figure 12: GPPGA Pustulation Sub Score Over Time by Randomised Treatment at Day 1 and Open-Label Spesolimab Treatment at Day 8



Key: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; ITT, intention-to-treat.
Notes: dashed line represents the proportion of patients achieving GPPGA pustulation subscore of 0 (no visible pustules). Analyses conducted on randomised ITT population with patients receiving escape medication, or non-randomised spesolimab at any point from Day 8 categorised separately as non-response for this analysis (grey bars).
Source: Bachelez et al. 2021.[36]

Figure 13: GPPGA Total Score Over Time by Randomised Treatment at Day 1 and Open-Label Spesolimab Treatment at Day 8



Key: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; ITT, intention-to-treat.
Notes: dashed line represents the proportion of patients achieving GPPGA total score of 0 or 1 (clear or almost clear skin). Analyses conducted on randomised ITT population with patients receiving escape medication, or non-randomised spesolimab at any point from Day 8 categorised separately (grey bars) as non-response for this analysis.
Source: Bachelez et al. 2021.[36]

B.2.6.3.1.2. Patient-reported outcomes

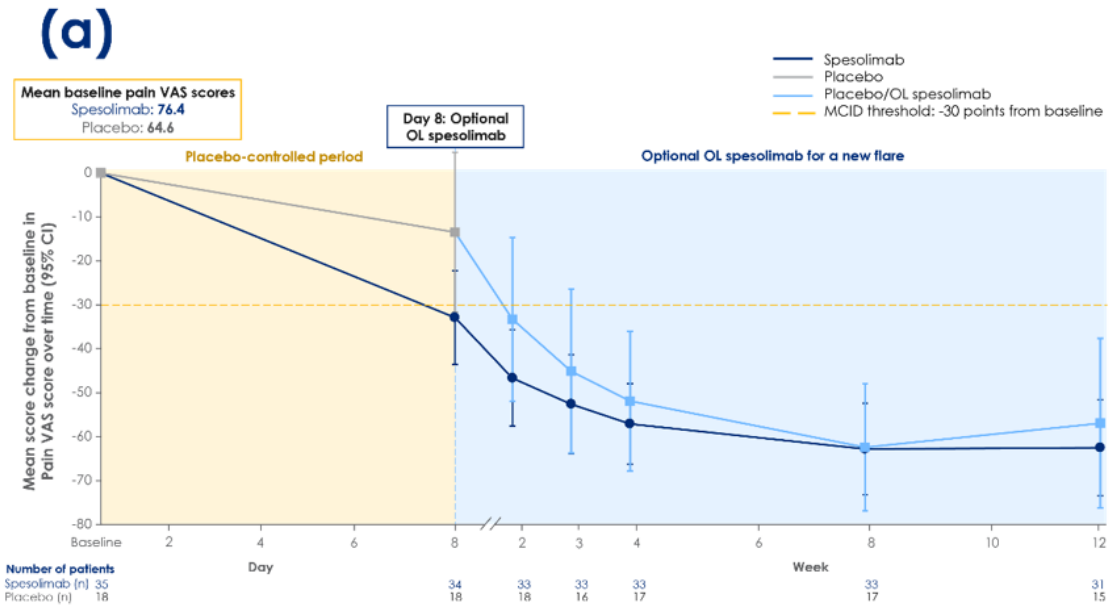
Changes in patient-reported outcome (PRO) scores from baseline to Week 12 for patients randomised to spesolimab are shown in Figure 14.

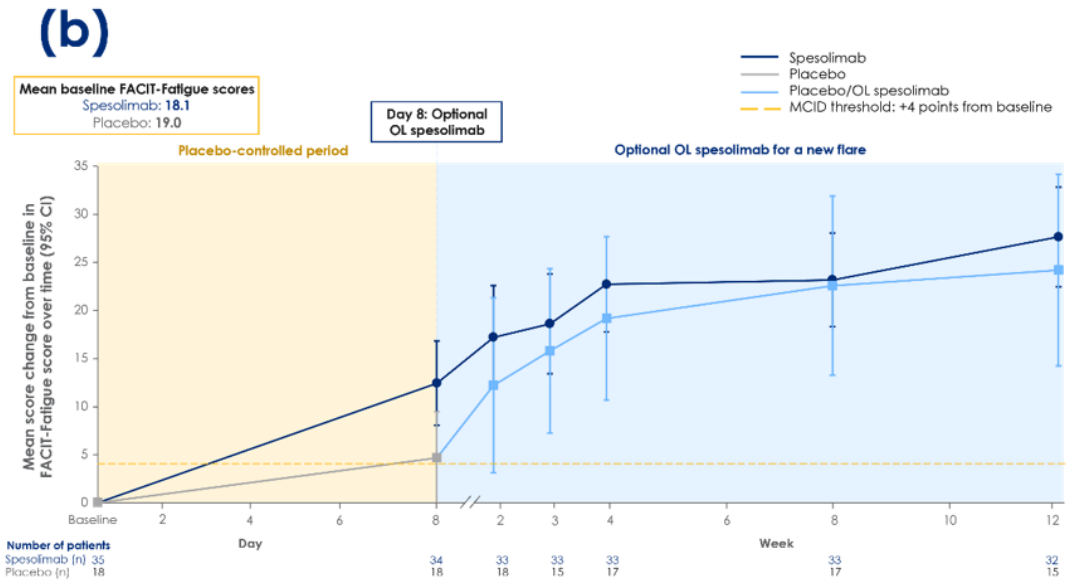
Spesolimab treatment resulted in rapid and sustained clinically meaningful improvements in pain VAS, FACIT-Fatigue, DLQI and PSS from baseline. The mean score change from baseline were all above the minimal clinically important difference (MCID) thresholds for each PRO by Week 1 in the spesolimab arm (Figure 14).[44] Additional data showing the proportion of patients achieving the MCID threshold over time are provided in Appendix E.

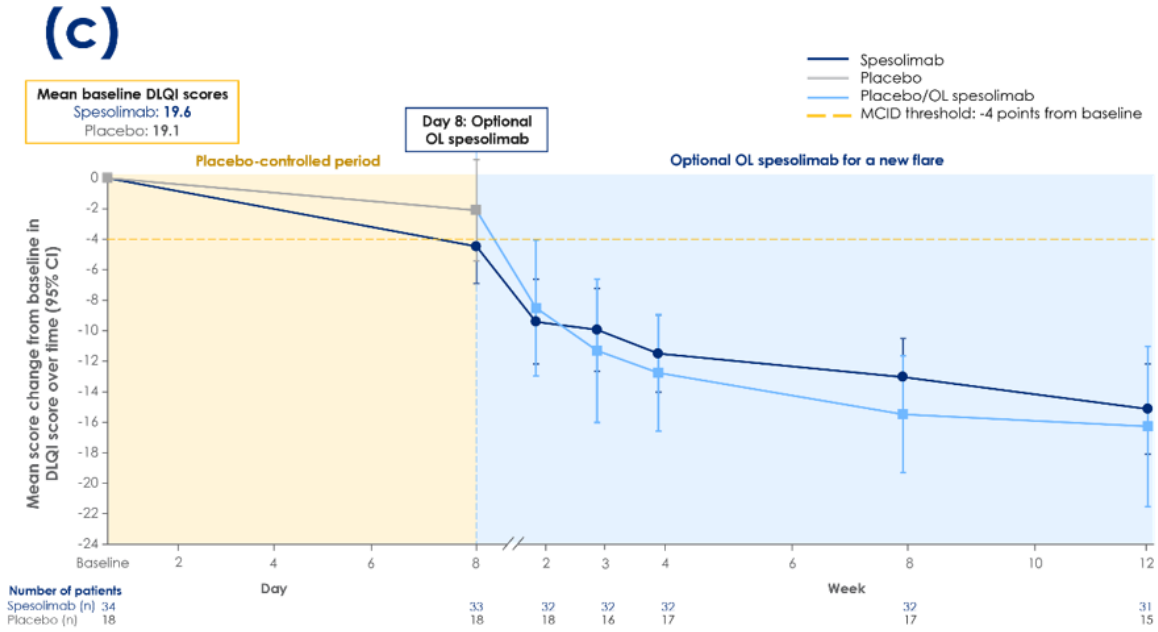
Clear separation of the spesolimab and placebo curves occurred early in the placebo-controlled treatment period for all PRO scores, but particularly for pain VAS scores, and PRO scores continued to improve up to Week 4 and were sustained through Week 12 (Figure 14).[44]

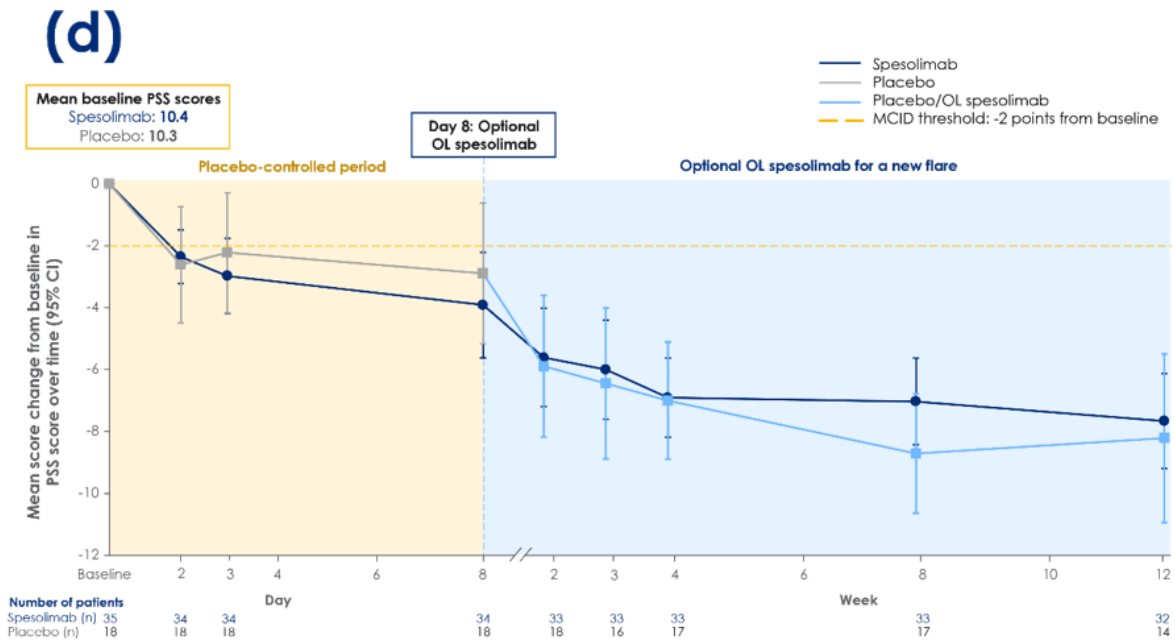
At Week 4, a significant correlation (Spearman's rank correlation coefficient) was observed between GPPGA total score and all PROs, except for FACIT-Fatigue (pain VAS:$p < 0.05$; DLQI: $p < 0.001$; and PSS: $p < 0.05$).[44] The proportion of patients achieving a GPPGA pustulation sub score of 0 (no visible pustules) and GPPGA total score of 0 or 1 (clear or almost clear skin) also mirrored the improvements in PRO scores from baseline over time.[44]

Figure 14: Absolute changes in PRO scores from baseline over time in (a) Pain VAS (b) FACIT-Fatigue (c) DLQI (d) PSS









Key: CI, confidence interval; DLQI, Dermatology Life Quality Index; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; ITT, intention-to-treat; VAS, visual analogue scale; MCID, minimal clinically important difference; OL, open-label; PRO, patient-reported outcome; PSS, Psoriasis Symptom Scale.
Notes: dashed line represents the MCID threshold. Analyses conducted on randomised ITT population. At Day 8, 12 patients randomised to the spesolimab arm and 15 patients randomised to the placebo arm received OL spesolimab. After Day 8, 4 patients in the spesolimab arm and two in the placebo arm received spesolimab for a new flare.
Source: Navarini et al. 2023[44]

Exploratory analyses of the EQ-5D health index of patients showed a general trend of improved quality of life in the week following treatment with spesolimab, as depicted by the in Figure 15, but observations were inconsistent through Week 12.[45] As a general health measure, the EQ-5D may not be as sensitive in acute conditions where health status can change rapidly.[46]

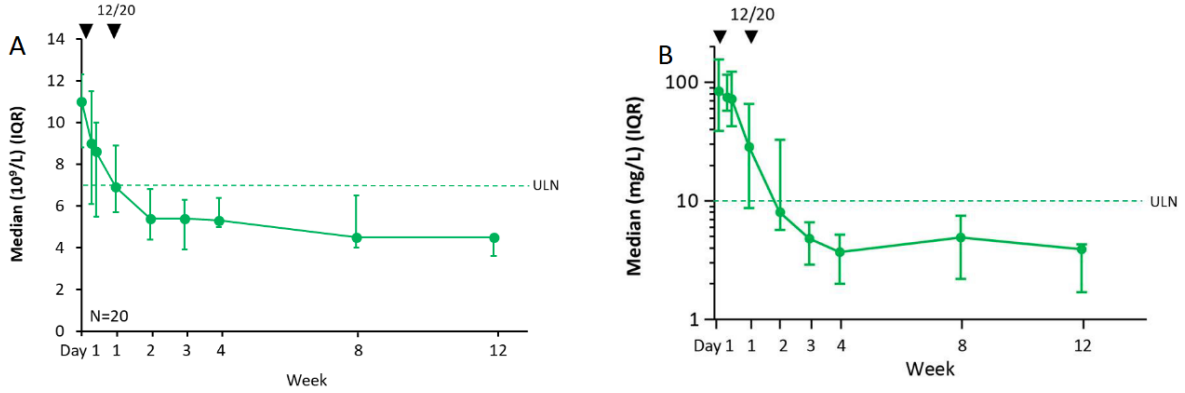
Figure 15: Median absolute change from baseline in EQ-5D health index status over time

Key: IV, intravenous; NR, non-response; Q1, first quartile; Q3, third quartile; SD, standard deviation.
Notes: Values after death, escape medication, open-label spesolimab or rescue medication are imputed as non-response. The denominator for percentages and proportions is the number of patients in the analysis set. Minimal clinically important difference in EQ-5D health index is estimated at 0.07.
Source: Clinical Trial Report.[45]

B.2.6.3.1.3. Systemic features of GPP

Treatment with spesolimab resulted in rapid and sustained improvements in markers of inflammation from baseline.[36] Median CRP levels normalised within 2 weeks, and median ANC normalised within 1 week, as shown in Figure 16**.**

Figure 16: Median neutrophils (A) and C-reactive protein (B) levels over time in patients who had >ULN at baseline and were randomised to spesolimab



Key: IQR, interquartile range; IV, intravenous; ULN, upper limit of normal.
Notes: Data collected after open-label spesolimab at Day 8 are used as observed, but data collected after escape medication or rescue medication are censored. Arrowhead indicates day of spesolimab IV infusion. ULN of neutrophils defined as ≥7 x 109/L; ULN of CRP defined as ≥10 mg/L.
Source: Bachelez et al. 2021.[36]

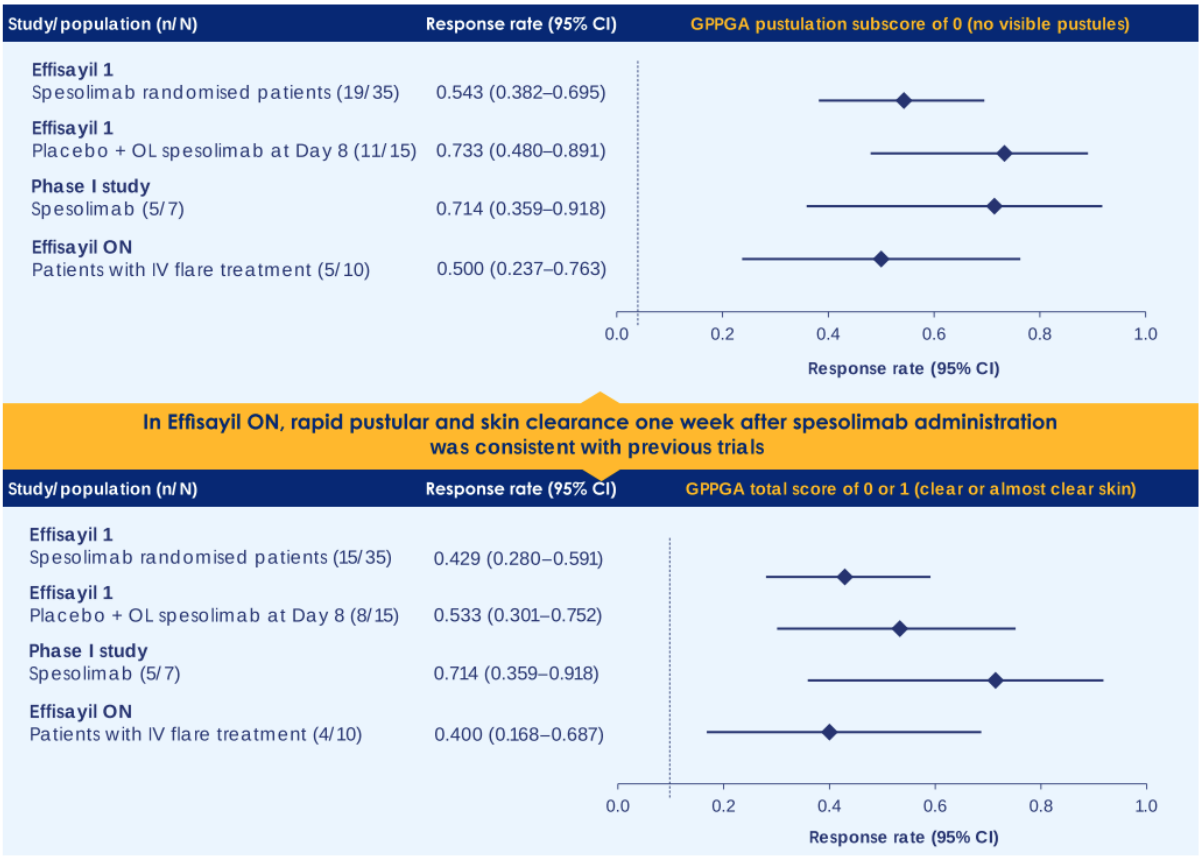
B.2.6.4. Effisayil™ ON interim results for flare treatment

Of 39 patients from Effisayil™ 1 who entered Effisayil™ ON, 10 were treated for a recurrent GPP flare by the cut-off date for this interim analyses.[47]

One week after the first recurrent GPP flare treatment with spesolimab IV infusion, 50% of patients (n = 5/10) achieved a GPPGA pustulation subscore of 0, indicating no visible pustules, and 40% of patients (n = 4/10) achieved a GPPGA total score of 0 or 1, indicating clear or almost clear skin.[47]

As shown in Figure 17, these data showing rapid pustular and skin clearer one week after spesolimab IV infusion was consistent with the Week 1 results of the Effisayil™ 1 trial and Phase I study data.[47]

Figure 17: GPPGA pustulation subscore of 0 (no visible pustules) and GPPGA total score of 0 or 1 (clear or almost clear skin) at Week 1



Key: CI, confidence interval; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; OL, open-label.
Source: Navarini et al. 2023.[47]

B.2.6.5. Effisayil™ 2 early results for flare treatment

A total of [redacted] patients enrolled to Effisayil™ 2 experienced a GPP flare during the trial period which was treated with spesolimab IV infusion.[48] Of these patients, [redacted] had been originally randomised to spesolimab SC treatment for prevention of flares and [redacted] had been randomised to placebo.[48]

Following spesolimab IV infusion for GPP flare, [redacted] achieved complete pustular clearance (GPPGA pustulation sub score of 0) by Week 1, increasing to [redacted] by Week 4 (data on file).[48] [redacted] percent of patients [redacted] achieved clear or almost clear skin (GPPGA total score of 0 or 1) by Week 1, increasing to [redacted] by Week 4 (data on file).[48]

Despite the difference in patient groups with several of these patients receiving spesolimab SC treatment prior to spesolimab IV infusion for GPP flare, data are generally consistent with the Week 4 results of the Effisayil™ 1 trial.

B.2.7. Subgroup analysis

Pre-specified subgroup analyses were conducted based on by sex, age, race, BMI category, GPPGA pustulation sub score at baseline, GPPGA total score at baseline, plaque psoriasis at baseline, background treatment prior to randomisation, JDA GPP severity score at baseline, and mutation status in *IL36RN*.[49]

All subgroup analyses were exploratory, but treatment effect estimates were generally comparable to the estimates of the primary analyses.[49] Despite the small sample sizes, treatment effects were observed in all pre-specified subgroups in a positive trend with a large overlap in CIs. Specifically, for both the primary and the key secondary endpoint, treatment effect was observed for all patients regardless of the IL-36RN mutation status (positive vs negative) and race (Asian vs White).[49]

Subgroup analyses are provided in Appendix E.

B.2.8. Meta-analysis

The Effisayil™ 1 trial is the only trial providing data on spesolimab treatment of GPP flares, and therefore meta-analysis is not applicable.

B.2.9. Indirect and mixed treatment comparisons

In the absence of robust comparator data for formal indirect treatment comparison, supportive evidence is provided by:

- Effisayil™ 1 historical cohort: historical cohort data characterising patients' GPP flares prior to their enrolment to the Effisayil™ 1 trial[50]
- Central and Eastern Europe (CEE) GPP Expert Network: retrospective case series study evaluating characteristics and management of GPP[24]
- Structured expert elicitation to identify the efficacy and safety of current treatments for GPP flares in the UK.[33]

B.2.9.1. Effisayil™ 1 historical cohort

Investigators in the Effisayil™ 1 trial collected historical data to describe the characteristics and outcomes of GPP flares prior to patients enrolment to the Effisayil™ 1 trial.[50] At screening, information on the characteristics and clinical course of past GPP flares was obtained from each patient and substantiated by retrospective clinical chart review. Investigators collected information on flares prior to consent using a standard study questionnaire. Data collected included (i) the average number of flares per year or whether the patient was constantly flaring with persistent pustules; (ii) the duration of affected and clear skin over the past year; (iii) treatments given for past GPP flares; and (iv) clinical and laboratory characteristics of identified typical, most severe, and longest flares, as well as treatment instituted, duration of hospitalisation, and outcome of the three categories of flares identified. There was no standard definition of a typical, most severe, and longest flare: assignment of flares to each category was based on investigator interpretation.

For GPP flares where a trigger event was identified, the most common were stress (19-21%), infections (19-21%) and treatment withdrawal (7-20%). For two patients, long flares were triggered by pregnancy.

Clinical characteristics of historical GPP flares are summarised in Table 12. For the categorisation of flares as presented, no standard definitions/criteria were applied; rather the assignment of flares to each category was based on investigator interpretation.[50] Across all flare categories, the majority of patients experienced flares of moderate-to-severe intensity (based on investigator assessment). Around a third of patients experienced flares affecting at least 30% of their body surface area and flares were often associated with systemic symptoms and increases in biological markers of inflammation and infection (Table 12).

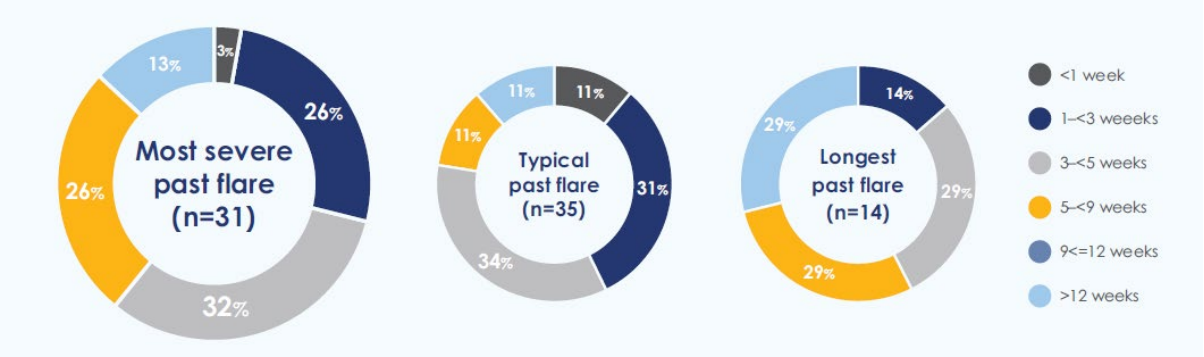
Table 12: Clinical features of past GPP flares in the Effisayil™ 1 historical cohort

Clinical feature, n (%)	Typical past flare (n = 37)	Most severe past flare (n = 31)	Longest past flare (n = 14)
Flare intensity at baseline:			
Mild	5.0 (13.5)	0.0 (0.0)	1.0 (7.1)
Moderate	13.0 (35.1)	8.0 (25.8)	3.0 (21.4)
Severe	14.0 (37.8)	23.0 (74.2)	9.0 (64.3)
Unknown	5.0 (13.5)	0.0 (0.0)	1.0 (7.1)
BSA of skin affected ≥30%	24.0 (64.9)	21.0 (67.7)	9.0 (64.3)
CRP ≥7 mg/dL	7.0 (25.9)*	14.0 (45.2)	4.0 (28.6)
Leukocytosis ≥15,000 WBC/μL	3.0 (11.1)*	9.0 (29.0)	3.0 (21.4)
Body temperature >38.5°C	5.0 (18.5)*	12.0 (40.0)^	6.0 (46.2)#
Albumin <3.0 g/dL	3.0 (11.5)$	6.0 (20.0)^	1.0 (7.1)
Fatigue	20.0 (74.1)*	23.0 (74.2)	11.0 (78.6)
Malaise	13.0 (48.1)*	12.0 (38.7)	6.0 (42.9)
Asthenia	16.0 (59.3)*	19.0 (61.3)	9.0 (64.3)
Myalgia	12.0 (44.4)*	13.0 (41.9)	6.0 (42.9)
Oedema	10.0 (37.0)*	10.0 (32.3)	4.0 (28.6)
Pain	17.0 (63.0)*	23.0 (74.2)	13.0 (92.9)
Neutrophilia	7.0 (25.9)*	13.0 (41.9)	4.0 (28.6)

Key: BSA, body surface area; CRP, C-reactive protein; GPP, generalised pustular psoriasis; WBC, white blood cells.
Notes: *Data available for 27 patients; ^ Data available for 30 patients; # Data available for 13 patients; $ Footnote not provided in manuscript
Source: Choon et al. 2023[50]

Time to resolution of GPP flare ranged from <1 week to >12 weeks.[50] The longest flare prior to enrolment took more than 3 weeks to resolve for most patients (86%) and lasted for over 12 weeks in 29% of patients (Figure 18).

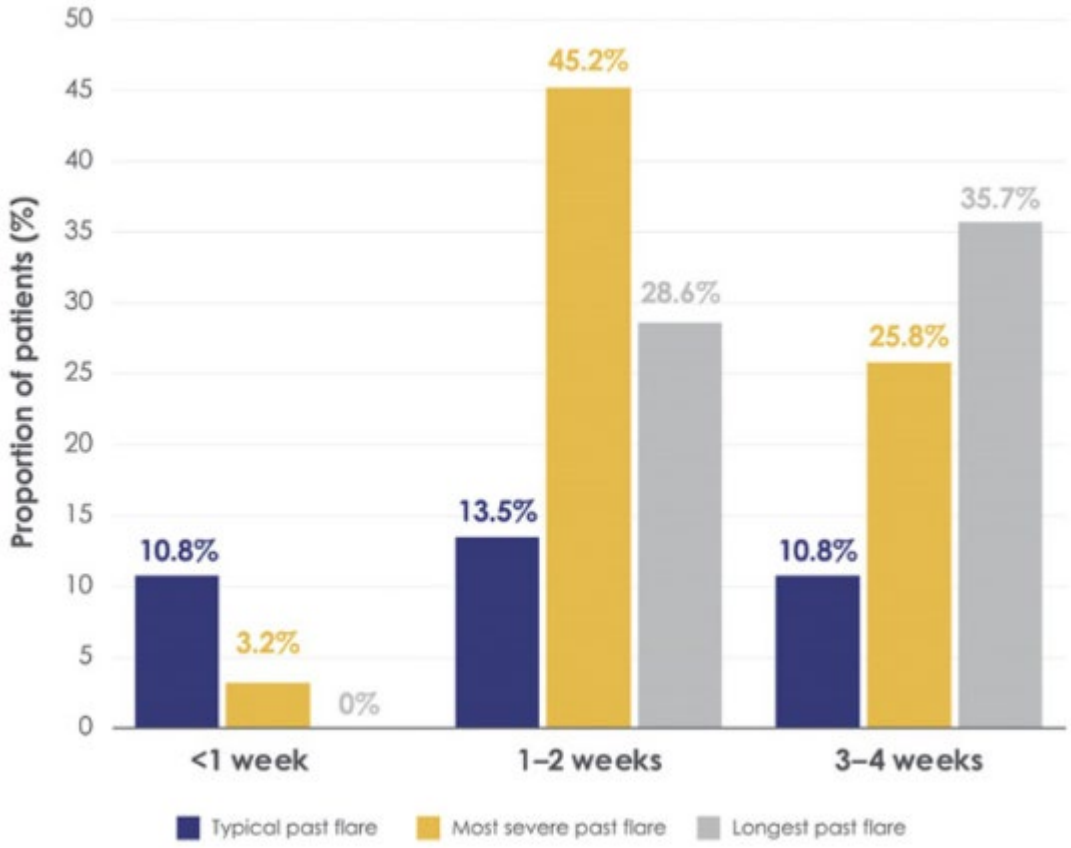
Figure 18: Duration of past flares in the Effisayil™ 1 historical cohort



Source: Choon et al. 2023[50]

Almost two-thirds of patients (64%) required hospitalisation for their longest flare and were hospitalised for 1-4 weeks, as depicted in Figure 19. The most severe flare prior to enrolment took more than 3 weeks to resolve for 71% of patients and lasted for over 12 weeks in 13% of patients (Figure 18). Approximately three-quarters of patients (74%) required hospitalisation for their most severe flare, with most (71%) being hospitalised for 1-4 weeks (Figure 19).

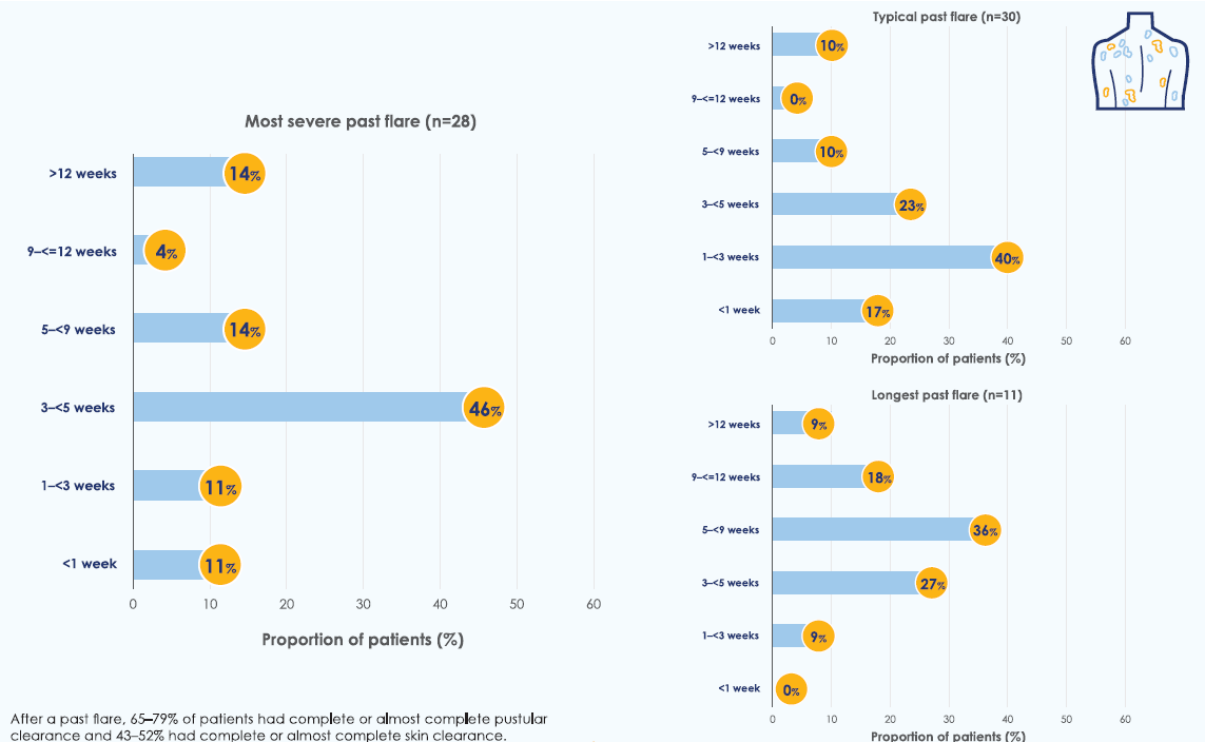
Figure 19: Duration of hospitalisation for past GPP flares in the Effisayil™ 1 historical cohort



Key: GPP, generalised pustular psoriasis
Notes: Typical past flare, n=37 but hospitalisation data are unknown for four patients; most severe past flare, n=31; longest past flare, n=14.
Source: Choon et al. 2023[50]

The majority of GPP flares were of 1-4 weeks duration and required lengthy hospitalisation despite patients receiving treatment for their GPP flare.[50] At least two-thirds of flares were treated with systemic therapies: 64% of the longest past flare, 71% of the most severe past flare and 70% of the typical past flare. An additional 29%, 19% and 14% of the longest past flare, most severe past flare and typical past flare, respectively, were treated with topical therapies. The typical time to pustular clearance for each flare category are presented in Figure 20. These data reflect dermatologist survey conclusions that existing treatments are too slow to control GPP flares and do not adequately resolve flares.[34]

Figure 20: Time to clearance of pustules related to past GPP flares in the Effisayil™ 1 historical cohort



Key: GPP, generalised pustular psoriasis.
Source: adapted from Choon et al. 2023.[50]

B.2.9.2. CEE GPP Expert Network – Wolf and colleagues

A retrospective case-series study evaluating demographic information for patients with GPP in CEE was conducted between March and December 2022 in 12 sites across nine CEE countries.[24] Patients were included in the study if they met ERASPEN criteria for GPP diagnosis; in total, 58 patients were included.[24] Information from medical records was extracted using a case report form, collecting data on patient demographics at the most recent observation and past treatments. Clinical characteristics were provided for a patient's last flare and most severe flare, designated at clinician's discretion from all documented episodes[24]

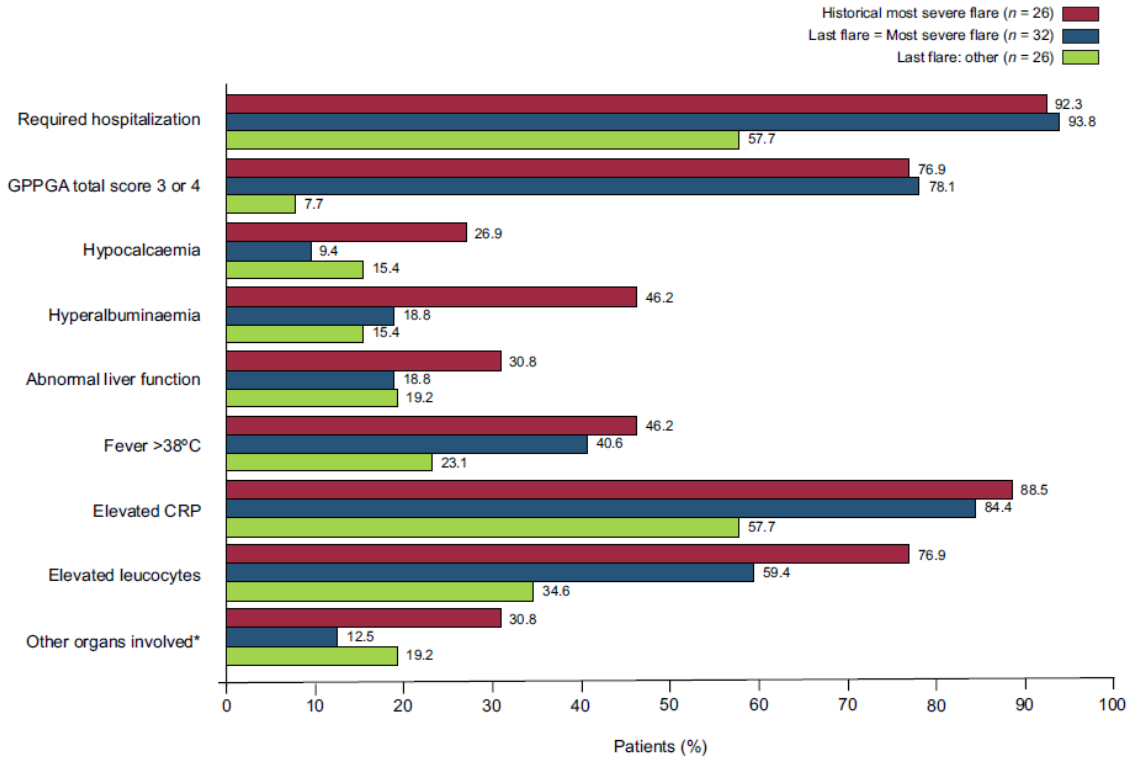
Demographic data for patients at the most recent observation are provided in Appendix M. There was a slight predominance of female patients (n = 35; 60.3%) and the median (range) age was 61 (16–92) years.[24] Median (range) disease

duration was 8 (0.25–51) years and the mean (SD) flare frequency was 0.98 (0.93) flares per year.

For the 58 patients included, data were available for 84 individual flare episodes.[24] Although systemic symptoms could be present in patients with a GPPGA total score or GPPGA pustulation sub score of 1, a significant correlation was observed between combined systemic disease score and both GPPGA total score ($p< 0.001$) and GPPGA pustulation subscore ($p< 0.05$), as well as the duration of hospitalisation ($p< 0.05$). GPPGA total score and GPPGA pustulation subscore also significantly correlated with levels of CRP and neutrophils ($p<0.05$). Leucocyte levels were not significantly correlated.

Patients were most likely to require hospitalisation for their historical most severe flare (92%) and last flare = most severe flare (94%) compared with last flare = other (58%), as depicted in Figure 21.[24] Flare duration ranged from 1 to 48 weeks across flare subgroups with a median flare duration of 4 weeks for all flare subgroups.[24] Median hospitalisation duration was highest in the historical most severe flare subgroup at 2.3 weeks (range: 0.4–28 weeks) but was still as high as 1.3 weeks (range: 0.1–9.0 weeks) for ‘other’ flare (Table 7).

Figure 21: Clinical characteristics and hospitalisation requirements of flare subgroups



Key: CRP, C-reactive protein; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment.
Note: *Other organs involved include acute respiratory distress syndrome, kidney failure, metabolic disorders, osteoarthritis and sepsis.
Source: Wolf et al. 2024[24]

Retinoids were the most frequently used treatment (47%) following by biologics (29%), methotrexate (17%), phototherapy (17%), systemic steroids (14%), TNF inhibitors (12%) and cyclosporin (10%); anti-IL agents of various types were used to treat 22% of patients.[24] Biologics were used to treat the last most severe flare more than historical severe flares, suggesting an increased use of biologics over time. Of all individual flare episodes, 23% (19/84) were unresolved with treatment, and for those that did resolve, the median time from treatment initiation to flare resolution was 4 weeks (range: 1–54 weeks).[24]

B.2.9.3. Structured Expert Elicitation – BAC efficacy and safety

Identifying an evidence gap in 2022, Boehringer Ingelheim carried out an SEE exercise to identify the treatments used for GPP flares in the UK and the efficacy and safety profiles of current treatments, including the mortality rate for people experiencing a flare beyond 4 weeks.[33]

Dermatologists in the UK and Ireland, with experience treating GPP patients at specialist centres participated in the SEE. Their predictions for BAC efficacy were generally aligned with the RWE outcomes observed in the Effisayil™ 1 historical cohort and CEE GPP Expert Network data. Consensus outputs indicated that the majority of patients who will respond to BAC will not do so until [redacted] after treatment. A summary of the SEE results are provided in Appendix M, and the full report, with details of the methodology, is included in the submission reference pack.[33]

Although the SEE data provide supportive evidence for the efficacy of BAC, these estimates are from a lower quality source than the RWE, which was published subsequently. The data provided by the experts filled an evidence gap at the time, but they highlighted throughout the SEE exercise that the survey was complicated and unintuitive due to the rarity of the disease. As such, the data are not sufficient for decision making and are not used to inform the economic modelling.

B.2.10. Adverse reactions

Safety analyses in the Effisayil™ 1 trial were performed on the safety analysis set, which included all randomised patients who received at least one dose of study medication.[36] Outcomes for the following analysis periods are presented in Table 13:

- Adverse events (AE) at Week 1 (data collected during the first 8 days), consistent with the timing of the primary efficacy analysis.
- AEs up to Week 12, including the residual effect period (data collected up to Day 113, which is 16 weeks after the Day 1 treatment).

B.2.10.1. Adverse events at Week 1

At Week 1, the proportion of AEs, drug-related AEs and serious adverse events (SAEs) were comparable between treatment groups (Table 13). AEs were reported in 66% of the patients in the spesolimab group and 56% in the placebo group. Infections were reported with a higher rate in the spesolimab group compared to placebo (17% vs 6%) but there was no distinct pattern in terms of pathogen or type of infection.[36] Of spesolimab patients reporting infection (n = 6), there were two cases of urinary tract infection (UTI) and one case each of various other infections.

SAEs were reported in two patients (6%) who received one dose of spesolimab and in none of the patients who received placebo.[36] SAEs reported were DRESS, serious UTI, drug-induced hepatic injury, and arthritis.

B.2.10.2. Adverse events at Week 12

At Week 12, a total of 82% of the patients who received at least one dose of spesolimab experienced an AE and 55% experienced a drug-related AE (Table 13). There was no increase in the incidence rates of AEs over time, or after administration of a second spesolimab dose.[36] Infections were reported in 47% of patients treated with spesolimab up to Week 12 (n = 24); there were three cases each of UTI and influenza; two cases each of folliculitis, otitis externa, upper respiratory tract infection, and pustule; and one case each of other infections.

SAEs were reported in six patients (12%) who received at least one dose of spesolimab; one patient experience three events so the total SAEs experienced

were eight.[36] SAEs reported were DRESS (two events), UTI, drug-induced hepatic injury, arthritis, worsening of chronic plaque psoriasis, influenza, and squamous cell carcinoma of the skin. In both cases of DRESS, symptoms were experienced at a time of GPP flare and symptoms were consistent with clinical manifestations of a GPP flare. Independent external expert assessment was undertaken in both cases. Applying RegiSCAR scoring criteria, one of the cases is classified as 'no DRESS' and the other as 'possible DRESS'.[36] Symptoms resolved without drug treatment in both cases.

Table 13: Summary of AEs reported in Effisayil™ 1

	Week 1				Week 12*	
	Spesolimab (N = 35)		Placebo (N = 18)		Spesolimab (N = 51)	
	No. (%)	Rate per 100 patient-yr	No. (%)	Rate per 100 patient-yr	No. (%)	Rate per 100 patient-yr
Patients with AE	23 (66)	5874.7	10 (56)	4623.4	42 (82)	981.5
Patients with severe AE (RCTC grade 3 or 4)	2 (6)	309.5	1 (6)	304.4	5 (10)	40.9
Patients with investigator-defined drug-related AEs	10 (29)	1747.6	5 (28)	1773.1	28 (55)	353.5
Patients with SAE	2 (6)	309.5	0	N/A	6 (12)	49.7
Patients with AE leading to discontinuation of trial drug	0	N/A	0	N/A	0	N/A
Death	0	N/A	0	N/A	0	N/A
Common AEs reported for more than 10% of patients in either treatment group						
General disorders and administration site conditions	9 (25.7)	1543.3	5 (27.8)	1756.0	13 (25.5)	127.5
Pyrexia	2 (5.7)	313.5	4 (22.2)	1404.8	5 (9.8)	41.3
Infections and infestations	6 (17.1)	987.2	1 (5.6)	292.2	24 (47.1)	262.8
Skin and subcutaneous tissue disorders	5 (14.3)	822.6	2 (11.1)	593.9	14 (27.5)	137.9
Nervous system disorders	4 (11.4)	655.2	3 (16.7)	961.2	7 (13.7)	60.5
Dizziness	0	0	2 (11.1)	619.1	0	N/A
Investigations	4 (11.4)	664	2 (11.1)	619.1	7 (13.7)	61.5
Musculoskeletal and connective tissue disorders	(11.4)	627.0	2 (11.1)	624.4	11 (21.6)	101.6
Metabolism and nutrition disorders	3 (8.6)	484.8	2 (11.1)	624.4	4 (7.8)	32.4
Blood and lymphatic system disorders	1 (2.9)	154.1	2 (11.1)	640.8	4 (7.8)	32.9

	Week 1				Week 12*	
	Spesolimab (N = 35)		Placebo (N = 18)		Spesolimab (N = 51)	
	No. (%)	Rate per 100 patient-yr	No. (%)	Rate per 100 patient-yr	No. (%)	Rate per 100 patient-yr
Gastrointestinal disorders	2 (5.7)	309.5	1 (5.6)	292.2	13 (25.5)	118.5
Serious adverse events						
Drug reaction with eosinophilia and systemic symptoms	1 (3)	154.1	0	N/A	2 (4)	15.9
Urinary tract infection	1 (3)	154.1	0	0	1 (2)	7.8
Drug-induced hepatic injury^	1 (3)	154.1	0	0	1 (2)	7.8
Arthritis	1 (3)	152.2	0	0	1 (2)	7.8
Worsening of chronic plaque psoriasis†	0	0	0	0	1 (2)	7.8
Influenza	0	0	0	0	1 (2)	7.7
Squamous cell carcinoma of skin	0	0	0	0	1 (2)	7.7

Key: AE, adverse event; N/A, not applicable; RCTC, Rheumatology Common Toxicity Criteria.
Notes: Shown are AEs that occurred between the start of spesolimab or placebo administration and the end of the residual effect period (16 weeks after the placebo dose or the last dose of spesolimab). AEs were coded with the use of the Medical Dictionary for Drug Regulatory Activities, version 23.1. The severity of AEs was graded according to the RCTC, version 2.0. Pustular psoriasis was excluded as an AE from this safety analysis.
*The data set at Week 12 includes patients assigned to the spesolimab group who received up to three doses of spesolimab and patients assigned to the placebo group who received open-label spesolimab at or after Day 8. All AEs from the first use of spesolimab to the residual effect period of the last spesolimab dose are included. ^Drug-induced hepatic injury was reflected by an increase in aminotransferase levels and was considered to be a systemic symptom of drug reaction with eosinophilia and systemic symptoms. †Events involving the worsening of chronic plaque psoriasis are reflective of non-pustular psoriasis; these events were not captured in the efficacy end points.
Source: Bachelez et al. 2021.[36]

B.2.10.3. Effisayil™ ON interim results for flare treatment

During the first flare episode, nine of the ten patients treated for a new GPP flare by the cut-off data for the interim analyses of the Effisayil™ ON trial reported an AE.[47] There was one report of a severe AE and serious AE (required or prolonged hospitalisation), which were both pustular psoriasis in the same patient.

B.2.10.4. Safety summary

No additional safety issues to those identified in the Effisayil™ 1 and Effisayil™ ON trials are anticipated with the use of spesolimab in clinical practice.

As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for spesolimab to detail the potential risks, how these risks can be minimised, any uncertainties / missing information, and how more information will be obtained about the important risks and uncertainties.[2] As for all new active substance medicines, spesolimab is labelled with a black triangle to highlight it is subject to additional monitoring. This is to allow quick identification of new safety information and healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.[3]

Based on data available to date, regulatory agencies conclude there is a positive benefit/risk ratio for spesolimab IV infusion in the treatment of GPP flares.[1, 2]

B.2.11. Ongoing studies

Longer-term efficacy and safety data collection are ongoing in the Effisayil™ ON study and the Effisayil™ REP study, data from which form part of the CMA agreement.

B.2.12. Interpretation of clinical effectiveness and safety evidence

B.2.12.1. Principal findings from the clinical evidence

Effisayil™ 1 is the first and largest randomised controlled, Phase II trial in patients with GPP.[51] It provides substantial evidence on the efficacy of spesolimab IV infusion versus placebo for treatment of GPP flares in adults. Spesolimab was superior over

placebo for all tested endpoints.[36] A statistically significant higher proportion of patients in the spesolimab group achieved the primary endpoint of GPPGA pustulation sub score of 0, indicating complete pustular clearance, and the key secondary endpoint of GPPGA total score of 0 or 1, indicating clear or almost clear skin at Week 1.[36] Patients treated with spesolimab rapidly achieved this complete pustular clearance with response observed as early as Day 2 and treatment effect sustained up to Week 12.[36, 42]

Improvements in skin manifestations of GPP flare were accompanied by clinically meaningful benefits in PRO measures, including pain levels, severity of symptoms, fatigue levels, and quality of life.[44] PRO benefits were similarly rapid to efficacy benefits, particularly for pain levels with a clinically meaningful improvement reported within the first week of treatment and maintained through Week 12.[44] Biological markers of inflammation and infection were also seen to rapidly drop below ULN following spesolimab treatment, indicating a positive impact of spesolimab on systemic manifestations of GPP flare as well as skin manifestations.[36]

Overall, spesolimab IV infusion demonstrated an acceptable safety profile in the Effisayil™ 1 trial.[36] AE rates were generally comparable between treatment groups during Week 1. Although there was a higher rate of non-serious infections observed in the spesolimab group, there was no apparent pattern regarding pathogen and affected organs suggestive of a systemic safety concern.[36] There was no increase in AE rates with higher exposure to spesolimab (2 to 3 doses) or after longer observation time (through Week 12 end of trial timepoint).[36]

Effisayil™ 1 historical cohort data characterising patients' GPP flares prior to enrolment to the Effisayil™ 1 trial show that current BAC is slow to take effect, with 40% of typical past flares taking 1–<3 weeks to resolve and 46% of severe past flares taking 3–<5 weeks to resolve.[50] Ten percent of typical flares and 14% of severe flares had not resolved by 12 weeks. CEE GPP Expert Network support the conclusions of the Effisayil™ 1 historical cohort data, similarly reporting slow treatment effect with a median duration of flare resolution from treatment initiation of 4 weeks.[24] Twenty-three percent of flares did not resolve with current BAC. In comparison, response to spesolimab in the Effisayil™ 1 trial was observed as early

as Day 2 and by Week 1, 54% of patients randomised to spesolimab in the Effisayil™ 1 trial achieved pustular clearance (GPPGA pustulation sub score of 0).[36, 42] Of patients who received a single dose of randomised spesolimab (n = 23), 83% achieved pustular clearance by Week 1 and 65% maintained this over the 12 week study period.[36]

B.2.12.2. Strengths and limitations of the clinical evidence base

The aim of treatment of GPP flares is to achieve rapid and sustained clearance of pustules and other skin features of the disease, rapidly alleviate systemic symptoms and reduce pain, while maintaining a favourable safety profile.[5] Effisayil™ 1 provides data built around these aims of treatment specific to the GPP patient, with GPP-specific clinical measures that assess key manifestations of the disease established to evaluate treatment efficacy.[51] Further to its design and first use in a proof-of-concept study, the GPPGA has been validated as a robust, reliable and reproducible assessment of disease severity, specific to GPP.[21]

The primary and key secondary endpoint assessments conducted at Week 1 directly measure outcomes that are most meaningful to patients and healthcare providers, that is, rapid resolution of pustulation and additional skin eruptions. The achievement of a GPPGA pustulation sub score of 0, indicating no visible pustules, as per the primary endpoint assessment of Effisayil™ 1 is an intentionally ambitious treatment goal and in clinical practice, a GPPGA pustulation sub score of 0 or 1 is considered a good response for patients presenting with a GPPGA pustulation sub score of 3 or 4, as per the Effisayil™ 1 trial population.[46]

While the high levels of crossover from placebo to open-label spesolimab at Day 8 prevented controlled efficacy analyses after Week 1, the Week 1 controlled trial period is of most relevance in the medical emergency setting under which GPP flares are treated. No active control arm was included in the Effisayil™ 1 trial due to the absence of licensed treatments specific to GPP flares (prior to spesolimab) and no recognised standard of care. Concomitant medication with off-label treatment that may be used in clinical practice were also prohibited due to the lack of known effect of such treatments, which have not been tested in clinical trials or for which there are limited published RWE supporting use. Placebo arm data at Day 8 are generally

consistent with BAC efficacy data from the Effisayil™ 1 historical cohort which report 3-11% of flares resolve within 1 week depending on flare severity, compared to a flare resolution rate of 6% in the placebo arm of Effisayil™ 1 when using a flare resolution definition of GPPGA pustular sub score of 0.[36, 50]

The setting in which patients presented for randomisation to the Effisayil™ 1 trial was not specified and it was not designed to evaluate hospitalisation rates and LOS. Across the Effisayil™ 1 historical cohort data and CEE GPP Expert Network data, we observe hospitalisation rates of 35–58% for typical / other flares, increasing to 74–94% for severe flares with current BAC.[24, 50] Median flare duration across these datasets was approximately 4 weeks and median hospital LOS ranged from 1-2 weeks for typical / other flares to 1-4 weeks for severe flares.[24, 50] Clinical experts are aligned in their expectation that rapid resolution of GPP flares, as provided by spesolimab, will reduce hospitalisation rates and hospital LOS.[46]

In recognition of data gaps, Boehringer Ingelheim have conducted several studies to compliment the Effisayil™ 1 trial data set. These include RWE and SEE exercises specific to England / UK that provide insight to GPP flare characteristics and flare management. It can be concluded from the totality of evidence that there is a clear unmet medical need for treatments specifically targeted for GPP that provide rapid control and fast resolution of flares with tolerable side effects which spesolimab can address.

B.2.12.3. Applicability of the clinical evidence to UK practice

The GPPGA is a novel measurement designed for the spesolimab trial programme but is a modification of a well-established measurement used in other psoriasis types (PGA) and its use is supported by the clinical community.[13] In real world practice, multiple factors alongside skin symptoms are considered when assessing flare severity and treatment response, including body surface area affected, pain, fatigue and other quality of life factors, systemic symptoms and complications.[46] GPPGA scores were shown to correlate well with PRO outcomes and systemic outcomes in the Effisayil™ 1 trial [36, 44] and clinical experts feel it is reasonable to use a GPPGA pustular subscore of 0 or 1 to represent flare resolution.[46] Pustules are also reported

to be the most bothersome symptom of a GPP flare and one of the most important to manage from the patient perspective.[23]

Due to the rare nature of disease, the Effisayil™ 1 trial population was small and there were a high proportion of patients enrolled outside of Europe (Table 9). Nonetheless, the demographics and clinical characteristics of the trial population closely reflect those reported for patients in the UK across RWE studies, and clinical experts in England have validated that the study results provide relevant evidence for the effectiveness of spesolimab.[46] Pre-planned sensitivity and subgroup analyses which included analyses based on gender and race among other characteristics showed no difference in effect of spesolimab across different patient types (Appendix E).

Spesolimab is intended as a single dose treatment for most GPP flares, and this is aligned with its use in the Effisayil™ 1 trial with 66% of patients (n = 23/35) randomised to spesolimab receiving a single 900mg IV infusion dose.[36] There was the possibility of receiving a second dose of spesolimab in the trial if flare symptoms persisted at Week 1, aligning with the license terms of spesolimab (Appendix C). While placebo was used in lieu of a recognised standard of care to provide an active control arm, placebo outcomes at Day 8 are generally consistent with RWE outcomes, supporting the use of placebo data as a proxy for BAC efficacy.

B.3. Cost-effectiveness

- Spesolimab was evaluated using a Markov state transition model for the treatment of adult patients with GPP presenting with flares:
  - Analyses were conducted over a 12-week time horizon from the perspective of the UK NHS and Personal Social Services
  - Spesolimab was compared with BAC, which included a mixture of systemic and biological treatments informed by UK clinical experts
  - Effisayil™ 1 trial data are used to model spesolimab and BAC outcomes up to Week 1, with placebo data representing BAC
  - Effisayil™ 1 trial data are used to model spesolimab after Week 1; Effisayil™ historical cohort data are used to model BAC outcomes after Week 1
  - Data gaps are filled from the wider evidence base available in the literature and from the HCRU SEE exercise
- In the base case analyses and the majority of sensitivity and scenario analyses, spesolimab dominates BAC
- Spesolimab is thus more effective and cost saving compared to BAC
- The key drivers of uncertainty in the cost-effectiveness results were the efficacy of BAC, the proportion of BAC patients who are treated as inpatients, LOS for ICU and daily inpatient costs.

B.3.1. Published cost-effectiveness studies

A de novo economic SLR was conducted on 27 December 2022, with an update on 6 May 2024 to identify cost-effectiveness studies, health-related quality of life data, costs and health care resource studies for the treatment of patients with GPP. There was no restriction by treatment. Further details are provided in Appendix G.

The economic SLR did not identify any cost-effectiveness studies for patients with GPP. There are also no prior NICE assessments specific to GPP.

Given the limited available evidence, a de novo Markov model was developed. The model concept and its justification are described in detail in Section B.3.2.2.

B.3.2. Economic analysis

The de novo model described in the following sections was developed to assess the cost-effectiveness of spesolimab compared with BAC for treating adult patients with GPP presenting with flares from the perspective of the UK National Health Service (NHS) and Personal Social Services.

B.3.2.1. Patient population

Spesolimab is indicated for the treatment of adult patients with GPP presenting with flares, as described in Section B.1.2. Spesolimab, as a treatment for GPP flares, has been evaluated in a Phase II randomised controlled trial, Effisayil™ 1[36], which is discussed in more detail in Section B.2.

The baseline clinical characteristics of patients entering the model are based on the Effisayil™ 1 trial population, as summarised in Table 14. Patient weight influences some drug costs. Age and sex do not directly influence the results of the cost-effectiveness analysis, but they allow for both calculations of the severity modifier (Section B.3.6) and a comparison of estimated utility values against age- and sex-matched general population utilities (Section B.3.4.5).

Table 14: Patient baseline characteristics based on the Effisayil™ 1 trial cohort

Characteristic	Baseline values
Average age (years)	43.00
Proportion female (%)	67.90
Average weight (kg)	72.03
Source: Bachelez et al. 2021[36]	

B.3.2.2. Model structure

A Markov state transition model was developed that used a 12-week time horizon to align with the design of Effisayil™ 1, where patients were followed up for 12 weeks.[36] A daily cycle was used to reflect the transition of patients between the intervention and comparator arms and to capture the healthcare resource and quality of life impact. A Markov structure provides a simple and transparent modelling approach that is easy to validate. The dynamics of the GPP patient pathway are well-captured within this model, and the added complexity of a patient-level simulation model

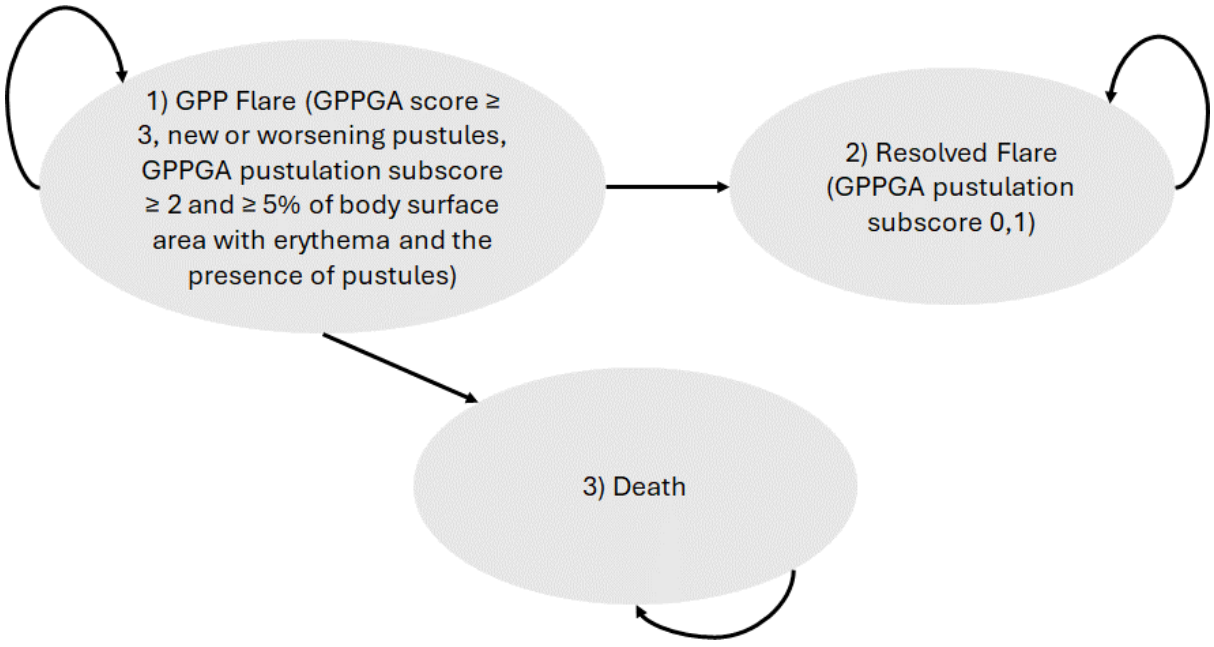
would not necessarily provide more accurate results. Particularly when past events do not significantly affect patient outcomes and when recurrent flares are assumed to not occur within the modelled time horizon.

The cost-effectiveness model comprises a three-state Markov model with health states designed to reflect resolution of GPP flares, defined by GPPGA pustulation subscores of either 0 or 1, representing skin that is clear or almost clear of pustules (see Figure 22):

1. GPP flare (defined as per the Effisayil™ 1 trial: GPPGA score ≥ 3, new or worsening pustules, GPPGA pustulation subscore ≥ 2 and ≥ 5% of body surface area with erythema and the presence of pustules).[36] Everyone begins in this health state
2. Resolved flare (GPPGA pustulation subscore 0, 1)
3. Death

A schematic of the cost-effectiveness model is provided in Figure 22, and a summary of the model health states is provided in Table 15. The flow of patients through the model is further described below.

Figure 22: Schematic of the cost-effectiveness model



Key: GPP, generalised pustular psoriasis; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment.

Table 15: Descriptions of the model health states

Health state	Description
GPP flare	All patients enter the model in the flare state, which is defined as GPPGA score ≥ 3, new or worsening pustules, GPPGA pustulation subscore ≥ 2 and ≥ 5% of body surface area with erythema and the presence of pustules
Resolved flare	GPPGA pustulation subscore 0, 1
Death	Death represents the absorbing health state in the model. Patients experiencing a flare and in a high dependency unit have a probability of dying in each cycle. This mortality probability reflects both all-cause and disease-related mortality

Key: GPP, generalised pustular psoriasis; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment.

Three mutually exclusive states represent the GPP flare health state, resolved flare health state and death. Health state membership is based on GPPGA pustulation subscores. Based on clinical advice, response was defined as a score of 0 or 1.[46] While this definition is broader than the primary outcome measure used in the pivotal Effisayil™ 1 trial (GPPGA pustulation subscore of 0),[36] it reflects the impact of, and treatment for, GPP in UK clinical practice (Section B.3.3.1). UK clinicians consulted as part of the model development for this submission validated the use of 0 or 1 to represent a resolved flare and that any patients who had been in hospital would likely be discharged at this stage.[46]

The health care resource use associated with a GPP flare is also captured as a proportion of patients are assumed to be treated as inpatients. Of these patients, a further proportion are assumed to require high dependency care, with or without mechanical ventilation (MV). Clinicians noted that the majority of patients requiring high dependency care in England would be treated in a high dependency unit (HDU) and not an ICU. As there was no evidence to distinguish between the costs and utility impact of being in ICU or HDU, these were viewed as interchangeable for the purposes of the modelling (and referred to as ICU). Further details are provided in Section B.3.5.3.

The key features of the base case economic analysis are presented in Table 16.

Table 16: Features of current economic analysis

Factor	Chosen values	Justification
Population	Patients having a GPP flare (defined as a GPPGA total score of ≥ 3, new or worsening pustules, a GPPGA pustulation subscore of ≥ 2, and ≥ 5% of body surface area with erythema and the presence of pustules)	Aligned to the eligibility criteria of the Effisayil™ 1 trial
Modelling approach	Cohort Markov state transition	Incorporates key GPP outcomes
Time horizon	12 weeks	Aligned to the follow-up period of the Effisayil™ 1 trial Period of most relevance in the medical emergency setting
Cycle length	Daily	Capture daily changes in outcome
Half-cycle correction	Not included	Use of daily cycle means that the impact of a half-cycle correction will be negligible
Treatment waning effect	Not applicable	Not relevant in the context of flare treatment
Source of efficacy and safety (AE incidence rate)	Efficacy and safety of spesolimab: Effisayil™ 1 trial [36] Efficacy and safety of comparator: Effisayil™ 1 trial and historical cohort[36, 50]	Effisayil™ 1 is the most appropriate source of evidence for the spesolimab arm and provides the best available comparative evidence for the same patient cohort for the first week. Beyond this time, the high crossover meant that an alternative source (the historical cohort) was required for longer-term BAC outcomes
Source of utilities	Health state utilities: Effisayil™ 1 AE disutilities: literature[52, 53]	Most appropriate data source, as EQ-5D was used to obtain utilities in the Effisayil™ 1 trial. Due to the short time horizon and small patient numbers, the trial did not reliably capture the impact of AEs on utility, so evidence was taken from the literature
Source of costs	Drug costs: Monthly Index of Medical Specialties and the electronic Market Information Tool Resource use: NHS reference costs 2020/21 (published 2022)[54]	The most recent costs relevant to England and Wales (accessed July 2024).

Factor	Chosen values	Justification
Source of resource use	Effisayil™ 1[36], literature[24] and HCRU SEE[25]	Best available evidence
Discount rate for costs and effects	Nominally 3.50% but not applied given the short time horizon	NICE methods guide.[55] Modelled time horizon of 12 weeks means that the impact of discounting will be negligible
Key: AE, adverse event; BAC, best available care; GPP, generalised pustular psoriasis; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; HCRU, healthcare resource use; NHS, National Health Service; SEE structured expert elicitation.		

B.3.2.3. Intervention technology and comparators

B.3.2.3.1. Spesolimab

Consistent with the NICE scope, spesolimab is modelled for the treatment of GPP flares. Thus, spesolimab is expected to be used in first-line treatment and administered by IV infusion. On Day 1, an IV infusion of spesolimab (900 mg) was administered to all patients randomised to receive spesolimab. In the trial, patients in either arm with persistent symptoms could receive an open-label dose of spesolimab (900 mg) IV infusion on Day 8.[36] In the model, an assumption is made that 80% of patients who initially received spesolimab and have persistent symptoms on Day 8 receive this second IV infusion of spesolimab. This 80% is based on 12 patients receiving a second IV infusion of spesolimab, with 15 patients who did not achieve a GPPGA pustulation subscore of 0 or 1 on Day 8, and corresponds to 34% of the overall spesolimab cohort. Patients who did not achieve a GPPGA pustulation subscore of 0 or 1 on Day 8 and who did not receive a second IV infusion of spesolimab were assumed to receive treatment with ciclosporin.

B.3.2.3.2. Best available care GPP flare treatments

In the UK, no licensed treatments are specifically approved for GPP apart from spesolimab, and no standard, evidence-based, GPP treatment options have been established. In Effisayil™ 1, the comparator arm was placebo, and baseline medications for GPP were restricted.[36] Patients received no active drug during the first week (but could be admitted to hospital for supportive care), and after Day 8 patients were given the opportunity to receive open-label spesolimab. Hence, while Effisayil™ 1 represents the only randomised trial of spesolimab, it only provides

comparative effectiveness data for Week 1. To make best use of the trial data, the first week of the economic model aligns with Effisayil™ 1, with BAC informed by placebo arm data.

Beyond the first week, the outcomes and treatments for BAC were based on the best available evidence – the Effisayil™ 1 historical cohort, which reports observed outcomes for the same patient cohort as the Effisayil™ 1 trial.[50] The primary limitations are that it is based on retrospective data collection and reports time to pustular clearance; the GPPGA was not available at the time. The assumption that pustular clearance is equivalent to a GPPGA pustulation subscore of 0-1 was validated by UK clinicians. Further details are provided in Section B.3.3.2.

While information on treatments received was collected in the Effisayil™ 1 historical cohort, this was for any prior flare treatment and hence it was not possible to derive the treatment composition for an individual flare. Hence, evidence on the treatments received for a GPP flare, and how these change over time, were based on information from the experts provided in the SEE. Further details are provided in Section B.2.9.2

B.3.3. Clinical parameters and variables

The pivotal Effisayil™ 1 trial represents the primary evidence source for the clinical effectiveness of spesolimab. As noted in Section B.3.2.3.2, in Effisayil™ 1 all patients were eligible to receive spesolimab at Day 8 if they demonstrated persistent symptoms. As crossover occurred in the placebo arm (15/18, with rescue spesolimab treatment received by two patients after Day 8), Effisayil™ 1 outcomes could only be used for spesolimab after Day 8.

Therefore, for BAC a chained evidence approach is used, whereby the short-term trial outcomes are supplemented by additional data beyond the first week from the historical Effisayil™ 1 cohort. The approaches to modelling spesolimab and BAC are discussed in turn.

B.3.3.1. Response to treatment: spesolimab

As per the schedule of assessments for Effisayil™ 1, evidence on flare response was available at Day 2, Day 3, Day 8, Week 2, Week 3, Week 4 and by Week 12.

No single definition for GPP flare resolution is available and in real world practice, multiple factors are considered when assessing treatment response.[46] Consistent with the outcomes measured in Effisayil™ 1, the model uses the GPPGA pustulation subscore to define response. Pustulation is the key characteristic of a GPP flare (see Section B.1.3.1) and one of the most important symptoms to manage from both the patient and clinician perspective.[23, 33, 46] GPPGA scores were shown to correlate well with PRO outcomes and systemic outcomes in the Effisayil™ 1 trial [36 , 44] and clinical experts feel it's reasonable to use a GPPGA pustular subscore of 0 or 1 to represent flare resolution and that flare resolution would result in discharge from hospital.[46]

It was assumed that once patients responded to treatment, they would remain flare free for the remainder of the model time horizon (12 weeks). The derivation of efficacy inputs and the assumptions applied are detailed in Table 17. As a daily cycle is used in the economic model, it was assumed that there would be no responders on Day 1, with a linear cumulative response in between weeks. It was further assumed that all patients would have responded by the end of Week 12. This assumption was motivated by the lack of evidence beyond Week 12, and validated by UK clinicians.[46]

Table 17: Derivation of efficacy for spesolimab (n = 35) based on Effisayil™ 1

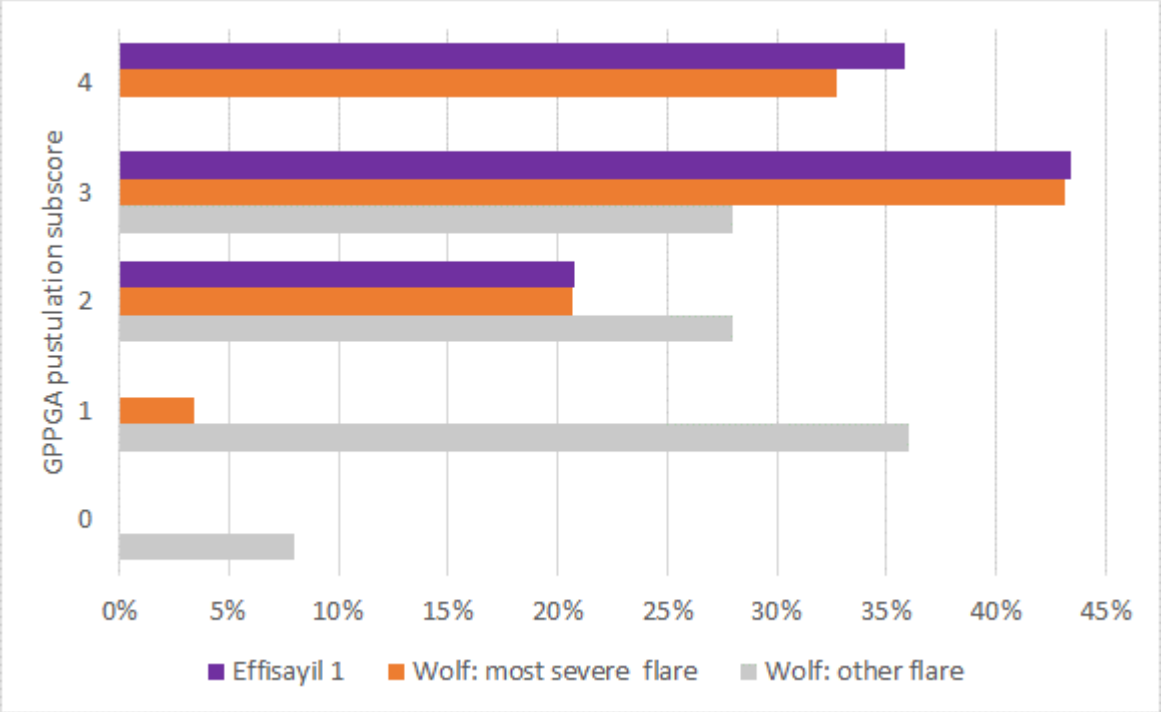
Timepoint	GPPGA subscore 0 or 1
Day 2	13 responders in total: 13/35 = 37.1%
Day 3	19 responders in total (assumed 6 new): 6/35 = 17.1%
Day 3–8	20 responders in total (assumed 1 new): 1/35 = 2.9%
Week 2	8 new responders (among those who could also receive second OL dose of spesolimab): 8/35 = 22.9%
Week 3	No new responders: 0/35 = 0.0%
Week 4	No new responders: 0/35 = 0.0%
No response by end of Week 4	Assumed all 'new responders' for each timepoint are unique patients. Hence, the number of non-responders is the remainder: 7/35 = 20%
Key: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; OL, open-label. **Source:** Bachelez et al. 2021[36]	

B.3.3.2. Response to treatment: BAC

For the first week of the model the response to BAC was modelled using the same approach as for spesolimab: using the observed Effisayil™ 1 outcomes at Days 2, 3, and 8, and also assuming no response on Day 1.[36] The observed number of responders was 0, 1, and 2 at Days 2, 3, and 8, respectively (hence there was 1 additional responder between Days 3 and 8).

After the first week, evidence on response to BAC was obtained from the Effisayil™ 1 historical cohort.[50] This approach has the benefit of using the same patient population as included in the Effisayil™ 1 trial. Details on the historical cohort are provided in Section B.2.9.1. Of the outcomes collected, time to pustular clearance was used as being the most similar to the Effisayil™ 1 trial outcome of a GPPGA pustulation subscore of 0-1. Time to pustular clearance was collected for patients' typical flare, most severe flare and longest past flare. Time to pustular clearance was categorised as < 1 week, 1–2 weeks, 3–4 weeks, 5–8 weeks, 9–12 weeks and > 12 weeks, as shown in Table 18. The time to pustular clearance is expected to depend on the severity of the flare. While information on flare severity was reported for the Effisayil™ 1 historical cohort, this was based on investigator assessment, and so it is unclear how the investigator-assigned flare categories (typical, most severe, longest) relate to the flares that were included in the Effisayil™ 1 trial. An alternative source of RWE that used investigator-assigned flare categories (last flare assigned to 'most severe' or 'other') is provided by Wolf and colleagues, details of which are provided in Section B.2.9.2.[24] In this retrospective study of patients with GPP in Central and Eastern European countries, evidence for the GPPGA pustulation subscore was also collected. A comparison of GPPGA pustulation subscores by flare type with the baseline scores observed in the Effisayil™ 1 trial is provided in Figure 23, and demonstrates that the 'most severe flare' cohort is more aligned with the trial cohort.

Figure 23: GPPGA pustulation subscores by evidence source



Key: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment.
Source: Bachelez et al. 2021[36]; Wolf et al. 2024[24]

This evidence from Wolf suggests that the 'most severe past flare' should be used from the Effisayil™ 1 historical cohort. However, there is uncertainty in the alignment of investigator-assigned flare categories in the two observational studies. Hence, a conservative approach was taken, with the proportion of most recent flares that were categorised as 'most severe' in Wolf (55%) being used to weight the 'most severe' flare in the Effisayil™ 1 historical cohort. The proportion of 'other' flares in Wolf (45%) was used for the proportion of 'typical' flares in the Effisayil™ 1 historical cohort. Resulting estimates are provided in Table 18.

Of note, clinicians indicated that they would prefer to see spesolimab used earlier to treat GPP flares, before they became too severe.[46] They suggested that this would lead to a lower proportion of 'most severe' flares, with approximately 20% most severe and 80% typical flares.[46] However, Figure 23 suggests that investigator-assigned typical flares would include a large proportion of flares with a GPPGA pustulation subscore <2; these patients were not enrolled in the Effisayil™ 1 trial, so the effectiveness of spesolimab in patients with these flares is unclear. Instead, in a

scenario use of 100% weight for the 'most severe' flare was assessed, with evidence used from Day 0, as this may provide a more realistic comparison to the spesolimab outcomes in the Effisayil™ 1 trial.

Table 18: Efficacy of BAC – RWE based on Effisayil™ 1 historical data

Timepoint	Time to pustular clearance, n (%)			
	Typical past flare (N=30)	Most severe past flare (N=28)	Longest past flare	Pooled (weights 0.45 for typical, 0.55 for most severe past flare)
< 1 week	5 (16.7%)	3 (10.7%)	0 (0.0%)	13.40%
1–2 weeks	12 (40.0%)	3 (10.7%)	1 (9.1%)	23.89%
3–4 weeks	7 (23.3%)	13 (46.4%)	0 (0.0%)	36.01%
5–8 weeks	3 (10.0%)	4 (14.3%)	4 (36.4%)	12.37%
9–12 weeks	0 (0.0%)	1 (3.6%)	3 (27.3%)	1.98%
> 12 weeks	3 (10.0%)	4 (14.3%)	3 (27.3%)	12.37%

Key: BAC, best available care; RWE, real-world evidence.
Source: Choon et al. 2023[50]

As these timepoints are not the same as those used in the Effisayil™ 1 trial, the following conservative assumptions were made:

- Responses for Weeks 1 and 2 are informed by "1–2 weeks" by assuming that half of the proportion responds in Week 1 and the other half in Week 2
- Responses for Weeks 3 and 4 are informed by "3–4 weeks" by assuming that half of the proportion responds in Week 3 and the other half in Week 4
- For consistency with the approach to modelling spesolimab efficacy, it was assumed that all flares would have resolved by Week 12, with a linear cumulative response in between Week 4 and Week 12.

The corresponding model inputs are shown in Table 19.

Table 19: Efficacy of BAC – model inputs derived from Effisayil™ 1 historical data

Timepoint	Time to pustular clearance	
	Assumption	**Result**
Day 2	No response	0.00%
Day 3	by <1 week *(3/7)	5.74%
Day 3–8	by <1 week-(D2 + D3))+(1-2 weeks/2)	19.60%
Week 2	by 1-2 weeks/2	11.94%
Week 3	by 3-4 weeks/2	18.00%
Week 4	by 3-4 weeks/2	18.00%
No response by end of Week 4	1-SUM(rest)	26.71%
Key: BAC, best available care.		

B.3.3.3. AE incidence

Within the model, there is a weekly probability of experiencing an AE while receiving treatment. Three types of AEs are included in the model: serious infection, tuberculosis reactivation, and liver injury. Serious infection and tuberculosis reactivation were identified as important AEs via a Cochrane review of biological side effects and a via review of related NICE technology appraisals for psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, and Crohn's disease.[56-64] The Cochrane review presented evidence showing that people receiving biological therapies were more likely to experience serious infections or tuberculosis than people receiving placebo treatment.[56] In addition, the only AEs of treatment considered in TA375 and TA383 (both appraisals of biologics) were serious infection and tuberculosis reactivation.[61, 62] Liver injury was included based on clinical advice. DRESS was considered for inclusion as it was reported in two patients receiving spesolimab during the 12 weeks of Effisayil™ 1.[36] However, an independent external expert assessment ruled that one of the AEs was not a DRESS, and the second was a possible DRESS. In addition, they found a lack of causal relationship between spesolimab and DRESS in Effisayil™ 1. In both patients, the symptoms occurred during or in close temporal relation to a reported GPP flare and are consistent with the potential clinical manifestations of a GPP flare.

Thus, it was not included as an AE.[35] This exclusion was also validated by clinical experts.

For the BAC arm, the weekly rates of AEs were based on the literature for rates of serious infection, and tuberculosis.[61, 62] As no evidence was identified for liver injury, this was based on the SEE exercise (Section B.2.9.3), with beta distributions fitted to the output in R using the SHELF software package.[65] For the spesolimab arm, rates of serious infection and liver injury are assumed to be equal to the probability of experiencing an event over the first week of treatment (after the first dose of spesolimab) based on Effisayil™ 1 data. Due to a lack of evidence, rates of tuberculosis were assumed to be equal to that for BAC. The incidence rates for each AE are summarised in Table 20.

Table 20: Adverse event rates

Adverse event	**Spesolimab arm**	**BAC arm**
	n (%, Effisayil™ 1 N = 35)	**Value from literature**
Serious infection	1 (2.86%)	3.5% (biologics), 2.6% (non-biologics)[61]
Tuberculosis	Assumed equal to BAC	0.2% (biologics), 0.04% (non-biologics)[62]
Liver injury	1 (2.86%)	[redacted]%[33]
Key: BAC, best available care.		

B.3.3.4. Mortality

In rare cases, a GPP flare can result in death due to systemic complications.[8] In the model, an increased mortality risk associated with a flare is applied for patients in ICU. The daily probability of death was derived from a French SNDS study, in which 2.6% of patients (15 of 569) died within four weeks after their last flare.[20] This probability of death due to a GPP flare is aligned with published European studies.[66, 67] In the study by Augey et al., two deaths were reported among 99 patients (approximately 2%),[66] and in the study by Kromer et al. two deaths were reported among 66 patients (approximately 3%).[67]

B.3.4. Measurement and valuation of health effects

As discussed in Section B.1.3.2.2, most GPP flares present as medical emergencies, with fever, fatigue, joint swelling pain and oedema often reported. As such, GPP flares can have a significant impact on patient's quality of life.

B.3.4.1. Health-related quality of life data from clinical trials

The 5-level version of the EQ-5D (EQ-5D-5L) and the DLQI data were both collected in Effisayil™ 1.[36] Both questionnaires were collected at Day 1 and on a weekly basis until Week 4 and at least in Week 8 and 12. The EQ-5D-5L was additionally collected daily during the first week.

B.3.4.2. Mapping

Individual domain scores are mapped to a single utility index score using tariffs for the UK. As per the NICE reference case, the EQ-5D-3L from EQ-5D-5L data are mapped using the mapping function developed by the NICE DSU using the Policy Research Unit in Economic Methods in Health and Social Care Intervention (EEPRU) dataset.[68]

B.3.4.3. Health-related quality of life studies

An SLR was conducted on 27 December 2022 to identify the available health-related quality of life evidence in patients with GPP, with an update on 6 May 2024. No studies were found that reported on health state utility or disutility values. Further details are provided in Appendix I.

B.3.4.4. Adverse reactions and disutilities

The AEs relating to pharmaceutical treatments considered (see Section B.2.10) for the analysis were serious infection, tuberculosis, and liver injury. The duration of each disutility was assumed to be 4 weeks (28 days). The disutility associated with a serious infection (0.156) was obtained from NICE TA375 (which considered biologics for rheumatoid arthritis).[53] In the absence of similar values for tuberculosis, the same disutility (0.156) was assumed. For liver injury, the value of 0.0956 for liver disorders was sourced from a UK study by Sullivan et al.[52] For all AEs, the standard error was assumed to be 5% of the mean. Patients in the BAC arm of the model did not

experience any AEs in Week 1 as they did not receive any active treatments until Week 2.

B.3.4.5. Health-related quality of life data used in the cost-effectiveness analysis

A summary of the base case utility inputs is provided in Table 21. The values for a GPP flare health state were derived using the utility at baseline, regardless of treatment. This utility is applied for patients experiencing a GPP flare utility until they respond to treatment. It represents a reduced quality of life due to the impact of symptoms (pustule formation, open lesions, high-grade fever, myalgia, joint pain and erythema symptoms) and the need for hospitalisation. The utility values for patients who recovered from a GPP flare are based on a repeated-measures mixed effects model, accounting for multiple measures per patient. Disutilities due to treatment-related AEs are also included in the analysis base case. Consistent with previous economic evaluations, it was assumed that patients in ICU had a zero utility.[69] This may be a conservative assumption, as another evaluation used a utility of -0.402 for patients in ICU.[70]

Table 21: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Active flare	[redacted]	[redacted]	B.3.4.1	Effisayil™ 1 trial data
Resolved flare	[redacted]	[redacted]	B.3.4.1	Effisayil™ 1 trial data
Hospitalisation ICU	0 (0)	(0, 0)	-	Assumption
Key: GW, general ward; ICU, intensive care unit; MV, mechanical ventilation.				

As a comparison, the general population utility values for a 43 year old (the average age of the Effisayil™ 1 trial participants[36]) are 0.85 and 0.87 for females and males, respectively.[71] Using the proportion of females from Effisayil™ 1 (Table 14) provides a weighted average general population utility value of 0.85, [redacted] the estimated utility for a resolved flare of [redacted].

B.3.5. Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted on 27 December 2022 to identify cost and resource use data associated with patients with GPP from the published literature, with an update on 6 May 2024 (Appendix H). The focus of the SLR was on HCRU amongst patients with GPP that was both applicable to the UK and also differentiated HCRU for GPP patients by whether or not they were experiencing a flare. As no UK-specific studies were identified, it was assumed that evidence for European studies would also be applicable to the UK. Two relevant studies were identified. Both were retrospective studies; one used the SNDS to identify HCRU for patients who were hospitalised with GPP in France.[20] The second identified rates of hospitalisation along with LOS for patients with a GPP flare in Central and Eastern European countries.[24] Evidence on the HCRU from these studies is provided in Table 7. Evidence used in the economic modelling is described further in Section B.3.5.3.

Two additional European studies were identified as potentially relevant, but not considered further due to limitations in the reported outcomes. In a retrospective observational study conducted in Portugal, 68% of the 59 patients with GPP were hospitalised due to GPP symptoms.[72] However, not all patients experienced a flare during the study period; hence the actual hospitalisation rate amongst the subset of patients with a GPP flare is unknown. The severity of flares is also unknown. A retrospective study of GPP patients in Italy experiencing a flare provided rates of hospitalisation, but only when patients also had a comorbidity (infection or hepatitis).[22] Therefore the overall hospitalisation rate is unknown.

Costs were obtained from published literature, 2021/2022 NHS reference costs,[54] the electronic Monthly Index of Medical Specialities (MIMS),[73] and the drugs and pharmaceutical electronic market information tool (eMIT).[74] The base case includes eMIT data, where available. In line with NICE requirements, the model only considers direct medical costs. Cost and health care resource use inputs comprised drug acquisition, administration costs, resource use costs, and costs associated with the management of AEs.

Specific details for all treatments are provided in Appendix K: Price details of treatments included in the submission.

B.3.5.1. Intervention and comparators' costs and resource use

The model includes separate costs for drug acquisition and administration. A summary of the route of administration, pack cost, pack size, and strength for each treatment is provided in Table 22. As noted in Section B.3.2.3, in the base case, the comparator treatments after the first week have been selected in alignment with the results of an SEE exercise conducted to understand the treatment patterns and disease complications observed by UK experts in practice.

Table 22: Summary of pack cost, pack size, and strength

Treatment (route of administration)	Pack cost (£)*	Pack size	Strength (mg)	Source[75]
Spesolimab (IV infusion, simple)	15,000 (list) [redacted] (with PAS)	2 vials	900	BNF, generalised pustular psoriasis
Acitretin (oral)	17.92	60 capsules	1500	BNF, severe extensive psoriasis
Ciclosporin (oral)	41.59	30 capsules	3000	BNF, severe psoriasis
Clobetasol propionate (topical)	7.51	1 tub (100 g)	50	BNF, moderate-to-severe plaque psoriasis
Guselkumab (SC)	2,250.00	1 vial	100	BNF, plaque psoriasis
Infliximab (IV, complex)	755.32	2 vial	240	BNF, severe psoriasis
Methotrexate (SC)	14.55	1 vial	30	BNF, plaque psoriasis
Secukinumab (SC)	1218.78	2 vials	300	BNF, plaque psoriasis
Ustekinumab (SC)	2147.00	1 vial	45	BNF, short-term treatment only of severe resistant inflammatory skin disorders

Key: BNF, British National Formulary; IV, intravenous; PAS, patient access scheme; SC, subcutaneous.
Notes: * The lowest cost per mg unit was chosen if multiple strengths were available.

Drug acquisition costs are estimated for each intervention/comparator by multiplying the drug consumption (dose per administration and number of administrations) by the cost per mg of each intervention/comparator. For all treatments, the minimum cost per mg is used. With the exception of spesolimab, there are no recommended

treatment dosing regimens for GPP. For spesolimab, the dosing schedule followed the licensed indication, with evidence from Effisayil™ 1 informing the proportion of eligible patients who receive a second dose (80%; 12 out of 15 patients who had not responded by Day 8).[36] It was assumed that if patients were eligible for a second dose of spesolimab but did not receive it, this was because of previous adverse events. Hence these patients instead received ciclosporin on Day 8.

For comparator treatments, the dosing schedule was sourced from the British National Formulary (BNF) for the BAC comparators, assuming the same dosing as severe psoriasis or plaque psoriasis, where available.[75] Escalated doses were used if available to represent GPP treatment. The dose for ciclosporin and for infliximab was obtained using the average weight (72.03 kg) of patients from Effisayil™ 1.[36] A summary of treatment dosing schedules is provided in Table 23. The total weekly acquisition costs for spesolimab and the drugs that comprise BAC are presented in Table 25.

Table 23: Treatment dosing schedules

Treatment	Dosing details	Source
Spesolimab	Initial 900 mg IV infusion at Day 1. At Day 8, an additional 900 mg IV infusion for patients who have not responded (i.e. those with a GPPGA pustulation subscore ≥2)	Generalised pustular psoriasis
Acitretin	Initially 25–30 mg daily for 2–4 weeks, then adjusted according to response to 25–50 mg daily, increased to up to 75 mg daily, dose only increased to 75 mg daily for short periods in psoriasis	Severe extensive psoriasis
Ciclosporin	Initially 1.25 mg/kg twice daily (max. per dose 2.5 mg/kg twice daily), increased gradually to maximum if no improvement within 1 month, initial dose of 2.5 mg/kg twice daily justified if condition requires rapid improvement; discontinue if inadequate response after 3 months at the optimum dose; max. duration of treatment usually 1 year unless other treatments cannot be used. 5 mg/kg twice daily	Severe psoriasis
Clobetasol propionate	1–2 times a day, maximum 50 g of 0.05% preparation per week	Short-term treatment only of severe resistant inflammatory skin disorders

Treatment	Dosing details	Source
Guselkumab	Initially 100 mg, then 100 mg after 4 weeks, then maintenance 100 mg every 8 weeks, consider discontinuation of treatment if no response after 16 weeks	Moderate-to-severe plaque psoriasis
Infliximab	Initially 5 mg/kg, then 5 mg/kg, to be taken at Week 2 and 6 after initial dose, then 5 mg/kg every 8 weeks, discontinue if no response after 14 weeks of initial infusion (after 4 doses)	Plaque psoriasis
Methotrexate	Initially 2.5–10 mg once weekly, then increased in steps of 2.5–5 mg, adjusted according to response, dose to be adjusted at intervals of at least 1 week; usual dose 7.5–15 mg once weekly, stop treatment if inadequate response after 3 months at the optimum dose; maximum 30 mg per week	Severe psoriasis
Secukinumab	300 mg every week for five doses, then maintenance 300 mg every month, review treatment if no response within 16 weeks of initial dose	Plaque psoriasis
Ustekinumab	Initially 45 mg, then 45 mg after 4 weeks, then 45 mg every 12 weeks, consider discontinuation if no response within 28 weeks	Plaque psoriasis

Key: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; IV, intravenous; SC, subcutaneous; SmPC, summary of product characteristics.
Source: BNF indication[75]; Spevigo SmPC[3]

Table 24: Composition of comparator treatments

Treatment*	Week 1 (no treatment)	Weeks 2–4	Weeks 5+
TNF inhibitors (infliximab**)	0%	[redacted]	[redacted]
IL-23 inhibitors (guselkumab^)	0%	[redacted]	[redacted]
IL-17 inhibitors (secukinumab^)	0%	[redacted]	[redacted]
Ustekinumab	0%	[redacted]	[redacted]

Key: IL, interleukin; TNF, tumour necrosis factor.

Notes: *The use of systemic and topical treatments was considered in a scenario. ** Experts highlighted that infliximab would be the preferred anti-TNF therapy. ^Representative treatment in class

Source: Data on file.[33]

Table 25: Weekly acquisition costs – list price

Treatment	Weekly cost	Source
Spesolimab	£15,000.00	BNF[75]
Immunosuppressant (ciclosporin)	£35.76	eMIT database last updated 22 March 2023. [74]
TNF inhibitors (infliximab)	£1,159.73	
Methotrexate	£14.55	

Treatment	Weekly cost	Source
Retinoid (acitretin)	£6.27	
IL-23 inhibitors (guselkumab)	£2,250.00	
IL-17 inhibitors (secukinumab)	£1,218.78	
Ustekinumab	£2,147.00	
Topical steroids (clobetasol propionate)	£3.76	
Key: BNF, British National Formulary; eMIT, electronic market information tool; IL, interleukin; TNF, tumour necrosis factor.		

Administration costs were dependent on mode of administration (IV, SC, oral or topical) and the number of administrations required with each treatment. Orally and topically administered drugs (including clobetasol propionate) were assumed to have no administration cost. The cost of SC administration is £3.61, obtained from TA375, inflated to 2020/2021 using the Personal Social Services Research Unit (PSSRU) inflation index.[61, 76] The cost of IV infusion administration is split by complexity of administration into simple (£361.53) and complex (£482.91); IV infusion administration costs were obtained from NHS reference costs.[54] A summary of administration unit costs is provided in Table 26.

Table 26: Summary of administration unit costs

Administration	Cost	Source
Oral and topical	£0.00	Assumption
SC	£3.61	Average administration cost per SC injection according to the assessment group for TA375 (£3.05, 2011/2012), inflated to 2020/2021 using the PSSRU inflation index[61, 76]
IV, simple	£361.53	National schedule of NHS costs 2020/2021. Total HRGs, SB12Z (deliver simple parenteral chemotherapy at first attendance)[54]
IV, complex	£482.91	National schedule of NHS costs 2020/2021. Total HRGs, average of SB13Z-SB14Z (deliver more complex parenteral chemotherapy at first attendance and deliver complex chemotherapy, including prolonged infusion treatment, at first attendance)[54]
Key: HRG, healthcare resource group; IV, intravenous; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; SC, subcutaneous.		

B.3.5.2. Structured expert elicitation – HCRU for a GPP flare

Boehringer Ingelheim carried out an SEE exercise in 2024 to identify the HCRU for GPP patients presenting with a flare and receiving BAC.[25]

[redacted] English dermatologists, with experience treating GPP patients at specialist centres participated in the SEE exercise. Full details of the methodology adopted are provided in the report included in the submission reference pack, but in summary it comprised of two rounds of elicitation. In each round experts individually completed the exercise. In the first round there was no insight on other experts' responses. In the second round experts could view the pooled experts' responses from the first round.[25]

Resulting estimates that were of relevance to the economic modelling are provided in Table 27 (this includes values that were used to validate outcomes and assumptions). Further details, including graphs of individual and pooled responses are provided in the report.[25] In general there was consistency in responses across the English participants. For use in the model, mean values were used.

Table 27: Selected elicited estimates of HCRU for a flare

Description	Fitted distribution	Pooled distribution	
		Parameters	Mean
What is the number of outpatient visits for flare-free patients per year?	Log-normal	[redacted]	[redacted]
What is the number of outpatient visits for moderate-severe patients per week?	Log-normal	[redacted]	[redacted]
What is the proportion of moderate-severe patients treated as inpatients?	Beta	[redacted]	[redacted]
What is the proportion of patients treated in the ICU with mechanical ventilation?	Beta	[redacted]	[redacted]
What is the proportion of patients treated in the ICU without mechanical ventilation?	Beta	[redacted]	[redacted]
What is the expected number of nights for patients treated in the ICU with MV?	Log normal	[redacted]	[redacted]
What is the expected number of nights for patients treated in the ICU without MV?	Log normal	[redacted]	[redacted]
What is the expected number of nights for patients treated in the General Ward, post-ICU care?	Log normal	[redacted]	[redacted]
Key: HCRU, health care resource use; ICU, intensive care unit; MV, mechanical ventilation.			

B.3.5.3. Health state unit costs and resource use

The model includes disease management costs comprising outpatient and inpatient hospital visits, emergency room visits, and ICU. Clinical advice was that patients requiring critical care would be more likely to be admitted to a HDU than an ICU. As NHS reference costs do not distinguish between critical care settings, this distinction does not impact on the costs used. A summary of resource use unit costs is provided in Table 28.

Table 28: Summary of resource use unit costs

Resource item	Unit cost (£)	Source
Outpatient appointment	174.89	National Schedule of NHS Costs 2021–2022. WF01A: Non-Admitted Face-to-Face Attendance, Follow-up. Dermatology (Service Code 330). Outpatient procedure. Inflated to current price year[54]
Daily care of inpatient care	857.00	Unit Costs of Health and Social Care 2023[76]
Daily cost of ICU care	1,704.84	National schedule of NHS costs 2021/2022. Adult Critical Care, 0-1 Organ Supported, weighted average of XC06Z and XC07Z for elective and non-elective patients. Inflated to current price year [54]
Daily cost of MV care	2,685.24	National schedule of NHS costs 2021/2022. Adult Critical Care, 2+ Organ Supported, weighted average of XC01Z to XC05Z for elective and non-elective patients. Inflated to current price year[54]
Terminal care	5,877.88	Georghiou and Bardsley. 2014. https://www.nuffieldtrust.org.uk/files/2017-01/end-of-life-care-web-final.pdf Per-patient estimated costs in the last three months of life. Secondary (acute) hospital care (n = 1,286,005). Cost of all hospital contacts for all patients. (Table 4). Inflated to current price year[77]
Cost of day care	1,110.00	Unit Costs of Health and Social Care 2023[76]
Key: ICU, intensive care unit; MV, mechanical ventilation; NES, non-elective short stay; NHS, National Health Service.		

In clinical practice, resource use is expected to differ between the spesolimab and the BAC arms, given the rapid response of spesolimab. During a flare it is assumed that a proportion of patients will be treated as inpatients, with the remainder treated as outpatients. Of the inpatients, a proportion will be treated in an ICU, with a further

proportion of these patients also requiring MV. An overview of the relevant European sources for HCRU is provided in Table 7 (with further details on the SEE provided in Section B.3.5.2). These sources were considered preferentially to the evidence from the Effisayil™ 1 historical cohort, since the location of treatment centres was predominantly non-European.

Some of the studies defined a GPP flare based on time spent in hospital, and so by definition inpatient rates for GPP flares were 100% for these sources. The only identified European study that collected evidence on rates of hospitalisation for GPP flares was that by Wolf and colleagues. This study collected evidence based on two types of flare: 'most severe' and 'other'. A comparison of GPPGA pustulation subscores by flare type with the baseline scores observed in the Effisayil™ 1 trial was previously shown in Figure 23, and demonstrated that the 'most severe flare' cohort is more aligned with the trial cohort. Use of this cohort suggests an inpatient rate of 93%, which is [redacted] than the [redacted] elicited for moderate/severe flares from the SEE exercise. Hence for the base case, an inpatient rate of 78% was used, corresponding to the overall inpatient rate for a patient's last flare in the study by Wolf and colleagues. The alternative values of 93% and [redacted] were explored in scenario analyses.

Clinical advice was that due to its rapid onset of action, use of spesolimab would lead to a significant reduction in inpatient admissions. There were no data available to inform the impact of spesolimab on reducing inpatient admissions. Instead, the impact of spesolimab on flare response (defined as GPPGA pustulation subscore of 0-1) in the Effisayil™ 1 trial was considered as a proxy measure.[36] At Day 2 – the earliest time-point with outcomes – the proportion of patients with a flare was 94.4% and 45.7% for the placebo and spesolimab arms, respectively, a relative reduction of 48.4%. Hence, a 50% reduction in inpatient rates for spesolimab was assumed, with the impact of assuming alternative reductions assessed via scenario analyses. A consequence of this approach is that the effect of spesolimab on the GPPGA pustulation subscore is used twice; to inform both the reduction in inpatient rates and the time to flare resolution. This approach was used due to a lack of short-term evidence on both PRO and systemic outcomes (which are likely to influence the

decision to admit) along with the known correlation between GPPGA scores and PRO outcomes and systemic outcomes in the Effisayil™ 1 trial.[36, 44]

Within the model, it is assumed that inpatients will be discharged once their pustules have resolved, (which is based on a GPPGA pustulation subscore of 0-1 in the model). While clinical advice was supportive of this assumption, it was noted that a patient needs to be systemically stable too. Systemic markers are not included in the economic model; however, PRO data in Effisayil™ 1 were correlated with the GPPGA pustulation subscore (see Section B.2.6.3.1.2).[44]

The proportion of BAC inpatients requiring ICU (with or without MV) was [redacted]% and obtained from the HCRU SEE exercise.[25] Two alternative values were available from the literature. In the French SNDS study (see Section B.1.3.2) 25.0% (142 out of 569) of patients experiencing a GPP flare were to admitted to an ICU or resuscitation unit. In the study by Wolf and colleagues, 11.5% (three of 26 patients) experiencing a GPP flare required ICU care. This is less than half that reported in SNDS study; however, it is based on much smaller numbers, so is more uncertain. As these alternative evidence sources provide proportions higher and lower than the base case, this uncertainty was explored via deterministic sensitivity analyses. It was further assumed that, due to its rapid onset of action, patients receiving spesolimab would not require treatment in the ICU.

Clinical advice was that, while patients would likely remain in hospital until their flare has resolved, a stay in an ICU would only last until the complications of the flare stabilises. From the HCRU SEE exercise, mean length of stay in ICU was estimated to be [redacted] days without MV and [redacted] days with MV. Mean length of stay is not explicitly modelled, instead a maximum length of stay was included, which was derived from the elicited mean length of stay and response rates over time for BAC. The purpose of this was to ensure that the modelled mean length of stay for BAC was similar to the elicited values. In a scenario analysis the maximum length of stay restriction was removed.

Based on the HCRU SEE exercise, it was assumed that all patients with flares who were not treated as inpatients would be treated as outpatients, with an average (mean) of [redacted] visits per week. For patients with a resolved flare the elicited average

(mean) of [redacted] outpatient appointments per year was used.[25] No other evidence was identified to inform how the number of outpatient appointments varies depending on a GPP patient's flare status.

A summary of healthcare resource use for a GPP flare is provided in Table 29.

Table 29: Modelled healthcare resource use

Resource use during a flare	Value	Source of resource use
Proportion of patients treated as inpatients (spesolimab)	38.8%	Assumed 50% reduction in inpatient rates.
Proportion of patients treated as inpatients (BAC)	77.6%	Wolf et al.[24]
Proportion of patients treated as outpatients (spesolimab)	61.2%	Assumption that all patients that did not have a hospitalisation would be treated as outpatients.
Proportion of patients treated as outpatients (BAC)	22.4%	Assumption that all patients that did not have a hospitalisation would be treated as outpatients.
Average weekly number of outpatient appointments: active flare	[redacted]	HCRU SEE[25] (mean value)
Average annual number of outpatient appointments: resolved flare	[redacted]	HCRU SEE[25] (mean value)
Proportion of inpatients treated in ICU: spesolimab	0%	Assumption based on the fact that rapid resolution of flares as observed with spesolimab would alleviate the risk of the need for ICU care
Proportion of inpatients treated in ICU: BAC	[redacted]	HCRU SEE[25] (mean value)
Proportion of patients in ICU requiring mechanical ventilation	[redacted]	HCRU SEE[25] (mean value)
Key: BAC, best available care; HCRU, healthcare resource use; ICU, intensive care unit.		

B.3.5.4. Adverse reaction unit costs and resource use

The cost-effectiveness analysis included costs of AEs in the form of serious infection, tuberculosis reactivation and liver injury. A summary of the unit costs for the treatment of AEs is provided in Table 30.

Table 30. Summary of the unit costs for the treatment of AEs

AE	Unit cost	Source
Serious infection	£2,895.14	Unable to mimic HRG codes outlined in TA375 (WA03Y, DZ23C, LA04F, PA16B, DZ22X, DZ21K). National schedule of NHS costs 2020/2021. Total HRGs, weighted average of DZ11K-DZ11V and WJ06A-WJ06J (sepsis and pneumonia)[54]
Tuberculosis reactivation	£4,733.08	Unable to mimic HRG codes used in TA383 (codes DZ14C-DZ14E). National schedule of NHS costs 2020/2021. Total HRGs, weighted average of DZ14F-DZ14J (pulmonary, pleural or other tuberculosis)[54]
Liver injury	£2,322.55	National schedule of NHS costs 2020/2021. Total HRGs, weighted average of GC01E-GC01F (liver failure disorders without interventions)[54]
Key: AE, adverse event; HRG, Healthcare Resource Group; NHS, National Health Service.		

B.3.5.5. Miscellaneous unit costs and resource use

An end-of-life (terminal care) cost of £5,877.88 was implemented as a one-off cost upon death. This cost was adjusted for inflation from the original cost of £4,580 reported in Georghiou et al. 2014.[77]

B.3.6. Severity

The QALY shortfall calculator was used to generate estimates of expected total QALYs for the general population.[71] This used the patient characteristics of the Effisayil™ 1 trial as reported in Table 14 (average age 43, 68% female) and gives a remaining discounted QALYs of 17.91.

To be applicable for a severity modifier, GPP flares should be associated with an absolute QALY shortfall of at least 12 or a proportional QALY shortfall of at least 0.85 (equivalent to an absolute QALY loss of 15.22).

From the economic model, patients receiving BAC have a mean flare duration of 3.2 weeks, with UK evidence suggesting that patients with GPP experience between 0.9 to 1.79 flares per year (Section B.1.3.2.2.1). Using the higher estimate of 1.79 flares a year then even if a flare were associated with a utility of 0, the maximum undiscounted QALY loss in a year would be 0.09. To be eligible for a severity modifier, a patient would have to experience 1.79 flares per year for over 100 years

(the true number will be higher as flares are associated with an average utility greater than zero and these calculations do not account for discounting). Hence, a severity modifier is not applicable for this appraisal.

B.3.7. Uncertainty

The rarity of GPP and lack of recommended treatments, with no licensed treatments beyond spesolimab in the UK, has had an impact on the ability to generate evidence to inform the cost-effectiveness analysis. Effisayil™ 1, the pivotal trial for spesolimab, demonstrated that it has a rapid onset of action, leading to resolution of flares and addressing an important unmet need. However, the comparator arm did not include active treatments, and it was not possible to perform any indirect comparisons to inform the relative effectiveness of spesolimab. Given the inherent uncertainties in evidence generation for rare diseases, best practice was followed to identify additional supportive evidence in the literature, including RWE (primarily from the Effisayil™ 1 historical cohort). Nevertheless, the lack of recommended treatments for GPP along with the lack of a direct randomised comparison between spesolimab and any active treatments leads to uncertainty in the relative effectiveness, and hence cost-effectiveness, of spesolimab.

As well as the deterministic and probabilistic sensitivity analysis, where possible, the uncertainty in the economic inputs has been assessed via scenario analyses. As GPP is a rare disease, then consistent with the current NICE guidance, “the committee may be able to make recommendations accepting a higher degree of uncertainty” (Section 6.2.34).[55]. Based on a willingness to pay threshold of £30,000 per QALY, spesolimab remained cost-effective in all scenarios when incorporating the confidential discount.

B.3.8. Managed access proposal

Not applicable

B.3.9. Summary of base case analysis inputs and assumptions

B.3.9.1. Summary of base case analysis inputs

An overview of the key inputs included in the base case analysis are summarised in Table 31 below; full details are provided in Appendix O.

Table 31: Summary of variables applied in the economic model

Variable	Value	Standard error	Measurement of uncertainty and distribution	Reference to section in submission
Model parameters				
Time horizon (days)	85	Fixed	No sampling	B.3.2
Discount rate (costs and effects)	0.00%	Fixed	No sampling	B.3.2
Efficacy				
Intervention: % people whose GPP flare responds at Day 2	37.1%	1.9%	Beta	B.3.3
Comparator: % people whose GPP flare responds at Day 2	0.0%	0.0%	Beta	B.3.3
Intervention: % people whose GPP flare responds at Day 3	17.1%	0.9%	Beta	B.3.3
Comparator: % people whose GPP flare responds at Day 3	5.6%	0.3%	Beta	B.3.3
Intervention: % people whose GPP flare responds at Day 8	8.6%	0.4%	Beta	B.3.3
Comparator: % people whose GPP flare responds at Day 8	11.1%	0.6%	Beta	B.3.3
Intervention: % people whose GPP flare responds by Week 2	22.9%	1.1%	Beta	B.3.3
Comparator: % people whose GPP flare responds by Week 2	34.1%	1.7%	Beta	B.3.3

Variable	Value	Standard error	Measurement of uncertainty and distribution	Reference to section in submission
Intervention: % people whose GPP flare responds by Week 3	0.0%	0.0%	Beta	B.3.3
Comparator: % people whose GPP flare responds by Week 3	14.0%	0.7%	Beta	B.3.3
Intervention: % people whose GPP flare responds by Week 4	0.0%	0.0%	Beta	B.3.3
Comparator: % people whose GPP flare responds by Week 4	14.0%	0.7%	Beta	B.3.3
Intervention: % people whose GPP flare responds by Week 12	14.3%	0.7%	Beta	B.3.3
Comparator: % people whose GPP flare responds by Week 12	21.3%	1.1%	Beta	B.3.3
Utilities				
Active flare	[redacted]	0.0148	Beta	B.3.4
Resolved flare	[redacted]	0.0418	Beta	B.3.4
Drug costs (£)				
Cost of spesolimab (IV infusion, simple)	15,000	Fixed	No sampling	B.3.5
Cost of acitretin	17.92	Fixed	No sampling	B.3.5
Cost of ciclosporin	41.59	Fixed	No sampling	B.3.5
Cost of clobetasol propionate	7.51	Fixed	No sampling	B.3.5
Cost of guselkumab	2,250.00	Fixed	No sampling	B.3.5
Cost of infliximab	755.32	Fixed	No sampling	B.3.5
Cost of methotrexate	14.55	Fixed	No sampling	B.3.5
Cost of secukinumab	1218.78	Fixed	No sampling	B.3.5
Cost of ustekinumab	2147.00	Fixed	No sampling	B.3.5
Resource use unit costs (£)				
Outpatient appointment	174.89	16.34	Gamma	B.3.5
Daily care of inpatient care	857.00	85.70	Gamma	B.3.5
Daily cost of ICU care	1,704.84	159.29	Gamma	B.3.5
Daily cost of MV care	2,685.24	250.89	Gamma	B.3.5

Variable	Value	Standard error	Measurement of uncertainty and distribution	Reference to section in submission
Terminal care	5,877.88	4.33	Gamma	B.3.5
Cost of day care	1,110.00	111.10	Gamma	B.3.5
Resource use				
Outpatient appointments per week, GPP flare	[redacted]	0.52	Log-normal	B.3.5
Outpatient appointments per year, resolved flare	[redacted]	0.56	Log-normal	B.3.5
% patients treated as inpatients, GPP flare, BAC	77%	3.9%	Beta	B.3.5
% reduction in patients treated as inpatients, GPP flare, spesolimab	50%	2.5%	Beta	B.3.5
% of inpatients treated in ICU: spesolimab	0%	Fixed	No sampling	B.3.5
% of inpatients treated in ICU: BAC	[redacted]	1.1%	Beta	B.3.5
% of ICU patients requiring MV	[redacted]	1.5%	Beta	B.3.5
Key: AE, adverse event; BAC, best available care; GPP, generalised pustular psoriasis; ICU, intensive care unit; IV, intravenous; MV, mechanical ventilation; SC, subcutaneous.				

B.3.9.2. Assumptions

The assumptions for the inputs included in the base case analysis are summarised in Table 32.

Table 32: Key modelling assumptions

Assumption	Justification
Model structure	
Relapse of a GPP flare is not modelled	Patients who respond to treatment are assumed to remain responders for the remainder of the modelled time horizon. Evidence on flare frequency (see Section B.1.3.2.2.1) shows that patients are unlikely to have more than two flares per year

Assumption	Justification
Severity of a GPP flare (based on GPPGA pustulation subscore) was not modelled	This was a simplifying assumption designed to increase the transparency and interpretability of the model
No half-cycle correction	Use of a daily time cycle removes the need for a half-cycle correction
No discounting of outcomes	The short (12-week) time horizon means that the impact of discounting would be negligible
Model inputs	
SEE is an appropriate proxy for the BAC composition	While no treatments are licensed for GPP flare treatment apart from spesolimab, BAC would usually include active treatments in practice, as validated by clinical experts. Information regarding the treatments received was obtained via an SEE exercise
Time spent in hospital is informed by GPPGA pustulation subscore	Clinicians consulted as part of the model development for this submission validated the use of 0 or 1 to represent a resolved flare and that any patients who had been in hospital would likely be discharged at this stage
Spesolimab leads a reduction in inpatient rates	Clinical advice was that due to its rapid onset of action, use of spesolimab would lead to a significant reduction in inpatient admissions
Patients receiving spesolimab will not require ICU admission	Assumption due to spesolimab's rapid onset of action
Maximum flare duration is 12 weeks.	Patients are assumed to respond by Week 12. This was a pragmatic assumption validated by clinicians. This is a conservative assumption as evidence from the Effisayil™ 1 historical cohort shows that for BAC 11% of typical flares and 29% of 'longest flares' had not resolved by 12 weeks[50]
Rates of tuberculosis are the same for spesolimab and BAC	This is an assumption in the absence of evidence

Key: BAC, best available care; GPP, generalised pustular psoriasis; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; ICU; intensive care unit.

B.3.10. Base case results

B.3.10.1. Base case incremental cost-effectiveness analysis results

The full incremental cost-effectiveness results when using list prices and with PAS applied for spesolimab are presented in Table 33 and Table 34, respectively.

Spesolimab dominates BAC, that is, it is more effective and cost saving with a positive incremental net health benefit (INHB) at standard willingness-to-pay

thresholds, implying that overall population health would be increased with the introduction of spesolimab.

Table 33: Base case results at list prices

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	INHB at £20,000 / QALY	INHB at £30,000 / QALY
BAC	[redacted]	[redacted]					
Spesolimab	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	[redacted]	[redacted]

Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life years gained; QALYs, quality-adjusted life years.

Table 34: Base case results incorporating confidential spesolimab discount

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	INHB at £20,000 / QALY	INHB at £30,000 / QALY
BAC	[redacted]	[redacted]					
Spesolimab	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	[redacted]	[redacted]

Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.11. Exploring uncertainty

B.3.11.1. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was performed to account for joint uncertainties in the key model inputs, in which multiple input parameters were varied simultaneously by sampling their values from uncertainty distributions for 1,000 iterations. Convergence plots indicated that 1,000 simulations of the model was more than sufficient to ensure that results to converged to a sufficient degree of accuracy.

Whenever available, the standard error of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on parameter variability, a standard error of 5% of the mean was assumed.

The ICER scatterplots for the base case analysis at list price and with confidential discount, arising from 1,000 simulations of the model with all parameters sampled, are presented in Figure 24 and Figure 25, respectively. The cost-effectiveness acceptability curve at list price and with confidential discount are presented in Figure 26 and Figure 27, respectively.

Figure 24: Cost-effectiveness plane, spesolimab vs BAC – list price

Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 25: Cost-effectiveness plane, spesolimab vs BAC – PAS price

Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 26: Cost-effectiveness acceptability curve – list price

Key: WTP, willingness-to-pay.

Figure 27: Cost-effectiveness acceptability curve – PAS price

Key: PAS, patient access scheme; PAS, patient access scheme; WTP, willingness-to-pay.

Based on this analysis, the probability that spesolimab is cost-effective is estimated to be [redacted]% at list price and [redacted]% with the confidential discount, both for a WTP of £30,000 per QALY.

The probabilistic base case results at list price and with PAS applied for spesolimab are presented in Table 35 and Table 36, respectively.

Table 35: Probabilistic base case results at list prices

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	INHB at £20,000 / QALY	INHB at £30,000 / QALY
BAC	[redacted]	[redacted]					
Spesolimab	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	[redacted]	[redacted]

Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life years gained; QALYs, quality-adjusted life years.

Table 36: Probabilistic case results incorporating confidential discount

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	INHB at £20,000 / QALY	INHB at £30,000 / QALY
BAC	[redacted]	[redacted]					
Spesolimab	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	[redacted]	[redacted]

Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.11.2. Deterministic sensitivity analysis

The results of the OWSA are presented in the form of a tornado diagram of the 10 parameters with the most influence on the ICER, using both the list price and the confidential discount in Figure 28 and Figure 29, respectively. For both analyses, the cost of spesolimab, the proportion of BAC patients who are treated as inpatients, and the daily cost of an inpatient stay are the three influential parameters.

Figure 28: Deterministic sensitivity analysis tornado diagram – list price

Key: BAC, best available care; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; ICER, incremental cost-effectiveness ratio; IV, intravenous; W, week.

Figure 29: Deterministic sensitivity analysis tornado diagram – PAS price

Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; IV, intravenous; PAS, patient access scheme; W, week.

B.3.11.3. Scenario analysis

Table 37 describes the scenarios tested and presents the impact on the ICER with spesolimab at list price. The most impactful scenarios across all comparisons are the efficacy of BAC, LOS for ICU and inpatient costs.

Table 37: Results of scenario analyses at list price

	Scenario	Justification	ICER versus BAC
	Base case		Spesolimab dominates
1	BAC efficacy: RWE from Day 0	Alternative approach to estimating BAC efficacy	[redacted]
2	LoS for ICU with MV not capped	Reflect uncertainty in how long patients stay in ICU	Spesolimab dominates
3	Inpatient costs: non-elective short stay	Alternative approach to costing inpatient day costs	[redacted]
4	BAC inpatient percentage based on literature (proportion of patients treated as inpatients: most severe flare)	Uncertainty in how many patients require hospitalisation for their flare	Spesolimab dominates
5	BAC weightings: 100% most severe from Day 0	Alternative approach to estimating BAC efficacy	Spesolimab dominates
6	BAC inpatient percentage based on SEE	Uncertainty in how many patients require hospitalisation for their flare	Spesolimab dominates
7	Inpatient costs: GPP-specific admissions	Alternative approach to costing inpatient day costs	Spesolimab dominates
8	BAC efficacy: Typical flare from day 8	Alternative approach to estimating BAC efficacy	Spesolimab dominates
9	Spesolimab % of inpatients treated in ICU equivalent to comparator	Uncertainty in the impact of spesolimab on ICU admissions	Spesolimab dominates

Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; LOS, length of stay; RWE, real world evidence; SEE, structured expert elicitation.

Table 38 describes the scenarios tested and presents the impact on the ICER with the confidential discount for spesolimab. The most impactful scenarios across all comparisons are the efficacy of BAC, LOS for ICU and inpatient costs.

Table 38: Results of scenario analyses (PAS price)

	Scenario	Justification	ICER versus BAC
	Base case		Spesolimab dominates
1	BAC efficacy: RWE from Day 0	Alternative approach to estimating BAC efficacy	[redacted]
2	LoS for ICU with MV not capped	Reflect uncertainty in how long patients stay in ICU	Spesolimab dominates
3	Inpatient costs: non-elective short stay	Alternative approach to costing inpatient day costs	Spesolimab dominates
4	BAC inpatient percentage based on literature (Proportion of patients treated as inpatients: most severe flare)	Uncertainty in how many patients require hospitalisation for their flare	Spesolimab dominates
5	BAC inpatient percentage based on SEE	Uncertainty in how many patients require hospitalisation for their flare	Spesolimab dominates
6	Inpatient costs: GPP-specific admissions	Alternative approach to costing inpatient day costs	Spesolimab dominates
7	BAC weightings: 100% most severe from Day 0	Alternative approach to estimating BAC efficacy	Spesolimab dominates
8	Spesolimab % of inpatients treated in ICU equivalent to comparator	Uncertainty in the impact of spesolimab on ICU admissions	Spesolimab dominates
9	BAC efficacy: Typical flare from day 8	Alternative approach to estimating BAC efficacy	Spesolimab dominates

Key: BAC, best available care; GPP, generalised pustular psoriasis; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; LOS, length of stay, RWE, real-world evidence; SEE, structured expert elicitation.

B.3.12. Subgroup analysis

There are no relevant subgroups; hence, subgroup analyses were not performed.

B.3.13. Benefits not captured in the QALY calculation

There is a clear unmet medical need for treatments specifically targeted for GPP that provide rapid control and fast resolution of flares with tolerable side effects. Spesolimab addresses this need and represents a ‘step change’ in GPP flare management, providing a standard of care to patients who are experiencing a medical emergency with no established care pathway.

The innovation of spesolimab was recognised with a Prix Galien award in the Best Orphan/Rare Diseases category in 2023.[78] The Galien Foundation fosters, recognises and rewards excellence in scientific innovation to improve the state of human health. Spesolimab also received Breakthrough Therapy Designation in the US., China mainland and Taiwan, Priority Review in the US. and China mainland, Orphan Drug Designation in the US, Korea, Switzerland and Australia, and Rare Disease Designation and fast track in Taiwan.[79]

Although the key clinical, patient and health service benefits of rapid resolution of GPP flares are captured in the economic model, the impact on patients' quality of life is unlikely to be fully captured. It is also worth noting that the impact on carers is not considered at all in the model.

Patients living with GPP are typically in their mid-fifties and are likely to have multiple responsibilities in daily life across family, work and other commitments. On acute onset of a GPP flare, they will need to arrange unexpected cover for these responsibilities – and the longer the flare persists, the longer such cover is needed. Alongside such practical implications, there is an emotional and societal implication of experiencing a GPP flare; patients report wanting to hide away when in the midst of a GPP flare, at least in part due to others' reactions to GPP flare symptoms, given their highly visible nature.[30, 31] Quick resolution of symptoms allows patients to resume social interactions as well as reducing the risk of hospitalisation and a lengthy stay in hospital.

The reassurance of having a standard of care treatment available with proven effect should also not be overlooked. The constant worry of flares has a considerable impact on patients' mental health, as does the despair of knowing that there is little the health service can currently offer to alleviate symptoms and resolve the flare.[31] Making spesolimab available as an option would reassure patients, carers and healthcare services alike that in the event of a GPP flare, quick resolution is possible.

Based on the cost-effectiveness modelling, there is a reduction in mortality associated with the use of spesolimab. Accurately quantifying the long-term QALY benefit associated with this mortality reduction was deemed to not be feasible, so

has not been included. Hence, the current results may be viewed as providing conservative estimates of the cost-effectiveness of spesolimab.

B.3.14. Validation

B.3.14.1. Validation of cost-effectiveness analysis

The approach to the cost-effectiveness analysis, including model structure, key assumptions and evidence sources, were validated via consultations with clinical experts and health economic experts. This allowed the model approach to be validated and permitted areas of disagreement to be resolved prior to generation of model results and ensure that results were relevant to UK clinical practice. In addition, quality control was undertaken, whereby a cell-by-cell verification process was conducted to allow checking of all input calculation, formulae and Visual Basic code.

B.3.15. Interpretation and conclusions of economic evidence

The economic SLR did not identify any cost-effectiveness studies for patients with GPP. Therefore, a de novo economic model was developed to support this submission. The economic analysis drew relevant inputs from the pivotal Effisayil™ 1 trial, real world evidence from the Effisayil™ 1 historical cohort, structured expert elicitation, and published literature.

The economic evaluation compared spesolimab with BAC. It made the best use of the available evidence, with key assumptions and inputs validated with clinical experts to ensure that the analysis is relevant to clinical practice in England. Uncertainty in these assumptions and inputs was assessed via sensitivity and scenario analyses.

Cost-effectiveness results demonstrated that spesolimab dominated BAC, both when using the list price of spesolimab and when using the confidential discount for spesolimab. Probabilistic results were consistent with the deterministic results. During uncertainty analyses, spesolimab remained dominant in the majority of scenarios considered (seven of the nine scenarios at list price and eight of the nine

scenarios with the confidential discount). When using the confidential discount for spesolimab it remained dominant in all of the deterministic sensitivity analyses. The key drivers of uncertainty in the cost-effectiveness results were the efficacy of BAC, the proportion of BAC patients who are treated as inpatients, LOS for ICU and daily inpatient costs.

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B.5. Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection, and synthesis of clinical evidence

Appendix E: Effisayil™ 1 additional analysis

Appendix F: Proof-of-concept trial results

Appendix G: Published cost-effectiveness studies

Appendix H: Cost and healthcare resource identification, measurement, and valuation

Appendix I: Health-related quality of life studies

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: RWE and SEE data from Europe

Appendix N: Effisayil™ 1 study design

Appendix O: Additional cost-effectiveness information

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It's a plain English summary of their submission written for patients participating in the evaluation. It's not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it's sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

Notes for authors: Please complete the template using plain language, taking time to explain all scientific terminology. As you draft your response, please do not delete the intro text included in each section. It might be a useful reference for patient reviewers.

However, any text preceded by the words '**Notes for authors**' simply contains additional prompts for the company to advise them on the type of information that may be most relevant, and the level of detail they need to include. **You may delete this text where indicated.**

Section 1: submission summary

1a) Name of the medicine

Both generic and brand name.

Generic name: Spesolimab Brand name: Spevigo®

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

Spesolimab is indicated for the treatment of flares in adult patients with generalised pustular psoriasis (GPP) as monotherapy.[1]

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Spesolimab received a conditional marketing authorisation from the Medicines & Healthcare products Regulatory Agency (MHRA) in July 2023.[2]

Conditional marketing authorisations are intended for medical products that address an unmet medical need but where comprehensive clinical data are not yet complete. Additional data for spesolimab on the treatment of repeated GPP flares are being collected as part of this conditional marketing authorisation.

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Boehringer Ingelheim provided financial support to the Psoriasis Association to support its annual conference in 2024 (£2,500) and as a corporate member (£2,000). The Psoriasis Association receives funding from Boehringer Ingelheim and several other pharmaceutical companies to support some of its activities and projects. These pharmaceutical companies have no influence over the conduct or content of any of the Psoriasis Association’s activities and projects.

Section 2: current landscape

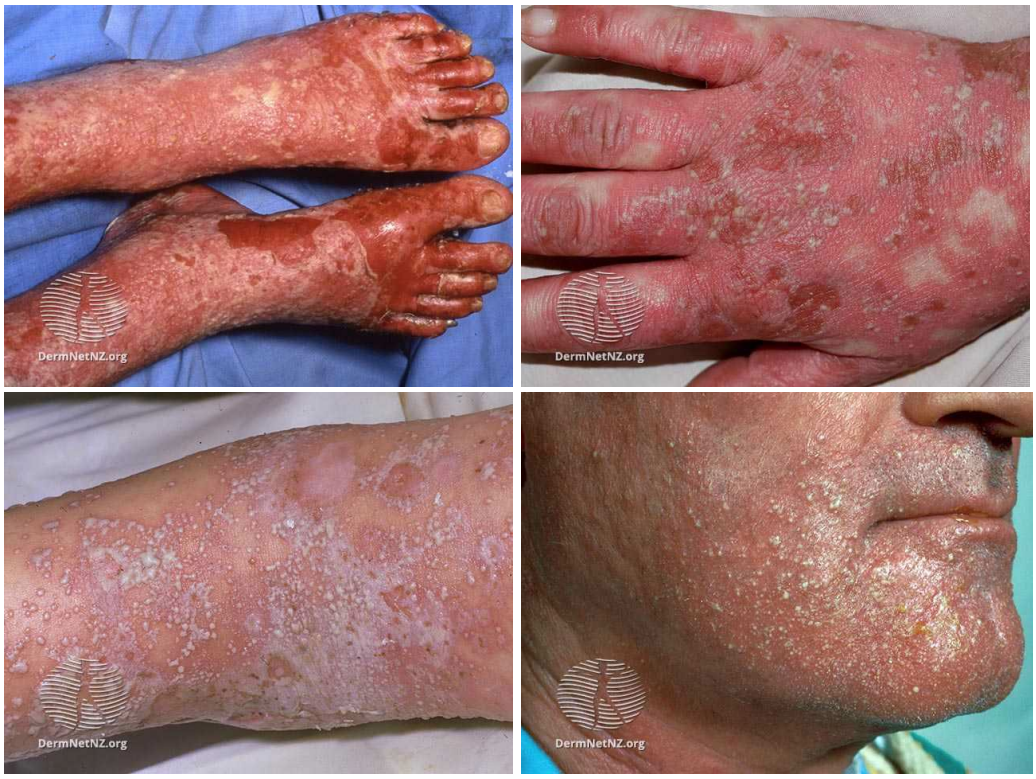
2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

GPP is a rare, severe inflammatory skin disease that affects approximately 1,900 people living in England.[3] It is characterised by episodes of widespread eruption of painful skin blisters filled with pus, known as GPP flares.[4] These blisters, also known as pustules, can affect large and varied areas of the body, see Figure 1.

Figure 1: Skin pustules in patients with generalised pustular psoriasis



Source: DermNet™.[5]

Other symptoms experienced during a GPP flare may include additional skin eruptions of redness, severe itchiness, a burning sensation of the skin and dry, cracked or scaly skin; and other general symptoms such as fever, sickness, extreme tiredness, swelling and pain.[6]

GPP is an inflammatory disease that can have widespread effects on the body. This includes the heart, lungs, and nerves.[7] In extreme cases, this can lead to a range of life-threatening conditions of the kidneys, liver, lungs and heart. Additionally, if left untreated, pustules can become infected, with the potential to develop sepsis – a life-threatening condition where the immune system attacks the body's own cells.[7] Studies have shown that 2–16% of people with GPP die from such complications.[7-9]

Although the exact cause of GPP is not yet known, the IL-36 pathway is central to its disease process. *IL36RN* is the gene that provides instructions for making a protein called interleukin-36 receptor antagonist (IL-36Ra).[10] This protein is part of the IL-36 pathway of the immune system and helps control inflammation. Specifically, it acts as a 'brake' to prevent too much inflammation by blocking the signals that tell immune cells to become active. When this gene doesn't work properly, it can lead to excessive inflammation. It is linked to some inflammatory diseases. In the case of GPP, the IL-36 pathway is overactivated, which results in a build-up of cells under the skin that cause the pustules of a GPP flare.[10]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Patients experiencing a GPP flare typically present at Accident & Emergency and are often misdiagnosed, with many seeing multiple specialists before receiving an accurate diagnosis.[11, 12]

GPP should be suspected in any patients with acute onset of skin eruptions that include redness and pustules.[13] In 2017, the European Rare And Severe Psoriasis Expert Network (ERASPEN) published their consensus definition of pustular psoriasis[10], which defined GPP as:

- Primary sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques);
- With or without systemic inflammation;
- With or without plaque psoriasis;

- Either relapsing (> 1 episode) or persistent (> 3 months)

These criteria, alongside physical assessment, medical and family history review, laboratory evaluations and genetic testing help diagnosis GPP.[13]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Given their potential severity, GPP flares are normally treated as a medical emergency.[11, 14] However, prior to spesolimab there were no treatments specifically licensed for the treatment of GPP in the UK, and there are no clinical guidelines or established standard of care treatment for GPP flares.

On presentation, patients are most likely to receive treatment with therapies developed to treat other types of psoriasis.[15] Therapies most commonly prescribed are immunosuppressant therapies (drugs that lower the body's immune response) including ciclosporin; methotrexate; acitretin; or biological therapies such as infliximab, guselkumab, ustekinumab or secukinumab.[15] Topical therapies such as corticosteroids may also be used alongside immunosuppressant or biological systemic therapy.

These therapies do not target the underlying cause of GPP and can therefore be ineffective and/or slow to take effect.[15-17] There is a clear unmet medical need for treatments specifically targeted for GPP that provide rapid control and clear-up of flares with tolerable side effects.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Symptoms associated with a GPP flare have a substantial negative impact on patients' daily activities, social interactions and mental wellbeing.[18-21] Patients living with GPP report not wanting to go out or be seen during a flare episode due to the disfiguring nature of their condition and the fear and revulsion it can invoke in others, who often mistake GPP as contagious.[22] Mothers report not being able to pick up their children because of the pain of their touch and partners report being unable to share a physical relationship.[22] Work can be challenging and some career paths are even closed off to patients with GPP due to the unpredictable nature of the disease and its day-to-day impact.[22] The constant worry of flares, the intensity of flares and peoples' reactions to GPP symptoms further add to the mental burden of disease.[22, 23]

Testimonies from patients living with GPP in the UK (n = 3) are summarised in the word clouds given in Figure 2. The huge impact of this condition on patients' mental health and wellbeing is sadly prominent in these testimonies, alongside their despair around the lack of treatment options.[23]

Figure 2: Quotes from patients with GPP

Key: GPP, generalised pustular psoriasis.
Source: Patient Experience with GPP (data on file).[23]

In a recent patient experience study that included primary data collection via a web-based survey, as well as qualitative telephone interviews with adult participants living with GPP across Canada, China, Japan, the UK and the US, pustules were most often reported among the three most bothersome symptoms (n = 10/21; 48%) and one of the most important to manage (n = 4/9; 44%).[12]

All participants in this study (n = 9/9; 100.0%) reported an impact on their mental and physical health, and nearly all participants (n = 8/9; 88.9%) reported impacts on their sleep.[12] More than three-quarters reported impacts on dressing/clothing choices, finances, social life, and work (each reported by n = 7/9; 77.8%).[12]

Section 3: the treatment

3a) How does the new treatment work? What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body.

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Spesolimab is the first treatment available to patients in the UK that specifically targets the underlying cause of GPP. It is a monoclonal antibody treatment, which is a type of medicine that helps the body's immune system to control inflammation.[1]

Spesolimab works by attaching to the IL-36 receptor to stop it being activated; essentially replacing the natural 'brake' that is missing in patients with GPP to stop the overactivation of the IL-36 pathway that causes the pustules of a GPP flare.[1]

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Spesolimab is not intended to be used in combination with any other medicines for the treatment of GPP flares.[1]

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Spesolimab is administered in a single intravenous (IV) infusion (drip into the vein).[1] A total of 900 mg is administered over 90 minutes. However, the infusion can last up to 180 minutes if it is slowed or paused.[1]

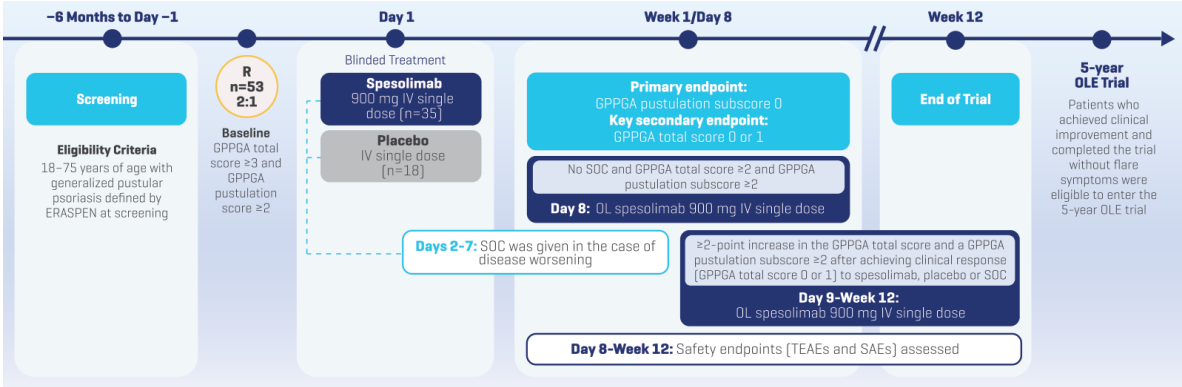
If flare symptoms persist, an additional 900 mg dose may be administered 1 week after the initial dose. Again, this is as an IV infusion and typically lasts 90 minutes.[1]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The main trial providing evidence for the use of spesolimab to treat GPP flares is Effisayil™ 1 (NCT03782792). The trial was designed to test how well spesolimab works compared with placebo (a replica solution with no active medicine) and how safe it is in adults with GPP who are experiencing a flare of moderate-to-severe intensity.[24] The trial took place across multiple hospitals, and patients and clinicians were ‘blinded’ to treatment, which means they did not know if spesolimab or placebo was being used.[24] The study design is presented in Figure 3.

Figure 3: Effisayil™ 1 study design



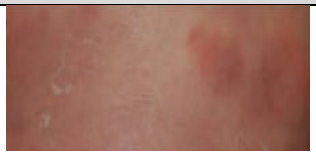
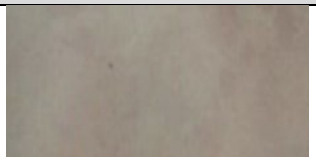
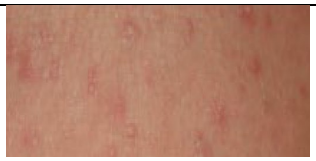
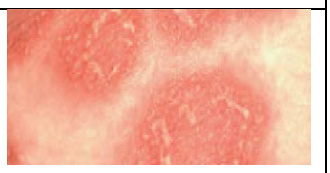
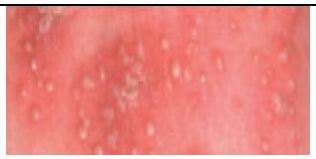
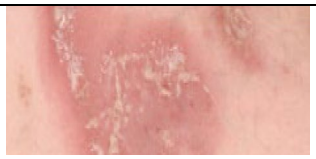
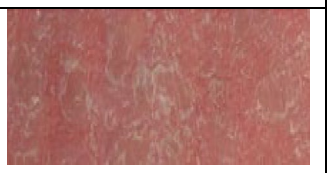
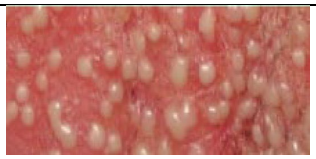
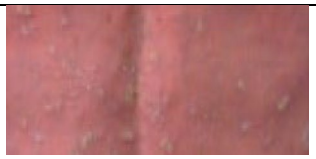
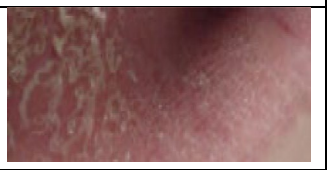
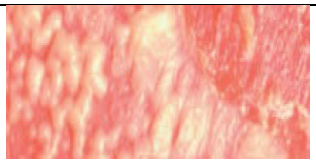
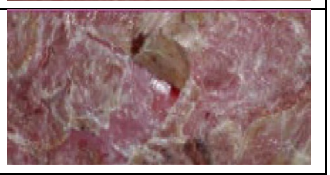
Key: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; ERASPEN, European Rare And Severe Psoriasis Expert Network; IV, intravenous; OL, open-label; OLE, open-label extension; SAEs, serious adverse events; SD, single dose; SOC, standard of care; TEAEs, treatment-emergent adverse events.
Source: adapted from Bachelez et al. 2021.[24]

The trial was conducted between February 2019 and January 2021 and enrolled 85 patients at 37 sites in 12 countries across Europe, North America, North Africa, and Asia.[24] Patients aged 18–75 were enrolled (screened) into the trial, if they met at least one of three pre-defined criteria for GPP diagnosis; for subsequent randomisation to treatment, patients had to experience a GPP flare of moderate-to-severe intensity, defined by the emergence of:

- A Generalised Pustular Psoriasis Physician Global Assessment (GPPGA) score of at least 3 (moderate) (Table 1); and
- Presence of new pustules (new appearance or worsening of existing pustules); and
- A GPPGA pustulation subscore of at least 2 (mild) (Table 1); and
- At least 5% of body surface area covered with abnormal redness of the skin or mucous membranes and the presence of pustules

The GPPGA is a measurement tool designed to assess the severity of GPP flares. Three key skin features (pustules, erythema [redness], and scaling/crusting) are scored separately to give GPPGA sub scores, and the average is calculated to give a GPPGA total score.[25] Scores range from 0 (clear) to 4 (severe) for each skin feature, as depicted in Table 1.

Table 1: Skins features relating to GPPGA subscores

GPPGA subscore	Pustules	Erythema (redness)	Scaling / crusting
0, clear			
1, almost clear			
2, mild			
3, moderate			
4, severe			

Key: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment.
Source: Burden et al. 2023[25]

Patients were randomised to receive spesolimab 900 mg IV infusion or placebo (2:1 ratio).[24] This means that the decision about which treatment is received is made at random, i.e. based on chance, rather than decided by the doctor or patient. Randomised treatment was started on Day 1, and primary and key secondary endpoint analyses were conducted at Day 8. These analyses were designed to test the most important measures of clinical benefit. At Day 8, all patients could receive spesolimab 900 mg IV infusion if they met certain criteria specified in the trial design, regardless of which treatment they received at Day 1. After Day 8 and through Week 12, patients who had a GPP flare recurrence could receive a further dose of spesolimab 900 mg IV infusion.[24]

The primary endpoint in Effisayil™ 1 was a GPPGA pustulation sub score of 0, indicating no visible pustules at Week 1. The key secondary endpoint was a GPPGA score of 0 or 1 indicating clear or almost clear skin at Week 1.[24]

In total, 53 patients were randomised: 35 to the spesolimab arm and 18 to the placebo arm.[24]

- **Before Day 8**, two patients (6%) in the spesolimab group and one patient (6%) in the placebo group received 'off-trial' treatment of the physician's choice to treat disease worsening
- **At Day 8**, 12 patients (34%) in the spesolimab group and 15 patients (83%) in the placebo group received an open-label dose of spesolimab
- **After Day 8**, 32 patients (91%) originally randomised to the spesolimab group and 17 patients (94%) originally randomised to the placebo group completed the 12-week follow-up period
  - During this time, four patients originally randomised to spesolimab and two patients originally randomised to placebo received a dose of spesolimab for a GPP flare recurrence

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

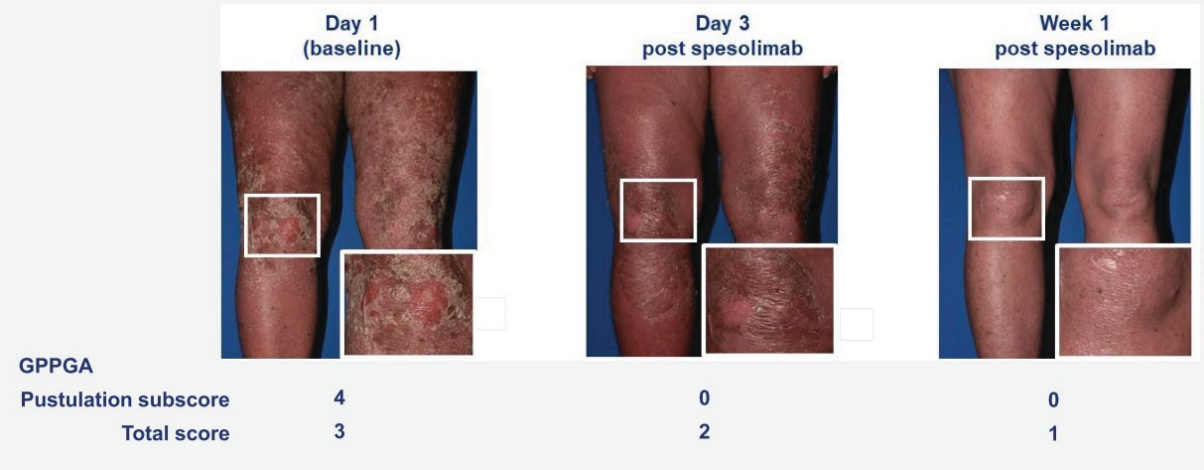
Primary endpoint

In the Effisayil™ 1 trial, more than half of the patients, 54% (n = 19/35), who were randomised to Spesolimab had no visible pustules (GPPGA pustular subscore of 0) at Week 1. In contrast, only 6% (n = 1/18) of patients randomised to placebo treatment had no visible pustules at Week 1.[24] This represents a statistically significant ($p < 0.001$) and clinically meaningful difference in efficacy.

Following spesolimab treatment, complete pustular clearance was rapid, starting as early as Day 2 in four patients and taking no longer than 1 week.[24] This can be seen in the patient case study pictures shown in Figure 4. This patient presented with a moderate GPP flare (GPPGA total score of 3) with severe pustulation (GPPGA

pustulation subscore of 4) at baseline (Day 1). One week after receiving a single dose of spesolimab, the patient had almost clear skin (GPPGA total score of 1) with no visible pustules (GPPGA pustulation subscore of 0).[26]

Figure 4: Patient case study pictures



Key: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment.
Source: Bachelez et al. 2021.[26]

Key secondary endpoint

In the Effisayil™ 1 trial, 43% (n = 15/35) of patients randomised to spesolimab had clear or almost clear skin (GPPGA total score of 0 or 1) at Week 1. Of patients randomised to placebo treatment, only 11% (n = 2/18) had clear or almost clear skin at Week 1.[24] This represents a statistically significant (p = 0.002) and clinically meaningful difference in efficacy between spesolimab and placebo.

Following spesolimab treatment, the onset of skin clearance was rapid, starting as early as Day 3 in two patients and taking no longer than 1 week for most patients.[24] This can be seen in the patient case study pictures above (Figure 4).

Exploratory endpoints after Week 1

The benefits of spesolimab on the GPPGA pustulation subscore and the GPPGA total score were sustained through Week 12 (see Figures 12 and 13 of the NICE Document B).[24] There was also a strong link between improvement in skin clearance (GPPGA total score) and improvement in pain; symptoms including fatigue; and quality of life.[27]

Treatment with spesolimab additionally resulted in fast and long lasting improvements in signs that show there is inflammation in the body, called markers of inflammation.[24] In patients who had levels of neutrophils and C-reactive protein above normal levels before treatment, levels returned to normal within 1–2 weeks of

spesolimab treatment, indicating inflammation reduction (see Figure 16 of the NICE Document B).[24]

Comparative efficacy

In the absence of a standard of care treatment for GPP flares in the current management pathway, it is difficult to compare the effect of spesolimab with other medicines currently available.

Insight into the expected benefit of best available care (BAC) for GPP is provided by a study of historical cohort data of patients' GPP flares prior to their enrolment to the Effisayil™ 1 trial.[16] For a typical past flare, as determined by the doctor or nurse treating the patient, the time taken for skin to clear was most commonly 1–2 weeks (40% of flares), though it could be as long as 12+ weeks (10% of flares).[16] For the most severe past flare, this time taken for skin to clear was longer – most commonly 3–4 weeks (46% of flares).[16] These data clearly show a lower rate of response and a slower time to response to treatment with BAC compared with those observed for spesolimab in the Effisayil™ 1 trial.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Spesolimab treatment resulted in rapid and sustained clinically meaningful improvements in pain, fatigue, quality of life, and other symptoms, as reported by patients in the Effisayil™ 1 trial.

Pain scores were recorded by patients on a visual analogue scale of 0 to 100; 0 indicates no pain, while 100 indicates severe pain. For patients randomised to spesolimab treatment, the average pain score decreased from 75 at baseline to 44

at Week 1. This indicates a clinically meaningful improvement in pain, defined as a reduction of at least 30 points from baseline.

Fatigue scores were recorded by patients using a 13-item questionnaire, with a total score of 0 to 52; 0 indicates high impact of fatigue, while 52 indicates low impact on fatigue. For patients randomised to spesolimab treatment, the average fatigue score increased from 19 at baseline to 32 at Week 1. This indicates a clinically meaningful improvement in fatigue, defined as an increase of at least 4 points from baseline.

Dermatology Quality of Life (DLQI) scores were recorded by patients using a 10-item questionnaire, with a total score of 0 to 30; 0 indicates low impact on quality of life, while 30 indicates high impact on quality of life. For patients randomised to spesolimab treatment, the average DLQI score decreased from 19 at baseline to 15 at Week 1. This indicates a clinically meaningful improvement in quality of life, defined as a reduction of at least 4 points from baseline.

Symptom severity scores were recorded by patients using a 4-item questionnaire with a total score of 0 to 16; 0 indicates low symptom severity, while 16 indicates high symptom severity. For patients randomised to spesolimab treatment, the average symptom severity score decreased from 10 at baseline to 8 at Week 1. This indicates a clinically meaningful improvement in symptom severity, defined as a reduction of at least 2 points from baseline.

These patient-reported outcome scores continued to improve up to Week 4 and were sustained through Week 12 (see Figure 14 of the NICE Document B).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like all medicines, spesolimab can cause side effects, and medical help should be sought if there are any signs or symptoms of an allergic reaction or infection during or after treatment. These may include[1]:

- Difficulty breathing or swallowing
- Swelling of the face, lips, tongue or throat
- Severe itching of the skin, with a red rash or raised bumps that differ from GPP
- Feeling faint
- Fever, cough
- Frequent urination, pain or burning while urinating, or bloody urine

The most common side effects reported with spesolimab treatment are redness, swelling, hardening, or warmth or pain at the injection site (may affect ≥ 1 in 10 people); and itching or feeling tired (may affect ≥ 1 in 100 people to < 1 in 10 people).[1]

In the Effisayil™ 1 trial, the most common side effect experienced by patients treated with spesolimab was infection (17.1%), compared with 5.6% of patients treated with placebo. Urinary tract infection was reported as serious in one patient (2.9%) treated with spesolimab and no patients in the placebo group.[24] Infections observed with spesolimab were generally mild to moderate, with no distinct pattern in the type of infection.[24]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

- Spesolimab is a first-in-class monoclonal antibody, developed to target the IL-36 signalling pathway that is involved in GPP
- Effisayil™ 1 is a clinical trial that investigated the use of spesolimab IV infusion for the treatment of GPP flares in adults
- Spesolimab IV infusion was more effective than placebo for all tested endpoints:

  - 54% of patients treated with spesolimab had complete pustular clearance (GPPGA pustulation sub score of 0) at Week 1, compared with 6% of patients in the placebo group ($p < 0.001$)
  - 43% of patients treated with spesolimab had clear or almost clear skin at Week 1 (GPPGA total score of 0 or 1), compared with 11% of patients in the placebo group ($p = 0.02$)
- The onset of response to spesolimab was rapid. Pustular clearance was observed as early as Day 2 and lasted until the end of the 12-week trial
  - Such rapid response is critical to preventing potentially life-threatening complications of a GPP flare from developing
- Improvements in skin manifestations were accompanied by clinically meaningful benefits in patient-reported outcomes and biological markers of inflammation and infection
- Spesolimab IV infusion demonstrated an acceptable safety profile in the Effisayil™ 1 trial, with medically manageable common side effects
  - Infections were the most common side effect in the spesolimab arm (reported in 17% of patients) but they were generally mild to moderate with no distinct pattern regarding pathogen or type of infection
- Rapid resolution of GPP flares, as provided by spesolimab, reduces the risk of hospitalisation and the potential length of stay if patients are hospitalised
  - This reduces the impact of disease of patients daily lives and the burden on carers / family members as well as alleviating burden on healthcare services
- Spesolimab offers a standard of care treatment to patients who are experiencing a medical emergency with no established care pathway
  - The availability of an effective treatment provides reassurance to patients, carers and healthcare services alike

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration

- What is the impact of any disadvantages highlighted compared with current treatments

- Spesolimab, like other biological therapies, can be associated with side effects. Medical help should be sought for any signs or symptoms of an allergic reaction or infection
  - Longer-term safety data are being collected in ongoing studies
- Spesolimab requires IV infusion for administration, which requires patients to have a small needle inserted into a vein and sit for 90 minutes while the medicine is delivered directly into the bloodstream

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

To assess the value and economic considerations of using spesolimab compared with BAC, a cost-effectiveness model was developed. A cost-effectiveness model is a tool that helps determine which healthcare interventions provide the most value for money by comparing the costs and benefits of different treatment options. The model uses a simplified representation of a GPP flare and how this is

treated, including any hospital stays, over 12 weeks. Two health states were used in this cost-effectiveness model for alive patients, each associated with a certain amount of costs and quality of life:

GPP flare: Patients with an active flare, based on the definition used in Effisayil™ 1. Costs in this health state are associated with the treatment received, treatment administration costs, management of flare and side effects. Most patients experiencing a GPP flare are assumed to be admitted to hospital and some may require treatment in an intensive care unit (ICU) or high dependency unit (HDU). Quality of life is lower compared with patients not experiencing a flare.

Resolved flare: This represents clearance or near-clearance of pustules. It is assumed that following resolution there will be no further flares within the time covered by the model (12 weeks). Costs in this health state are associated with monitoring, and quality of life is higher compared with patients experiencing a flare.

In addition, there is an extra cost associated with end-of-life care for patients who die with a GPP flare.

The model uses the best available evidence for spesolimab and BAC to estimate how fast patients respond to treatment when experiencing a flare and consequently the duration of the flare. This includes the Effisayil™ 1 trial and the Effisayil™ 1 historical cohort data (described in Section 3e). The time spent in each health state is then adjusted for the quality of life of a patient in that health state, to estimate the total number of quality-adjusted life years (QALYs) gained by a patient as a result of the GPP treatment received. This is compared with the total costs associated with that treatment (as described above). This then allows for an assessment of whether the costs associated with using spesolimab are justifiable based on the additional QALYs patients gain.

Clinical benefits included in the model

The model predicted that treatment with spesolimab would lead to more clinical benefit (i.e. more QALYs) gained than treatment with BAC (please note that the exact QALY results are confidential). The advantage of spesolimab treatment is that it reduces the duration of GPP flare, leading to a prolonged 'resolved flare' state which is associated with better quality of life.

Costs included in the model

The model considers the direct cost of treatment (drug acquisition costs) as well as health care resource use costs such as hospitalisation needs, and side effect management costs.

Model results

The model determined that spesolimab treatment was associated with additional benefit to patients (QALYs) at a lower overall cost of treatment. Cost savings were mainly driven by a reduced need for overnight hospitalisation (inpatient care) and for those patients who are hospitalised, both a shorter length of stay in hospital and a reduction in patients requiring an ICU or HDU stay.

Results were sensitive to model assumptions including those relating to the proportion of patients requiring hospitalisation, and the efficacy of BAC, but in nearly all sensitivity and scenario analyses, spesolimab remained a cost saving treatment option.

Uncertainty

The key uncertainties are:

- **Inpatient admissions.** There is a lack of UK data relating to the management of GPP flares for patients treated with either spesolimab or BAC. Therefore, the relative proportion of patients receiving inpatient care, and the duration of inpatient care is a source of uncertainty that influences model results.
- **Efficacy of BAC:** As there is no defined standard of care for GPP flares in the UK, and the pivotal trial for spesolimab did not include a BAC arm, the relative efficacy of BAC compared with spesolimab is uncertain. Both the Effisayil™ 1 trial and the Effisayil™ 1 historical cohort were used to estimate BAC efficacy in the model.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a ‘step change’ in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

There is a clear unmet medical need for treatments specifically targeted for GPP that provide rapid control and fast resolution of flares with tolerable side effects. Spesolimab addresses this need and represents a ‘step change’ in GPP flare management, providing a standard of care to patients who are experiencing a medical emergency with no established care pathway.

The innovation of spesolimab was recognised with a Prix Galien award in the Best Orphan/Rare Diseases category in 2023.[28] The Galien Foundation fosters, recognizes and rewards excellence in scientific innovation to improve the state of human health.

Although the key clinical, patient and health service benefits of rapid resolution of GPP flares are captured in the economic model, the impact on patients' quality of life is unlikely to be fully captured. It is also worth noting that the impact on carers is not considered at all in the model.

Patients living with GPP are typically in their mid-fifties and are likely to have multiple responsibilities in daily life across family, work and other commitments. On acute onset of a GPP flare, they will need to arrange unexpected cover for these responsibilities – and the longer the flare persists, the longer such cover is needed. Alongside such practical implications, there is an emotional and societal implication of experiencing a GPP flare; patients report wanting to hide away when in the midst of a GPP flare, at least in part due to others' reactions to GPP flare symptoms, given their highly visible nature.[22, 23] Quick resolution of symptoms allows patients to resume social interactions as well as reducing the risk of hospitalisation and a lengthy stay in hospital.

The reassurance of having a standard of care treatment available with proven effect should also not be overlooked. The constant worry of flares has a considerable impact on patients' mental health, as does the despair of knowing that there is little the health service can currently offer to alleviate symptoms and resolve the flare.[23] Making spesolimab available as an option would reassure patients, carers and healthcare services alike that in the event of a GPP flare, quick resolution is possible.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

No equality issues are foreseen.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Spesolimab (BI 655130):IL36 antibody

Effisayil-1™ trial publication: efficacy and safety

Effisayil-1™ trial publication: quality of life

Spesolimab Patient Information Leaflet (PIL)

Spesolimab: Summary of Product Characteristics (SPC)

Further information on NICE and the role of patients:

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EFPIA – Working together with patient groups (PDF)
- National Health Council Value Initiative

4b) Glossary of terms

Cost-effectiveness: Evaluation of the relative costs and benefits of treatment options that help make informed decisions on the best value for money health care options for the NHS.

Clinically meaningful: A term used to demonstrate that a treatment results in real, noticeable, or self-reported change in patients' lives.

C-reactive protein (CRP): A substance produced by the liver in response to inflammation; elevated levels of CRP indicate the presence of inflammation in the body.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): A rare but severe side effect characterised by eosinophilia and widespread systemic symptoms such as fever, rash, swollen lymph nodes and symptoms of involvement of internal organs such as the liver, kidney, lungs and heart.

Eosinophilia: Elevated levels of eosinophils, a type of white blood cell involved in the body's immune response.

Generalised pustular psoriasis: A rare, chronic, severe neutrophilic inflammatory skin disease, characterised by episodes of widespread eruption of sterile pustules that can occur with or without systematic inflammation.

Generalised Pustular Psoriasis physician Global Assessment (GPPGA): A modification of the well-established Psoriasis physician Global Assessment (PGA) tool used to assess psoriatic lesions, adapted to assess GPP lesions.

IL-36 pathway: Pathway within the immune system that helps control inflammation through 'start' and 'stop' triggers. When the pathway doesn't work properly, it can lead to excessive inflammation which in the case of GPP results in a build-up of cells under the skin that cause the pustules of a GPP flare.

Inflammatory disease: A group of conditions characterised by inflammation, which is the body's response to injury, infection or irritation. Inflammation can occur in various tissues and organs, leading to symptoms such as redness, swelling, pain and loss of function.

Intravenous (IV) infusion: Intravenous usually refers to a way of administering a drug or other substance into the bloodstream through a needle or tube inserted into a vein.

Neutrophils: A type of white blood cell critical to the body's immune response; elevated neutrophil counts indicate ongoing infection or inflammation.

Pustules: Pus-filled lesions / blisters on the skin that can affect large and varied areas of the body, potentially merging to form ‘lakes of pus’.

Structured expert elicitation: A systematic, reliable and transparent method used to collect and analyse expert judgements on a particular topic. Normally used to inform decision making where direct evidence is lacking and expert insight is needed.

Quality-adjusted life year: A measurement that shows how many additional months or years of life of a reasonable quality a patient may gain due to treatment.

Quality of life: An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.

Statistical significance: A measure used to determine whether observed results are likely due to chance or reflect a true effect. An observed result is said to be statistically significant if the probability of it occurring by chance is estimated as being less than one in 20.

Visual analogue scale: A horizontal or vertical line, usually 10 cm (100 mm) in length, which is anchored by word descriptors at each end. Respondents are asked to pace a mark on the line to indicate where they would place themselves.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Boehringer Ingelheim International GmbH. Summary of Product Characteristics. Spevigo 450 mg concentrate for solution for infusion (SPC). 2023. Available at: https://mhraproducts4853.blob.core.windows.net/docs/a309d0aa2dd806ac31c5ee92f28f67abe63e5a3f. Accessed: 25 June 2024.
2. Medicines & Healthcare products Regulatory Agency (MHRA). Public Assessment Report: Spevigo 450mg concetrate for solution for infusion. Available at: https://mhraproducts4853.blob.core.windows.net/docs/3739fe4ccdfdd4c807c575a53c0ce69e613c5158. Accessed: 25 June.
3. Frysz M, Patel S, Li MOY, et al. Prevalence, incidence, mortality, and healthcare resource use for generalised pustular psoriasis, palmoplantar pustulosis, and plaque psoriasis in England: a population-based cohort study. *Br J Dermatol*. 2024.
4. Rivera-Díaz R, Daudén E, Carrascosa JM, et al. Generalized Pustular Psoriasis: A Review on Clinical Characteristics, Diagnosis, and Treatment. *Dermatol Ther (Heidelb)*. 2023; 13(3):673-88.
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11. Boehringer Ingelheim. Patient pathway analysis in Generalised Pustular Psoriasis (GPP). 2022. Data on File.
12. Boehringer Ingelheim. Experience of Adults with Generalized Pustular Psoriasis (GPP) or Palmoplantar Pustulosis (PPP). (EVA-26261) 2024. Data on File.
13. Barker JN, Becher G, Burden DA, et al. Clinical course, treatment and management of generalised pustular psoriasis from a United Kingdom extension of a global Delphi panel. *Skin Health and Disease*. 2024; 4(3):e359.

14. Boehringer Ingelheim. Observational and Non-Interventional Study (ONIS) Report. (Clinical Study Report: Study number: 1368-0085) 2022. Data on File.
15. Boehringer Ingelheim. Structured expert elicitation in general pustular psoriasis report. (2903462) 2022. Data on File.
16. Choon SE, Lebwohl MG, Turki H, et al. Clinical Characteristics and Outcomes of Generalized Pustular Psoriasis Flares. *Dermatology*. 2023; 239(3):345-54.
17. Strober B, Kotowsky N, Medeiros R, et al. Unmet Medical Needs in the Treatment and Management of Generalized Pustular Psoriasis Flares: Evidence from a Survey of Corrona Registry Dermatologists. *Dermatol Ther (Heidelb)*. 2021; 11(2):529-41.
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20. Kotowsky N, Feldman SR, Garry EM, et al. 439 Characteristics of patients with generalized pustular psoriasis compared to those with psoriasis vulgaris: A claims database study. *J Invest Dermatol*. 2020; 140(7):S58.
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26. Bachelez H, Barker J, Ghoreschi K, et al. Efficacy of spesolimab for the rapid control of generalized pustular psoriasis flares: Results from the placebo-controlled Effisayil 1™ study. EADV Congress. 29 September - 2 October 2021. 345.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Clarification questions

September 2024

File name	Version	Contains confidential information	Date
ID3963 Spesolimab clarification questions from EAG - Response CIC REDACTED	1	Yes	17th September 2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Technology being evaluated

A1. CS B.1.2 Table 2 and the SmPC state that one dose 900mg of spesolimab would be administered and that if flare symptoms persist another dose of 900mg may be given one week after the initial dose.

i. If flare symptoms continue beyond another week, how long would it be before another (3rd) dose of spesolimab could be administered, if this is permissible, or before the clinician should switch to an alternative treatment?

The Effisayil™ 1 trial investigated up to two doses of spesolimab per flare. There are no data available on the use of a third dose of spesolimab for the same flare. Patients in the Effisayil™ 1 trial could receive an additional dose of intravenous (IV) spesolimab any time beyond Day 8 to treat recurrent flares.

Two patients received a total of three doses of spesolimab IV infusion in the Effisayil™ 1 trial (two doses for the first flare and one dose for the second flare). Spesolimab was safe and well tolerated in these two patients. If a flare were to remain unresolved after 2 doses of spesolimab, the choice of therapy would be at the discretion of the treating physicians.

ii. If the flare resolves, how long an interval is required from the previous spesolimab dose before another flare may be treated with spesolimab?

In Effisayil™ 1 and Effisayil™ ON up to the cut-off date of 30 Sep 2021, the shortest duration between two flares was 13 days, which happened during the course of the Effisayil™ 1 trial. BI does not recommend a minimum time period between spesolimab dosage courses due to the following considerations:

- In the Effisayil™ 1 trial, there was no such minimum time period specified
- Patients could receive additional spesolimab IV infusion any time beyond Day 8 to treat recurrent flares
- Spesolimab was safe and well tolerated in the two patients who received a total of three spesolimab IV infusions (two doses for the first flare and one dose for the second flare)

Clinical pathway of care

A2. B.1.3.3 CS Figure 4 outlines the clinical pathway of care for GPP flares in the UK.

i. Does CS Figure 4 illustrate the pathway for flares of all severities or is it specifically for moderate-to-severe flares?

The clinical pathway of care presented was based on clinical expert opinion of best available care (BAC) for treatment of moderate-to-severe flares, collected via Structured Expert Elicitation (SEE) and subsequent workshop discussion.

The question posed as part of this SEE and subsequent discussion was intended to provide insight into the likely alternative treatments used in practice for patients who were eligible for and thus treated with spesolimab in the Effisayil™ 1 trial.

ii. CS Figure 4 does not show the proposed position of spesolimab in the care pathway. CS section B.3.2.3.1 states that spesolimab is expected to be used in first-line treatment of GPP flares. Please clarify where spesolimab is positioned in relation to the pathway in CS Figure 4, e.g. whether it would displace (and so precede) the first-line treatments or be considered an alternative to them.

The current care pathway often requires multiple lines of treatment to be administered for resolution of a GPP flare. Spesolimab provides rapid resolution of GPP flares and therefore is proposed as a first-line treatment, but its use would prevent the need for current first-line and subsequent-line treatments. It therefore provides an alternative treatment option to the multiple lines of treatment approach.

iii. [redacted] text in CS B.1.3.3 states “topical treatments such as corticosteroids may also be used in combination with systemic therapy”. Does the company believe that topical steroids are used in combination with the treatments listed in CS Figure 4 [redacted] and if so, in what proportion of patients?

As noted in the company submission, the clinical pathway of care presented is a necessary simplification of an undefined clinical pathway due to a lack of standard of care and based on clinical expert opinion. All patients are estimated to receive combination treatment with topical steroids and systemic therapy for treatment of GPP flare initially, but where there is an inadequate response to such treatment, patients are typically switched to biological treatments. Topical steroids may or may not be discontinued based on clinician and patient choice, but for the simplified pathway, we assume they are discontinued. This also allows for more conservative costing of BAC with use of these data in the economic modelling.

Identification and selection of evidence

A3. Please supply the list of excluded studies noted at CS Appendix D.1.4 – with reasons for exclusion.

The list of excluded studies and reasons for exclusion are provided in Table 1.

Table 1: List of excluded studies

No.	Study	Title	Exclusion reason
Studies excluded during the original SLR			
1	Li et al. 2020	Clinical efficacy of thalidomide combined with avermectin a in the treatment of generalized pustular psoriasis	Outcome
2	Author not listed 2018	A study to test BI 655130 in patients with a flare-up of a skin disease called generalized pustular psoriasis	Superseded by full-text

No.	Study	Title	Exclusion reason
3	Morita et al. 2022	Design of Effisayil™ 2: A randomized, double-blind, placebo-controlled study of spesolimab in preventing flares in patients with generalized pustular psoriasis	Trial protocol
4	Uchida et al. 2022	A real-world, single-center experience and the immediate impact of granulocyte and monocyte adsorption apheresis on generalized pustular psoriasis	Study design
5	Gudjonsson et al. 2022	34617 Imsidolimab in the treatment of adult subjects with generalized pustular psoriasis: Design of a pivotal phase 3 clinical trial and a long-term extension study	Trial protocol
6	Navarini et al. 2022	33005 Clinically significant improvements in patient-reported outcomes (PROs) in patients with a generalized pustular psoriasis (GPP) flare treated with spesolimab	Outcome
7	Elewski et al. 2022	32924 Sustained treatment effect of spesolimab over 12 weeks for generalized pustular psoriasis flares; results from the Effisayil 1 study	Superseded by full-text
8	Ohata et al. 2022	Clinical characteristics of Japanese pustular psoriasis: A multicenter observational study	Outcome
9	Burden et al. 2022	Symptom experience and content validity of the Psoriasis Symptom Scale (PSS) in patients with generalized pustular psoriasis (GPP)	Outcome
10	Agerberg et al. 2022	Debut of psoriasis is usually before debut of concomitant inflammatory bowel disease: A population-based retrospective study	Population
11	Manone-Zenke et al. 2022	Characteristics of patients with generalized pustular psoriasis and psoriatic arthritis: A retrospective cohort study	Outcome
12	Wang et al. 2022	Profiling and multivariate analysis of serum cytokines in patients with generalized pustular psoriasis	Outcome
13	Choon et al. 2022	Clinical course and characteristics of generalized pustular psoriasis	Study design
14	Tosukhowong et al. 2021	Epidemiology and clinical features of pustular psoriasis: A 15-year retrospective cohort	Outcome

No.	Study	Title	Exclusion reason
15	Sachdeva et al. 2021	Management of pediatric generalized pustular psoriasis using biologics: An evidence-based review	Study design
16	Honma et al. 2020	Relationship between rapid skin clearance and quality of life benefit: Post hoc analysis of Japanese patients with moderate-to-severe psoriasis treated with ixekizumab (UNCOVER-J)	Outcome (no results reported for GPP patients only)
17	Suleiman et al. 2020	Exposure-response relationships for the efficacy and safety of risankizumab in Japanese subjects with psoriasis	Outcome (there were no results reported for GPP patients only)
18	Namiki et al. 2020	Thyroid dysfunction in patients with psoriasis: Higher prevalence of thyroid dysfunction in patients with generalized pustular psoriasis	Outcome
19	Kishimoto et al. 2020	Drug survival of biologic agents for psoriatic patients in a real-world setting in Japan	Outcome (there were no results reported for GPP patients only)
20	Singer et al. 2020	Medication use during hospitalizations for generalized pustular psoriasis	Superseded by full-text
21	Chabchoub et al. 2020	Pustular psoriasis in Tunisia : A 10-year review	Outcome
22	Ramalingam et al. 2020	Psoriasis: A decade of experience in a state hospital in peninsular Malaysia	Population (plaque, pustular and erythrodermic psoriasis; GPP not specified)
23	Zhou et al. 2020	Generalized pustular psoriasis: A systematic review of systemic treatments	Study design
24	Polat Ekinci et al. 2020	Successful treatment of recalcitrant pediatric generalized pustular psoriasis patients with anti-TNF-alpha therapy: A case series from a tertiary center in Turkey	Study design
25	Kura et al. 2020	Successful treatment of pustular psoriasis with itolizumab a novel cd6 blocking antibody in 3 cases	Outcome
26	Honma et al. 2020	Rapid skin clearance leads to better quality of life outcomes: A post hoc analysis of a Japanese study on patients with moderate-to-severe psoriasis (Uncover-J)	Outcome (there were no results reported for GPP patients only)
27	Rabhi et al. 2020	Childhood psoriasis : A descriptive study	Population (plaque, guttate, pustular and arthropathic psoriasis; GPP not specified)

No.	Study	Title	Exclusion reason
28	Laamari et al. 2020	Dermoscopy of ungueal psoriasis	Population
29	Hanna et al. 2020	PRO41 Indirect burden of illness in patients with generalized pustular psoriasis in the United States	Outcome
30	Zenke et al. 2020	17881 Characteristics of seven cases generalized pustular psoriasis with arthritis	Outcome
31	Twelves et al. 2019	Clinical and genetic differences between pustular psoriasis subtypes	Outcome
32	Plachouri et al. 2019	The role of IL-17 and IL-17 receptor inhibitors in the management of generalized pustular psoriasis	Study design
33	Lau et al. 2017	Juvenile generalized pustular psoriasis is a chronic recalcitrant disease: an analysis of 27 patients seen in a tertiary hospital in Johor, Malaysia	Study design
34	Torii et al. 2016	Safety profiles and efficacy of infliximab therapy in Japanese patients with plaque psoriasis with or without psoriatic arthritis, pustular psoriasis or psoriatic erythroderma: Results from the prospective post-marketing surveillance	Population (plaque psoriasis with or without psoriatic arthritis, pustular psoriasis or psoriatic erythroderma; GPP not specified)
35	Fawaz et al. 2016	Pustular psoriasis eruption with dabrafenib, a BRAF inhibitor	Study design
36	Lotfi et al. 2015	Assessment of serum levels of IgE in psoriasis: The relationship with clinical types of the disease	Population (plaque psoriasis, pustular psoriasis, erythrodermic psoriasis; GPP not specified)
37	Mansouri et al. 2015	Treatment of two patients with generalized pustular psoriasis with the interleukin-1beta inhibitor gevokizumab	Study design
38	Popadic et al. 2014	Pustular psoriasis in childhood and adolescence: A 20-year single-center experience	Study design
39	Posso-De Los Rios et al. 2014	A systematic review of systemic medications for pustular psoriasis in pediatrics	Study design
40	Gallo et al. 2013	Refractory generalized pustular psoriasis responsive to a combination of adalimumab and acitretin	Study design
41	Mehren et al. 2012	Dose-creep of infliximab during psoriasis treatment: An observational study	Population (psoriasis in general; GPP not specified)

No.	Study	Title	Exclusion reason
42	Shmidt et al. 2012	Psoriasis and palmoplantar pustulosis associated with tumor necrosis factor-alpha inhibitors: the Mayo Clinic experience, 1998 to 2010	Outcome (there were no results reported for GPP patients only)
43	Maza et al. 2011	Oral cyclosporin in psoriasis: A systematic review on treatment modalities, risk of kidney toxicity and evidence for use in non-plaque psoriasis	Study design
44	Sbidian et al. 2011	Efficacy and safety of oral retinoids in different psoriasis subtypes: A systematic literature review	Study design
45	Borges-Costa et al. 2011	Clinical and laboratory features in acute generalized pustular psoriasis: A retrospective study of 34 patients	Outcome
46	De Oliveira et al. 2010	Generalized pustular psoriasis in childhood	Study design
47	Palomo Arellano et al. 2009	Generalized pustular psoriasis: Treatment. With etanercept	Study design
48	Weishaupt et al. 2007	Treatment of pustular psoriasis with infliximab	Study design
49	Kaur et al. 2008	Systemic methotrexate treatment in childhood psoriasis: Further experience in 24 children from India	Outcome (there were no results reported for GPP patients only)
50	Ghosh et al. 2008	Generalized pustulosis	Study design
51	Fan et al. 2007	Childhood psoriasis: A study of 277 patients from China	Outcome (there were no results reported for GPP patients only)
52	Xiao et al. 2007	Juvenile generalized pustular psoriasis	Study design
53	Seyhan et al. 2006	Psoriasis in childhood and adolescence: Evaluation of demographic and clinical features	Outcome
54	Sharma et al. 2004	Hydroxyurea as an alternative therapy for psoriasis	Outcome
55	Creamer et al. 2002	Mediation of systemic vascular hyperpermeability in severe psoriasis by circulating vascular endothelial growth factor	Outcome
56	Kundakci et al. 2002	The evaluation of the sociodemographic and clinical features of Turkish psoriasis patients	Outcome (there were no results reported for GPP patients only)
57	Haustein et al. 2000	Methotrexate in psoriasis: 26 years' experience with low-dose long-term treatment	Outcome

No.	Study	Title	Exclusion reason
58	Magis et al. 2000	The treatment of psoriasis with etretinate and acitretin: A follow up of actual use	Outcome (there were no results reported for GPP patients only)
59	Ozawa et al. 1999	Treatments of generalized pustular psoriasis: A multicenter study in Japan	Outcome
60	Tay et al. 1997	The profile and outcome of pustular psoriasis in Singapore: A report of 28 cases	Outcome
61	Kumar et al. 1994	Methotrexate in childhood psoriasis	Outcome (there were no results reported for GPP patients only)
62	Cimatan et al. 1989	Clinical trial with cyclosporin A	Study design
63	Tsankov et al. 1992	Rifampicin therapy in severe forms of psoriasis	Outcome (there were no results reported for GPP patients only)
64	Zelickson et al. 1991	Generalized pustular psoriasis in childhood. Report of thirteen cases	Outcome
65	Piamphongsant et al. 1985	Treatment of generalized pustular psoriasis - clinical trials using different therapeutic modalities	Outcome
66	Hubler et al. 1984	Familial juvenile generalized pustular psoriasis	Study design
67	DesGroseilliers et al. 1981	The importance of patient selection for photochemotherapy in psoriasis	Outcome
68	Marquis et al. 1980	Photochemotherapy of psoriasis with oral 8-methoxypsoralen (8-MOP) and solar irradiation (Puvasol therapy)	Outcome (there were no results reported for GPP patients only)
69	Staughton et al. 1977	Infantile generalized pustular psoriasis responding to dapsone	Study design
70	Baker et al. 1976	Corticosteroids and pustular psoriasis	Study design
71	Hellgren et al. 1976	Induction of generalized pustular psoriasis by topical use of betamethasone dipropionate ointment in psoriasis	Study design
72	Tan et al. 1974	Pustular psoriasis with adrenal suppression following topical corticosteroids	Study design
73	Navarini et al. 2022	Spesolimab improves patient-reported outcomes in patients with generalized pustular psoriasis: results from the Effisayil 1 study	Outcome
74	Chiricozzi et al. 2022	Psoriasis: Talking points from recent clinical trials	Study design

No.	Study	Title	Exclusion reason
75	Wang et al. 2021	Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and other hematological parameters in psoriasis patients	Outcome
76	Shimauchi et al. 2013	Serum interleukin-22 and vascular endothelial growth factor serve as sensitive biomarkers but not as predictors of therapeutic response to biologics in patients with psoriasis	Outcome (there were no results reported for GPP patients only)
77	Ikeda et al. 2013	Therapeutic depletion of myeloid lineage leukocytes in patients with generalized pustular psoriasis indicates a major role for neutrophils in the immunopathogenesis of psoriasis	Intervention
78	Fujisawa et al. 2015	Granulocyte and monocyte adsorption apheresis for generalized pustular psoriasis: Therapeutic outcomes in three refractory patients	Intervention
Studies excluded during the SLR update			
1	Burden et al. 2024	Psychometric validation of the Psoriasis Symptom Scale, Functional Assessment of Chronic Illness Therapy–Fatigue and pain-Visual Analogue Scale in patients with generalized pustular psoriasis	Outcome
2	Higashi et al. 2024	Systemic therapy for psoriasis and the risk of cutaneous infections.	Population
3	Feldman et al. 2024	Poor adherence to and persistence with biologics in generalized pustular psoriasis: A claim-based study using real-world data from two large US databases.	Outcome
4	Tada et al. 2024	Treatment patterns and drug survival for generalized pustular psoriasis: A patient journey study using a Japanese claims database.	Outcome
5	Mastorino et al. 2024	Drug survival, effectiveness and safety of ixekizumab for moderate-to-severe psoriasis up to 5 years.	Outcome
6	Rastaghi et al. 2024	Epidemiology and clinical presentation of psoriasis in southeast Iran.	Outcome
7	Asilian et al. 2023	Value of adding betamethasone pulse therapy to methotrexate in treating patients with psoriasis.	Population
8	Distel et al. 2022	Long-Term effectiveness and drug survival of apremilast in treating psoriasis: A real-world experience.	Population
9	Qiao et al. 2023	Low-dose interleukin-2 for psoriasis therapy based on the regulation of	Outcome

No.	Study	Title	Exclusion reason
		Th17/Treg Cell balance in peripheral blood.	
10	Potestio et al. 2023	Efficacy and safety of spesolimab for the management of generalized pustular psoriasis: a drug safety evaluation.	Study design
11	Nie et al. 2023	Spesolimab in generalised pustular psoriasis flares: a profile of its use.	Study design
12	Uzuncakmak et al. 2023	Demographic and clinical characteristics of geriatric patients with psoriasis: A single-center, cross-sectional, retrospective study in Turkish population.	Population
13	Gonulal et al. 2023	Effectiveness and safety of ustekinumab for the treatment of psoriasis; six years of clinical experience.	Population
14	Burden et al. 2023	Psychometric validation of the generalized pustular psoriasis physician global assessment (GPPGA) and generalized pustular psoriasis area and severity index (GPPASI).	Outcome
15	Wang et al. 2023	Treatment persistence of interleukin-17 inhibitor class drugs among patients with psoriasis in Japan: a retrospective database study.	Population
16	Cetkovska et al. 2023	Apremilast use in severe psoriasis: Real-world data from Central and Eastern Europe.	Population
17	Onsun et al. 2023	Comparison of survival and retention rates between infliximab and adalimumab for psoriasis: 10-year experience at a single tertiary center.	Population
18	Montero-Vilchez et al. 2023	Epidemiology and geographic distribution of generalized pustular psoriasis in Spain: A national population-based study of hospital admissions from 2016 to 2020.	Duplicate
19	Kishimoto et al. 2023	Drug survival of Tumor Necrosis Factor-Alpha Inhibitors and switched subsequent biologic agents in patients with psoriasis: A retrospective study.	Outcome
20	Zitouni et al. 2023	Effectiveness and safety of adalimumab, etanercept and ustekinumab for severe psoriasis in children under 12 years of age: A French-Italian daily practice cohort (BiPe Jr).	Outcome
21	Ali et al. 2023	Spesolimab in the treatment of generalized pustular psoriasis: a critically appraised research paper.	Outcome

No.	Study	Title	Exclusion reason
22	Caldarola et al. 2023	Drug survival of methotrexate and predictor factors for discontinuation in psoriasis.	Outcome
23	Hugo et al. 2023	Long-Term efficacy, safety, and drug survival of guselkumab in patients with psoriasis: Real-world data from the Czech Republic BIOREP Registry.	Population
24	Wang et al. 2023	Different clinical features of pediatric generalized pustular psoriasis in patients with or without IL36RN variants.	Outcome
25	Jonak et al. 2023	Characteristics and outcomes of patients with psoriasis treated with apremilast in the real-world in Austria - results the APPRECIATE study.	Population
26	Yiu et al. 2022	Drug survival associated with effectiveness and safety of treatment with guselkumab, ixekizumab, secukinumab, ustekinumab, and adalimumab in patients with psoriasis.	Population
27	Yamanaka et al. 2023	Efficacy and safety of risankizumab in Japanese patients with generalized pustular psoriasis or erythrodermic psoriasis: Primary analysis and 180-week follow-up results from the phase 3, multicenter IMMspire study.	Duplicate
28	Lockshin et al. 2022	Outcomes in ixekizumab patients following exposure to secukinumab and other biologics in the CorEvitas Psoriasis Registry.	Population
29	Chiu et al. 2023	Predictors of time to relapse following ustekinumab withdrawal in patients with psoriasis who had responded to therapy: An 8-year multicenter study.	Population
30	Mahe et al. 2022	Biologics combined with conventional systemic agents for the treatment of children with severe psoriasis. Real-life data from the BiPe cohorts and a practice survey among French and Italian pediatric dermatologists.	Outcome
31	Mashor et al. 2022	A retrospective study on drug survival of biologics among patients with psoriasis seen in tertiary hospital in Johor Malaysia.	Outcome
32	Puig et al. 2023	Generalized pustular psoriasis: A global Delphi consensus on clinical course, diagnosis, treatment goals and disease management.	Outcome

No.	Study	Title	Exclusion reason
33	Prajapati et al. 2023	44100 A 3-year population-based incidence study of the burden of generalized pustular psoriasis in Canadian patients hospitalized or seen in emergency departments and hospital- or community-based outpatient clinics.	Duplicate
34	Lynde et al. 2023	43266 A 10-year population-based prevalence study of the burden of generalized pustular psoriasis in Canadian patients hospitalized or seen in emergency departments and hospital- or community-based outpatient clinics.	Duplicate
35	Gottlieb et al. 2023a	Healthcare resource utilization and costs among patients with generalized pustular psoriasis: A US claims analysis	Outcome

A4. Priority question. Please clarify the eligibility criteria applied to the 79 included trials to identify those with "data specific to GPP flares" (CS Appendix D.1.2) that culminated in the list of 15 studies in CS Appendix Table 11, and please supply a list of the [64] excluded studies with exclusion reasons. Additionally, please explain how the studies POLARIS and SCRIPTOR are not in the set of 15 studies with "data specific to GPP flares" when they are providing GPP flare data in CS section B.1.3.2.2.1

The criteria for selecting publications that primarily included a GPP flare population (aligning to the target population for spesolimab IV infusion treatment of patients with GPP experiencing a flare) were based on the publication's description of the inclusion/exclusion criteria for the study population. The 15 studies described as reporting "data specific to GPP flares" are those that describe in the publication that the population includes patients experiencing a GPP flare, either in the title, abstract or full text. Studies reporting GPP flare as an outcome or as a subgroup population were not deemed to meet this criterion if the study population was not described as a GPP flare population. These criteria led to the exclusion of 64 studies.

The POLARIS and SCRIPTOR studies include a broader GPP population and therefore, they do not meet the above criteria. They provide some information on flares experienced by the broader GPP population enrolled (hence their inclusion in CS section B.1.3.2.2.1 where flare frequency and severity are described), but they

do not provide efficacy or safety findings in the target population of GPP patients experiencing flares.

A5. Please clarify whether the feasibility assessment for indirect treatment comparison was performed on the broader set of 79 studies or the set of 15 studies relevant to the Decision Problem as it is unclear in the discussions of risk of bias (D.1.3) and of the relevance of the evidence base (D.1.5) why studies excluded as irrelevant to the Decision Problem are being assessed.

Quality assessment of included studies (D.1.3) was performed for all studies included in the broader scope of the clinical SLR, as part of the SLR process and best practice within SLR conduct.

Relevance of evidence base and heterogeneity assessment (D.1.5) was also performed for all studies included in the broader scope of the clinical SLR to identify potentially relevant studies to inform BAC efficacy and safety. The two real-world evidence (RWE) studies identified that were conducted in Europe and provided data on efficacy or safety outcomes for patients with GPP experiencing flares were formally compared for heterogeneity to the Effisayil™ 1 trial, as summarised in Table 13 of the CS Appendix D.1.5.

The Effisayil™ 1 trial

A6. CS section B.2.3.1 states that patients were eligible for the trial if they were experiencing their first episode of GPP flare of moderate-to-severe intensity. How many patients in the trial were enrolled on this basis?

To identify patients who were randomised upon their first flare, entries in the electronic case report form (eCRF) regarding the dates of the first GPP diagnosis, the current GPP flare, and the randomisation visit as well as further feedback from the sites were considered. Seven patients were identified who were randomised upon their first flare (five to the spesolimab arm and two to the placebo arm).

A7. CS Figure 5. Please confirm that the box labelled 'Days 2-7: SOC was given in the case of disease worsening' corresponds to escape treatment and

that the box labelled 'Day 9-Week12: OL spesolimab 900mg IV single dose' corresponds to spesolimab rescue treatment.

Apologies for the mixed use of terminology. We can confirm this interpretation is correct.

A8. Please confirm if:

- Patients who received escape treatment during week 1 were permitted to receive open-label spesolimab at Day 8.

Patients who received escape treatment during Week 1 were **not** permitted to receive open-label spesolimab at Day 8.

- Patients who received open-label treatment with spesolimab on or after Day 8 were permitted to also receive escape medication

Patients who received open-label treatment with spesolimab on or after Day 8 **were** permitted to also receive escape medication.

A9. Priority question. Patients who had a recurrent of GPP flare (defined as at least a 2-point increase in GPPGA score and GPPGA pustular subscore after achieving a clinical response to initial treatment) could receive a rescue dose of spesolimab 900mg. How was "clinical response to initial treatment" defined in this circumstance?

Clinical response was defined as achieving a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score of 0 or 1.

A10. Priority question. Did any trial participants receive three doses of spesolimab during the 12-week trial period (e.g. randomised to spesolimab 900mg, open-label spesolimab on Day 8, spesolimab rescue medication after Week 4). If so, how many participants received three doses of spesolimab?

As noted in the response to A1, two patients received a total of three doses of spesolimab IV infusion in the Effisayil™ 1 trial: two doses for the first flare (randomised and open-label spesolimab) and one dose for the second flare (spesolimab rescue treatment). Spesolimab was safe and well tolerated in these two patients.

A11. Please confirm if our understanding is correct that patients with flare symptoms graded as mild (total GPPGA score of 2 but also including a GPPGA pustulation subscore of at least 2) were eligible for open label spesolimab 900mg treatment at Day 8. Similarly, patients with a recurrence of flare graded as mild (total GPPGA score increased from 0 to 2, GPPGA subscore increased from 0 to 2) would have been eligible for a single rescue dose of spesolimab 900mg after Day 8 and through to Week 12.

Yes, that is correct.

A12. CS B.2.6.1 Figure 6

i. Please would the company confirm if our understanding is correct that three participants in the spesolimab arm (1 discontinued before completing week 1; two receiving escape medication) and one participant in the placebo arm (1 receiving escape medication) were assumed not to have responded (i.e. that in the spesolimab arm the participant who discontinued before completing week 1 was a different participant to either of the two who received escape medication)

This is correct for the primary endpoint and key secondary endpoint analyses, which assumed patients withdrawing or receiving escape medication were assumed not to have responded.

ii. Please provide a breakdown of numbers of participants by country for the 53 randomised participants.

Please find the breakdown requested in Table 2.

Table 2: Participants by country (screened and randomised)

Country	Participants screened	Participants randomised
China	9	6
France	18	10
Germany	6	5
Japan	7	2
Korea, Republic of	1	0
Malaysia	20	12
Singapore	1	1
Switzerland	1	1

Country	Participants screened	Participants randomised
Taiwan	7	5
Thailand	1	1
Tunisia	9	7
United States	5	3

A13. CS B.2.4 Table 10 states that the last observation carried forward (LOCF) method was used for data imputation in the case of missing continuous outcome data. For the patient reported outcomes presented in CS section B.2.6.3.1.2 does Figure 14 include LOCF data for missing patients?

Figure 14 is a descriptive analysis and hence, as per the trial protocol, based on observed cases including values after rescue therapy or treatment discontinuation. The last observation carried forward (LOCF) approach would not be appropriate for patients initially randomised to placebo due to the high crossover onto spesolimab after Day 8. Outcomes for patients initially randomised to spesolimab which include LOCF for missing patients are provided in Figure 1.

Figure 1: Patient-reported outcomes for patients randomised to spesolimab (last observation carried forward)

Key: DLQI, Dermatology Life Quality Index; IQR, interquartile range; MCID, VAS, visual analogue scale.
Notes: 1. Scores on the pain-VAS range from 0 (no pain) to 100 (very severe pain); Scores on the DLQI range from 0 (no effect) to 30 (extremely large effect); 2. MCID threshold for pain-VAS set at -30 points from baseline; MCID threshold for DLQI set at -4 points from baseline.
Source: data on file.

A14. CS B.2.6.1 Figure 7. One patient in the placebo group achieved the primary endpoint of GPPGA pustulation sub score of 0 at Week 1. Please confirm that this patient received no medication for the psoriasis flare (as per

trial protocol) and therefore this was a spontaneous resolution of the disease flare without treatment.

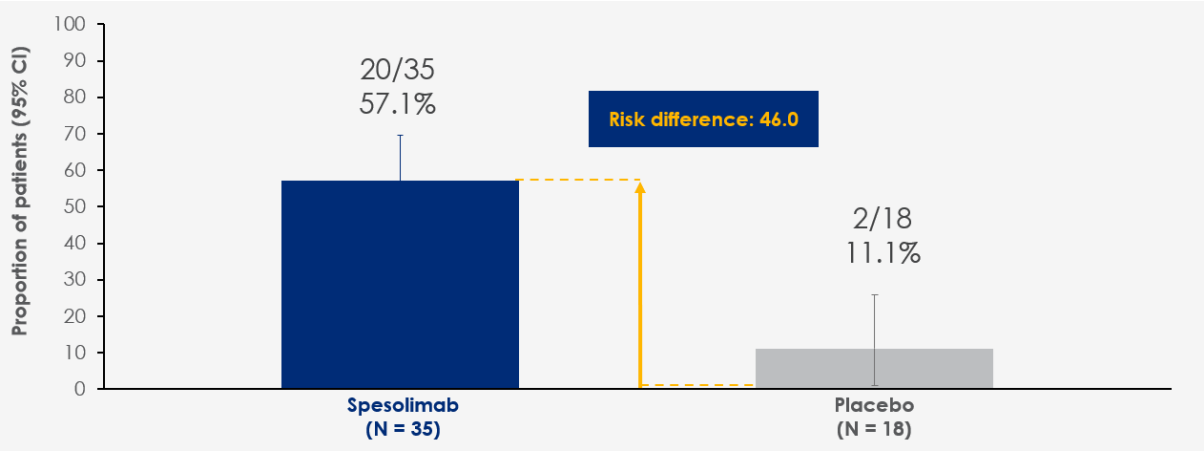
This patient was documented to fulfil the inclusion criteria for the Effisayil™ 1 trial on 29 June 2020. Under symptoms and status, the patient was reported as 'worsened' for change in pustules, erythema, scaling and systemic components. It is not documented when the flare had started for the patient. At screening, on 1 July 2020, the patient was documented to have had a GPPGA pustulation sub score of 2 and a GPPGA total score of 3. At Day 8, the patient had a pustulation sub score of 0 and a GPPGA total score of 1. This patient received no documented medication.

A15. Priority question. Please provide results for the model outcome of GPPGA pustulation subscore 0 or 1 in a format the same as CS Figure 7 and CS Figure 8.

Please find a replica of the CS Figure 7 for the model outcomes of GPPGA pustulation sub score of 0 or 1 presented in Figure 2. As this was not a predefined primary or key secondary endpoint in the Effisayil™ 1 trial, statistical between-group difference analyses are not available; however, the risk difference was 46.0 percentage points.

The CS Figure 8 provides data for time to first achievement of all GPPGA pustulation scores. Please therefore refer to the original figure (CS Figure 8) to see data requested for GPPGA pustulation sub score of 1. Following spesolimab treatment, a GPPGA pustulation subscore of 0 or 1 was observed as early as Day 2 in 13 patients, Day 3 in 19 patients and Day 8 in 22 patients (data reported are observed cases without censoring for patients receiving escape medication).[1]

Figure 2: GPPGA pustulation sub score of 0 or 1 at Week 1



Key: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; ITT, intention-to-treat.

Notes: Analyses conducted on randomised ITT population with patients withdrawing or receiving escape medication assumed not to have responded.

One patient in the spesolimab arm discontinued before completing Week 1; two patients in the spesolimab arm received rescue medication during Week 1. One patient in the placebo arm received escape medication during Week 1.

Source: Adapted from Bachelez et al. 2021[2]

A16. CS B.2.6.3 states the descriptive analyses of secondary endpoints at week 4 are provided for the treatment groups described post-hoc in Appendix E. Are the results presented in CS section B.2.6.3.1.1 through to Week 12 also for this post-hoc population and is our understanding correct that it includes part of the randomised ITT population that received rescue treatment?

Results presented in CS Section B.2.6.3.1.1 through to Week 12 are reported descriptively for the following groups:

- Patients randomised to spesolimab (n = 35)
- Patients randomised to receive spesolimab and received one dose of randomised spesolimab (n = 23)
- Patients randomised to receive spesolimab and received two doses (randomised and open-label) (n = 12)
- Patients randomised to placebo who received open-label spesolimab (n = 15)

Results presented in CS section B.2.6.3.1.1 are conducted on the randomised intention-to-treat (ITT) population, with patients receiving escape treatment (during

Week 1) or rescue treatment with spesolimab (after Day 8) categorised separately as non-response.

A17. Please clarify whether the ITT results reported in CS B.2.6.3.1.2 are also considered to be comparatively noninformative after Week 1 since they also report results through Week 12, when the majority of patients in the comparator arm had received spesolimab on Day 8.

Yes. As noted in CS Section B.2.4, due to the high spesolimab open-label use in patients randomised to placebo at Day 8, randomisation to trial groups no longer pertained after Week 1. Therefore, all comparisons according to randomised treatment as originally planned are non-informative after Day 8. This includes the patient-reported outcome (PRO) scores in CS Figure 14 from Day 8 through Week 12.

Spesolimab arm data and placebo arm data instead are both more reflective of the positive impact spesolimab has on PRO scores through Week 12.

A18. CS B.2.6.3.1.3 only reports results for patients randomised to the spesolimab arm for neutrophil and C-reactive protein levels. What are the results for the placebo arm at Week 1?

Markers of inflammation data from baseline to Day 8 for patients randomised to spesolimab or placebo are provided in Table 3.

Table 3: Median C-reactive protein and neutrophils up to Day 8 in patients who had >ULN at baseline

	Placebo		Spesolimab	
	n	**Median (IQR)**	**n**	**Median (IQR)**
C-reactive protein (mg/L)				
Baseline	16	25.6 (13.0, 64.8)	32	36.6 (8.3, 125.5)
Day 2	17	37.1 (9.9, 118.0)	32	51.0 (8.8, 90.8)
Day 3	16	34.4 (12.7, 113.0)	30	28.0 (6.6, 82.0)
Day 8	17	25.0 (9.4, 34.9)	32	13.0 (5.1, 40.3)
Neutrophils (10^9/L)				
Baseline	10	10.2 (8.5, 11.7)	20	11.0 (8.8, 12.3)
Day 2	9	10.2 (7.4, 13.0)	19	9.0 (6.1, 11.5)
Day 3	8	9.4 (7.3, 12.9)	18	8.6 (5.5, 10.0)

	Placebo		Spesolimab	
	n	**Median (IQR)**	**n**	**Median (IQR)**
Day 8	8	6.7 (6.2, 7.9)	17	6.9 5.7, 8.9)
Key: IQR, interquartile range; ULN, upper limit of normal. **Source:** Clinical Trial Report[3]				

A19. CS B.2.6.3.1.2 Figure 15. Please confirm if the thick solid red (or thick blue dashed) line shows the median absolute change over time with the Q1 and Q3 values shown in the thin red (or thin blue dashed) lines.

The thick solid red line in CS Figure 15 shows the median absolute change in EQ-5D health index status for patients randomised to spesolimab through Week 12, with the thin red lines showing the Q1 and Q3 values.

The thick blue dashed line in CS Figure 15 shows the median absolute change in EQ-5D health index status for patients randomised to placebo through Week 1, with the thin blue dashed lines showing the Q1 and Q3 values.

The Effisayil™ ON trial

A20. What was the severity of the 10 recurrent flares treated in the Effisayil™ ON study?

All 10 recurrent flares treated in the Effisayil™ ON study were moderate in severity, with a GPPGA total score of 3 and a GPPGA pustulation sub score ranging from 2 to 4. This is summarised in Table 4.

Table 4: Characteristics of flares prior to treatment in the Effisayil™ ON study

Characteristic	**Spesolimab (n = 10)**
GPPGA total score, n (%) 3	 10 (100)
GPPGA pustulation sub score, n (%) 2 3 4	 7 (70) 2 (20) 1 (10)
Key: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment. **Source:** Navarini et al. 2023[4]	

The Effisayil™ 2 study

A21. Priority question. Can the company provide results separately for the Effisayil™ 2 study participants who were originally randomised to placebo for the prevention of flares who then experienced a flare and were treated with spesolimab IV infusion for it? This group would appear to be most similar to those in the Effisayil™ 1 trial who received spesolimab for a moderate-to-severe flare. We would like to know what severity of flare they had and the proportions achieving complete pustular clearance and GPPGA total scores of 0 or 1 by week 1 and week 4.

In the Effisayil™ 2 trial, a flare was defined by an increase in GPPGA total score by ≥ 2 from baseline and GPPGA pustulation sub score by ≥ 2 from baseline. Of the [redacted] patients randomised to placebo who experienced flare, [redacted] patients had a GPPGA total score ≥ 3. [redacted] patient had a GPPGA pustulation sub score of 2 at flare baseline, [redacted] patients had a GPPGA pustulation sub score of 3 at flare baseline and [redacted] patients had a GPPGA pustulation sub score of 4 at flare baseline.

Of these [redacted] patients, [redacted] patients ([redacted]) achieved a GPPGA total score of 0–1 by Week 1 following treatment with spesolimab IV infusion, increasing to [redacted] patients ([redacted]) by Week 4. These data are supportive of the Effisayil™ 1 trial conclusions, but there are differences in patient groups that warrant caution when comparing the data.

The Effisayil™ 1 historical cohort

A22. CS B.2.9.1. Please provide the time period (i.e. date range) over which historical flares occurred in the Effisayil™ historical cohort.

There was no time period captured. The CRF included questions on “Typical Flare”, “Most Severe Flare”, “Longest Flare” and “Most recent flare prior to consent”, but no question assessed the time of these events. The first patient in Effisayil™ 1 was randomized on 11 March 2019 and the last patient was randomized on 16 September 2020. So, the date range for the case report forms, where historical flare data was captured, is March 2019 to September 2020.

A23. Priority question. CS B.2.9.1 please provide quality assessments for the Effisayil™ historical cohort study (Choon et al. 2023, CS document B reference 50) and the Wolf and colleagues retrospective case-series (Wolf et al, CS document B reference 24) covering the key risks of bias as set out in the NICE real-world evidence framework ideally using the ROBINS-I tool as suggested in NICE health technology evaluations: the manual, section 3.3.12.

An independent evidence review specialist conducted quality assessments according to the ROBINS-I tool. Please refer to the excel file provided alongside this response document for the complete risk of bias assessment.

The overall risk of bias of both studies was concluded to be low, as detailed in the summary Table 5

Table 5: Summary of overall risk of bias assessed using the ROBINS-I tool

	Effisayil™ 1 historical cohort Choon et al. 2023[5]	**CEE GPP Network Wolf et al. 2024[6]**
Bias due to confounding	Moderate	Moderate
	The study acknowledges various confounding factors such as stress, infections, and treatment withdrawal that can trigger GPP flares. However, no adjustment has been made; retrospective nature of data collection and lack of control for these confounders may introduce bias.	The study acknowledges various confounding factors such as sex and age at GPP diagnosis, with cases of drug or infection flare triggers (SARS-CoV-2 virus (COVID-19), urinary tract infection or upper respiratory tract infection, and initiation or withdrawal of treatment (including systemic steroids and antibiotics). However, no adjustment has been made; retrospective nature of data collection and lack of control for these confounders may introduce bias.
Bias in selection of participants into the study	Low	Low
	53 participants were selected based on specific inclusion criteria related to their history of GPP and systemic inflammation, which were clearly defined. This reduces the risk of selection bias.	58 participants from 12 sites in nine countries were selected based on clearly defined inclusion criteria of GPP diagnosis and follow-up time within past 10 years. This reduces the risk of selection bias.
Bias in classification of interventions	Low	Low
	The classification of interventions was based on historical medical data and standardized	The classification of interventions was based on historical medical records

	questionnaires, reducing the risk of misclassification.	extracted using a case report form, reducing the risk of misclassification.
Bias due to deviations from the intended intervention	Moderate	Moderate
	The study relies on retrospective data, and deviations from intended interventions were not systematically recorded or controlled.	The study relies on retrospective data, and deviations from intended interventions were not systematically recorded or controlled.
Bias due to missing data	Moderate	Low
	There were instances of missing data for several parameters. No analysis was done to assess the effect of missing data, which could affect the study's conclusions.	No missing data reported
Bias in measurement of outcomes	Moderate	Moderate
	Outcome measurements were based on patient recall, chart review and investigator interpretation, which could introduce measurement bias.	Outcome measurements were based on chart review which could introduce measurement bias.
Bias in selection of the reported result	Low	Low
	The study appears to report relevant outcomes related to GPP flares comprehensively.	The study and supplementary appendices appear to report relevant outcomes related to GPP flares comprehensively.
Overall risk of bias	Low	Low
	The study provides valuable insights into GPP flares, but the retrospective design introduces some bias. The overall risk of bias is assessed as Low.	The study provides valuable insights into GPP flares, but the retrospective design and instances of missing data introduce some bias. The overall risk of bias is assessed as Low.
Key: GPP, generalized pustular psoriasis. CEE, Central and Eastern Europe.		

A24. Priority question. Please provide evidence to show how representative the Effisayil™ 1 historical cohort is of the generalised pustular psoriasis patient population experiencing flares in England.

As described in the CS Section B.1.3, GPP is a heterogeneous disease with a variable clinical course that is poorly studied.

RWE pertaining to the patient population experiencing flares in England is limited. While the POLARIS and SCRIPTOR studies provide some data on patients

diagnosed with GPP, they do not provide demographic and clinical characteristics specific to the patient population experiencing flares. Demographic and flare characteristics data that are available are summarised in Table 6, but these data vary in definition and collection method. As a result, caution should be applied when making any comparisons across data sources.

In addition to RWE data collection, BI conducted several expert elicitation and opinion exercises to validate the applicability of the Effisayil™ 1 trial historical cohort data to clinical practice. An SEE informed by dermatologists in the UK and Ireland with experience treating GPP at specialist centres estimated that the average flare duration is [redacted][7] This is generally aligned with the Effisayil™ 1 historical cohort data where a 'typical past flare' most commonly lasted for 3–4 weeks and second most commonly lasted for 1–2 weeks, and is within the range of the SCRIPTOR flare duration data, which reported flares as lasting between [redacted] days (Table 6).

At a more recent clinical validation meeting, dermatologists in the UK were asked to comment on the generalisability of the patient population of Effisayil™ 1 trial to clinical practice.[8] Overall, the experts considered they were representative, although noted some demographic differences in race and gender. These are not reported prognostic factors, and pre-planned sensitivity and subgroup analyses showed no difference in treatment effect based on race, gender or other demographic and clinical characteristics (see CS Appendix E). At the same validation meeting, experts were also presented with data from the Effisayil™ 1 trial historical cohort. While they did highlight a risk of recall bias and variation in definitions applied to 'pustular clearance' in these cohort data, they were generally aligned that in the absence of better data, the Effisayil™ 1 historical cohort provides a suitable proxy for efficacy estimates of BAC used in the economic modelling.[8]

Table 6: Demographic and flare characteristics of patients enrolled to Effisayil™ 1 trial, POLARIS and SCRIPTOR

	Effisayil™ 1 trial historical cohort GPP patients experiencing flare (n = 53)[5]	**POLARIS[9] Incident GPP patients from 2008-2019 (n = 206)**				**SCRIPTOR GPP diagnosis after 2011 (n = 27)[10]**
		Hospital admission with any GPP code and ≥3 days hospitalisation	**Hospital admission with primary GPP code and ≥3 days hospitalisation**	**Hospital admission with primary GPP code of any duration**	**Emergency (non-elective) hospital admission with primary GPP code of any duration**	
Age, years Mean (SD)	At Effisayil™ 1 trial baseline: 43.0 (10.9)	At index date: 57.3 (19.0)				
Female, n (%)	36 (67.9)	136 (66.0)				
Ethnicity, n (%) Asian White	 29 (54.7) 24 (45.3)	All GPP patients (n = 373) 32 (8.6) 172 (46.1)				
BMI kg/m^2, n (%) <18.5 18.5–<25 25–<30 ≥30 Missing	At Effisayil™ 1 trial baseline: <25: 24 (45.3) 16 (30.2) 13 (24.5) 0	All GPP patients (n = 373) 10 (2.7) 93 (24.9) 83 (22.3) 98 (26.3) 89 (23.9)				
Comorbidities, n (%) ≥1 comorbidity	 NR	All GPP patients (n = 373) 285 (76.4)				
Number of flares, n (%)						
0 1 2 ≥3	NR	77 (37.4) 104 (50.5) 16 (7.8) 9 (4.4)	125 (60.7) 66 (32.0) 12 (5.8) <5 (1.5)	101 (49.0) 84 (40.8) 10 (4.9) 11 (5.4)	115 (55.8) 77 (37.4) 9 (4.4) 5 (2.4)	

	Effisayil™ 1 trial historical cohort GPP patients experiencing flare (n = 53)[5]	POLARIS[9] Incident GPP patients from 2008-2019 (n = 206)				SCRIPTOR GPP diagnosis after 2011 (n = 27)[10]
		Hospital admission with any GPP code and ≥3 days hospitalisation	Hospital admission with primary GPP code and ≥3 days hospitalisation	Hospital admission with primary GPP code of any duration	Emergency (non-elective) hospital admission with primary GPP code of any duration	
GPP flare duration						
Mean days (SD) Median days (range)	NR	NR	NR	NR	NR	[redacted]
<1 week, % 1–2 weeks, % 3–4 weeks, % 5–8 weeks, % 9–12 weeks, % >12 weeks, %	11.4^ 31.4^ 34.3^ 11.4^ 0^ 11.4^	NR	NR	NR	NR	NR
Notes: *data available for 29 patients; of patients who did not provide the number of flares per year, six had constant flares with persistent pustules; ^data presented for the 'typical past flare'; $White, Caucasian and/or of European descent.						

A25. Priority question. What are the prognostic factors in the generalised pustular psoriasis patient population experiencing flares?

There are limited data formally exploring prognostic factors that can be used to predict flare duration and severity, and consensus opinion is that there is a general lack of predictability of flaring frequency in most cases of GPP and the spectrum of flare severity.[11] In the UK delphi panel on clinical course, treatment and management of GPP, there was uncertainty around the prognostic value of age, which can arguably be correlated to complication-related morbidity but not necessarily to flare frequency.[12]

While GPP flare triggers are known, there are no data to suggest these are also predictive of flare severity and duration. These triggers include stress, certain medications, pregnancy, hormonal changes, infection, substance misuse and environmental factors.[10, 11, 13]

A26. Priority question. Please provide further details for the RCTs in Appendix D.1.3 Table 12 (i.e. treatment, comparators, population characteristics, numbers in each group).

Please refer to Table 1 of the embedded 'Clinical SLR Tables' document in Appendix D.1.2 for full details of the RCTs identified in the clinical SLR.

Summary details requested are provided in Table 7.

Table 7: Summary details of RCTs identified in the clinical SLR

Study (Region)	Population	Intervention (n)	Comparator (n)
Effisayil™ 1 trial Bachelez 2021 (Global)	Patient with GPP flare Age 18 to 75 years	Spesolimab (n=35)	Placebo (n=18)
Effisayil™ 2 trial Morita 2023 (Global)	Patients with GPP Age 12 to 75 years	Spesolimab low dose (n=31) Spesolimab medium dose (n=31) Spesolimab high dose (n=30)	Placebo (n=31)
Okubo 2022 (Japan)	Patients were ≥20 years of age with a diagnosis of GPP	CZP 400mg Q2W (n=3)	CZP 200mg Q2W (n=4)
Wolska 1983 (Poland*)	Patients with GPP Age: NR	Etretinate (n=4)	Placebo (n=1)
IMMspire Yamanaka 2022 (Japan)	Patients with GPP Age≥20 years	Risankizumab (75 mg) (n=4)	Risankizumab (150 mg) (n=4)

Key: CZP, certolizumab pegol; GPP, generalised pustular psoriasis; NR, not reported; Q2W, every 2 weeks.
*The country of the trial population is not specified

A27. Priority question. Please explain the rationale for not conducting unanchored population matching using RCT or real-world data? Please explain why this is not feasible for e.g. the Okubo 2022, Yamanaka 2022, Vigiuier 2024, HES data, POLARIS studies / databases (i.e. all the studies reported in CS Appendix D Table 11, Table 12, and Appendix M Table 57). Those listed here or other sources might appear preferrable to using the data on historical flares for the patient cohort from Effisayil 1 (which only appears to report on a maximum of 37 flares).

With the exception of the Effisayil™ 1 trial, the Effisayil™ 1 historical cohort study and Central and Eastern Europe (CEE) GPP Expert Network study, no RCT or real-world studies reported efficacy or safety findings for BAC in the target population of GPP patients experiencing flares that is comparable to the definition of flares used in the Effisayil™ 1 trial (which was based on several factors such as GPPGA total score and GPPGA pustulation subscore). For example, UK RWE for POLARIS

identified flares based on hospital admissions with a GPP diagnosis and reported health care use in this cohort; however not all flares will require hospitalisation and not all hospitalisations for patients with GPP will be due to a flare. Unanchored population matching would not therefore provide outcome data of relevance to this technology appraisal.

Please see Table 8 for a summary of trial and population characteristics and outcomes from the example studies listed in this question compared with the Effisayil™ 1 trial to illustrate this rationale.

Table 8: Trial and population characteristics and outcomes from example studies

	Effisayil™ 1 trial Bachelez 2021	**Okubo et al. 2022**	**IMMspire Yamanaka et al. 2022**	**Viguier et al. 2024**	**HES data**	**POLARIS**
Trial characteristics						
Population	Patients with GPP flare Age ≥18 years	Patients were ≥20 years of age with a diagnosis of GPP	Patients with GPP Age≥20 years	Patients hospitalised with GPP flares Mean age: 58 years	Patients with a diagnosis of GPP based on ICD-10 code L401 Mean age: [redacted] years	Patients with a diagnosis of GPP based on ICD-10 code L401 Mean age: 56 years
Intervention	Spesolimab Placebo	CZP 400mg Q2W (n=3) CZP 200mg Q2W (n=4)	Risankizumab 75 mg (n=4) Risankizumab 150 mg (n=4)	Topical Vitamin-D derivatives, Retinoids (acitretin), any biologics (n=569)	NR	NR
Study design	Phase II double blind RCT	Phase II/III double blind RCT	Phase III, randomised, open-label, parallel-design study	Retrospective, longitudinal, population-based study	Retrospective cohort study of longitudinal electronic health record data in the HES database	Retrospective cohort study of longitudinal electronic health record data in the CPRD database and linked hospital and mortality data from the HES and ONS databases
Baseline characteristics						
GPPGA total score, n (%)	Score of 3: 43 (81.1) Score of 4: 10 (18.8)	NR	NR	NR	NR	NR
GPPGA pustulation subscore, n (%)	Score of 2: 11 (20.7) Score 0f 3: 23 (43.3) Score of 4: 19 (35.8)	NR	NR	NR	NR	NR

	Effisayil™ 1 trial Bachelez 2021	Okubo et al. 2022	IMMspire Yamanaka et al. 2022	Viguier et al. 2024	HES data	POLARIS
GPPASI total score, median (IQR)	Spesolimab: 27.4 (15.5 to 36.8) Placebo: 20.9 (12 to 32)	NR	NR	NR	NR	NR
IL36RN mutation, n (%)	7 (13.2)	NR	NR	NR	NR	NR
Outcome data						
GPPGA subscore	Primary outcome: Proportion of patients with GPPGA pustulation subscore of 0 (range, 0 [no visible pustules] to 4 [severe pustulation]) at the end of week 1 Secondary outcome: Proportion of patients who achieved MCIDs in GPPGA pustulation subscore score of ≥1 point over 12 weeks	NR	NR	NR	NR	NR
GPPGA total score	Secondary outcome: Proportion of patients with GPPGA total score of 0 or 1 (clear or almost clear skin) at the end of week 1; scores range from 0 to 4, with higher scores	NR	NR	NR	NR	NR

	Effisayil™ 1 trial Bachelez 2021	Okubo et al. 2022	IMMspire Yamanaka et al. 2022	Viguier et al. 2024	HES data	POLARIS
	indicating greater disease severity Secondary outcome: Proportion of patients who achieved MCIDs in GPPGA total score of ≥1 point over 12 weeks					
Treatment response	Secondary outcome: PASI 75 response (75% improvement in GPPASI total score) PASI 50 response (50% improvement in GPPASI total score) Assessment time point: Day 1, Day 2, Day 3, Day 4, Week 8 and Week 12	CGI response (defined as remission or improved) Global improvement score response (defined as 'very much improved, much improved, or minimally improved') Assessment points: Week 2, Week 16 and Week 52	CGI response (defined as at least "Slightly Improved" in the overall improvement rating from baseline according to JDA total score) Assessment points: Week 16, Week 52, Week 124, Week 160, Week 180 PASI 90 defined as at least a 90% reduction in PASI score compared with the baseline PASI score) Assessment points: Week 16, Week 52,	NR	NR	NR

	Effisayil™ 1 trial Bachelez 2021	Okubo et al. 2022	IMMspire Yamanaka et al. 2022	Viguier et al. 2024	HES data	POLARIS
			Week 124, Week 160, Week 180			
Rationale for not conducting unanchored population matching	-	Population not specific to GPP flare Treatment not reflective of BAC Outcome data not comparable	Population not specific to GPP flare Treatment not reflective of BAC Outcome data not comparable	Population not specific to GPP flare No outcome data reported	Population not specific to GPP flare No treatment or outcome data reported	Population not specific to GPP flare No treatment or outcome data reported

Key: BAC, best available care; CGI, Clinical Global Impression; CPRD, Clinical Practice Research Datalink; CZP, certolizumab pegol; GPP, generalised pustular psoriasis; GPPASI, Generalised Pustular Psoriasis Area and Severity Index; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; HES, hospital episodes statistics; JDA, Japanese Dermatological Association; IQR, interquartile range; MCID, minimal clinically important difference; NR, not reported; ONS, Office for National Statistics; PASI, Psoriasis Area Severity Index; RCT, randomised controlled trial; Q2W, every 2 weeks.

Structured Expert Elicitation

A28. CS reference 33 [Boehringer Ingelheim. Structured expert elicitation in general pustular psoriasis report. (2903462) 2022.] The results shown in Table 2 and Table 3 seem counterintuitive. Is the correct table under the correct table header? [redacted]

Apologies for the confusion. There is a labelling error such that Table 2 and Table 3 headers are inverted. Please find the corrected tables below.

CS Table 2: Derivation of efficacy inputs for spesolimab and placebo based on Effisayil™ 1 trial data – complete response only (GPPGA subscore 0)

Timepoint	Moderate flare at baseline		Severe flare at baseline	
	Spesolimab (n=22)	**Placebo (n=12)**	**Spesolimab (n=13)**	**Placebo (n=6)**
Day 2	3 responders in total 3/22 = 13.6%	0 responders in total 0/13 = 0%	1 responder in total 1/13 = 7.7%	0 responders in total 0/6 = 0%
Day 3	8 responders in total (assumed 5 new) 5/22 = 22.7%	0 responders in total 0/12 = 0%	3 responders in total (assumed 2 new) 2/13 = 15.4%	0 responders in total 0/6 = 0%
Day 3-8	12 responders in total (assumed 4 new) 4/22 = 18.2%	1 responder in total 1/12 = 8.3%	7 responders in total (assumed 4 new) 4/13 = 30.8%%	0 responders in total 0/6 = 0%
Week 2-4	2 new responders among patients receiving second OL dose of spesolimab 2/22 = 9.1%	N/A as most patients receive OL spesolimab after week 1	3 new responders among patients receiving second OL dose of spesolimab 3/13 = 23.1%	N/A as most patients receive OL spesolimab after week 1

Timepoint	Moderate flare at baseline		Severe flare at baseline	
	Spesolimab (n=22)	**Placebo (n=12)**	**Spesolimab (n=13)**	**Placebo (n=6)**
No response by end of Week 4	Assumed all 'new responders' derived for each timepoint are different patients, therefore, the number of non-responders is the remainder 8/22 = 36.4%	N/A as most patients receive OL spesolimab after week 1	Assumed all 'new responders' derived for each timepoint are different patients, therefore, the number of non-responders is the remainder 3/13 = 23.1%	N/A as most patients receive OL spesolimab after week 1
Key: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; N/A, not applicable; OL, open label.				

CS Table 3: Derivation of efficacy for spesolimab and placebo based on Effisayil™ 1 trial data – complete or partial response (GPPGA subscore 0 or 1)

Timepoint	Moderate flare at baseline		Severe flare at baseline	
	Spesolimab (n=22)	**Placebo (n=12)**	**Spesolimab (n=13)**	**Placebo (n=6)**
Day 2	11 responders in total 11/22 = 50%	0 responders in total 0/13 = 0%	2 responders in total 2/13 = 15.4%	0 responders in total 0/6 = 0%
Day 3	15 responders in total (assumed 4 new) 4/22 = 18.2%	1 new responder in the 'placebo + OL D8' arm 1/12 = 8.3%	4 responders in total (assumed 2 new) 2/13 = 15.4%	0 responders in total 0/6 = 0%
Day 3-8	13 responders in total (assumed no new responder) 0/22 = 0%	1 responder in the 'placebo only' arm (assumed no new responder) 0/12 = 0%	7 responders in total (assumed 3 new) 3/13 = 23.1%	1 responder in total 1/6 = 16.7%
Week 2-4	Among patients receiving a second OL dose of spesolimab: 5 responders in total, assumed 4 new responders (as there was 1 responder at a previous timepoint) 4/22 = 18.2%	N/A as most patients receive OL spesolimab after week 1	Among patients receiving a second open label dose of spesolimab: 4 new responders 4/13 = 30.8%	N/A as most patients receive OL spesolimab after week 1

Timepoint	Moderate flare at baseline		Severe flare at baseline	
	Spesolimab (n=22)	**Placebo (n=12)**	**Spesolimab (n=13)**	**Placebo (n=6)**
No response by end of Week 4	Assumed all 'new responders' derived for each timepoint are different patients, therefore, the number of non-responders is the remainder 3/22 = 13.6%	N/A as most patients receive OL spesolimab after week 1	Assumed all 'new responders' derived for each timepoint are different patients, therefore, the number of non-responders is the remainder 2/13 = 15.4%	N/A as most patients receive OL spesolimab after week 1
Key: D8, Day 8; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; N/A, not applicable; OL, open label.				

Section B: Clarification on cost-effectiveness data

Time horizon

B1. In CS section B.2.2, it is mentioned that Effisayil™ ON will provide long-term safety and efficacy data on spesolimab subcutaneous maintenance treatment. Are there any early results available that can inform a scenario analysis with a longer time horizon (>12 weeks)?

There are currently no early results available from Effisayil™ ON that could inform a scenario analysis for a longer time horizon. In addition, it should be noted that as Effisayil™ ON is a trial of maintenance spesolimab treatment, it is not of relevance to this appraisal.

As spesolimab treatment is shown to improve time to pustular clearance, use of a longer time horizon in a scenario analysis is expected to show improved estimates of cost-effectiveness for spesolimab compared to the current base case.

Comparator

B2. Priority question. The UK experts enrolled in the SEE exercise suggested that a basket of drugs is used in the first week after a flare (Table 7 of CS reference 33). Also, CS Tables 22, 23 and 25 shows the costs of all the drugs

listed in Table 7 of CS reference 33. Please explain why the company assume that no drugs are used in week 1 as part of the best available care (BAC).

As noted in the CS, the Effisayil™ 1 trial is the most appropriate source of evidence for spesolimab outcomes, and the only source to provide directly observed comparative evidence for spesolimab. As the comparator in the Effisayil™ 1 trial is placebo, then for consistency between the source of evidence for the comparative effectiveness estimates and drug costs, the comparator is placebo in Week 1. Beyond Week 1, comparative evidence from the Effisayil™ 1 trial could not be used due to the high levels of crossover from placebo to spesolimab. Hence, the Effisayil™ 1 historical cohort was used for the comparator outcomes after the first week; as this represents outcomes for patients receiving active treatment, after the first week drug costs are incurred for the comparator.

B3. In the model (Data Library!U194:U239), the proportion of patients having infliximab in weeks 2-4 are split by week 1 cohort ([redacted]) and week 2 cohort ([redacted]). Please explain what the week 1 cohort refers to, as the company assumed that no drugs are used during the first week in the comparator arm.

As noted in the response to B2, the comparator is modelled as placebo in the first week and active treatment in subsequent weeks. This is to ensure alignment with the sources for efficacy data; the placebo arm of the Effisayil™ 1 trial in week 1, and the Effisayil™ 1 historical cohort (which received active treatments) after week 1. This approach was chosen as using the best available evidence on comparative effectiveness. In a scenario analysis, use of the Effisayil™ 1 historical cohort for BAC outcomes from Day 0 was explored; for consistency with this scenario, drug costs were incurred for BAC in the first week. See also the response to B14 (page 53).

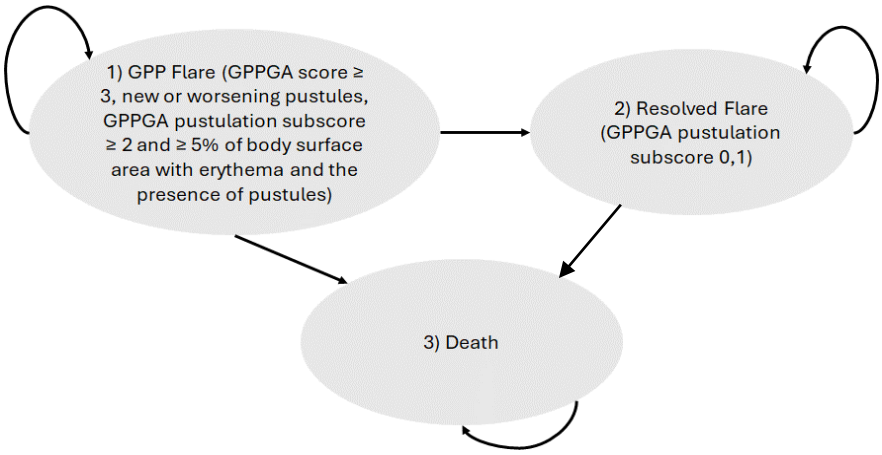
Clinical inputs

B4. Priority question. Please include the general population mortality in the economic model, to reflect the mortality of patients that recover from flares.

We have included non-disease-specific general population mortality in the updated economic model (i.e., “Data Library” row 53) for patients resolved from a GPP flare in both the intervention and comparator arms (see “Intervention trace” column O&P, and “Comparator Trace” column O&P). These data are based on the UK Office of

National Statistics for 2017-2019 in England (pre-COVID), with yearly mortality rates of 0.001851 for males and 0.001098 for females. The weighted averages of these mortality rates, based on the model's gender proportions, were integrated into the model. The yearly rates have been converted to daily rates to fit the model's daily cycle (see “Mortality inputs” E10). Given the minimal daily mortality risk (0.0004%) for patients at age 43, this adjustment did not significantly alter the results. The model structure figure has also been updated to reflect this, please see Figure 3.

Figure 3: Updated model structure



B5. Priority question. Please discuss whether there are any alternative studies that can inform the efficacy data of the comparator arm in the economic model.

In the base case, evidence from the Effisayil™ 1 trial and historical cohort were used to inform the efficacy data of the comparator, as the trial is the only source of comparative effectiveness data, and the historical cohort provides outcomes for the same patient cohort. As discussed in response to questions A26 and A27, it was not possible to use any other studies to inform the efficacy of the comparator.

B6. Priority question. The EAG are unable to identify the sources of several model input parameters which are reported in the CS and used in the company’s model (Table 1 below). Please clarify how these values were derived from the corresponding sources, by stating where they can be found in the source and, if applicable, the calculations needed to derive the model input value. Where required, please update the economic model.

Answers have been directly included in Table 1 below.

EAG Table 1 – EAG queries on sources of model input parameters

Parameters	Location in company submission	Location in company model	Source	Describe how the values for the input parameters were derived (providing detail where they are in the source and any calculations needed)
Efficacy of spesolimab	CS Table 17	Data Library!U26:U32	Bachelez et al. 2021	These were derived from an analysis of the Effisayil™ 1 trial, the results of which are provided separately.
Efficacy of BAC: (longest past flare for 3-4 weeks, 9-12 weeks, and >12 weeks, and total number of patients)	CS Table 18	Efficacy inputs	Choon et al. 2023 – Figure 4a	The correct values in CS Table 18 for longest past flares should read; 27.3% for 3-4 weeks, 18.2% for 9-12 weeks, and 9.1% for >12 weeks. The total number of patients (11) is from the footnote to Figure 4. Note that these data were not used in the economic model.
Adverse event rates: tuberculosis	CS Table 20	Data Library! U416:U436	TA383	TA383 derives the values from the Cochrane review DOI: 10.1002/14651858. CD008794.pub2: “Among people who took any biologic, 20 out of 10,000 had tuberculosis compared with 4 people out of 10,000 who took placebo.”
Mortality	CS B.3.3.4	Mortality inputs!E7	Viguier et al. 2024	The correct source is Table 2 from: https://www.avancesenppg.com/arxius/imatgesbutlleti/Bachelez-H-AAD-2021-Poster-26591.pdf
Healthcare resource use: proportion of patients treated as inpatients (BAC)	CS Table 29	Hospital inputs!F20	Wolf et al. 2024	Supplementary Figure 4 of Wolf et al. 2024
Drug costs: acitretin	CS Table 22	Acquisition costs!F7	BNF	The correct source is eMIT, this has also been updated to 2023 costs (£17.10)

B7. Priority question. Different input values are reported in the company submission and in the company’s model for several input parameters (Table 2

below). Please clarify which of the values should be considered in the company's base case. Where required, please update the economic model.

Answers have been directly included in Table 2.

EAG Table 2 – EAG queries on discrepancies between reported model input parameters

Parameters	Location in company submission	Location in company model	Source	Which value (company submission or model) should be considered in the company's base case?
Clinical effectiveness				
Efficacy of BAC: model inputs Day 8	CS Table 31 (11.1%)	Data Library!U38 (5.56%)	Effisayil 1™ trial	5.56% to reflect the 1 additional responder between Days 3 and 8 (as per Section B.3.3.2; no change to economic model)
Efficacy of spesolimab: % people whose GPP flare responds at Day 8	CS Table 17 (2.9%); CS Table 31 (8.6%)	Data Library!U28 (2.9%)	Effisayil 1™ trial data	2.9% (no change to economic model)
Efficacy of spesolimab: % people whose GPP flare responds by Week 12	CS Table 17 (20%); CS Table 31 (14.3%)	Data Library!U32 (20%)	Effisayil 1™ trial data	20% (no change to economic model)
Efficacy of BAC: % people whose GPP flare responds by Week 12	CS Table 31 (21.3%)	Data Library!U42 (40.94%)	Effisayil 1™ trial plus Effisayil 1™ historical data	40.94% (no change to economic model)
Resource use and costs				
Drug costs: ciclosporin	CS Table 22 (£41.59)	Acquisition costs!F8 (£68.28)	BNF	£41.59 (economic model has been updated). Note CS Table 22 should read '100' for the strength (mg)
Drug costs: infliximab	CS Table 22 (£755.32 for 240mg)	Acquisition costs!F10 (£377.66 for 100mg)	BNF	£377.66 for 100mg (no change to economic model)

Parameters	Location in company submission	Location in company model	Source	Which value (company submission or model) should be considered in the company's base case?
Treatment dosing schedule: clobetasol propionate	CS Table 23 (every week)	Acquisition costs!K14 (week 1-4)	BNF	Both are based on the BNF, which states for up to 4 weeks. Note that since the BNF is not specific to GPP, for implementation in the model treatment dosing was aligned with the pathway of care in Figure 4 (so only used during week 1, and only in a scenario where active treatment in the first week is modelled).
Treatment dosing schedule: ustekinumab	CS Table 23 (Day 1, Week 4)	Acquisition costs!K13 (week 1-4)	BNF	This should match the BNF; as per the CS Table 23. The economic model has been updated to reflect this (sheet 'Drug Dosage').
Weekly acquisition cost: clobetasol propionate	CS Table 25 (£3.76)	Acquisition costs!J14 (£0.04)	BNF	£3.76; economic model has been updated accordingly.

Utility inputs

B8. Priority question. Please explain how the company have derived the health state utility values used in the economic model. Please provide details on the methods used.

As outlined in the CS, values for an active flare were based on baseline utility, regardless of treatment. The utility value for resolved flares was based on a repeated-measures mixed effects model, accounting for multiple measures per patient. In the Effisayil™ 1 trial, data on EQ-5D-5L was collected daily during the first week and then weekly until weeks 4, 8, and 12. The base-case analysis utilized EQ-5D-5L to calculate health state utilities. Specifically, the EQ-5D-5L data from the Effisayil™ 1 trial was leveraged to estimate utilities for "GPP flare". Similarly, EQ-5D-5L data from the Effisayil™ 2 trial was employed to assess the health state of "Resolved flare" given that patients spent most of their time in the trial without experiencing a GPP flare. Utility data were mapped to EQ-5D-3L from EQ-5D-5L

data based on the individual patient data, using patients' 5 Dimension scores, age and sex in line with the approach described in Hernandez et al.14

Resource use and cost inputs

B9. Please provide details on how the proportion of patients hospitalised in a day care were calculated (see model Data Library!U90)

This was obtained via an analysis of Hospital Episodes Statistics (HES) data for GPP Non elective events, April 2016 – February 2022. Of [redacted] inpatient admissions where the primary patient diagnosis was GPP (ICD-10 code L401), [redacted] ([redacted]) were day cases.

B10. Please explain the adjustment made to the number of days for length of stay in intensive care units (model Data Library!U87, U89) and why the company adjusted it rather than using the mean number of days estimated by UK experts as part of the SEE exercise.

Within the economic model, length of stay is based on GPPGA pustulation subscore, with a value of 0 or 1 representing a response, and hence discharge from hospital. This approach was validated by UK clinicians. As a result, mean length of stay was not a model input, but a model output – and the maximum length of stay in intensive care (which is a model input) was therefore adjusted so that mean length of stay in intensive care was similar to the elicited values.

B11. The adverse event costs shown in CS Table 30 and used in the model were obtained from the National Schedule of NHS costs 2020/21. Please update these costs using the National Schedule of NHS costs 2021/22.

The adverse event costs have been updated using the National Schedule of NHS Costs 2021/2022 (see "Data Library" rows 489 to 491). The mean costs are £2,718.58 for serious infection, £4,253.13 for tuberculosis reactivation, and £2,262.30 for liver injury. These figures are based on the weighted average of total HRG costs based on NHS currency code for each respective adverse event (see "Data Library" F489 to F491 for the NHS currency code used).

B12. Priority question. The company model assumes that no patients on spesolimab are admitted to intensive care units and provide an insufficient

justification for this assumption in CS Table 29. Please provide literature- or trial-based data to support this justification.

There was no planned collection of data on intensive care unit administrations. Spesolimab has demonstrated rapid and sustained control of disease, with skin clearance as early as Day 3 and pustulation clearance as early as Day 2 (see Section B.2.6 of the CS for further details). The effectiveness of spesolimab is also demonstrated by clinically meaningful improvements in patient reported outcomes and markers of inflammation. Collectively this suggests that, due to the efficacy and rapid onset of spesolimab, it is not unreasonable to assume that spesolimab will also be effective at stopping patients from requiring admission to an intensive care unit. During clinical validation, UK clinicians agreed that they expect the treatment with spesolimab to reduce hospitalisations. Given spesolimab's rapid onset of action, they expected a lower rate compared to BAC.[8]

B13. Priority question. The administration costs and sources used in the model are inconsistent with those reported in the company submission. Table 3 below provides a summary of the costs provided by the CS and the model. Please provide a table identifying the administration costs for each drug that should be used in the company model and update the economic model if required.

EAG Table 3 – Comparison of administration costs in the company submission and company model

Administration	Cost in company submission	Source in company submission	Cost in company model	Source in company model
Subcutaneous	£3.61	TA375	£57.00	PSSRU 2023, community-based nurse as per TA935
IV, simple	£361.53	National schedule of NHS costs 2020/21: SB12Z (deliver simple parenteral chemo at first attendance)	£174.89, no difference between simple or complex IV administration	Cost of dermatology outpatient as per TA907, National schedule of NHS costs 2021/22: WF01A.
IV, complex	£482.91	National schedule of NHS costs 2020/21: avg of SB13Z-SB14Z		

		(deliver more complex parenteral chemo at first attendance and deliver complex chemo, including prolonged infusion treatment, at first attendance)		

The below table provides an overview of the administration costs that are used in the model. Note that the subcutaneous dose was erroneously given as for 1 hour instead of 3, and not based on the latest costs – the economic model has now been updated to include this.

Table 9: Administration costs used in the model

Administration	Cost in model	Source and justification
Oral	£0	Assumption: TA442, TA475, TA511, TA907
Subcutaneous (first dose)	£141.00	PSSRU 2023, unit costs of health and social care 2022/23, Nurse (Community-based band 5 without qualifications), wage cost per hour (3 hours); Cost incurred only once on the first use of SC therapy, as patients self-administer thereafter. As per TA935.
Subcutaneous (subsequent dose)	£0	See above
IV	£174.89	Assumed to be the total unit cost of a dermatology outpatient appointment (as per TA907) applied for each IV administration. National Schedule of NHS Costs 2021–2022. WF01A: Non-Admitted Face-to-Face Attendance, Follow-up. Dermatology (Service Code 330). Outpatient procedure

Below is an overview of the updated cost-effectiveness results (for the base-case and uncertainty analyses). This incorporates the updates outlined in the response to B4, B6, B7, B11, B13.

Results at list price

Spesolimab continues to dominate BAC in the base case and in the majority of sensitivity and scenario analyses. The most influential inputs are the spesolimab IV infusion costs, the proportion of patients treated as inpatients and the daily cost of inpatient care. In scenario analyses, when RWE is used to model the efficacy of BAC from Day 0, or when alternative approaches to inpatient day costs or different inpatient percentages are applied, spesolimab no longer dominates BAC.

Table 10: Base case results at list prices

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	INHB at £20,000 / QALY	INHB at £30,000 / QALY
BAC	[redacted]	[redacted]					
Spesolimab	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	[redacted]	[redacted]

Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life years gained; QALYs, quality-adjusted life years.

Table 11: Probabilistic base case results at list prices

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	INHB at £20,000 / QALY	INHB at £30,000 / QALY
BAC	[redacted]	[redacted]					
Spesolimab	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	[redacted]	[redacted]

Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 4: Cost-effectiveness plane, spesolimab vs BAC – list price

Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 5: Cost-effectiveness acceptability curve – list price

Key: WTP, willingness-to-pay.

Figure 6: Deterministic sensitivity analysis tornado diagram – list price

Key: BAC, best available care; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; ICER, incremental cost-effectiveness ratio; IV, intravenous; W, week.

Table 12: Results of scenario analyses at list price

	Scenario	Justification	ICER versus BAC
	Base case		Spesolimab dominates
1	BAC efficacy: RWE from Day 0	Alternative approach to estimating BAC efficacy	[redacted]
2	LoS for ICU with MV not capped	Reflect uncertainty in how long patients stay in ICU	Spesolimab dominates
3	Inpatient costs: non-elective short stay	Alternative approach to costing inpatient day costs	[redacted]
4	BAC inpatient percentage based on literature (proportion of patients treated as inpatients: most severe flare)	Uncertainty in how many patients require hospitalisation for their flare	Spesolimab dominates
5	BAC weightings: 100% most severe from Day 0	Alternative approach to estimating BAC efficacy	Spesolimab dominates
6	BAC inpatient percentage based on SEE	Uncertainty in how many patients require hospitalisation for their flare	[redacted]
7	Inpatient costs: GPP-specific admissions	Alternative approach to costing inpatient day costs	Spesolimab dominates
8	BAC efficacy: Typical flare from day 8	Alternative approach to estimating BAC efficacy	Spesolimab dominates
9	Spesolimab % of inpatients treated in ICU equivalent to comparator	Uncertainty in the impact of spesolimab on ICU admissions	Spesolimab dominates

Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; LOS, length of stay; RWE, real world evidence; SEE, structured expert elicitation.

Results at PAS price

Spesolimab continues to dominate BAC in the base case, in all of the deterministic sensitivity analyses and in all of the scenario analyses apart from when RWE is used to model the efficacy of BAC from Day 0. For this scenario, the ICER is £[redacted].

Table 13: Base case results – PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	INHB at £20,000 / QALY	INHB at £30,000 / QALY
BAC	[redacted]	[redacted]					
Spesolimab	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	[redacted]	[redacted]

Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life years gained; QALYs, quality-adjusted life years.

Table 14: Probabilistic case results – PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	INHB at £20,000 / QALY	INHB at £30,000 / QALY
BAC	[redacted]	[redacted]					
Spesolimab	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	[redacted]	[redacted]

Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 7: Cost-effectiveness plane, spesolimab vs BAC – PAS price

Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 8: Cost-effectiveness acceptability curve – PAS price

Key: PAS, patient access scheme; PAS, patient access scheme; WTP, willingness-to-pay.

Figure 9: Deterministic sensitivity analysis tornado diagram – PAS price

Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; IV, intravenous; PAS, patient access scheme; W, week.

Table 15: Results of scenario analyses (PAS price)

	Scenario	Justification	ICER versus BAC
	Base case		Spesolimab dominates
1	BAC efficacy: RWE from Day 0	Alternative approach to estimating BAC efficacy	[redacted]
2	LoS for ICU with MV not capped	Reflect uncertainty in how long patients stay in ICU	Spesolimab dominates
3	Inpatient costs: non-elective short stay	Alternative approach to costing inpatient day costs	Spesolimab dominates
4	BAC inpatient percentage based on literature (Proportion of patients treated as inpatients: most severe flare)	Uncertainty in how many patients require hospitalisation for their flare	Spesolimab dominates
5	BAC inpatient percentage based on SEE	Uncertainty in how many patients require hospitalisation for their flare	Spesolimab dominates
6	Inpatient costs: GPP-specific admissions	Alternative approach to costing inpatient day costs	Spesolimab dominates
7	BAC weightings: 100% most severe from Day 0	Alternative approach to estimating BAC efficacy	Spesolimab dominates
8	Spesolimab % of inpatients treated in ICU equivalent to comparator	Uncertainty in the impact of spesolimab on ICU admissions	Spesolimab dominates
9	BAC efficacy: Typical flare from day 8	Alternative approach to estimating BAC efficacy	Spesolimab dominates

Key: BAC, best available care; GPP, generalised pustular psoriasis; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; LOS, length of stay, RWE, real-world evidence; SEE, structured expert elicitation.

Scenario analyses

B14. Priority question. CS Table 24 notes that "The use of systemic and topical treatments was considered in a scenario". The EAG are unable to find this scenario in CS Table 37 or CS Table 38. Please provide us with an explanation of this scenario and the results.

This is explored in the scenario 'BAC efficacy: RWE from Day 0' where, for consistency with the approach to estimating BAC efficacy from RWE (which is based

on patients receiving active treatments), drug costs are incurred for the first week – this includes systemic and topical treatments based on the proportions reported in Figure 4 of the CS. Please note that due to an error in the economic model these costs were not incurred in the scenario; updated scenario results are provided in response to question B13.

Additional question

B15. All patients in ICU have utility value 0, is this for all patients IN ICU or only for those on MV?

This is for all patients in intensive care unit, irrespective of whether they require mechanical ventilation.

Section C: Textual clarification and additional points

C1. Please provide an abbreviations list for CS document B.

Please find below an abbreviations list.

A&E	Accident and emergency
AE	Adverse event
ANC	Absolute neutrophil count
BAC	Best available care
BNF	British National Formulary
CEE	Central and Eastern European
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CRP	C-reactive protein
DLQI	Dermatology Life Quality Index
DRESS	Drug reaction with eosinophilia and systemic symptoms
DSU	Decision Support Unit
EEPRU	Policy Research Unit in Economic Methods in Health and Social Care Intervention
eMIT	Drugs and pharmaceutical electronic market information tool
ERASPEN	European Rare And Severe Psoriasis Expert Network
FACIT	Functional Assessment of Chronic Illness Therapy

GPP	Generalised pustular psoriasis
GPPGA	Generalised Pustular Psoriasis Physician Global Assessment
HCRU	Healthcare resource use
HDU	High dependency unit
HES	Hospital Episode Statistics
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IgG	Immunoglobulin G
IL-36R	Interleukin-36 receptor
IL-36R	Interleukin-36
IL-36Ra	Interleukin -36 receptor antagonist
INHB	Incremental net health benefit
IRT	Interactive response technology
ITT	Intention-to-treat
IV	Intravenous
JDA	Japanese Dermatological Association
LOS	Length of stay
mAb	Monoclonal antibody
MCID	Minimal clinically important difference
MIMS	Monthly Index of Medical Specialities
MV	Mechanical ventilation
NHS	National Health Service
PGA	Physician Global Assessment
PRO	Patient-reported outcome
PSS	Psoriasis Symptom Scale
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RMP	Risk Management Plan
RWE	Real-world evidence
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SEE	Structured expert elicitation
SLR	Systematic literature review

SmPC	Summary of product characteristics
SNDS	French National Health System database
TNF	Tumour necrosis factor
ULN	Upper limit of normal
UTI	Urinary tract infection
VAS	Visual analogue scale
WBC	White blood cell
WTP	Willingness-to-pay

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Psoriasis and Psoriatic Arthritis Alliance (PAPAA)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	PAPAA is a national charity, which provides information and support to people affected by psoriasis and psoriatic arthritis. The current incarnation followed the merger of two separate organisations, with the oldest dating back to 1992. Although the charity has no formal membership, it has a supporter register of >13,000 people, which includes both patients and healthcare professionals. In a changing 21st century, activity and support has evolved with more taking place online, with most interaction via that medium. The main charity website has >8,000 members and has had >800,000-page views during the past year. Our information of generalised pustular psoriasis has been viewed >19,000 (around 2.5% of the total site engagement) times over that period, this includes downloads of patient information for off-line use. Regular use of feedback forms and online surveys help to direct the charity's work and how it represents its constituent group. Funding is via donations, subscriptions, other income generation and from the sale of promotional items. Financial support is not accepted from the pharmaceutical industry, either as direct payment or in-kind, this includes third-party work via PR or research agencies. The organisation values its independence and feels this provides an agenda which is patient-centred and not driven by marketing or promotional activities, that may be behind such support, however arms-length or segmented.

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Data for this submission has been gathered via a specific survey about GPP. The survey and need for views for this submission was added to our circulation list, news feed and was widely circulated via our social media. Our ongoing online general PAPAA survey along with previous feedback, also added to the content.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Generalised pustular psoriasis (GPP) is a rare condition, that presents as painful erupting pustules, if left untreated it has the potential to be life threatening, and often appears or develops alongside the more common plaque type. Although, distinctly different from plaque psoriasis, it does pose similar issues of having a very visible chronic skin disease. As with other variants, the condition can come and go, with sudden flares and remission. Other symptoms can include: fatigue, fever, headaches, muscle weakness and joint pain. People will adapt their behaviour to avoid embarrassment. The psychological impact is equally as is with widespread plaque psoriasis. Avoidance of situations that expose skin, this includes relationships, work, social and leisure activities. A general misunderstanding of the causes, that it's not contagious and the limited knowledge amongst some healthcare professionals, can cause delayed diagnosis, treatment, care and anxiety about the condition. In our small qualitative survey (n=12), we asked a number of questions including basic demographic data, how GPP affected education, work, relationships, social life, self-esteem and future plans, most of the respondents reported that all those domains, were moderately to severely affected by having GPP. In free text answers the following comments were given: *"People comment all the time on my skin. Including strangers who pass me in the street. I am 50-75% covered in plaque and pustular psoriasis."* (Male aged 46). *"I am usually able to hide my psoriasis with clothing*." (Female aged 60). *"I don't know how I will be feeling or what I can do, as it can flare."* (Female aged 26). *"I'm conscious of puss filled spots as well as red blotches and burst spots, which look ugly."* (Male aged 71). *"It comes and goes, I could have pustules on all fingers and on hands but, as is now, only one stubborn pustule on one finger that won't go away"* (Female aged 57).

	"I'm in severe pain. I have to plan my days as to what work I can do. I wish I could reduce hours as there are days I feel I cannot get out of bed, but finances do not allow. PiP don't agree I suffer enough for mobility allowance." (Male aged 46). "…the fact that it is always in awkward places makes it a nuisance and difficult to treat and live with…" (Female aged 76). *"Comes and goes. Can be all over hands and feet or, as now, concentrated on one finger."* (Male aged 54). *"Fortunately, I only have mild pustular psoriasis, but it does get me down."* (Male aged 66). *"I had general psoriasis and then I developed pustular psoriasis, which I had never had before and was unable to walk nor use my hands (have to open doors with elbows).* (Female aged 71). *"I mostly have this on my hands. This makes caring for myself difficult." (*Female aged 58). This of course is a small self-selected group of people who took time to complete a survey, but provides an insight into some lived-experiences and chimes with those that people report to us via our information line, and within our larger data collection process.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	For GPP, patients report the lack of effective available treatments, for the more common plaque psoriasis there has been a huge advance and availability of newer therapies, sadly these prove ineffective in GPP. The nature of GPP, its presentation and rarity can make diagnosis difficult. The appearance, which is very different to plaque psoriasis can lead to misdiagnosis, which does leave those affected frustrated.
8. Is there an unmet need for patients with this condition?	The lack of any specific treatment for GPP, means that those therapies trialled in general plaque psoriasis will be the only available options. A targeted therapy for GPP would provide a much-needed solution in the treatment pathway.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We have no information from patients on the merits of this technology. The evidence within the trial suggests that the issues patient would want to see from a therapy, could provide some advantages.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As with similar class therapies used currently for plaque psoriasis, the product is a self-administered subcutaneous injection, this may pose difficulties for some people with limited hand dexterity, GPP does commonly affect the hands.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	None that are obvious.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None covered by the Equality Act, as far as we can see.

Other issues

13. Are there any other issues that you would like the committee to consider?	None

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Rare variant of psoriasis • Limited dedicated therapy • Unpredictably flares and remits • Impacts on self-care due to location • High psychological effect of visible disease

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Psoriasis Association
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Patient Support Organisation and Charity. The reach of the Psoriasis Association now extends much further than that of the original member. The Psoriasis Association currently has around 2000 members who help to fund the organisation via an annual fee. Other sources of income include fundraising (individuals, legacies and trusts), Gift Aid, investments and unrestricted educational grants from the Pharmaceutical Industry for projects (there is a policy that no more than 15% of the total income of the Psoriasis Association can come from the Pharmaceutical Industry). The Psoriasis Association has three main aims; to provide information advice and support, to raise awareness and to fund and promote research. In addition to traditional members, the Psoriasis Association regularly communicates with, or offers a platform enabling people whose lives are affected by the condition to communicate with one another via online forums on their own websites (~17,500 registered users), and Social Media (~7,200 registered users on closed Facebook group). The main Psoriasis Association website averages 48,000 visits per month. Other social media channels used by the Psoriasis Association that lend themselves more to "raising awareness" include Twitter (~14,000 followers) and Instagram (~12,450 followers), along with a YouTube channel offering further information. The Psoriasis Association has been passionate about research throughout its 50+ year history. Regularly funding PhD studentships, alongside supporting the PPI of bigger research collaborations (including the James Lind Alliance Top 10 Research Priorities for Psoriatic Arthritis), always seeking to improve the lives of those affected by psoriatic disease and in 2021 awarded £1 million to the Biomarkers and Stratification to Optimise outcomes in Psoriasis (BSTOP) research project based at Kings College, London.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the	Yes Psoriasis Association has received funding from Boehringer Ingelheim - £2,000 towards annual conference costs (they and the other companies who supported the event had no control / input to the programme agenda). Other pharmaceutical funding in the last 12 months includes:-

comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Abbvie (£600 – Honorarium) Bristol Myers Squibb (BMS) (£4,500 – Core funding and Conference costs) Janssen (£2,500 Conference costs) LEO Pharma (£2,000 – Core funding) Medac Pharma (£2,000 – Core funding) UCB (£5,160 – Core funding, Conference costs and honorarium)
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	This submission has been informed by informal, anecdotal information that we hear from patients and carers themselves, through the following channels provided by the Psoriasis Association:- the Psoriasis Association website (517,359 visitors in 2023) helpline (1,038 enquiries in 2023) online forums (20,219 registered users in 2023) social media channels (including Facebook Group, Twitter / X, Instagram and LinkedIn, 57,624 followers / users in 2023) The Psoriasis Association analyses the data gathered from all communication channels (mentioned above) and monitors for trends in addition to interesting new requests. We have completed a Priority Setting Partnership on Psoriasis which gave valuable insight into issues affecting people living with psoriasis and supported the Priority Setting Partnership on psoriatic arthritis (including membership of the Steering Committee). The Psoriasis Association also ran a questionnaire (open for 4 weeks in July / August 2024) advertised on the website and social media channels, inviting people with GPP to share their experiences of living with the condition. The questionnaire contained both quantitative and qualitative questions and was answered by 21 people.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	One respondent to the Psoriasis Association survey described GPP in the following way:- (It) "travels like a slow-burning flame over my body with pustules appearing as it goes. Extremely painful and messy". Whilst another explains "it's demoralising and dictates your life down to how you feel with the pain, the clothes you wear, how people look at you, restricts everything you do". The condition itself causes "pus-filled blisters over arms, hands, chest, thighs and stomach then burst and leave my skin peeling. It makes my skin feel tight and red raw and I can't move without pain. High temperature and feeling sick accompany bad flares." Most people in the Psoriasis Association survey reported they feel dirty "all the time" with the majority describing how sore, painful and uncomfortable the condition is. People feel that their skin is on fire, and they are very scared. GPP impacts on all aspects of people's lives including their relationships. Many people explained how their homelife and relationships suffer, they withdraw from society and "struggle to do anything", "I can't work, I can barely leave my house. I find it hard to cope outside my home environment when I have flare ups". Intimate relationships with loved ones suffer – "I cannot bare to have anyone touching me, which my husband finds very difficult when he wants to comfort me", "my husband and I cannot be intimate", as do relationships with other family members – "my youngest son doesn't understand why he can't cuddle his Mummy". As mentioned above, the ability to work also suffers "I lost my job because I was so ill for such a long period of time". People's choice of clothes is limited – cloth against the inflamed skin irritates and hurts, clothes get damaged by topical treatments – yet understandably people also feel they want to cover their skin, to hide the physical symptoms of the condition. Pain and discomfort are reported frequently, along with itching – "Everything is difficult as I'm so consumed with itching". Over 90% of participants (19/21) reported that GPP has prevented them from doing things from exercising and socialising, wearing nice clothes, working and even sitting (due to eruptions on back and buttocks). The condition rarely flares once – the people in our survey all had had more than 2 flares, with over half having had more than 10 flares. Owing to this, the fear and anxiety people live with regarding when the next flare will occur is huge (over 40% of participants described worry about it coming back). Answers about the impact of the condition between flares included:- • It's dreadful – watching and waiting for the next flare • Scared of every blotch on skin • Constant living nightmare

	• There's always a bit of dread looming • Gives me anxiety thinking it may just appear at any time and always on my mind • I have left my old life behind now, unable to do the things I loved, like taking my dogs out, swimming with my family Depending on when GPP presents (the age of diagnosis ranged from under 16 years of age up to 74 years of age) impacts on different aspects of life. One respondent missed all their secondary school education (which clearly has knock on effects regarding life-achievements and accomplishments) whilst others have lost jobs owing to the time it takes to treat GPP. Family life suffers also, with lots of missed holidays and social withdrawal. When asked how it (GPP) makes you feel, one response was "like I'm going to die".

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	From our survey, the insights people gave regarding the care within the NHS system in order to get treatments:- • 14% reported long waits to see a Dermatologist, with a further 10% of respondents having to report to A&E and 10% of respondents being 'stuck in primary care (with one person resorting to seeking treatment abroad). • Sadly, 20% of respondents felt the care they received lacked empathy, with respondents feeling that 'no-one understands'. • There was frustration with how slow it can be to advance to further therapies (from topicals), and the processes people must go through:- o 'Have to jump through hoops to be taken seriously' o 'As a patient we have to go through years of an embarrassing dance before we get to biologics. It's a waste of everyone's time and NHS resources' o I am tired of going back and forth to the doctor and hospital – I feel like it's a constant battle I have to fight' o 'Having to go through a long list of creams or tablets before you get to biologics is very wearing' When it comes to the treatments themselves, respondents found that the ointments and creams 'make it worse' and 'leave marks on everything I own'.
8. Is there an unmet need for patients with this condition?	Yes

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	That it could give them back their life – improve their mental health – start living again.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	That it may not work for everyone – the cycle of hope and despair is difficult to manage

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The recent survey by the Psoriasis Association of people with GPP found there was a large impact on people's mental health following diagnosis. Two things in particular were highlighted; the anxiety and fear of when the GPP would flare again and the withdrawal from social situations (including work and exercise). To help ease the mental health burden of living with GPP, those newly diagnosed may benefit more from the new technology. However, those who have lived with GPP for many years would certainly benefit citing overwhelmingly in the survey the technology would allow them to have a normal life / get life back / start living again.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	If the prescribing of Spesolimab is dependent on severity scores, and the scores required include a measure for erythema, erythema presents differently in different skin types and this should be taken into account. More regarding the measuring of GPP severity can be found in the following paper:- https://doi.org/10.1093/bjd/ljad071

Other issues

13. Are there any other issues that you would like the committee to consider?	Many people with GPP will have been treated on specialist inpatient wards, most of which have now closed. People with GPP feel that they no longer have anywhere to go for specialist care. This treatment can help to restore trust that they are receiving the best treatment available, which should also limit the time people would need inpatient care for. By treating people quickly and appropriately, they will be able to return to or continue living their lives (including work) as the time spent in hospital will lessen

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• GPP is a devastating skin condition that is life threatening and life ruining • This treatment could have a positive life-changing result for people with GPP • GPP affects every aspect of someone's life; some cannot even sit down owing to the pain of the condition, let alone walk, exercise, study, work, socialise or have relationships. • The threat of GPP returning or flaring is devastating and consuming – if there was a treatment available to help alleviate the symptoms of a flare, this would in-turn help to treat the anxiety that people experience.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted] and [redacted], on behalf of the on behalf of the BAD Therapy & Guidelines sub-committee, and [redacted] on behalf of the BAD Guideline Development Group on biologics for psoriasis.
2. Name of organisation	British Association of Dermatologists (the BAD)
3. Job title or position	Consultant Dermatologists
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** A specialist in the treatment of people with this condition? **Yes** A specialist in the clinical evidence base for this condition or technology? **Yes** Other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD is a not-for-profit organisation whose charitable objectives are the practice, teaching, training, and research of dermatology. It works with the Department of Health and Social Care, patient bodies and commissioners across the UK, advising on best practice and the provision of dermatology services across all service settings. It is funded by the activities of its members.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	The BAD is a registered charity and owns various companies. The British Association of Dermatologists Biologic Interventions Register (BADBIR) is the national psoriasis biologic and systemic treatment registry (and an NIHR portfolio study) run by the BAD as a non-profitmaking limited company. This company receives funding from most manufacturers of biological drugs for psoriasis on the registry to collect pharmacovigilance data. The BAD does not receive any funding from BADBIR.

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	• To control flare/the acute phase of generalised pustular psoriasis (GPP), i.e. rapid and sustained clearance of pustules, redness, alleviate symptoms of pain and distress, to control systemic aspects (fever, shock, acute respiratory distress syndrome (ARDS), cardiovascular disease (CVD) and renal failure, infection) https://pubmed.ncbi.nlm.nih.gov/36606566/. • To prevent new flares. • To improve the quality of life and reduce disease burden. • To reduce reliance on systemic immunosuppressive strategies that result in long-term, drug-induced morbidity (e.g. ciclosporin, methotrexate, retinoids).

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Rapid resolution of acute flares; prevention of recurrent flares; reduction in use of systemic immunosuppressive strategies (e.g. corticosteroids; ciclosporin particularly); reduction or avoidance of hospital admissions. In the acute phase, recommended measures of GPP activity include: • Generalised Pustular Psoriasis Area and Severity Index • Generalised Pustular Psoriasis Physician Global Assessment (GPPGA; https://pubmed.ncbi.nlm.nih.gov/37075220/) • Body surface area (BSA) involvement • Pain scores • DLQI • Alongside measures of systemic features depending on individual characteristics of the patient including fever, levels of C-reactive protein, white cell count and albumin A clinically significant response in an acute flare would include: • 0 or 1 in the GPPGA or GPPASI pustular sub-score • Global assessment of at least mild • Resolution of skin pain • Resolution of systemic features • Becoming/remaining afebrile A clinically significant indicator of flare prevention includes: • Reduction in number flares (e.g. by at least 50%) • Reduction in severity of flares (e.g. absent systemic symptoms, no hospital admissions) • Reduction in use of systemic immunosuppressants with long-term, associated morbidity (e.g. ciclosporin) Given the rarity of GPP, the cited disease severity scores may not be in routine clinical practice in all centres. However, PASI and BSA are widely used in routine clinical care as part of disease severity assessments for

	plaque-type psoriasis so adoption of GPPASI (and BSA) to assess impact of spesolimab can be implemented rapidly.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. GPP is a severe, potentially life-threatening condition for which there are no licensed therapeutic interventions with proven efficacy. It is episodic, unpredictable, painful and incapacitating, associated with severe systemic features, often requiring hospital admission and organ support in an intensive care setting. It is associated with major morbidity – and in some cases, mortality. The unpredictable nature of the condition further compounds the long-term psychological impact of the disease.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Current NICE guidelines state (CG153) that: *"People with generalised pustular psoriasis should be referred immediately for same-day specialist assessment and treatment"* This means that all patients with GPP are under the care of specialist dermatology services. During an acute flare, patients are often/usually admitted for inpatient supportive management (specialist nursing care with topicals, pain management, and for associated systemic upset including fluids, management of infection, liaison with relevant specialists depending on organ involvement; severe cases are managed in HDU/ITU). There are no licensed therapeutic interventions for GPP flares. Commonly used strategies include ciclosporin and infliximab/TNF antagonists. In acute cases, methylprednisolone is deployed occasionally and, in less severe cases, methotrexate and retinoids may be used (often in combination). Targeted immunomodulatory therapies developed for plaque-type psoriasis have also been used with variable – and unpredictable – success, including IL17 and IL23 antagonists, the evidence for which is based primarily upon case reports and small case series.

	Ciclosporin and TNF antagonists are probably the most widely used approach to prevent flares, although with variable success, and (in the case of ciclosporin) substantial long-term risk. https://pubmed.ncbi.nlm.nih.gov/34626330/, https://pubmed.ncbi.nlm.nih.gov/38114719/, https://pubmed.ncbi.nlm.nih.gov/36219603/ Given the rarity of the condition and the lack of clinical trials, coupled with a lack of specific guidelines https://pubmed.ncbi.nlm.nih.gov/38114719/ treatment can be highly individualised, relying on the clinical expertise of healthcare professionals at specialised centres.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE CG 153 recommends immediate referral to specialist care. The BAD guidelines cover GPP in the systematic review scope (currently being updated – last published in 2020) but there was inadequate evidence to produce strong recommendations. Weak evidence for TNF antagonists justified consider use of TNF antagonists (and integrated into pathways of care, e.g. Southeast London ICS https://www.selondonics.org/wp-content/uploads/dlm_uploads/2022/11/Psoriasis-Biologic-Pathway-Adults-FINAL-January-2022.pdf). In the US and Japan, in light of evidence on spesolimab, spesolimab is strongly recommended https://pubmed.ncbi.nlm.nih.gov/37838256/.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In general, the treatment pathway includes a combination of topical and systemic treatments and supportive care, but this may vary depending on the severity of skin and systemic involvement and the extent of affected skin areas. See also section 9 above.

9c. What impact would the technology have on the current pathway of care?	Spesolimab is the first, targeted intervention for GPP, developed as a result of understanding the disease biology, with evidence for benefit from trials that have been well designed, especially in the context of it being a rare disease, with heterogenous clinical manifestations, and its episodic and unpredictable disease course. Following approval in the US and Europe, it is recognised as the "first-in-class" medication, setting the standard of care for treating GPP flares in adults. Given the benefit in acute flares in very rapidly resolving symptoms, signs and systemic upset (within days), this technology would have a very major impact on the current pathway https://pubmed.ncbi.nlm.nih.gov/34936739/. CG153 already states that patients with GPP should be referred immediately to secondary care. At the point of referral, if spesolimab is approved for use first line, then access to facilities for IV administration will be required. Use of spesolimab would be expected to reduce the need for hospital admission, reduce the length of stay, reduce escalation of care to HDU/ITU and reduce or prevent systemic complications (from GPP as well as drug-related toxicity) and the significant psychological impact of the disease. If approved for *prevention* of flares, this would be expected to reduce the need for repeated follow-up appointments, and the use of interventions of unproven/variable benefit.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This technology can be used within the current NHS care pathway. Within specialist care, administration of IV drugs is well established for dermatological conditions and the SmPC (posology, administration, adverse effects) do not pose any specific or unique challenges.
10a. How does healthcare resource use differ between the technology and current care?	See above. This is the first technology specifically available for the management of acute GPP. Within specialist care, administration of IV drugs is well established for dermatological conditions. Use of spesolimab would be expected to reduce the need for hospital admission, reduce the length of stay, reduce escalation of care to HDU/ITU and reduce or prevent systemic complications (from GPP as well as drug-related toxicity) and the significant psychological impact of the disease.

	If approved for *prevention* of flares, this would be expected to reduce the need for repeated follow-up appointments, and the use of interventions of unproven/variable benefit.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care with specialist dermatology (and multi-disciplinary) expertise.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nothing specific other than development of guidelines for safe and effective use (as with any new intervention).
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes.
11a. Do you expect the technology to increase length of life more than current care?	Yes.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology appears to be effective in patients with a clinical diagnosis of GPP. Individuals carrying the IL36RN mutation *may* have specific additional benefit, although more research is required. See results presented at the EADV 2022 in poster format (not yet published in full) https://www.avancesenppg.com/arxius/imatgesbutlleti/Burden-D-EADV-2022-Poster-1224.pdf.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It would be easier for patients and healthcare professionals than current care. The treatment acts rapidly, is easy to administer, should negate the need for concomitant therapies, and requires no additional tests or monitoring. Current strategies are unpredictably effective, burdensome, and may be associated with significant drug-related toxicity.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The BAD will be integrating the evidence for spesolimab in the upcoming update of our guideline on the use of targeted immunomodulatory therapies for psoriasis. Spesolimab is likely to be recommended for patients with an acute, severe flare of GPP in the absence of any other licensed or effective treatment. This is a rare disease with a very substantial health burden.

	No additional testing required.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Time lost at work. Social impact and burden.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes.
16a. Is the technology a 'step-change' in the management of the condition?	Yes, for reasons stated above. This is the first technology specifically available for the management of acute GPP. In the US and Europe where its use has been approved, it is recognised as the "first-in-class" medication, setting the standard of care for treating GPP flares in adults.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8801408/. GPP is a severe, potentially life-threatening condition. This group of patients' acute healthcare needs have not been adequately met due to the lack of licensed therapeutic interventions with proven efficacy.
17. How do any side effects or adverse effects of the	The overall number of patients treated with spesolimab is limited, as this is rare disease. As with any new intervention, vigilance will be required to ensure drug-related problems are identified early and managed. To date,

technology affect the management of the condition and the patient's quality of life?	the side effect profile of spesolimab is favourable; infection has been cited as a potential complication (also a problem with GPP itself) and will be managed in line with current practice when using targeted immunomodulatory therapy for other indications.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Largely yes; however, there is no established pathway of care for GPP in the UK. Consideration should be made for the use of the technology at a much earlier stage in the pathway. https://pubmed.ncbi.nlm.nih.gov/34936739/ https://pubmed.ncbi.nlm.nih.gov/37738999/ https://pubmed.ncbi.nlm.nih.gov/36282833/ https://pubmed.ncbi.nlm.nih.gov/36527385/ https://pubmed.ncbi.nlm.nih.gov/37140190/ https://pubmed.ncbi.nlm.nih.gov/36870370/
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Resolution of flares, and prevention of flares. Both these key outcomes are captured using accepted standards in the trials. The trials were designed and supported by acknowledged experts in the field of GPP.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical	None that we are aware of.

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	This is a rare disease. There seems to be variation in the epidemiology of GPP with it being more common in Asia so inclusion of all languages in the search strategy will be important.
20. How do data on real-world experience compare with the trial data?	Not available yet.

Equality

21. Are there any potential equality issues that should be taken into account when considering this treatment?	As with all skin disease, commonly used tools may underestimate redness in people with darker skin tones. There are major challenges in the delivery of dermatology services post-Covid pandemic and in light of escalating skin cancer burden, expertise in management of complex rare conditions such as GPP may not be widely available. Equality of access may be difficult in certain areas. It is also worth noting that epidemiological evidence suggests that GPP may be more prevalent in non-white populations particularly East Asians (trials do include these populations).
22. Consider whether these issues are different from issues with current care and why.	These issues are similar for the current standard of care for patients with GPP.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• GPP is a severe, rare and life-threatening condition for which there are currently no licensed treatments or established standard of care. • This is a first-in-class, effective intervention targeting known pathological drivers of GPP. • We strongly support adoption of this technology into NHS care as it is likely to reduce length of hospital stay, reduce or prevent systemic complications (from GPP as well as drug-related toxicity), prevent flares of GPP after the acute phase hence reducing the need for follow-up appointments, use of interventions with unproven or variable benefit, thereby reducing mortality and morbidity due to GPP, including its psychological impact.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

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In part 1 we are asking you about living with generalised pustular psoriasis flares or caring for a patient with generalised pustular psoriasis flares. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **14 November 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Patient expert statement

Part 1: Living with this condition or caring for a patient with generalised pustular psoriasis flares

Table 1 About you, generalised pustular psoriasis flares, current treatments and equality

1. Your name	Helen McAteer
2. Are you (please tick all that apply)	☐ A patient with generalised pustular psoriasis flares? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with generalised pustular psoriasis flares? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Psoriasis Association
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: This submission has been informed by informal, anecdotal information that the Psoriasis Association

Patient expert statement

	hears from patients and carers themselves, through the following channels provided by the Psoriasis Association:- the Psoriasis Association website (517,359 visitors in 2023) helpline (1,038 enquiries in 2023) online forums (20,219 registered users in 2023) social media channels (including Facebook Group, Twitter / X, Instagram and LinkedIn, 57,624 followers / users in 2023) The Psoriasis Association also ran a questionnaire (open for 4 weeks in July / August 2024) advertised on the website and social media channels, inviting people with GPP to share their experiences of living with the condition. The questionnaire contained both quantitative and qualitative questions and was answered by 21 people. ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6a. What is your experience of living with generalised pustular psoriasis flares? **6b. Have you experienced recurrent flares?** **6c. Have you experienced a GPP flare within the space of 12 weeks from a prior flare?** **6d. How long after receiving treatment does it take for the flares to resolve, in weeks?**	

6e. Have you ever been untreated/ gone without treatment during a GPP flare and if so, what was the impact? **If you are a carer (for someone with generalised pustular psoriasis flares) please share your experience of caring for them**	
7a. What treatments have you received for generalised pustular psoriasis flares? **7b. What do you think of the current treatments and care available for generalised pustular psoriasis flares on the NHS?** **7c. Have you been treated with spesolimab?** **7d. Have you experienced GPP flares of different severity levels; if so, did you receive different treatments depending on the severity of the flare?**	
8. Are you aware if there are disadvantages for people of current NHS treatments for generalised pustular psoriasis flares? (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. Are you aware if there are advantages of spesolimab over current treatments in the NHS? If so, please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**	

9c. Does spesolimab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	
10. Are there any groups of patients who might benefit more from spesolimab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
11. Are there any potential equality issues that should be taken into account when considering generalised pustular psoriasis flares and spesolimab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
12. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- GPP is a devastating skin condition that that is life threatening and life ruining
- This treatment could have a positive life-changing result for people with GPP
- GPP affects every aspect of someone's life; some cannot even sit down owing to the pain of the condition, let alone walk, exercise, study, work, socialise or have relationships
- The threat of GPP returning or flaring is devastating and consuming – if there was a treatment available to help alleviate the symptoms of a flare, this would in-turn help to treat the anxiety that people experience
- Click or tap here to enter text.

Thank you for your time.

Your privacy

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Single Technology Appraisal

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Patient expert statement

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Your response should not be longer than 15 pages.

The deadline for your response is **12.30pm** on **Friday 06 December 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Patient expert statement

Part 1: Living with this condition or caring for a patient with generalised pustular psoriasis flares

Table 1 About you, generalised pustular psoriasis flares, current treatments and equality

1. Your name	Donna Lamour
2. Are you (please tick all that apply)	☒ A patient with generalised pustular psoriasis flares? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with generalised pustular psoriasis flares? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	The Psoriasis Association
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6a. What is your experience of living with generalised pustular psoriasis flares? **6b. Have you experienced recurrent flares?** **6c. Have you experienced a GPP flare within the space of 12 weeks from a prior flare?** **6d. How long after receiving treatment does it take for the flares to resolve, in weeks?** **6e. Have you ever been untreated/ gone without treatment during a GPP flare and if so, what was the impact?** **If you are a carer (for someone with generalised pustular psoriasis flares) please share your experience of caring for them**	I was diagnosed with Psoriasis at the age of 12/13. I have had various types, including palmoplantar on my hands and mainly feet, also scalp psoriasis and triggered the first time by a fall, grief and bullies - probably combined, for the next 40 years on and off. It's been torture. I have had recurrent flares, of different types. I am currently taking cosentyx (secukisumab), it has helped for a few years but is not effective at the moment. Current flares have not resolved and this treatment may be stopped. Without treatment the condition gets worse.
7a. What treatments have you received for generalised pustular psoriasis flares? **7b. What do you think of the current treatments and care available for generalised pustular psoriasis flares on the NHS?** **7c. Have you been treated with spesolimab?**	I've tried so many different things medically and not. A couple worked and then stopped working. I am now 54 and have more psoriasis in different places and it's a living hell. There are some good treatments but only available on the NHS if other treatments fail, so they are difficult to access. It's also hard to get face to face appointments and assessments. I have not been treated with spesolimab. I have had flares of different levels of severity and different types of treatment.

7d. Have you experienced GPP flares of different severity levels; if so, did you receive different treatments depending on the severity of the flare?	
8. Are you aware if there are disadvantages for people of current NHS treatments for generalised pustular psoriasis flares? (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Cosentyx lowers the immune system which means I am more susceptible to illnesses such as flu and Covid. This is a self-administered injection which easy to do, once a month.
9a. Are you aware if there are advantages of spesolimab over current treatments in the NHS? If so, please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does spesolimab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Not aware.
10. Are there any groups of patients who might benefit more from spesolimab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
11. Are there any potential equality issues that should be taken into account when considering generalised pustular psoriasis flares and spesolimab? Please	There are disadvantages due to this being a hidden disability, and there is a lack of awareness and understanding.

explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I've tried a lot of treatments that have failed and it's hard to access new treatments on the NHS.
12. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Spesolimab for treating generalised pustular psoriasis flares

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The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Ines Ribeiro critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Lois Woods critically appraised the clinical effectiveness systematic review and drafted the report; Asyl Hawa critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Joanna Picot critically appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator and guarantor.

Commercial in confidence (CIC) information in blue

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LIST OF ABBREVIATIONS

BAC	Best available care
BMI	Body mass index
BNF	British National Formulary
BSA	Body surface area
CEE	Central Eastern European
CI	Confidence interval
CIC	Commercial in confidence
CPRD	Clinical Practice Research Datalink
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
DLQI	Dermatology Life Quality Index
DRESS	Drug reaction with eosinophilia and systemic symptoms
DSA	Deterministic sensitivity analyses
EAG	External Assessment Group
eMIT	Electronic Market Information Tool
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue scale
GPP	Generalised pustular psoriasis
GPPASI	Generalised Pustular Psoriasis Area Severity Index
GPPGA	Generalised Pustular Psoriasis Physician Global Assessment
HCRU	Health care resource use
HES	Hospital Episode Statistics
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IL36	Interleukin-36
IL36Ra	Interleukin-36 receptor antagonist

IL36RN	Interleukin-36 receptor antagonist protein
ITT	Intent to treat
IV	intravenous
JDA	Japanese Dermatological Association
MCID	Minimum clinically important difference
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PAS	Patient Access Scheme
PGA	Physician Global Assessment
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Psoriasis Symptom Scale
PSSRU	Personal Social Services Research Unit
PV	Psoriasis vulgaris
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RWE	Real-world evidence
SD	Standard deviation
SEE	Structured expert elicitation
SLR	Systematic literature review
SmPC	Summary of product characteristics
SNDS	Système Nationale des Donneés de Santé = French National Health Data System
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TNF	Tumour necrosis factor
UK	United Kingdom
US	United States
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1 Summary of Key Issues

ID	Summary of issue	Report sections
1	The trial evidence is from a narrower population than defined in the NICE scope and company's decision problem.	2.3, 3.2.1, 4.2.3
2	Comparator in the Effisayil 1 trial is placebo not established clinical management without spesolimab	2.3, 3.2.1, 3.2.5.1, 3.2.5.2, 4.2.6
3	A second/recurrent GPP flare is not implemented in the model	4.2.2.2.1
4	Treatments included in the comparator arm	4.2.4
5	Short time horizon	4.2.5
6	Efficacy of the comparator arm (BAC): response to treatment	4.2.6.2
7	Proportion of patients treated as inpatients in the spesolimab arm	4.2.8.3

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the composition of the comparator in the first week of the model and the efficacy of BAC.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Following their response to the clarification questions, the company updated their economic model. The company revised base case deterministic cost-effectiveness results are shown in

Table 2 with a confidential PAS discount applied for spesolimab. The ICER is -£172,713 per QALY for spesolimab versus BAC (spesolimab dominates BAC), with a QALY gain of [redacted] and a reduced cost of [redacted].

Table 2 Company revised base case results after clarification responses using PAS price for spesolimab

Treatment	Total		Incremental		ICER
	Cost (£)	QALYs	Cost (£)	QALYs	(£/QALY)
BAC	[redacted]	[redacted]			-£172,713 (spesolimab dominates)
Spesolimab	[redacted]	[redacted]	[redacted]	[redacted]	

Source: Clarification response document Table 13, company revised economic model (Deterministic Results!F15)
BAC, best available care; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.

1.3 The decision problem: summary of the EAG's key issues

Although no key issues were identified with respect to the decision problem we note that the comparator in the company's key trial, Effisayil 1, comes from a narrower patient group (see Key Issue 1) and the comparator in the Effisayil 1 trial is placebo not established clinical management without spesolimab (see Key Issue 2 and Key Issue 4).

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 The trial evidence is from a narrower population than defined in the NICE scope and company's decision problem

Report section	2.3, 3.2.1, 4.2.3
Description of issue and why the EAG has identified it as important	The NICE scope and company's decision problem define the population for this appraisal as "*Adult patients with generalised pustular psoriasis presenting with flares*". This aligns with the therapeutic indication for spesolimab which is "*the treatment of flares in adult patients with generalised pustular psoriasis as a monotherapy*". However, the pivotal clinical trial that informs the company's submission and economic model, the Effisayil 1 trial, enrolled adult patients with generalised pustular psoriasis presenting with flares of moderate-to-severe intensity (section 3.2.1.1). Therefore, the trial evidence is drawn from a narrower population group (i.e. only people experiencing flares of moderate-to-severe intensity) than defined in the NICE scope and company decision problem. Additionally, the Structured Expert Elicitation (SEE) exercise for best available care efficacy and safety asked clinical experts to make estimates for patients with a moderate or a severe flare.

What alternative approach has the EAG suggested?	We do not suggest an alternative approach because there is no alternative source of trial evidence that is fully aligned with the NICE scope, company decision problem and economic model population.
What is the expected effect on the cost-effectiveness estimates?	Unknown, but the results from the cost effectiveness model may not be generalisable to a population of adults with generalised pustular psoriasis experiencing flares of any severity.
What additional evidence or analyses might help to resolve this key issue?	Clinical expert opinion about the patients expected to receive spesolimab in clinical practice and any potential for differences in spesolimab efficacy and best available care (BAC) efficacy for mild flares in comparison to moderate-to-severe flares.

Issue 2 Comparator in the Effisayil 1 trial is placebo not established clinical management without spesolimab

Report section	2.3, 3.2.1, 3.2.5.1, 3.2.5.2, 4.2.6
Description of issue and why the EAG has identified it as important	The NICE scope and company's decision problem define the comparator for this appraisal as established clinical management without spesolimab. The company's Figure showing the clinical pathway indicates which therapies are used at first-, second- and third-line or later in the treatment of moderate-to-severe GPP flares in the UK (section 2.2.3 of this report). However, the comparator arm in the company's pivotal clinical trial Effisayil 1 received placebo only (prior to randomisation, patients had to discontinue biologic therapies, systemic non-biological therapies and other treatments such as phototherapy and topical treatments). The economic model assumes that patients in the comparator arm receive no treatment during the first week (link with Key Issue 4). Therefore, clinical effectiveness evidence for the comparator arm in the first week of the trial and the associated period for the economic model does not align with clinical practice.
What alternative approach has the EAG suggested?	There is no alternative source of comparative trial evidence for spesolimab where the comparator is established clinical management without spesolimab.
What is the expected effect on the cost-effectiveness estimates?	The treatment effect for the first week for a comparison of spesolimab versus best available care is unknown. In the EAG's opinion the model may over-estimate the treatment difference between spesolimab and best available care in the first week because it is based on data from spesolimab and placebo treated trial participants. However, we acknowledge the absence of any reliable data to show whether there is a difference in effectiveness between best available care and placebo. Also see Key Issue 4
What additional evidence or analyses might help to resolve this key issue?	Given the nature of the available evidence it may be difficult to resolve this key issue. Clinical expert opinion may be able to provide an indication of the impact on flare symptoms when a patient does not receive any treatment for a week.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 3 A second/recurrent GPP flare is not implemented in the model

Report section	4.2.2.2.1
Description of issue and why the EAG has identified it as important	Patients who respond to treatment (i.e., have a GPPGA pustulation subscore of 0 or 1) are assumed to remain responders for the remainder of the modelled time horizon. However, evidence from the Effisayil 1 trial shows that 11.3% of patients received rescue treatment with spesolimab to treat second/recurrent flares, and eight patients received a standard of care escape treatment after day 8 although there is no information on how many of these patients have achieved a clinical response before getting worse. The company did not include second or recurrent flares in the model. We consider that understanding how modelling second/recurrent flares might affect the model conclusions is relevant for the committee's decision.
What alternative approach has the EAG suggested?	The EAG don't have data to model second or recurrent flares. It is unclear whether there is currently sufficient evidence (efficacy, safety, and costs) available to incorporate this in the model.
What is the expected effect on the cost-effectiveness estimates?	Uncertain; we note that the total costs will increase to account for the additional drugs used but we are unclear about the efficacy of the rescue treatments for patients with second/recurrent flares.
What additional evidence or analyses might help to resolve this key issue?	Evidence on the efficacy and safety of the rescue treatments and further clinical expert opinion on whether the company's assumption is reasonable or not.

Issue 4 Treatments included in the comparator arm

Report section	4.2.4
Description of issue and why the EAG has identified it as important	There are no licensed treatments specifically approved to treat GPP flares in the UK aside from spesolimab. In the company's model, it was assumed that patients in the comparator arm (BAC) do not receive any drugs during the first week (to align with the placebo data of the Effisayil 1 trial where patients in the placebo arm did not receive any active drugs during the first week). In the EAG's view, it is unlikely that patients in UK clinical practice would not receive any active drugs to treat GPP flares for a whole week (see Key Issue 2). Beyond that, data from the Effisayil 1 historical cohort study informed the efficacy of BAC (see Key Issue 6 for further details), although the treatments used to treat each flare in this study are not possible to derive. So, the treatments included in the BAC arm of the company's model beyond week 1 were obtained from a group of UK experts participating in a SEE exercise. We believe that modelling the treatments indicated by the UK experts as part of the

	SEE exercise is a reasonable approach in the absence of better UK evidence. However, it is unclear how closely these treatments match the treatments used to treat moderate-to-severe GPP flares in the Effisayil 1 historical cohort study (see Key Issue 6 for further details).
What alternative approach has the EAG suggested?	The EAG included active treatments in the comparator arm in the first week of the model in our base case, obtained from the SEE exercise. This is aligned with the EAG base case for the efficacy of the comparator arm (see Key Issue 6 below).
What is the expected effect on the cost-effectiveness estimates?	Including active treatments in the comparator arm in the first week of the model leads to ICERs of £15,680 (using the company's base case source of efficacy for BAC - Effisayil 1 1 historical cohort) and to £143,574 (using the EAG base case source of efficacy for BAC – SEE exercise).
What additional evidence or analyses might help to resolve this key issue?	Further clinical expert opinion on which treatments are currently considered the best available care in UK clinical practice to treat GPP flares.

Issue 5 Short time horizon

Report section	4.2.5
Description of issue and why the EAG has identified it as important	A time horizon of 12 weeks was implemented in the company's model, which is the follow-up period of the Effisayil 1 trial. The EAG notes that relevant evidence to inform the model is only available for a period of 12 weeks and therefore modelling a longer time horizon would be challenging. The company also stated that evidence on flare frequency shows that patients are unlikely to have more than two flares per year. However, it is possible that treating one flare with spesolimab might affect the efficacy and safety of spesolimab or other treatments in a subsequent flare, even if that only happens after a period of 12 weeks. Therefore, we consider the appropriateness of a 12-week time horizon to be uncertain and questionable because the long-term consequences of the treatment with spesolimab are still unclear.
What alternative approach has the EAG suggested?	The EAG is unable to model a longer time horizon as long-term data does not seem to be currently available.
What is the expected effect on the cost-effectiveness estimates?	Uncertain as we are unclear about the long-term effects of spesolimab.
What additional evidence or analyses might help to resolve this key issue?	Further clinical data on the long-term effects of spesolimab (if possible) and clinical expert opinion on the plausibility of assuming that spesolimab has similar incremental effectiveness/costs versus BAC in the treatment of individual flares, regardless of being the first or subsequent flares.

Issue 6 Efficacy of the comparator arm (BAC): response to treatment

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	For the first week of the model, treatment response to BAC was obtained from the Effisayil 1 trial and, beyond that, from the Effisayil 1 historical cohort, as crossover occurred for more than 80% of patients in the placebo arm on day 8 in the Effisayil 1 trial. Effisayil 1 trial provides a direct comparison between the intervention and the comparator. However, patients in the placebo arm of the Effisayil 1 trial do not receive any standard of care treatments although they may be admitted to hospital. It is unknown if receiving active treatments would have led to different effectiveness outcomes. Therefore, using trial data to inform the efficacy of BAC does not seem to appropriately reflect UK reality. The Effisayil 1 historical cohort uses the same cohort of patients as in the Effisayil 1 trial, however it is unclear how long in the past the flares have occurred and whether the standard of care at that time is similar to the standard of care currently used as we do not know which treatments were included in standard of care in this study. Therefore, it is uncertain how generalisable the results from Effisayil 1 historical cohort are to the current UK reality. The SEE exercise has limitations, such as being a low quality evidence source when compared to clinical trials and RWE studies; the lack of consistency in the definition of response to treatment; the discrepancy in the estimates of efficacy between clinicians; and the potential biased interpretation of best available care by the experts (see further details in section 4.2.6.2.). However, the SEE exercise provides relevant data to inform the economic model as the estimates elicited for the efficacy of BAC were in relation to the best available care as seen in the experts' practice, which would therefore be relevant to the NHS. Furthermore, we consider that it is more appropriate and relevant to the NHS to use the SEE estimates as they are related to the treatments included in the comparator arm in the model (also elicited by the SEE exercise experts).
What alternative approach has the EAG suggested?	The EAG uses the SEE exercise estimates from day 1 until the end of the time horizon, based on a GPPGA pustulation subscore of 0 or 1 in our base case. We explored the uncertainty around this assumption by conducting alternative scenario analyses, as follows: • Effisayil 1 trial (first week) + SEE exercise (GPPGA pustulation subscore of 0 or 1) • SEE exercise (GPPGA pustulation subscore of 0) • Effisayil 1 trial (first week) + SEE exercise (GPPGA pustulation subscore of 0)

	• Effisayil 1 trial (first week) + Effisayil 1 historical cohort (GPPGA pustulation subscore of 0 or 1, company's base case) • Effisayil 1 historical cohort (GPPGA pustulation subscore of 0 or 1, company's scenario)
What is the expected effect on the cost-effectiveness estimates?	Using the SEE exercise estimates for the efficacy of BAC from day 1 (based on a GPPGA pustulation subscore of 0 or 1) leads to an increase in the ICER of £311,357 per QALY (from -£167,783 to £143,574) for the EAG corrected company's base case.
What additional evidence or analyses might help to resolve this key issue?	Further clinical expert on which are the most appropriate estimates for the efficacy of BAC to be used in the economic model.

Issue 7 Proportion of patients treated as inpatients in the spesolimab arm

Report section	4.2.8.3
Description of issue and why the EAG has identified it as important	In the BAC arm, the proportion of patients treated as inpatients was based on the study by Wolf et al. (77.6%). For the spesolimab arm, the company assumed that only half of the proportion considered for BAC would be treated as inpatients (33.8%). This assumption was based on the relative reduction of 48.4% in the proportion of patients with an active flare (GPPGA pustulation subscore higher than 1) for spesolimab versus placebo in the Effisayil 1 trial. We note that the reduction of patients with an active flare directly leads to a reduction in the number of hospitalisations, as the clinical experts advising the company stated that patients with a resolved flare defined by a GPPGA pustulation subscore of 0 or 1 are discharged from hospital, and therefore we assume that they are not at risk of being hospitalised. Thus, it remains uncertain whether spesolimab has an additional residual benefit in reducing hospitalisation rates for patients not responding to treatment and therefore with an active flare. We note that there is no evidence showing such a benefit. Also, in the case of spesolimab having a benefit in reducing hospitalisation rates, the size of the benefit remains uncertain. Different inpatient rates for spesolimab changes the ICER considerably. So, in the absence of data, we consider the company's assumption is likely to be optimistic.
What alternative approach has the EAG suggested?	We have not changed our base case but we explored the uncertainty around this assumption by conducting alternative scenario analyses, as follows: • no reduction • reduction of 10% • reduction of 20% • reduction of 30%

What is the expected effect on the cost-effectiveness estimates?	Applying a reduction in inpatient rates for spesolimab versus BAC leads to the following results in the EAG corrected company's base case: • no reduction: ICER increases from -£167,783 to -£5,009 per QALY. • reduction of 10%: ICER increases from -£167,783 to -£37,564 per QALY. • reduction of 20%: ICER increases from -£167,783 to -£70,119 per QALY. • reduction of 30%: ICER increases from -£167,783 to -£102,674 per QALY.
What additional evidence or analyses might help to resolve this key issue?	Further clinical expert opinion on the potential residual benefit of spesolimab in reducing inpatient rates for patients with an active flare.

1.6 Other issues: summary of the EAG's view

There are two other issues to draw to the committee's attention. We deem these not sufficiently likely to affect decision making that they should be a 'key' issue, but we believe they should be noted.

- The full extent of the duration of the response to spesolimab is unknown. Duration of response is one of the outcomes listed in the NICE scope and the company's decision problem. The Effisayil 1 trial had a duration of 12 weeks and 60% of participants originally randomised to spesolimab had a GPPGA pustulation subscore of 0 (clear) at Week 12. However, we do not know how much longer this response endured beyond 12 weeks or whether spesolimab treatment has any effect on the length of the interval between GPP flares.
- We were not able to obtain any expert clinical input into our report. Of 20 clinicians or dermatology centres contacted, 12 responded but none were able to be of assistance (four were conflicted as they had contributed to the CS, three had no capacity to take on the task, and five were out of office for an extended period due to illness or work-related reasons). In addition to the areas noted above across our seven key issues where we think clinical expert opinion could be useful, there are other questions we would have asked clinicians to help inform the report. These include:
  - What are the prognostic factors associated with GPP flares. In particular do race or age affect either flare intensity or frequency or response to flare treatment?
  - Are the treatments in Figure 1 of this report a reasonable reflection of the standard of care for moderate-to-severe GPP flares in UK clinical practice. Would topical steroids be used alongside second- and third-line treatments?

- Is the Effisayil 1 trial population generalisable to the population of GPP patients experiencing moderate-to-severe flares in England? Are the characteristics of the economic model population representative of the patients who may receive spesolimab in UK clinical practice?
- If a patient was not treated in the first week of a flare what impact would this have? Would a delay in starting treatment mean the flare would take longer to resolve?
- Questions about the appropriateness of all the model assumptions.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Based on the EAG's critique of the company's model (discussed in section 4.2.2), we have identified the following key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

- **Composition of the comparator arm**: inclusion of active treatments during the first week of the model (linked to the following change in the efficacy of BAC).
- **Efficacy of BAC**: SEE exercise estimates based on a GPPGA pustulation subscore of 0 or 1 from day 1 until the end of the time horizon (see Table 19).

Table 3 shows the cost-effectiveness results of applying the EAG preferred model assumptions to the company's base case including the PAS discount for spesolimab. Incorporating the EAG assumptions, the ICER for spesolimab versus BAC increases to £143,574 per QALY.

The changes that have the most significant impact on the cost-effectiveness results are changing the assumptions for the efficacy of BAC, the proportion of inpatients on spesolimab, and the proportion of patients in the spesolimab arm with active flare by the end of the time horizon.

Table 3 EAG's preferred base case results using PAS price for spesolimab

Treatment	Total		Incremental		ICER
	Cost (£)	QALYs	Cost (£)	QALYs	(£/QALY)
BAC	[redacted]	[redacted]			£143,574
Spesolimab	[redacted]	[redacted]	[redacted]	[redacted]	

BAC, best available care; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Boehringer Ingelheim Ltd on the clinical effectiveness and cost effectiveness of spesolimab (Spevigo) for treating adults with generalised pustular psoriasis presenting with flares. It identifies the strengths and weaknesses of the CS.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 3 September 2024. A response from the company via NICE was received by the EAG on 18 September 2024 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on generalised pustular psoriasis

Generalised pustular psoriasis (GPP) is a chronic autoinflammatory disease affecting the skin with additional systemic symptoms.[1,2] It is phenotypically distinct from the most common type of psoriasis, plaque psoriasis (psoriasis vulgaris (PV)) although some patients may have both types.[3,4] GPP is characterised by intermittent flares with partial or complete remission occurring in between each flare episode.[1] A GPP flare typically develops rapidly and affects large areas of any part of the body. The skin becomes covered with sterile pus-filled blisters which can merge to become 'lakes' and there can be associated redness, itching, pain and scaling. Systemic features of flares are associated with inflammation and include fever, swelling, malaise, joint pain, fatigue, headache, increased white blood cell count, increased neutrophil count (a type of white blood cell) and increased c-reactive protein.[1,2,5] A GPP flare can be life-threatening and requires emergency treatment.[1,2,6]

Although the actual cause of GPP is unknown, it is known that interleukin-36 (IL36) signalling is part of the pathogenic process. In the skin, IL-36 contributes to host defence through inflammatory response, but if it becomes dysregulated it can induce psoriatic-like skin disorder; genetic mutations of antagonist IL-36Ra are associated with GPP.[5,7]

The only published data available for prevalence and incidence of GPP in England are from a recent cohort study (POLARIS) carried out by Boehringer Ingelheim in which data in the Clinical Practice Research Datalink (CPRD) Aurum database were linked with Hospital Episode Statistics (HES) data, as reported in CS section B.1.3.2.1.[8] GPP is rare. In England, between 2008 and 2019, there were 206 incident cases of GPP (in comparison the same

study identified 84,081 cases of plaque psoriasis over the same period): incidence was stable with an age- and sex-adjusted incidence rate of 0.14 to 0.34 cases per 100,000 person-years, and prevalence increased from 1.61 per 100,000 patients in 2008 to 3.00 per 100,000 patients in 2019.[8] During the twelve years analysed, 50.5% of patients experienced one flare (requiring three or more days of hospitalisation), 7.8% of patients experienced two flares, and 4.4% of patients experienced three or more flares.[8] GPP occurs more frequently in women than men: the POLARIS study found that females were 62.5% of the GPP population in England, which is reflective of the proportion of females with GPP in other epidemiological studies and reviews.[9,10]

The disease course for GPP is variable: for each patient GPP flares can be of different levels of intensity or severity and can recur more or less frequently.[1] Therefore, the periods of remission (when skin is clear) or partial remission in between flares are of varying lengths.[1] This appraisal is focused on treating patients who are experiencing a GPP flare.

The causes of GPP flares are not known, however, some, but not all, patients can identify triggers for the flares such as stress, alcohol, infections or other illnesses, menstruation, pregnancy, environmental triggers, or stopping high-dose steroids.[2 5,6]

There are limited data for prognostic factors for GPP disease course or for treatment outcomes for GPP flares, and Clarification Response A25 refers to the global consensus statement (Puig et al. 2023)[1] which shows a lack of predictability for flare duration, severity and frequency. The UK extension of the global consensus study (Barker et al. 2024)[11] noted uncertainty around the prognostic value of age because this could potentially be correlated to complication-related morbidity rather than flare frequency. The EAG has not been able to discuss prognostic factors associated with GPP with any clinical experts to verify this, and we agree that scientific literature investigating prognostic factors is lacking.

2.2.2 Background information on spesolimab

Spesolimab, brand name Spevigo, is a first in class humanised antagonistic monoclonal immunoglobulin 1 antibody. It blocks human interleukin-36 receptor (IL-36R) signalling by binding to IL-36R which prevents activation of the autoinflammatory response.

Spesolimab received a conditional marketing authorisation from the MHRA in July 2023. The authorisation was conditional because the data on treatment of subsequent flares was not considered comprehensive. Another study, Effisayil REP, is in progress to investigate the treatment of repeated flares with spesolimab.

Spesolimab is indicated for treatment of flares in adult patients with GPP as monotherapy (i.e. it should not be used in combination with other GPP treatments such as systemic immunosuppressants).[12] It is administered as an intravenous infusion of 900 mg. If flare symptoms persist, an additional 900 mg dose may be administered after one week. In response to clarification question A1 the company stated that there are no data on the use of a third dose of spesolimab for a specific flare and therapy choice if a flare remains unresolved after two doses of spesolimab would be at the discretion of the treating physician. It is not clear to us if clinicians would view a third spesolimab dose as an option in this circumstance. The company confirmed that they have not recommended a specified minimum period between spesolimab dosage courses for subsequent flares (response to clarification question A1ii) so there does not appear to be a maximum dose of spesolimab that can be received within a specified time period.

2.2.3 The position of spesolimab in the treatment pathway

There are no specific guidelines for treating GPP and GPP flares. The NICE Clinical Guideline for the assessment and management of psoriasis (CG153) refers specifically to GPP only in the context of referral to dermatology specialist advice and treatment which should be immediate and same-day, and in consideration of the use of acitretin for people with pustular forms of psoriasis.[13] Apart from spesolimab, there are no licensed treatments in the UK specifically for GPP so treatment typically draws on the licensed therapies used for treating other forms of psoriasis. The only information on the current treatment pathway for patients experiencing a GPP flare is from a global consensus study (Puig et al. 2023)[1], for which there is a UK consensus panel published (Barker et al. 2024),[11] and from the company's structured expert elicitation (SEE).[14]

The company's outline of the treatment pathway for GPP flares is shown in CS Figure 4, reproduced below in Figure 1. It shows a range of therapies are used at first-, second- and third-line or later including topical corticosteroids, systemic non-biological therapies such as ciclosporin, and biological therapies such as TNF-alpha inhibitors (infliximab), an IL-17 inhibitor (secukinumab), and IL-23 inhibitors (guselkumab, ustekinumab).

Figure 1 Clinical pathway of care for moderate-to-severe GPP flares in the UK

Source: Reproduced from CS Figure 4 with title amended by the EAG.
Abbreviations: 1L, first line; 2L, second line; 3L+, third- or later-line; GPP, generalised pustular psoriasis.

The company acknowledge that this diagram is simplified and represents an undefined clinical pathway. We agree, and this is due to a lack of clinical guidelines or licensed treatments as noted above. The pathway in Figure 1 does not appear to take into account whether the severity of a flare determines choice of treatment. Clarification Response A2i confirms that the pathway is based on evidence from the company's SEE (critiqued in section 3.3.2) and represents UK and Ireland clinical expert opinion of best available care for treatment of moderate-to-severe flares. The EAG has been unable to obtain further clinical expert opinion for verification, however, this illustration of the treatment pathway for flares does not contradict the global consensus study nor the UK additional panel to the global consensus study because they do not state what treatments should be used and instead agree on treatment goals and that treatments should have a rapid onset of action.[1,11]

The pathway in Figure 1 does not include the proposed position of spesolimab. The SmPC does not specify a line of treatment, but CS section B.3.2.3.1 states that spesolimab is expected to be used in first-line treatment of GPP flares, confirmed in Clarification Response A2ii, which further elaborates that it is expected to displace the current first-line and subsequent-line treatment options, providing an alternative option to the multiple lines of treatment approach.

The SmPC indicates use of spesolimab as a monotherapy.[12] It does not recommend using spesolimab in combination with immunosuppressants, including biologics, because combination treatment has not been evaluated systematically. Currently, topical steroids can be used alongside the other therapies ([redacted] at first line in Figure 1), but it is unclear whether they can be used alongside spesolimab. This is because the pivotal trial (see section 3.2.1 below) did not permit the use of therapies in addition to spesolimab: topical treatments could not be initiated in the week prior to visit 2 (treatment initiation) and washout periods ranging from seven days to 5.5 months were required for other medications (CS Appendix N). Therefore, it is unclear whether patients receiving preventive topical or systemic therapies for GPP will be able to receive emergency treatment for flares with spesolimab (when there is no opportunity for a washout period) and to what extent this affects the size of the eligible population. The EAG did not have access to clinical expertise to clarify the proportion of the UK GPP population that are on maintenance topical steroids or systemic therapies.

EAG conclusion on GPP and spesolimab in the treatment pathway

GPP is a rare systemic inflammatory disease and GPP flares require emergency treatment for which the company propose spesolimab as first-line therapy. The company accurately reports disease, pathogenesis and symptoms, and provides epidemiologic data relevant to England from their analysis of national CPRD Aurum and HES data. Due to the limitations of clinical guidelines which focus on PV, the company conducted a structured expert elicitation[14] which has informed the treatment pathway. There is limited information around some aspects of the dosing of spesolimab. For example, what is the minimum interval between treating subsequent flares with spesolimab and is there a maximum dose of spesolimab that can be received within a specified time period? There is also a lack of evidence on concomitant use of spesolimab with topical steroids and systemic treatments because these were not permitted in the clinical trial.

2.3 Critique of the company's definition of the decision problem

Table 4 summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE and the EAG's comments on this.

Table 4 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	Adult patients with generalised pustular psoriasis presenting with flares	Adult patients with generalised pustular psoriasis presenting with flares	Not applicable	CS Table 2 states the therapeutic indication is for the treatment of flares in adult patients with generalised pustular psoriasis as a monotherapy. However, in the company's pivotal trial, Effisayil 1,[a] only adult patients with GPP experiencing moderate-to-severe intensity flares were randomised to treatment.[b] The clinical evidence is therefore drawn from a narrower population than defined in the NICE scope and the company's decision problem. The patient cohort that start in the economic model are in the moderate-to-severe flare health state.
Intervention	Spesolimab	Spesolimab	Not applicable	The intervention matches the NICE scope and in the pivotal Effisayil 1 trial, the licensed dose of spesolimab was used.
Comparators	Established clinical management without spesolimab which may include: Systemic non-biological therapies such as ciclosporin Biological therapies (such as TNF-alpha	Established clinical management without spesolimab	Not applicable	The comparator in the company's Effisayil 1 trial was placebo. Prior to randomisation patients had to discontinue biologic therapies, systemic non-biological therapies and other treatments (e.g. phototherapy and topical treatments). Therefore, there is no direct comparative effectiveness evidence from the company's trial for spesolimab versus established clinical management without spesolimab. The economic model assumes that patients in the

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	inhibitors, IL-17 and IL-23 family inhibitors)			comparator arm receive no treatment during the first week and thereafter receive treatment from a basket of options (TNF inhibitors, IL-23 inhibitors, IL-17 inhibitors and ustekinumab in the base case) identified by a group of UK clinical experts who participated in the company's structured expert elicitation (SEE) exercise. Therefore, the EAG note that the comparator in the economic model is not fully aligned with the NICE scope and company definition of the decision problem
Outcomes	The outcome measures to be considered include: • Symptoms specific to GPP including pain • Severity of flares • Mortality • Response rate • Duration of response • Relapse rate • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Symptoms specific to GPP including pain • Severity of flares • Mortality • Response rate • Duration of response • Relapse rate • Adverse effects of treatment • Health-related quality of life	Not applicable	The outcomes listed by the company match those in the NICE scope and the majority are clearly reported in the CS. An exception is duration of response for which there is limited data due to the length of the Effisayil 1 trial (response was still ongoing for a proportion of patients at the end of this 12-week study).
Economic analysis	Not included in CS Table 1			The company's cost-utility analysis adheres to the NICE reference case. Whether the time horizon used is sufficiently long to reflect all important differences in

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
				costs or outcomes between spesolimab and BAC is unclear (Key Issue 5).
Subgroups	Not included in CS Table 1. No subgroups are noted in the NICE scope.			No comments.
Special Considerations including issues related to equity or equality	Not included in CS Table 1. No special considerations are noted in the NICE scope.			No comments.

Source: CS Table 1 with the addition of EAG comments in the final column.
BAC, best available care; CS, company submission; EAG, External Assessment Group; GPP, generalised pustular psoriasis; IL-17, interleukin-17; IL-23, interleukin-23; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SEE, structured expert elicitation; TNF, tumour necrosis factor.
[a] Throughout the CS the Effisayil trial names are followed by the trademark symbol (TM in superscript) but because the NICE style guide does not permit the use of this symbol we have not included this in our report and refer solely to the Effisayil 1, Effisayil 2,Effisayil ON and Effisayil REP trials.
[b] A moderate-to-severe intensity flare was defined as a Generalised Pustular Psoriasis Physician Global Assessment (GPPGA) score of at least 3 (moderate) and presence of fresh pustules (new appearance or worsening of existing pustules), and a GPPGA pustulation subscore of at least 2 (mild), and at least 5% of body surface area covered with erythema (abnormal redness of the skin or mucous membranes) and the presence of pustules (CS section B.2.3.1).

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review

The company conducted a systematic literature review (SLR) to identify all relevant evidence of clinical efficacy and safety associated with spesolimab and current available treatments for GPP (CS Appendix D). Bibliographic searches of the main healthcare databases and clinical trials registers were run in December 2022, with update searches run in May 2024. Several specific dermatology and psoriasis conferences were hand searched from 2022 to May 2024. Published search filters for randomised controlled trials (RCTs) and observational studies were used, and the searches were generally comprehensive. We do not believe that any relevant studies would be missed by the searches.

Screening was carried out according to eligibility criteria that were broader than the NICE scope and company decision problem because they included a population of all GPP patients (CS Appendix D Table 10) not just GPP patients presenting with flares (CS Table 1). A total of 79 unique studies were identified (CS Appendix D.1.2) or 81 unique trials according to CS section B.2.2; we are unable to explain the reason for this inconsistency. A further screening stage was carried out to identify the studies "*that reported data specific to GPP flare*s" to align with the company decision problem (CS Appendix D.1.2), and Clarification Response A4 confirms that the eligibility criterion was a population including patients experiencing a GPP flare. Therefore, the studies identified by this additional screening stage were identified based on the population only, not because of any specific outcomes related to GPP flare treatment. The company assessed fifteen studies as including data specific to a population experiencing a GPP flare (CS Appendix Table 11 and CS section B.2.2). A list of the excluded studies with reasons for exclusion was provided in Clarification Response A3.

Of the 15 studies that "*reported data specific to GPP flares and were thus aligned to the decision problem*" (CS Appendix D.12), the company identified four studies that evaluated the efficacy and safety of spesolimab. Of these, the Effisayil 1 study assessing spesolimab IV infusion for treatment of GPP flares, was considered by the company as most relevant to this submission (section 3.2 below). The other three studies evaluating spesolimab were the company's Phase I, Effisayil 2 and Effisayil ON studies. The Phase 1 and Effisayil ON open label extension study safety results are considered in section 3.2.5.5. Three of the remaining 11 studies, were considered further as a source of possible comparator data for an indirect treatment comparison (ITC) (see section 3.3 below).

In Clarification Response A5 the company confirm that the quality assessment, relevance of the evidence base, and heterogeneity assessment were performed for all 79 studies included in the broader scope of the SLR. This makes it more difficult to have clarity about the methods and criteria that were used to identify the evidence specific to the company's decision problem for this appraisal.

The EAG's summary appraisal of the company's review methods is provided in Appendix 1.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

The company's systematic literature review identified the four pivotal trials of spesolimab for the treatment of adults with GPP but only one of these, the Effisayil 1 trial, provides evidence fully relevant to this technology appraisal and informs treatment effectiveness in the economic model. The outcomes from Effisayil 1 that inform that company model are:

- Comparative effectiveness data for Week 1 in terms of the response to treatment (GPPGA pustulation subscore 0 or 1 representing flare resolution) for both the spesolimab and BAC treated model cohorts. The Effisayil 1 trial also informs efficacy of the spesolimab treated cohort beyond Week 1 to the end of the model time horizon.
- Rates of serious infection and liver injury (adverse events) in the spesolimab model cohort
- Utility values for the active flare state for both the spesolimab and BAC treated model cohorts. We note that the Effisayil 2 trial informed the utilities for the resolved flare health state (further details in section 4.2.7.2)

The key features and roles of the four spesolimab studies in this appraisal are summarised in Table 5.

Table 5 Summary of the company trials of spesolimab and their role in the appraisal

	NCT02978690	Effisayil 1 (NCT03782792)	Effisayil 2 (NCT04399837)	Effisayil ON (NCT03886246)
Role in this appraisal	Evidence provided in Appendix F for information.	Key source of clinical effectiveness evidence and informs the economic model.	Supportive clinical effectiveness evidence. Effisayil 2 informs the utilities for the resolved flare health state in the economic model. Effisayil ON does not inform economic model.	
Study type	Phase I, PoC study.	Phase II double-blind[a] RCT.	Phase IIb double-blind RCT	Open-label extension study
Patient group	Adult patients with GPP presenting with flare involving 10% or more of their BSA with erythema and the presence of pustules and a GPPGA score of 3 or higher.	Adult patients with GPP presenting with flares of moderate-to-severe intensity (GPPGA score of at least 3 and presence of fresh pustules, and a GPPGA pustulation subscore of at least 2, and at least 5% of BSA covered with erythema and the presence of pustules).	Patients aged ≥ 12–75 years at screening (weight ≥ 40 kg) with a history of at least two prior presentations of GPP flares with fresh pustulation. At screening and randomisation a GPPGA score of 0 or 1.[15]	Patients who completed treatment in either Effisayil 1 or Effisayil 2 without premature discontinuation (patients with evidence of moderate-to-severe flare at screening are excluded).
Intervention	Spesolimab IV infusion (10mg/kg, single dose) for treatment of GPP flares.	Spesolimab IV infusion, 900mg single initial dose for treatment of GPP flares. A second open-label dose at Day 8 if prespecified criteria were met[b] and one rescue dose for a recurrence of GPP flare.[c] were also permitted.	Spesolimab SC with randomisation to one of 3 arms for prevention of GPP flares: 600mg LD then 300mg q4w 600mg LD then 300mg q12w 300mg LD then 150mg q12w	Spesolimab SC (300mg) as a maintenance treatment: q4w q6w q12w
Comparator	None	Placebo. An open-label dose of spesolimab at Day 8 was permitted if prespecified criteria were met[b] and one rescue dose for a recurrence of GPP flare.[c] was also permitted.	Placebo SC q4w	None
Duration	20 weeks	12 weeks	48 weeks	252 weeks

Source: EAG generated table based on information presented in CS section B.2.2, CS Appendix F.1.1 and cited references.
BSA, body surface area; GPP, generalised pustular psoriasis; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; IV, intravenous; LD, loading dose; PoC, proof-of-concept; q4w, every 4 weeks; q6w, every 6 weeks; q12w, every 12 weeks; RCT, randomised controlled trial; SC, subcutaneous.

[a] Note the study was double-blind for the first week only and placebo-controlled for the first week only because most placebo arm participants received open-label spesolimab at Day 8.
[b] The criteria were a GPPGA total score and a GPPGA pustulation sub score of at least 2, and no receipt of escape treatment during Week 1.
[c] The criteria for a rescue dose of spesolimab after Day 8 and through to Week 12 were at least a 2-point increase in GPPGA score and GPPGA pustular sub score after achieving a clinical response to initial treatment (randomised treatment, escape treatment or open-label spesolimab)

3.2.1.1 Study characteristics

Effisayil 1 is the company-sponsored, multi-centre, randomised, double-blind phase II study of spesolimab versus placebo for the treatment of adult patients with GPP flares of moderate-to-severe intensity. The design of Effisayil 1 is described in CS section B.2.3.1 and shown in CS Figure 5. Patient flow is described in CS section B.2.3.2 and shown in CS Figure 6.

Eligible patients aged 18-75 years were first enrolled into the study if they met at least one of the three eligibility criteria summarised in CS section B.2.3.1 (the full trial eligibility criteria for enrolment are provided in CS Appendix N). Patients could be enrolled into the study if they satisfied the eligibility criteria regardless of their current flare status. However, to be randomised to either spesolimab or placebo, patients had to be currently experiencing a GPP flare of moderate-to-severe intensity. This was defined as:

- A GPPGA score of at least 3 (moderate), and
- Presence of fresh pustules (new appearance or worsening of existing pustules), and
- A GPPGA pustulation subscore of at least 2 (mild), and
- At least 5% of body surface area covered with erythema (abnormal redness of the skin or mucous membranes) and the presence of pustules

Prior to randomisation, participants had to stop receipt of their current therapies as described in detail in CS Appendix N Table 62 and were not permitted to use these therapies during the trial. In brief for the main types of therapy:

- Biological therapies had to stop at least 7 days (range 7 days to 5.5 months depending on the biological therapy) prior to randomisation.
- Other systemic immunomodulating treatments and other systemic psoriasis treatments were not permitted 30 days prior to randomisation.
- Methotrexate, cyclosporine and retinoids could not be started or have the dose escalated in the 2 weeks prior to randomisation and these therapies had to be discontinued prior to receipt of randomised treatment.
- Topical treatments and phototherapy for psoriasis or any other skin condition could not be started in the week prior to randomisation.
- Investigational products for psoriasis had to stop 3 months prior to randomisation and other investigational products or devices were not permitted 30 days prior to randomisation.
- IL-36R inhibitors were not permitted before or during trial participation.

Fifty-three trial participants were randomised 2:1 to either spesolimab (n=35) or placebo (n=18). In response to clarification question A12 the company provided a breakdown of the numbers of participants by country (both for enrolled and for randomised participants). The proportions of participants randomised from the various countries were: Malaysia (23%), France (19%), Tunisia (13%), China (11%), Germany (9%), Taiwan (9%), United States (6%), Japan (4%), Singapore, Switzerland and Thailand each 2% (percentages calculated by the EAG).

The key features of treatment and trial events after randomisation are shown in CS Figure 5 and summarised briefly below:

- Day 1: participants randomised to spesolimab received a single 900mg IV dose. This is the dose recommended in the Summary of Product Characteristics (SmPC). Participants randomised to placebo received a single IV dose.
- Days 2-7: Escape treatment (physician's choice) was permitted in the case of disease worsening.
- Day 8:
  - Primary and key secondary endpoint analyses were conducted. In these analyses participants who had received escape treatment during days 2-7 were assumed not to have responded.
  - Participants from both trial arms with a GPPGA score of at least 2 and a GPPGA pustulation subscore of at least 2 (flare graded at least as mild, confirmed in response to clarification question A11), and who had not received escape treatment during days 2-7 were eligible to receive an open-label spesolimab 900mg IV dose (i.e. participants from the placebo arm meeting the criteria could receive open label spesolimab and participants from the spesolimab arm meeting the criteria could receive a second dose of spesolimab).
- Day 8 – week 12: Safety endpoints were assessed.
- Day 9 – week 12: Participants with a recurrence of GPP flare (defined as "*at least a 2-point in GPPGA score and GPPGA pustular subscore after achieving a clinical response to initial treatment*") could receive a rescue dose of spesolimab 900mg IV. In response to clarification question A9, the company confirmed that clinical response to initial treatment was defined as a GPPGA total score of 0 or 1, and we note that the criteria for a flare mean that it is graded at least as mild. All participants (regardless of which randomised treatment they had received and whether they had received escape treatment or open-label spesolimab on Day 8) were able to receive

a rescue dose of spesolimab if they met the criteria. Only one rescue dose of spesolimab was permitted per patient.

- Beyond trial end at week 12: If participants with clinical improvement completed the trial up to week 12 and were without flare symptoms, they were eligible to enter the open-label extension study Effisayil ON.

As CS Figure 5 and the summary above indicate, it was possible for participants to receive three spesolimab doses during the trial – i) in the arm randomised to spesolimab, ii) open-label spesolimab on Day 8 providing criteria met, iii) rescue medication due to a recurrence of GPP flare. In response to clarification question A10 the company state that two patients received three spesolimab doses for these reasons.

Participant flow through the Effisayil 1 trial is described in CS section B.2.3.2 and shown in CS Figure 6. This shows that of the 53 participants who were randomised, 52 completed the first week of the trial. At day 8, 12 participants (34%) in the spesolimab group received open-label spesolimab (i.e. a second dose) and 15 of the 18 participants (83%) in the placebo group also received open-label spesolimab (their first dose).

3.2.1.2 Patients' baseline characteristics

Patients' baseline data are reported for demographic characteristics, disease severity characteristics associated with skin condition and quality of life, and IL36RN mutation in CS Table 9. Trial publication Table S1 additionally reports geographic region and systemic disease characteristics (baseline temperature (fever/no fever), white blood cell count, and C-reactive protein level).[16] We have combined them, and added [redacted] from the CSR, in Table 6 below:

Table 6 Patients' baseline characteristics in Effisayil 1

Characteristic	Spesolimab (n = 35)	Placebo (n = 18)
Age, mean years (SD)	43.2 (12.1)	42.6 (8.4)
Weight, kg (SD)	73.7 (24.0)	68.8 (26.6)
Female, n (%)	21 (60)	15 (83)
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Characteristic	Spesolimab (n = 35)	Placebo (n = 18)
Race, n (%)[a]		
Asian	16 (46)	13 (72)
White	19 (54)	5 (28)
Region, n (%)		
US, n (%)	2 (5.7)	1 (5.6)
Asia, n (%)	14 (40.0)	13 (72.2)
Europe, n (%)	14 (40.0)	2 (11.1)
Africa, n (%)	5 (14.3)	2 (11.1)
GPPGA total score, n (%)[b]		
3 (moderate)	28 (80)	15 (83)
4 (severe)	7 (20)	3 (17)
GPPGA pustulation subscore — n (%)[c]		
2 (mild)	6 (17)	5 (28)
3 (moderate)	16 (46)	7 (39)
4 (severe)	13 (37)	6 (33)
Median GPPASI total score (IQR) [d]	**27.4 (15.5–36.8)**	**20.9 (12.0–32.0)**
Median DLQI score (IQR)[e]	**19.5 (16–25)**	**19.5 (14–24)**
Median pain VAS score (IQR)[f]	**79.8 (70.5–87.8)**	**70.0 (50.0–89.4)**
Median PSS score (IQR)[g]	**11.0 (9–12)**	**10.5 (9–11)**
Median FACIT-Fatigue score (IQR)[h]	**14.0 (7–28)**	**18.0 (6–33)**
***IL36RN* mutation, n (%)[i]**	**8 / 29 (28)**	**6 / 17 (35)**
Baseline temperature[j]		
< 38.5 C, n (%)	29 (85.3)	18 (100.0)
≥ 38.5 C, n (%)	5 (14.3)	0 (0.0)
Baseline leucocytes[j] [k]		
< 10,000 µL, n (%)	14 (40.0)	6 (33.3)
≥ 10,000 µL, n (%)	18 (51.4)	10 (55.5)
Baseline C-reactive protein[j] [l]		
≥ 3mg/L-70 mg/L, n (%)	20 (58.8)	12 (66.7)
≥ 70 mg/L, n (%)	11 (31.4)	4 (22.2)

Characteristic	Spesolimab (n = 35)	Placebo (n = 18)
Sources: CS Table 9; Bachelez 2021 Table S1;[16] Effisayil 1 CSR.[17] Footnotes relabelled and reordered by EAG. Abbreviations: [redacted]DLQI, Dermatology Life Quality Index; FACIT, Functional Assessment of Chronic Illness Therapy; GPPASI, Psoriasis Area and Severity Index for Generalised Pustular Psoriasis; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; IQR, interquartile range; n, number; PSS, Psoriasis Symptom Scale; SD, standard deviation; VAS, Visual Analogue Scale. [a] Race was reported by the patient; [b] Scores on the GPPGA range from 0 (clear skin) to 4 (severe disease); [c] GPPGA pustulation subscores range from 0 (no visible pustules) to 4 (severe pustulation); [d] Scores on the GPPASI range from 0 (least severe) to 72 (most severe); [e] Scores on the DLQI range from 0 (no effect) to 30 (extremely large effect) – spesolimab n = 34; [f] Scores on the pain VAS range from 0 (no pain) to 100 (very severe pain); [g] Scores on the PSS range from 0-16, with higher scores indicating more severe symptoms; [h] Scores on the FACIT-Fatigue range from 0-52, with lower scores indicating greater impact of fatigue on daily activities; [i] Samples from seven patients were missing; [j] Data for 52 participants (34 spesolimab, 18 placebo); [k] Four patients had missing values at baseline; [l] Five patients had missing values at baseline.		

The Effisayil 1 trial population may not be representative of UK patients because 55% of patients in Effisayil 1 were Asian, 51% were at sites in Asia, compared to only 30% from Europe (France, Germany and Switzerland). There were no UK sites or patients. The company's clinical experts validated the evidence from Effisayil 1 as relevant (CS section B.2.12.3), however, the EAG was unable to obtain expert opinion to independently verify whether the baseline characteristics of the Effisayil 1 trial population are similar to GPP patients experiencing flares in England.

Characteristics were not balanced between trial arms. There were proportionally more Asian people in the placebo arm (72%) compared to the spesolimab arm (46%). The EAG was unable to obtain expert opinion on whether race could be a prognostic factor for treatment outcomes in GPP flares. Disease severity scores according to the GPPASI score and GPPGA pustulation subscore were slightly worse in the spesolimab arm, proportionally more patients had fever (Suppl. Table 1)[16] in the spesolimab arm (14% compared to 0%), and therefore there could be a bias in favour of the placebo arm. It may be that the characteristics aren't entirely balanced because of the small sample size and the especially small placebo group.

It is not clear whether all possible prognostic factors for flare severity and duration were assessed at baseline because there are very limited data about which prognostic characteristics predict flare severity and duration (as confirmed in company response to clarification question A25, see also section 2.2.1 above). Therefore, we cannot be certain if there was any further bias or consistent bias in favour of the placebo arm. Baseline

characteristics that informed participant selection for the pre-specified subgroup analyses but which are not reported in the CS are: BMI, presence of plaque psoriasis, background GPP treatment prior to randomisation, and the Japanese Dermatological Association (JDA) GPP severity score (though this characteristic is less relevant to UK clinical practice). These characteristics are reported in CSR Tables 10.4.1:1, 10.4.3:3, 10.4.5:1 and 10.4.2:1 respectively.[17] There are [redacted].

EAG conclusion on included studies

The Effisayil 1 trial provides evidence fully relevant to this appraisal and informs the economic model. It was one of four pivotal trials of spesolimab identified by the company's systematic review. Supportive clinical evidence is reported in the CS from two other studies, Effisayil 2 and Effisayil ON, and results from the fourth study, NCT02978690, are provided for information. The Effisayil 2 trial informed the utilities for the resolved flare health state (see section 4.2.7.2). Effisayil 1 compared spesolimab versus placebo for the treatment of adult patients with GPP flares of moderate-to-severe intensity. Therefore, the trial evidence is drawn from a narrower population than defined in the NICE scope and company's decision problem (Key Issue 1). The comparator in the Effisayil trial is placebo, not established clinical management without spesolimab which is the comparator defined in the NICE scope and company decision problem (Key Issue 2). No UK participants were recruited to the trial and a high proportion of the participants were Asian which could impact the generalisability of the evidence to patients experiencing moderate-to-severe GPP flares in England. Knowledge about prognostic factors for flare severity and duration is limited, and because we were unable to obtain clinical expert opinion to help inform this report there is uncertainty about whether the high proportion of Asian participants in the trial and the imbalance in the proportions of Asian people between trial arms (spesolimab arm 46% vs placebo arm 72%) could have affected treatment outcomes.

3.2.2 Risk of bias assessment

The company critically appraised Effisayil 1 using the RCT checklist from the Centre for Reviews and Dissemination. The level of risk of bias is reported in CS Appendix Table 12, and supporting statements are provided in CS Table 11. The company judged the risk of bias in Effisayil 1 as low in all domains except for detection bias where the risk of bias was 'unclear' but without any justification made, and this judgement is not reported in CS Table 11. The EAG agree the Effisayil 1 trial is mainly at low risk of bias overall, although because

prognostic factors for GPP flares are not defined it is unclear which characteristics are most important to be balanced between groups (and there was slight imbalance for some characteristics). Other characteristics were also not balanced between trial arms (GPPASI, GPPGA pustulation subscore and proportion with fever were slightly worse in the spesolimab arm) so there may be bias in favour of the placebo arm. A summary of our assessments for each domain are presented alongside the company assessments in Appendix 2 of this report.

CS Table 11 adds an assessment question asking whether the study reflects routine clinical practice in England which refers to generalisability rather than risk of bias and we discuss this aspect of the study in section 3.2.1.2.

3.2.3 Outcomes assessment

The company lists the reported outcomes that are specified in the decision problem in CS Table 8 with the outcomes that inform the economic model indicated by bold type: GPPGA pustulation subscore, the occurrence of treatment emergent adverse effects (TEAEs), EQ-5D. A full list of outcomes for the Effisayil 1 trial is provided in CS Appendix N Table 62 and a description (including summary of scoring) of the GPPGA, GPPASI, PSS, Pain VAS, DLQI, FACIT-Fatigue and EQ-5D-5L is provided in CS Appendix N Table 63. We therefore focus here on the efficacy outcomes, the EQ-5D and safety outcomes as these inform the economic model, and a description of the Pain VAS, FACIT-Fatigue, DLQI, and PSS outcomes is provided in Appendix 3.

3.2.3.1 Efficacy outcomes

Efficacy in the Effisayil 1 trial was primarily measured using the GPPGA pustulation subscore and the GPPGA total score. A GPPGA pustulation subscore of 0 at Week 1 was the primary outcome of the trial and a GPPGA total score of 0 or 1 at Week 1 was the key secondary endpoint (CS section B.2.3.1). For the economic model, response to treatment was modelled in terms of flare resolution, defined as a GPPGA pustulation subscore 0 or 1 (CS section B.3.3.1).

The GPPGA is a relatively recent modification of the Physician Global Assessment (PGA) which has been commonly used in clinical trials.[18] It was first described in use in the 2019 publication[19] for the NCT02978690 proof-of-concept study of spesolimab. The PGA has been criticised for being variable between trials, in terms of range of the scales used to evaluate the three aspects of psoriasis being assessed (erythema, induration and scale) and the definitions used for each point on the scale. In the GPPGA, which appears to have been developed by the company, the induration component of the PGA has been replaced by

pustulation. Since the Effisayil 1 trial was completed, the GPPGA has been assessed and validated in a company sponsored study. In this study GPP-experienced dermatologists participating in the Effisayil 2 trial were trained on the GPPGA using a guide that includes descriptions and photographs to illustrate how each component of the GPPGA is scored. Then they were asked to score 16 representative photographs twice (10-14 days apart) taken from patients with GPP who participated in the Effisayil 1 trial.[20] The inter-rater reliability between dermatologists (26 completing the first assessment and 20 completing both assessments), assessed by the intraclass correlation coefficient, was described as 'generally excellent'.[20]

The way in which erythema, pustules and scaling are scored and contribute to the GPPGA total score is shown in Table 7. To achieve a GPPGA total score of 0 or 1 at Week 1 (key secondary endpoint) the mean composite score has to be less than 1.5. This can be achieved by 35 different combinations of the component parts of the score as shown in Appendix 4.

Because the GPPGA is a relatively new measure it is not used in clinical practice.[14] When the company conducted their SEE exercise for efficacy[14] the participating clinicians were provided with pictures and definitions of the GPPGA components.

Table 7 Scoring for the Generalised Pustular Psoriasis Physician Global Assessment (GPPGA).

Score	Erythema	Pustules	Scaling
0 (clear)	Normal or post-inflammatory hyperpigmentation	No visible pustules	No scaling or crusting
1 (almost clear)	Faint, diffuse pink, or slight red	Low-density occasional small discrete pustules (noncoalescent)	Superficial focal scaling or crusting restricted to periphery of lesions
2 (mild)	Light red	Moderate-density groups discrete small pustules (noncoalescent)	Predominantly fine scaling or crusting
3 (moderate)	Bright red	High-density pustules with some coalescence	Moderate scaling or crusting covering most or all lesions
4 (severe)	Deep fiery red	Very-high-density pustules with pustular lakes	Severe scaling or crusting covering most or all lesions

Each component is graded separately and then the average composite mean score is used to produce a total GPPGA score		
Mean composite score	**Total GPPGA score**	**Description**
0	0	Clear
> 0 to < 1.5	1	Almost clear
≥ 1.5 to 2.5	2	Mild
≥ 2.5 to 3.5	3	Moderate
≥ 3.5	4	Severe

Source: EAG table drawing on information published in Burden et al. 2023[20] and CS Appendix N Table 63.
GPPGA, Generalised Pustular Psoriasis Physician Global Assessment

The GPPGA pustulation subscore of 0 at week 1 (primary outcome) is the score given based on the physician's assessment of pustules only. As Appendix 4 shows, a patient with a GPPGA pustulation subscore of 0 could still be assessed as having moderate GPP, for example, if their erythema and scaling scores were both 4 (severe).

3.2.3.2 EQ-5D

Effisayil 1 collected EQ-5D-5L assessments daily for the first week, then weekly until weeks 4, 8 and 12. No results are reported for the group originally randomised to placebo who received open label spesolimab at Day 8. MCID for the EQ-5D health index was estimated at 0.07 (CS Figure 15 footnote). The data were mapped to EQ-5D-3L using the NICE preferred mapping function (CS section B.3.4.2). The company suggest this outcome measure is not particularly sensitive in acute conditions, nonetheless the data inform the model as required for utilities but not for disutilities due to adverse events (CS Table 16). The EAG believe it is unlikely that that any single PRO for quality of life fully covers all aspects of a GPP flare in order to be an alternative to EQ-5D, and no alternative to EQ-5D was suggested by the company.

3.2.3.3 Safety outcomes

Effisayil 1 assessed mortality and adverse effects of treatment; occurrence of treatment emergent adverse events was used in the economic model (CS Table 8). Severity of adverse events was measured appropriately using the Rheumatology Common Toxicity Criteria (CS Table 13). Adverse events of special interest were pre-specified as hepatic injury, systemic hypersensitivity reactions (e.g. infusion reactions and anaphylactic reactions), severe infections, and opportunistic and mycobacterium tuberculosis infections (CSR 9.5.3.2.1),[17] which are relevant to IV infusion administration and a treatment that acts on the immune system.

The CS additionally reports adverse events from the Phase I spesolimab study in CS Appendix F.1.2, and interim safety results from the Effisayil ON open-label extension study for patients receiving maintenance spesolimab in CS section B.2.10.3 (also published in the Navarini et al. 2023 conference abstract).[21]

EAG comment on outcomes assessment

There is no standard definition of GPP flare resolution but the company's use of the GPPGA pustulation subscore seems acceptable. A GPPGA pustulation subscore of 0 (clear, no visible pustules) at Week 1 was the primary outcome of the trial and a GPPGA total score of 0 (clear) or 1 (almost clear) at Week 1 was the key secondary endpoint. A GPPGA pustulation subscore of 0 or 1 is the outcome that informs the economic model. The GPPGA (total score and subscores) do not appear to be used in clinical practice but clinical expert opinion on whether a GPPGA pustulation subscore of 0 or 1 appropriately reflects GPP flare resolution would be welcome.

The patient reported outcomes used in the Effisayil 1 trial are not specific to GPP but two, the Psoriasis Symptom Scale and the Dermatological Quality of Life Index, are specific for psoriasis and skin conditions respectively. Three generic measures were also used (pain VAS, Functional Assessment of Chronic Illness Therapy – Fatigue scale, and EQ-5D) with the EQ-5D informing the economic model.

3.2.4 Statistical methods of the included studies

The company's statistical methods for Effisayil 1 are reported in CS section B.2.4, CS Table 10 and section 9.7 of the clinical study report (CSR)[17]. We summarise the methods in Table 8 below.

Table 8 Summary and EAG critique of the statistical methods used in Effisayil 1

Analysis populations
Analyses were conducted on the randomised set for the primary outcome (GPPGA pustulation subscore, Week 1) and the key secondary outcome (GPPGA total score, Week 1) which compared spesolimab against placebo (CS section B.2.4). This is an appropriate ITT analysis. [redacted].
After Week 1, on Day 8 15/18 participants randomised to the placebo group received open label spesolimab and were therefore imputed with non-response or worst possible outcome. The company argue that an ITT analysis of outcomes after Week 1 would be

noninformative. Therefore, analyses are reported in the CS for four post-hoc groups where the original randomised ITT set is split (CS B.2.4):

- Patients randomised to spesolimab who received,
    - either 1 dose (Day1) or 2 doses (Day 1 and Day 8), n=35
    - 1 dose (Day 1), n=23
    - 2 doses (Day 1 and Day 8), n=12
- Patients randomised to placebo who received,
    - spesolimab (Day 8), n=15

The secondary outcomes assessed at Week 4, GPPASI score, pain VAS, PSS and FACIT-Fatigue, were reported descriptively according to these four post-hoc groups and the planned hierarchical statistical testing of these outcomes was abandoned. They are also reported descriptively for the ITT analysis in CSR section 11.1.2.2.[17]

Analyses of other outcomes beyond Week 1:

- GPPGA pustulation subscore and total score through Week 12 were analysed descriptively according to the four post-hoc subgroups (CS section B.2.6.3.1.1).
- PROs through Week 12 (pain VAS, FACIT-Fatigue, DLQI and PSS) were analysed descriptively for the randomised ITT populations (CS section B.2.6.3.1.2)
- Systemic features (neutrophil and CRP levels) are reported descriptively for the spesolimab group only (CS section B.2.6.3.1.3).

The safety set included all randomised patients who received at least one dose of study medication (CS section B.2.10) [redacted].

EAG comment: The ITT analysis used for the primary outcome and the secondary outcome is appropriate. Only the results for the primary outcome and key secondary outcome at Week 1 can be considered comparatively meaningful. All other results can only be considered illustrative because they are reported according to assignment to post-hoc groups, not per-protocol, which leads to increased risk of bias and the company have not explained the relevance of each group nor how the results should be interpreted. [redacted].

Sample size calculations

It was calculated that 51 patients were needed to provide ≥90% power (CS section B.2.4 and CS Table 10), and this was achieved. This only provides power for the primary outcome and the key secondary outcome.

EAG comment: The target sample size to achieve the required power for the primary outcome and key secondary outcome was achieved.

Methods to account for multiplicity

The primary outcome and key secondary outcome were tested hierarchically, i.e. the key secondary outcome was only tested if the primary outcome results were statistically meaningful. Hierarchical testing of the secondary outcomes was planned but abandoned due to 15/18 participants in the placebo arm receiving open label spesolimab on Day 8, whereby the analysis changed to assessing results descriptively according to four post-hoc population groups instead. The trial was not powered for statistical comparisons of the secondary outcomes, nor were the secondary outcomes statistically tested as planned, so the results of the secondary outcomes are uncertain.

EAG comment: due to cross-over at Day 8 multiplicity is only relevant to the primary outcome and key secondary outcome, and this has been accounted for. All other outcomes are not statistically analysed and are illustrative only.

Analysis of outcomes

The GPPGA pustulation subscore, GPPGA total score, and GPPASI score were analysed using the Suissa-Shuster Z-pooled method, which is an exact unconditional test suitable for these binary outcomes. Confidence intervals were determined using the Chan and Zhang method which is suitable for small sample sizes.

All outcomes, except for the primary outcome and key secondary outcome, were analysed descriptively. Clarification Response A17 confirms that all comparisons according to randomised treatment as originally planned are non-informative after Day 8.

EAG comment: the company have used standard statistical analyses appropriate to the type of outcome and suitable for small sample sizes.

Handling of missing data

Missing data for the binary outcomes (includes primary outcome and key secondary outcome) was imputed as non-response, [redacted].

The last observation carried forward (LOCF) method [redacted].was planned to handle missing data for the continuous outcomes (pain VAS, PSS, FACIT-Fatigue, DLQI). However, the high crossover of participants into spesolimab treatment after Day 8 meant that this was replaced with descriptive analysis based on observed cases, including values after rescue therapy or treatment discontinuation (Clarification Response A13). Therefore, results using the LOCF method were not reported in the CS, but are reported

for pain-VAS and DLQI in Clarification Response A13 for participants initially randomised to spesolimab.
EAG comment: the amount of missing data is not clear. However, the methods appear appropriate, the primary outcome and key secondary outcome are treated conservatively in the primary analysis, [redacted].
Sensitivity analyses
Sensitivity analyses were performed for the primary outcome and the key secondary outcome: - post-hoc use of linear regression and to adjust for the imbalance of covariates at baseline, incl. sex, race, and GPPASI score (CS Table 10). [redacted]
EAG comment: The sensitivity analyses are relevant, e.g. adjusting for imbalanced covariates at baseline, [redacted] due to small numbers could affect results more than if there was a larger sample size. We have not identified any other sensitivity analyses that would have been useful.

Source: CS Table 10, Clarification Response A13, CSR section 9.7.[17]
Abbreviations: CRP, C-reactive protein; CSR, clinical study report; DLQI, Dermatology Life Quality Index; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue scale; GPP, Generalised Pustular Psoriasis; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; GPPASI, Generalised Pustular Psoriasis Physician Area Severity Index; ITT, intention to treat; LOCF, last observation carried forward; PROs, patient reported outcomes; PSS, Psoriasis Symptom Scale; VAS, visual analogue scale.

EAG conclusion on study statistical methods

The EAG have not identified any methodological issues with the statistical methods of Effisayil 1. Only the results for the primary outcome and the key secondary outcome (both at Week 1) can be interpreted as statistically meaningful, because high crossover to spesolimab treatment after Day 8 rendered the planned statistical analysis of the other outcomes noninformative.

3.2.5 Efficacy results of the intervention studies

In this section we focus on the primary outcome (GPPGA pustulation subscore 0 at Week 1) and the key secondary outcome (GPPGA total score of 0 or 1 at week 1). We also report on the GPPGA pustulation subscore over time because within these data we can observe something of how the proportions with a GPPGA pustulation subscore 0 or 1 vary over time (response to treatment in the economic model is modelled in terms of flare resolution,

defined as a GPPGA pustulation subscore of 0 or 1). We do not report on the GPPASI 75 outcome here but descriptive post-hoc analyses for four participant groups, based on treatment received, are presented in CS Appendix E for this outcome.

3.2.5.1 GPPGA pustulation subscore 0 at Week 1 (Primary outcome)

At Week 1, 19 of the 35 participants in the spesolimab arm (54.3%) achieved a GPPGA pustulation subscore of 0 (i.e. they had no visible pustules). In the placebo arm only one participant (5.6%) achieved this (Table 9 below and CS Figure 7). The risk difference between the spesolimab and placebo arms of the trial was 48.7 percentage points (95% CI 22 to 67, p-value <0.001). In this analysis, any participants who withdrew from the study (one participant in the spesolimab arm) or who received escape medication during Week 1 (two participants in the spesolimab arm, one in the placebo arm) were assumed not to have responded.

A post-hoc sensitivity analysis was conducted with linear regression that adjusted for sex, race, and baseline GPPASI value because these were imbalanced covariates at baseline. As can be observed from Table 9, similar results were obtained.

Table 9 GPPGA pustulation subscore 0 at Week 1 and results of post-hoc sensitivity analysis

Primary outcome	**Spesolimab (N=35)**		**Placebo (N=18)**	
GPPGA pustulation subscore of 0 at week 1, n/N (%)	19/35 (54.3%)		1/18 (5.6%)	
Risk difference percentage points (95% CI), p-value	48.7 (21.5 to 67.2), p<0.001			
Post-hoc sensitivity analyses of primary outcome[a]				
	Spesolimab	**Placebo**	**Spesolimab**	**Placebo**
Sex	Female		Male	
Responders/total patients	11/21	1/15	8/14	0/3
Adjusted risk difference percentage points (95% CI), p-value for treatment difference	48.2 (26.9 to 69.5), p<0.001			
Race	Asian		White	
Responders/total patients	10/16	1/13	9/19	0/5
Adjusted risk difference percentage points (95% CI), p-value for treatment difference	52.2 (31.4 to 72.9), p<0.001			

Baseline GPPASI value	
Adjusted risk difference percentage points (95% CI), p-value for treatment difference	46.9 (25.4, 68.3), p<0.001[b]

Source: Based on CS Appendix E Table 14 with data from CS B.2.6.1 added.
CI, confidence interval; GPPASI, Generalised Pustular Psoriasis Area and Severity Index; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment
[a] The post-hoc sensitivity analyses are based on a linear regression model using the primary endpoint as the dependent variable, and treatment assignment plus the respective covariate (sex, race or baseline GPPASI value) as the independent variable. The 95% CI and p-value are based on robust standard errors.
[b] The EAG believes incorrect values are reported in CS Appendix E Table 14 and so we report the values from Bachelez et al. (2021)[16] Table S5.

3.2.5.1.1 Time to complete pustular clearance

This analysis, reported in CS Figure 8, was conducted without censoring for participants receiving escape medication. In the spesolimab arm, complete pustular clearance was achieved at Day 2 in four participants, Day 3 in 11 participants and day 8 in 21 participants. All the participants in the spesolimab arm who achieved a GPPGA pustulation subscore of 0 with a single dose of spesolimab (n=19/35) did this by Week 1 (Day 8). The single participant who achieved complete pustular clearance in the placebo arm did this at Day 8.

CS Figure 9 shows pictures of one participant's skin before (Day 1, baseline) and after treatment (Day 3 and Week 1) with a single dose of spesolimab and a second participant's skin before (Day 1, baseline) and after treatment with a single dose of spesolimab (Day 8, Week 4, Week 12).

3.2.5.1.2 GPPGA pustulation subscores over time by randomised treatment at Day 1 and open-label spesolimab treatment at Day 8

CS Figure 12 panel A shows the GPPGA pustulation subscores over time for the 35 participants randomised to spesolimab. Data from this panel informs the efficacy data that is used in the cost-effectiveness model (see section 4.2.6.1 and Table 14 of this report for further details). At Day 8, 57% (n=20/35) of participants had a GPPGA pustulation score of 0 or 1, rising to 80% (n=28/35) had a GPPGA pustulation subscore of 0 or 1 at week 2, this proportion was maintained at week 4 and then fell slightly such that at Week 12 71% (n=25/35) had a GPPGA pustulation score of 0 or 1. We note that an outcome in the NICE scope and company decision problem is duration of response. Because the trial ended at Week 12 we do not know how much longer the response endured for the 60% of participants who had a GPPGA pustulation subscore of 0 at Week 12 (Key issue 4).

CS Figure 12 panel B shows the GPPGA pustulation subscores over time for the 23 participants who were randomised to spesolimab and received only a single spesolimab dose during the trial. CS Figure 12 panel C shows the data for the remaining participants randomised to spesolimab (n=12) who received their initial randomised dose and then a second open-label spesolimab dose at Day 8 because they still had a GPPGA pustulation subscore of at least 2. CS Figure 12 panel D shows the GPP pustulation subscores over time for the 15 participants randomised to placebo who then received open-label spesolimab at Day 8.

These data provide some indication of the duration of response after receipt of spesolimab for the treatment of a moderate-to-severe flare of GPP but, as patients were only followed-up to Week 12 in the Effisayil 1 trial, the data on duration of response are limited.

3.2.5.2 GPPGA total score of 0 or 1 at week 1 (Key secondary outcome)

The proportion of participants with a GPPGA total score of 0 or 1 at Week 1 was 42.9% (15/35 participants) in the spesolimab arm compared to 11.1% (2/18 participants) in the placebo arm. The risk difference between the trial arms was 31.7 percentage points, statistically significantly in favour of spesolimab. The analysis was conducted by assuming that any participants who withdrew from the study or who received escape medication during Week 1 had not responded.

The EAG infers from CS Figure 11 that all the participants meeting the criteria for this outcome did so with a GPPGA total score of 1 (i.e. no participants had a GPPGA total score of 0 at week 1).

A linear regression that adjusted for sex, race, and baseline GPPASI value because these were imbalanced covariates at baseline was also conducted for this key secondary outcome as a post-hoc sensitivity analysis. Table 10 shows that similar results were obtained.

Table 10 GPPGA total score 0 or 1 at Week 1 and results of post-hoc sensitivity analysis

Key secondary outcome	Spesolimab (N=35)	Placebo (N=18)
GPPGA total score of 0 or 1, n/N (%) at week 1	15/35 (42.9%)	2/18 (11.1%)
Risk difference percentage points (95% CI), p-value	31.7 (2.2 to 52.7), p<0.02	
Post-hoc sensitivity analyses of key secondary outcome[a]		

Key secondary outcome	Spesolimab (N=35)		Placebo (N=18)	
	Spesolimab	Placebo	Spesolimab	Placebo
Sex	Female		Male	
Responders/total patients	10/21	2/15	5/14	0/3
Adjusted risk difference percentage points (95% CI), p-value for treatment difference	34.6 (11.3 to 57.9), p=0.005			
Race	Asian		White	
Responders/total patients	8/16	2/13	7/19	0/5
Adjusted risk difference percentage points (95% CI), p-value for treatment difference	35.4 (12.5 to 58.3), p=0.004			
Baseline GPPASI value				
Adjusted risk difference percentage points (95% CI), p-value for treatment difference	29.7 (5.8, 53.5), p=0.018			

Source: Based on CS Appendix E Table 15 with data from CS B.2.6.2 added.
CI, confidence interval; GPPASI, Generalised Pustular Psoriasis Area and Severity Index; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment
[a] The post-hoc sensitivity analyses are based on a linear regression model using the primary endpoint as the dependent variable, and treatment assignment plus the respective covariate (sex, race or baseline GPPASI value) as the independent variable. The 95% CI and p-value are based on robust standard errors.

3.2.5.2.1 Time to first achievement of a GPPGA total score of 0 or 1

This analysis was conducted without censoring for participants receiving escape medication. The earliest achievement of a GPPGA total score of 1 (almost clear) in the spesolimab arm was day 3 (in 2 participants). By Day 8, which is the next time point shown in CS Figure 11, 17 participants in the spesolimab arm had a GPPGA total score of 1. In contrast, the earliest achievement of a GPPGA total score of 1 in the placebo arm was at Day 8 (in 3 participants). As CS Figure 11 shows, no participants achieved a GPPGA total score of 0 or 1 during Week 1.

3.2.5.2.2 GPPGA total score over time by randomised treatment at Day 1 and open-label spesolimab treatment at Day 8 (exploratory outcome)

The proportion of participants randomised to spesolimab (CS Figure 13 panel A, n=35) with GPPGA total scores of 0 or 1 increases from 43% at day 8 to 66% at week 4 (which is the

first time point that scores of 0 are observed) before levelling off at 60% at week 8 and week 12.

CS Figure 13 panel B shows that among the 23 participants randomised to spesolimab who received a single dose of treatment 15 (65%) had a GPPGA total score of 1 at day 8. From Day 8 to Week 12 the proportion of participants with a GPPGA total score of either 0 or 1 reached a maximum of 74% at week 4 (3/23 participants with a GPPGA total score of 0 and 14/23 participants with a GPPGA total score of 1) dropping back down to 61% at week 12 (4/23 participants with a GPPGA total score of 0 and 10/23 participants with a GPPGA total score of 1). The pattern of response among participants who were randomised to placebo and who received open-label spesolimab on Day 8 was a little more variable (potentially due to the smaller numbers of participants) but supports these observations (CS Figure 13 panel D).

Among the 12 participants who received two doses of spesolimab (CS Figure 13 panel C), none achieved a GPPGA total score of 0 during the 12-week trial but 58% (n=7/12) had a GPPGA total score of 1 at week 12 (the remaining 42% received escape or rescue treatment).

3.2.5.3 HRQoL outcomes

3.2.5.3.1 Pain VAS, FACIT-Fatigue, DLQI, and PSS

CS section B.2.6.3.1.2 reports mean score change from baseline over time (through to Week 12, end of study) descriptively for the following PROs: pain VAS, FACIT-Fatigue, PSS and DLQI. This includes the first week of comparator placebo evidence. CS Figure 14 shows that in the first week by Day 8, the placebo-controlled period, the spesolimab group (n=35) mean score achieved the MCID, shown by the dashed orange line, in all PRO scores, though we note that the 95% confidence intervals crossed the MCID boundary for the Pain VAS and DLQI. Although the mean score for FACIT-Fatigue and PSS scores of the placebo group (n=18) also achieved the MCID 95% confidence intervals crossed the MCID boundary for both and the spesolimab group achieved a greater improvement in both mean scores. Median score change from baseline at Week 1 is reported in the CSR in addition and compiled in Table 11 below.

Table 11 PROs: median score change from baseline at Week 1 in Effisayil 1 (pain VAS, FACIT-Fatigue, DLQI, PSS)

Outcome	Spesolimab N=35	Placebo N=18
Pain VAS. CFB, median (Q1, Q3)	[redacted]	[redacted]
FACIT-Fatigue. CFB, median (Q1, Q3)	[redacted]	[redacted]
PSS. CFB, median (Q1, Q3)	[redacted]	[redacted]
DLQI. CFB, median (Q1, Q3)	[redacted]	[redacted]

Source: CSR Tables 11.1.3.1.4:1 (pain VAS), 11.1.3.1.4:2 (PSS), 11.1.3.1.4:3 (FACIT-Fatigue), 15.2.4.10.3:2 (DLQI). Use of escape medication represents non-response. Last observation carried forward imputation for any missing data.
Abbreviations: CFB, change from baseline; DLQI, Dermatology Life Quality Index; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapies – Fatigue scale; IQR, interquartile range; NA, not applicable; PSS; Psoriasis Symptom Scale; VAS, visual analogue scale.

Using median score change from baseline instead of mean score change from baseline shows that the spesolimab group [redacted] MCID for the pain VAS score (a [redacted] points, MCID is a decrease of =>30 points), and that the placebo group [redacted] MCID for the PSS score. Thus, the median score change from baseline is more conservative than the mean score change.

After Day 8, CS Figure 14 compares the placebo group who received open label spesolimab (15/18) with the group initially randomised to spesolimab (35/35, 12 of whom received a second (open label) dose of spesolimab). The group initially randomised to placebo met the MCID for the scores where they had not met it already, pain VAS and DLQI, within a week (by Week 2). Generally, both groups show continued improvement in all PRO scores until the end of the study with confidence intervals for the two groups overlapping from the Day 8 time point onwards. We note that all participants had received one or two doses of spesolimab for the results reported after Day 8 and so these results do not support efficacy of spesolimab against placebo nor against standard of care.

The per-protocol secondary outcomes for Week 4 are reported within CS Appendix E Table 16, but descriptively according to the post-hoc subgroups noted in CS section B.2.4 instead of the original randomised groups.

3.2.5.3.2 EQ-5D

CS Figure 15 shows that the group initially randomised to spesolimab achieved an increase in EQ-5D median score change from baseline [redacted] by Week 1,

[redacted]. After Week 1 the results for the group initially randomised to spesolimab are inconsistent, and there are no further results reported for the group originally randomised to placebo who received open label spesolimab at Day 8. EQ VAS score change from baseline, by visit, was not reported in the CS.

3.2.5.4 Subgroup analyses

No subgroups were specified in the NICE scope or the company decision problem. Pre-specified exploratory subgroup analyses for the Effisayil 1 trial are reported for the primary outcome and the key secondary outcome in CS section B.2.7 and CS Appendix E.1 Figures 5 and 6. These results have been published in the trial publication Burden et al. 2023.[22]

Results are reported for the pre-specified subgroups of sex, race (Asian/White), BMI, plaque psoriasis at baseline, IL36RN mutation status, baseline GPPGA total score, baseline GPPGA pustulation subscore, baseline GPPASI total score, baseline Japanese Dermatological Association (JDA) GPP Severity Index, and medication for GPP prior to randomisation. The trial publication explains that results for the pre-specified age subgroups were not reported because there were only two patients in the ≥65 years subgroup. [22]

For both the primary outcome (the proportion of participants achieving a GPPGA pustulation subscore of 0 at Week 1) and the key secondary outcome (the proportion of patients achieving a GPPGA total score of 0 or 1 at Week 1) the majority of the subgroups had similar treatment effect estimates to the overall trial population that are favourable for spesolimab.

Some of the subgroups were very small, particularly for the placebo group which only numbered 18 in total. Consequently, the subgroup confidence intervals tend to be wider than that for the overall trial population and often cross the null line making the results less certain. The subgroup analyses do not raise any significant concerns but should be viewed as illustrative.

3.2.5.5 Safety results

Safety results for Effisayil 1 are reported in CS sections B.2.10.1-2 and CS Table 13 for adverse events at Week 1 (to align with the timing of the primary outcome) and at Week 12 for all randomised patients who received at least one dose of the study drug.

At Week 1 the proportions of participants experiencing adverse events, severe adverse events, or drug-related adverse events were similar between the spesolimab and placebo groups. There were only slightly more adverse events in the spesolimab group (23/35, 66%) than in the placebo group (10/18, 56%). The placebo group fared much worse for pyrexia with 22.2% of participants experiencing pyrexia in the placebo group compared to 5.7% in the spesolimab group. The pyrexia events are discussed in the trial publication as occurring in the context of the underlying GPP flare but the authors were unable to rule them out as drug-related events (Bachelez et al. 2021).[16] Infections were the adverse events that occurred among a greater proportion of the spesolimab group (6/35, 17.1%) than the placebo group (1/18, 5.6%) in week 1. There were four serious adverse events among two participants in the spesolimab group and none in the placebo group. Three of the serious adverse events [redacted] being drug reaction with eosinophilia and systemic symptoms (DRESS), serious urinary tract infection, and drug-induced hepatic injury (the fourth was arthritis).

At Week 12 there were 51 participants in total, according to CS Table 13, who had received up to three doses of spesolimab during the course of the study. At Week 12 82% of participants had experienced an adverse event and 55% experienced drug-related adverse events. All incidence rates for adverse events had decreased since Week 1. There were eight serious adverse events experienced by six participants. Two of the serious adverse events were reported as DRESS but the CS states these were re-classified by independent external expert assessment as ‘no DRESS’ and as ‘possible DRESS’ which both resolved without drug treatment. The serious adverse events do not raise any further concerns.

The trial publication for Effisayil 1 reports on antidrug antibodies, the occurrence of which may lead to loss of efficacy of the study drug and potential risk for increased toxicity. Antidrug antibodies were detected in 46% of participants treated with spesolimab, at a median of 2.3 weeks after spesolimab administration.[16] This does not appear to have affected safety results at Week 12 whereby the incidence rate of adverse events decreased.

Throughout the Effisayil 1 trial there were no deaths and no adverse events that led to discontinuation of the trial drug.

Results of the Phase I spesolimab study show that all seven participants experienced an adverse event, all graded as mild or moderate, and there were no severe or serious adverse events (CS Appendix F.1.2). Interim results for Effisayil ON, the open label extension study, show that nine out of ten participants experienced an adverse event, and there was only one

severe adverse event and one serious adverse event both of which were pustular psoriasis in the same patient (CS section B.2.10.3). These studies do not raise any safety concerns.

EAG conclusion on the safety results

Spesolimab appears to be well tolerated and the safety results to date raise no concerns. However, we note that the data are limited.

3.2.6 Pairwise meta-analysis of intervention studies

Pairwise meta-analysis was not conducted because only one trial provides evidence fully relevant to this appraisal.

3.3 Critique of studies included in the indirect comparison and/or multiple treatment comparison

In CS section B.2.9 the company state that there was an absence of robust comparator data for formal indirect treatment comparison but did not elaborate further nor signpost to other parts of the company submission for this information. Our summary of the location and sources of evidence the company identified and included in their feasibility assessment for indirect treatment comparison is provided in Appendix 5.

The EAG has reviewed the information on the nine retrospective studies identified by the company and presented in CS Appendix D Table 11, the three real-world evidence sources and the two SEE sources (from CS Appendix M) but none could provide comparator data for formal indirect treatment comparison (Appendix 6). In addition, we asked the company to explain their rationale for not conducting unanchored population matching using trial or real-world data (clarification question A27). The company tabulated the trial and population characteristics for studies we listed in clarification question A27 in their response (Clarification response Table 8) and explained that there were no other studies (RCT or real-world) that reported efficacy or safety findings for a population of GPP patients experiencing flares as defined in the Effisayil 1 trial and receiving the comparator treatment for this appraisal, established clinical management (also described as best available care in the CS). We independently checked a proportion of the wider set of studies identified by the company's systematic literature review (clinical SLR tables embedded in CS Appendix D.1.2) and did not find any comparator data that would be suitable for use in a formal indirect treatment comparison.

3.3.1 The Effisayil 1 historical cohort.

In the absence of an indirect treatment comparison to inform the economic model the company used data from the Effisayil 1 historical cohort.[23] The way these data are used in

the model are described in more detail in section 4.2.6.2.1 of this report. We have some concerns about how well the flares and treatments received for flares represent current best available care/established clinical management in England.

3.3.1.1 Effisayil 1 historical cohort study aims and methods

The Effisayil 1 historical cohort,[23] (n=53) provides data on the characteristics and clinical course of past GPP flares. In this retrospective study, investigators used a standard study questionnaire to log data which included the clinical and laboratory characteristics of past flares that were identified as being the typical, most severe, and longest flares experienced by each patient. There was no standard definition for typical, most severe and longest flares so this was based on investigator interpretation. For these three categories of flares, the treatment used, duration of hospitalisation and time to clearance of pustules, erythema and scaling was also logged.

3.3.1.2 Effisayil 1 historical cohort study generalisability and patient characteristics

We asked the company to provide evidence to show how representative the Effisayil 1 historical cohort,[23] is of the generalised pustular psoriasis patient population experiencing flares in England (clarification question A24). The company provided patient demographic and flare characteristics data (clarification response Table 6) for the POLARIS[8] and SCRIPTOR[24] real-world evidence sources whilst also stating that caution should be applied when making comparisons across data sources because of differences in definitions and collection methods. We note that patients in the POLARIS study in England with incident GPP (n=206), who experienced a flare (n=129) had a higher mean age than those in the Effisayil 1 trial at baseline (mean 57.3 years, SD 19.0 in POLARIS versus 43.0, SD 10.9 in Effisayil 1). The patients in the SCRIPTOR study (n=27 from the UK) were also older than those in the Effisayil 1 trial at baseline (mean 53.1, SD 19.7 at diagnosis). Due to the locations where the Effisayil 1 trial took place (see section 3.2.1.1) over half of the participants (54.7%) were of Asian ethnicity with the remainder being White (45.3%). A similar proportion (46.1%) were White in the POLARIS study but the proportion of Asian patients was lower (8.6%) (the remaining patients' ethnicities were Black/Caribbean 2.1%, mixed 41.3% or other/unknown 1.9%).[8] In the SCRIPTOR study a much higher proportion were documented as White, Caucasian and/or of European decent (77.8%) with 14.8% as Central, South and/or East Asian descent[24] (we believe there is an error in Clarification response Table 6 which gives a value of 1.3%). The remaining two participants were either of mixed ethnicity or of unknown/not reported ethnicity). For the other characteristics it is

difficult to compare due to missing data or data for a particular characteristic not being reported in different sources or data being reported in a different format.

3.3.1.3 Effisayil 1 historical cohort study flare treatment

Most patients in the Effisayil 1 historical cohort,[23] (n=46/53, 86.6%) received treatment for past GPP flares with at least one medication and 24.5% of the cohort (n=13/53) received at least one biologic therapy. We note that the use of prior treatments for past GPP flares in the historical cohort is not specific for moderate-to-severe flares as data were not reported in this way in the publication. In the EAG's opinion the use of biologic treatments in the Effisayil 1 historical cohort (24.5%),[23] seems lower than might be expected with current treatment in England [CS Figure 4 shows [redacted]% at first-line (Week 1) and [redacted]% at second-line (weeks 2-4) and [redacted]% at third and later lines of therapy (Weeks 5+)] but the EAG acknowledges that three UK clinical experts consulted by the company confirmed the prior treatments for past GPP flares in the historical cohort was similar to the basket of treatments defined in the SEE. The time period during which the historical flares occurred is not known (clarification question A22) so it is possible that some flares could have occurred many years ago when biological treatments were not available or as widely used. We are concerned that time to pustular clearance in the Effisayil 1 historical cohort (CS Table 18) may have been longer than it would be for a similar patient group treated in the NHS because of these treatment differences. If this were the case it would disadvantage the comparator group, increasing the difference in time to flare resolution between the comparator and intervention groups.

Although the data on treatments received for past GPP flares were captured for the Effisayil 1 historical cohort,[23] the study did not report on which medications were received for the three categories of flare or the treatment composition for individual flares. Therefore, in the economic model, the evidence on treatments received during a GPP flare were based on the company's SEE exercise (CS Table 24). Consequently, the evidence on comparator efficacy and the composition of the comparator treatments received for a flare come from different sources. This is discussed further in section 4.2.6.2 of our report.

3.3.1.4 Effisayil 1 historical cohort outcomes

Descriptive results are presented which provide information on the length of time flares took to resolve. Data was not collected using the GPPGA, instead the proportions of patients with pustular, erythema and scaling resolution within different time bands (less than 1 week, 1-2 weeks, 3-4 weeks, 5-8 weeks 9-12 weeks and more than 12 weeks) were reported for each of the three types of flare category. In the economic model the company use time to

pustular clearance as a proxy for the GPPGA pustulation subscore of 0 or 1 which is used in the model as the measure of response to treatment (see section 4.2.6). It is unclear how well pustular clearance corresponds to a GPPGA pustulation subscore of 0 or 1. Duration of hospital treatment was similarly reported for each of the three types of flare category giving the proportions of patients with different durations of hospitalisation (less than 1 week, 1-2 weeks and 3-4 weeks).

3.3.1.5 Effisayil 1 historical cohort study risk of bias

The company had not conducted a risk of bias assessment for the Effisayil 1 historical cohort study[23] so we requested this (clarification question A23). The company judged four of seven domains as having a moderate risk of bias which, following the guidance on the use of the ROBINS-I[25] should have led to an overall risk of bias of moderate. However, the company gave an overall risk of bias judgement of 'Low' which we believe is inappropriate. After our independent risk of bias assessment (presented with that of the company in Appendix 7) we judged the Effisayil 1 historical cohort study[23] to be at a serious risk of bias.

3.3.2 Alternative comparator data sources

We reviewed the studies identified by the company (Appendix 6) to see if any provided data that could be used as an alternative to the Effisayil 1 historical cohort.[23] In particular we considered the CEE GPP Expert Network retrospective case-series by Wolf et al.[26] because information on this study is presented in CS section B.2.9.2. However, the focus of the Wolf et al. study is to describe GPP flares and treatments received rather than the outcomes of flare treatment. This study did not provide the level of detail required to inform effectiveness in the cost effectiveness model. Data from this study were used to help determine which flare category from the Effisayil 1 historical cohort.[23] was the most appropriate to use in the economic model and this is described in more detail in section 4.2.6.2.1 of our report.

The only other data source that does provide the level of detail needed to inform comparator effectiveness in the economic model is the company's SEE - BAC and efficacy,[14] which as noted above, provides the evidence for treatments received for a GPP flare in current UK practice. The company describe this SEE in CS section B.2.9.3 (with the summary of results in CS Appendix M.1.1). The company states "*predictions for BAC efficacy were generally aligned with the RWE outcomes observed in the Effisayil 1 historical cohort and CEE GPP Expert Network data*" however they ultimately decided that "*the data are not sufficient for decision making and are not used to inform the economic modelling*". Whilst we agree that the efficacy evidence elicited from the UK experts may be subject to a risk of bias and associated with uncertainty, we also recognise that it may better reflect the experience of

patients treated for moderate-to-severe GPP flares in the UK and be better aligned to the composition of comparator treatments. We therefore believe this data source should be considered and discuss this further in section 4.2.6.2.2 and 4.2.6.2.3. The SEE - BAC and efficacy report[14] states that [redacted].We note that an important potential source of bias is [redacted].

3.4 Conclusions on the clinical effectiveness evidence

The company's decision problem matches the NICE scope, however, the key clinical effectiveness evidence from the Effisayil 1 trial (spesolimab n=35, placebo n=18) differs from the NICE scope and company decision problem in two important areas:

- The population is adult patients with GPP flares of moderate-to-severe intensity which is a narrower population than defined in the NICE scope and company's decision problem (Key Issue 1)
- The Effisayil trial comparator is placebo, not established clinical management without spesolimab as defined in the NICE scope and company's decision problem (Key Issue 2)

The participants enrolled in the trial included a high proportion (55%) who were Asian which was partly a consequence of the countries from which participants were recruited. No participants were recruited from England. The company assessed the Effisayil 1 population as applicable to routine clinical practice [in the NHS] despite the high proportion of Asian people in the cohort (CS Table 11; CS section B.2.12.3), however, the EAG was unable to independently recruit clinical experts to verify this.

We agreed with the company's judgement that the risk of bias in the Effisayil 1 RCT was low. Although there were some differences in baseline characteristics between the groups, there is little published information about the prognostic factors for flare resolution. Some of the differences may bias the results in favour of the placebo arm.

There is no standard definition of flare resolution. In the Effisayil 1 trial the primary outcome was a GPPGA pustulation subscore of 0 (clear, no visible pustules) at Week 1. However,

clinical effectiveness (flare resolution) in the economic model is defined as a GPPGA pustulation subscore of 0 or 1 which is a less stringent response. Independent expert clinical opinion to verify the company's validation of the appropriateness of this definition of flare resolution would be welcome.

The Effisayil 1 RCT found that at Week 1 there was a statistically significant difference in favour of spesolimab in the proportion of participants who achieved a GPPGA pustulation subscore of 0 (primary outcome) and a GPPGA total score of 0 or 1 (Key secondary outcome). Similar results were obtained from post-hoc sensitivity analyses of these outcomes that adjusted for covariates that were not balanced at baseline (sex, race, baseline GPPASI value).

Participants in the placebo arm meeting pre-specified criteria were eligible to receive open label spesolimab on Day 8. The majority of placebo arm participants met the criteria and chose to receive open label spesolimab. Therefore, there is no comparative evidence for the efficacy of spesolimab in comparison to placebo beyond Week 1 of the trial. The planned testing of secondary outcomes, including for three patient reported outcome measures (Pain VAS, PSS and FACIT-Fatigue score), at Week 4 was abandoned and instead, outcomes after Day 8 were analysed descriptively. The EQ-5D-5L (health index and VAS) was an exploratory outcome and contributes data to the economic model, but in common with other trial outcomes, there is no comparative evidence beyond Week 1. The EAG view the PRO results from Effisayil 1 as illustrative. The total trial period was 12 weeks which means that we do not know the extent of the duration of the response to spesolimab.

The reported adverse events raised no concerns, although data both in terms of the number of people who had received spesolimab (n=51 participants in total) and the duration of the trial (12 weeks) are limited. There were no deaths during the trial and no adverse events that led to discontinuation of the trial drug (section 3.2.5.5).

In the absence of comparative data from the Effisayil 1 trial beyond Week 1 the company sought to identify studies that could be included in an indirect treatment comparison. No studies were identified that provided comparator data suitable for use in a formal indirect treatment comparison. The company therefore uses data from the Effisayil 1 historical cohort to inform cost-effectiveness modelling of the comparator arm beyond Week 1. We assessed this study as being at a serious risk of bias. The Effisayil 1 historical cohort provides data on the characteristics and clinical course of past GPP flares experienced by the participants who took part in the Effisayil 1 RCT. The past GPP flares were categorised by investigators as being either typical, the most severe or the longest flares experienced by

patients but there was no standard definition for these categories. It is difficult to know how representative the historical data on flare are to the GPP patient population experiencing flares in England. Additionally, the time period when the historical flares occurred is not known, and this may have impacted the range of treatments that people had received for their historic flares. In particular, the use of biologic treatments in the Effisayil 1 historical cohort seems lower than might be expected with current treatment in England. We have concerns that treatment differences could mean that pustular clearance in the historical cohort took longer than would be expected for a similar patient group receiving treatment in the NHS now. If this was the case this would disadvantage the comparator group in the economic model.

The company ruled out the use of their SEE – BAC and efficacy to inform comparator effectiveness in the economic model. Although we acknowledge that these data are also subject to a risk of bias as well as being associated with some uncertainty the results are relevant to the treatment of GPP flares in the NHS. Additionally, the composition of comparator treatments received that is used in the economic model also comes from the SEE – BAC and efficacy. We therefore use data from this source to inform comparator effectiveness in the EAG base case.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company reports their economic search strategy in CS section B.3.1 and CS Appendix G. They conducted simultaneous searches to identify cost-effectiveness studies, costs, and health care resource use studies for the treatment of patients with GPP. A single search strategy was carried out and consisted of an original search on 27 December 2022 and an updated search on 6 May 2024. CS Appendix G Table 31 presents the inclusion and exclusion criteria. The searches were well-constructed; the company searched relevant sources and used published search filters which they adapted by adding further search terms. Thus, we consider the searches to be sensitive, up-to-date, and not likely to miss any studies.

The systematic literature review did not identify any cost-effectiveness studies for patients with GPP, and there are no previous NICE appraisals assessing GPP. We are not aware of any cost-effectiveness studies that have been missed by the company.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

The company developed a de novo economic model to assess the cost-effectiveness of spesolimab compared with BAC in the treatment of adult patients with GPP presenting with flares.

4.2.1 NICE reference case checklist

The company's economic model fulfils the requirements of NICE's reference case (Table 12), except for the time horizon. It is unclear whether the time horizon used in the company's submission (12 weeks) is long enough to reflect all important differences in costs or outcomes between spesolimab and BAC. For further details, please see section 4.2.5.

Table 12 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and Personal Social Services	Yes

Element of health technology assessment	Reference case	EAG comment on company's submission
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Unclear
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and Personal Social Services resources and should be valued using the prices relevant to the NHS and Personal Social Services	Yes

Element of health technology assessment	Reference case	EAG comment on company's submission
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	No discounting applied due to the short time horizon

Source: EAG assessment based on the company submission.
EAG, External Assessment Group; NHS, National Health Service; NICE, The National Institute for Health and Care Excellence; QALY, quality-adjusted life-years; UK, United Kingdom.

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company developed a de novo cost-effectiveness model, which is described in CS section B.3.2.2. The model parameters are presented in CS sections B.3.3 to B.3.5, the base case inputs in CS section B.3.9.1, and the model assumptions in CS section B.3.9.2. The company developed a Markov state transition model with three mutually exclusive health states: GPP flare, resolved flare, and death. A daily cycle length was adopted, and the company did not apply a half-cycle correction. All patients start the model in the GPP flare health state, which is defined as a GPPGA score ≥ 3, new or worsening pustules, GPPGA pustulation subscore ≥ 2 and ≥ 5% of body surface area with erythema and the presence of pustules. At each cycle in the model, patients can remain in the GPP flare health state, move to the resolved flare health state (defined as a GPPGA pustulation subscore of 0 or 1) or die. We note that death was not initially modelled by the company for patients in the resolved flare health state. In response to clarification question B4, the company updated their model and included general population mortality to reflect the risk of death for patients with a resolved flare. The updated model structure is presented in Figure 2 below.

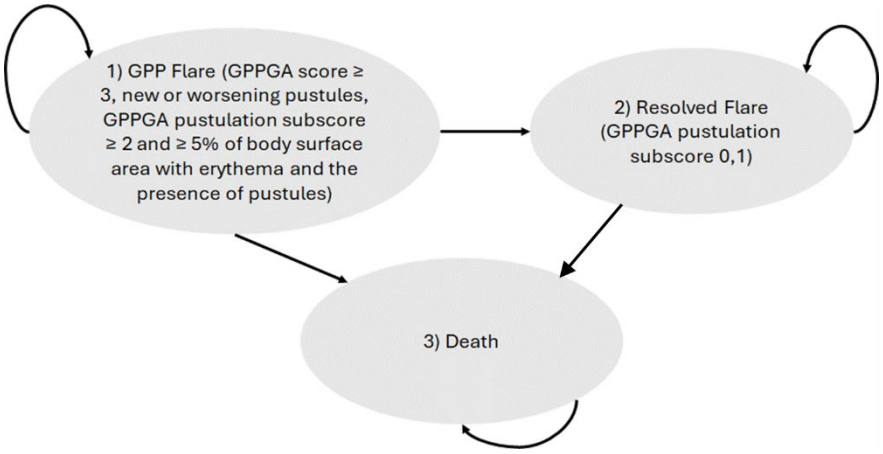

Figure 2 Updated model structure

Source: Reproduced from Figure 3 of the clarification response document.
GPP, generalised pustular psoriasis; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment.

In the company submission, response to treatment was defined as a GPPGA pustulation subscore of 0 or 1. The primary outcome of the Effisayil 1 trial is a GPPGA pustulation subscore of 0.[16] However, UK clinicians consulted by the company as part of the model developed for this submission validated the use of a pustulation subscore of 0 or 1 to represent a resolved flare as it better reflects the impact of GPP in UK clinical practice.[28] Also, the UK clinicians advising the company are of the opinion that any patients who had been in hospital would likely be discharged at this stage.[28] We were unable to confirm this assumption with clinical experts, but we consider that further clinical opinion would be relevant.

4.2.2.2 EAG critique of model assumptions

4.2.2.2.1 A second/recurrent GPP flare is not implemented in the model

Patients who respond to treatment (i.e., have a GPPGA pustulation subscore of 0 or 1) are assumed to remain responders for the remainder of the modelled time horizon. The company argues that evidence on flare frequency shows that patients are unlikely to have more than two flares per year. But the EAG notes that it does not mean that patients cannot have two flares in a 12-week period.

Based on information from the company submission and clarification response to question A1i, the EAG notes that within the 12-week Effisayil 1 trial period:

- Two patients in the spesolimab arm received a single dose of spesolimab (at baseline) for their first flare and then a rescue dose for a second/recurrent flare.

- Two patients in the spesolimab arm received two doses of spesolimab (at baseline and at day 8) for the first flare and then a rescue dose for a second/recurrent flare.
- Two patients in the placebo arm received a single dose of spesolimab at day 8 and then a rescue dose for a second/recurrent flare.
- Four patients in the spesolimab arm and another four patients in the placebo arm received standard of care escape treatment after day 8 – this was for patients with disease worsening after day 8 who either had not achieved a clinical response (GPPGA pustulation subscore of 0 or 1) and had disease worsening, or who had achieved a clinical response but subsequently experienced disease worsening that was not severe enough to meet criteria for flare recurrence and receive a rescue dose of spesolimab.

Therefore, 11.3% of patients in the Effisayil 1 trial received rescue treatment with spesolimab to treat second/recurrent flares, and eight patients received a standard of care escape treatment, [redacted]. The company did not include second or recurrent flares in the model. Although we acknowledge the low number of patients in this situation, we believe the company should have explored this in scenario analyses, as it would be valuable to see how modelling second/recurrent flares may affect the model conclusions. We also note that we were unable to confirm with clinical experts whether the company's assumption may be reasonable. We consider this to be a key issue (Key Issue 3) as we believe this uncertainty can be resolved with further clinical data and further clinical input.

4.2.2.2.2 Severity of a GPP flare (based on GPPGA pustulation subscore) is not implemented in the model

The company argued that this was a simplifying assumption designed to increase the transparency and interpretability of the model. The EAG agrees that modelling the severity of GPP flares would be challenging as the available data to inform the economic model does not seem to be categorised in that way.

Nevertheless, we note that most of the evidence informing the model is drawn from patients with moderate-to-severe GPP flares (Effisayil 1 trial and the SEE exercise). Therefore, it is unclear whether the model results are generalisable to the patients with mild flares. This is further discussed in section 4.2.3.

4.2.2.2.3 Maximum flare duration is 12 weeks

In the company's model, all patients are assumed to respond to treatment (spesolimab or best available care) by Week 12. The company considers this to be a conservative assumption as the study informing the efficacy of the comparator arm, the Effisayil 1 historical cohort, shows that around 12% of patients have not responded in 12 weeks.[23] We therefore tested this in a scenario analysis (see section 6).

Evidence from the Effisayil 1 trial shows that 25 of the participants at Week 12 had a GPPGA pustulation subscore of either 0 (n=21) or 1 (n=4) and the remaining 10 participants had received escape/rescue therapy; therefore there is no information on their Week 12 GPPGA pustulation subscore. In the best-case scenario, all patients achieved a GPPGA pustulation subscore of 0 or 1 by Week 12 (company's base case); in the worst-case scenario, none of them resolved their flare by Week 12. The EAG believes that it is likely that some of these patients have resolved their flares by Week 12 while others have not. Thus, we tested the following alternatives in scenario analyses (see section 6):

- The worst-case scenario (7 out of 35 patients have not responded to treatment by Week 12): 20.0%. According to the text above, the worst-case scenario is 10/35= 28.6%, however due to model limitations and the model assumption that patients cannot get a second/recurrent flare within the time horizon, it is only possible to model a maximum of 7 patients not responding to treatment by Week 12.
- The same proportion of patients as for the comparator arm have not responded to treatment by Week 12: 12.37%.
- The proportion of patients who received escape/rescue therapy at the latest time (between Week 8 and Week 12) have not responded to treatment by Week 12: 5.7%. This assumes that these patients did not have enough time to recover after receiving the escape/rescue therapy.

4.2.2.2.4 No half-cycle correction and no discounting of outcomes

The EAG agrees with these assumptions as the duration of both the cycle length (one day) and the time horizon (12 weeks) are short. Therefore, the impact of half-cycle correction and discounting would be negligible.

EAG comment on model structure

The EAG considers the model structure to be appropriate for this condition and to reasonably reflect its pathway. The company assumed that a GPP flare that appeared to initially improve cannot get worse again within a 12-week period, and that all

patients have responded to treatment (both to spesolimab and to BAC) by week 12. We are unclear whether these assumptions are appropriately representing UK reality, and therefore we consider that further clinical expert would be valuable.

4.2.3 Population

The population considered in the company model is described in CS section B.3.2.1 and consists of adult patients with GPP presenting with flares. This is aligned with the population defined in the NICE scope and the licensed population for spesolimab. However, we note that most of the evidence informing the model is drawn from the moderate-to-severe flare population (Effisayil 1 trial and the SEE exercise). It is unclear whether the model results are generalisable to the patients with mild flares and further clinical expert opinion would be helpful to clarify this. In the absence of that, we consider that the model conclusions are only relevant for the moderate-to-severe flare population.

The baseline characteristics of the model population are presented in CS Table 14. These were taken from the Effisayil 1 trial.[16] Table 13 shows the model inputs for baseline age, sex and weight. As we were not able to identify any clinical experts to advise the EAG, it is unclear whether the modelled baseline characteristics are representative of the patients who may receive spesolimab treatment in UK clinical practice. We note that using other values for the baseline characteristics has a limited impact on the model results.

Table 13 Baseline characteristics of the population

Characteristic	Baseline inputs
Average age (years)	43.00
Proportion female (%)	67.90
Average weight (kg)	72.03

Source: Reproduced from CS Table 14.

EAG comment on model population

The patient population included in the company's cost-effectiveness analysis aligns with the NICE scope and the licensed population. However, it is unclear whether the model results are generalisable to patients experiencing mild flares as the population from the studies informing the economic model is mainly a moderate-to-severe flare population. This is discussed in Key Issue 1. It is unclear whether the baseline characteristics based on the Effisayil 1 trial are reflective of UK clinical practice.

4.2.4 Interventions and comparators

CS section B.3.2.3 describe the intervention and comparators. The economic model compares spesolimab versus best available care (BAC).

Spesolimab is administered by intravenous infusion at the recommended dose of 900 mg on day 1. For patients with persistent symptoms, another dose of 900 mg can be offered on day 8. In the company's model, it was assumed that 80% of patients who received spesolimab on day 1 and have persistent symptoms on day 8 (GPPGA pustulation subscore ≥2) receive a second infusion of spesolimab. This was based on data from the Effisayil 1 trial, in which 12 out of 15 patients who did not achieve a GPPGA pustulation subscore of 0 or 1 received a second dose of spesolimab.[16] The remaining patients who have persistent symptoms on day 8 (20%) were assumed to receive treatment with ciclosporin.

There are no licensed treatments specifically approved to treat GPP flares in the UK aside from spesolimab. During the first week, the company used data from the placebo arm of the Effisayil 1 trial to inform the efficacy of the comparator arm (BAC). Beyond that, the company used data from the Effisayil 1 historical cohort study (further details are provided in section 4.2.6).[23] In the Effisayil 1 trial, patients in the placebo arm did not receive any active drugs during the first week although they could be admitted to hospital for supportive care.[16] For the Effisayil 1 historical cohort study, it was not possible to derive the treatment composition for an individual flare.

Therefore, in the company's model, it was assumed that patients in the comparator arm do not receive any drugs during the first week (to align with the placebo data of the Effisayil 1 trial) and, beyond the first week, evidence on the treatments received for a GPP flare in the UK were obtained from a group of UK experts participating in a SEE exercise (see Figure 1 above). The experts were asked to respond to the following question: "Please list up to 30 treatments that you believe would comprise currently best available care for first-line active treatment during a GPP flare, either moderate or severe (i.e., treatments used in practice)". Further clinical expert opinion on whether the treatments in Figure 1 reasonably reflect the standard of care for moderate-to-severe GPP flares in UK clinical practice would be useful as we were unable to confirm that with other clinical experts.

In the EAG's view, it is unlikely that patients in UK clinical practice would not receive any active drugs to treat GPP flares for a whole week. In the absence of better UK evidence for the composition of the BAC arm, we believe that modelling the treatments indicated by the UK experts as part of the SEE exercise is a reasonable approach. However, we are concerned that these treatments do not match the treatments used to treat GPP flares in the

Effisayil 1 historical cohort study, which is the study used to inform the efficacy of BAC after week 2 in the company's base case. It is therefore uncertain how generalisable the efficacy of the comparator (obtained from the Effisayil 1 historical cohort) is to the UK population (for further details, see section 4.2.6.2).

EAG comment on intervention and comparators

Although the intervention and comparators in the economic model appear to be broadly consistent with the NICE scope, the EAG is concerned that the composition of the comparator arm (BAC) is not aligned with UK clinical practice and/or the studies informing its efficacy. We therefore consider this to be a Key Issue (Key Issue 4).

4.2.5 Perspective, time horizon and discounting

The perspective of the analysis is the National Health Service (NHS) and Personal Social Services in England, in line with the NICE reference case. There is no discounting for costs and outcomes in the model as the time horizon is too short (12 weeks) (see section 4.2.2.2.4).

A time horizon of 12 weeks was implemented in the company's model. This is the follow-up period of the Effisayil 1 trial,[16] and the company considers this to be the period of most relevance in the emergency medical setting. Spesolimab is indicated to treat GPP flares. The company stated that evidence on flare frequency shows that patients are unlikely to have more than two flares per year.

The EAG notes that relevant evidence to inform the model is only available for a period of 12 weeks and therefore modelling a longer time horizon would be challenging. However, it is possible that treating one flare with spesolimab might affect the efficacy and safety of spesolimab or other treatments in a subsequent flare. Evidence on this does not seem to be currently available, and we are unclear whether any data are being collected to inform this (further information can be seen in the company's response to clarification question B1). We consider the appropriateness of a 12-week time horizon to be uncertain and questionable because the long-term consequences of the treatment with spesolimab are still unclear.

EAG comment on perspective, time horizon and discounting

The company uses the recommended perspective, which is in line with NICE guidelines. No discounting was applied in the company's model due to a short time horizon (<1 year), and we agree with this assumption. We are uncertain whether a time horizon of 12 weeks is long enough to capture all the costs and consequences of

the treatment with spesolimab. Therefore, we consider this to be a Key Issue (Key Issue 5).

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Response to treatment: spesolimab

The approach to modelling the response to spesolimab is discussed in CS section B.3.3.1. The company used data from the Effisayil 1 trial to model the effectiveness of spesolimab. Evidence on flare response was available at day 2, day 3, day 8, week 2, week 3, week 4 and week 12.

As no standard definition of GPP flare resolution is available, the company defined response to treatment as a GPPGA pustulation subscore of 0 or 1, as previously discussed in section 4.2.2. However, we were not able to confirm whether the use of a GPPGA pustulation subscore of 0 or 1 appropriately reflects the resolution of a flare and further expert opinion would be beneficial. We tested the impact of this assumption by running an alternative scenario in which the response to treatment is defined as a GPPGA pustulation subscore of 0 (primary endpoint of the Effisayil 1 trial).

The company adjusted the trial data to the model daily cycle by assuming that no patients would respond on Day 1 and then applying a linear cumulative response in between weeks (see Table 14 below for the model inputs).

Table 14 Efficacy of spesolimab based on Effisayil 1 trial

Timepoint	GPPGA subscore 0 or 1 (company's base case)	GPPGA subscore 0 (EAG scenario analysis)
Day 2	13/35 = 37.1% (13 responders)	4/35 = 11.4%
Day 3	6/35 = 17.1% (6 new responders)	7/35 = 20.0%
Day 3-8	1/35 = 2.9% (1 new responder)	8/35 = 22.9%
Week 2	8/35 = 22.9% (8 new responders)	4/35 = 11.4%
Week 3	0/35 = 0.0% (no new responders)	0/35 = 0.0%
Week 4	0/35 = 0.0% (no new responders)	0/35 = 0.0%
Week 12	7/35 = 20.0% (remaining)	12/35 = 34.3%

Source: Partially reproduced from CS Table 17.
GPPGA, Generalised Pustular Psoriasis Physician Global Assessment.

4.2.6.2 Response to treatment: BAC

The company's approach to modelling the response to BAC is discussed in CS section B.3.3.2. For the first week of the model, response to BAC was obtained from the Effisayil 1 trial using a similar approach as the one used for spesolimab (see section 4.2.6.1).

After the first week, response to BAC was not obtained from the Effisayil 1 trial because crossover occurred for more than 80% of patients in the placebo arm, who received spesolimab on Day 8. In their base case, the company used data from the Effisayil 1 historical cohort to model the efficacy of BAC after the first week.[23]

4.2.6.2.1 Effisayil 1 historical cohort (company's base case)

In Effisayil 1 historical cohort, investigators collected historical data from patients included in the Effisayil 1 trial to describe the characteristics and outcomes of GPP flares prior to patients' enrolment in the trial.[23] The Effisayil 1 historical cohort did not collect data on GPPGA pustulation subscores of 0 or 1 and the company used time to pustular clearance as a proxy to the Effisayil 1 trial GPPGA pustulation subscore outcome. It is not clear to us whether this is appropriate since we were not able to confirm it with clinical experts. Time to pustular clearance was collected for patients' typical flare, most severe flare and longest past flare and was categorised as <1 week, 1-2 weeks, 3-4 weeks, 5-8 weeks, 9-12 weeks and >12 weeks.[23] However, it is unclear how the investigator-assigned flare categories ("typical flare", "most severe flare" and "longest past flare") relate to the type of flares included in the Effisayil 1 trial.

The study by Wolf et al.,[26] details of which are provided in CS section B.2.9.2, reported GPPGA pustulation subscores by flare type ("most severe flare" and "other flare"). The company compared the baseline GPPGA pustulation subscores observed in the Effisayil 1 trial to the GPPGA pustulation subscores reported by flare type in Wolf et al.[26] CS Figure 23 shows this comparison and indicates that the trial cohort appears to be more aligned with the "most severe flare" cohort from Wolf et al.

However, the company were not certain whether the Effisayil 1 historical cohort investigator-assigned flare categories and the Wolf et al. flare categories were aligned. Therefore, the company's approach for their base case was to use a weighted average of the "most severe flare" and "typical flare" of the Effisayil 1 historical cohort based on the proportion of most recent flares that were categorised as "most severe" and "other flares" from the Wolf study (55% and 45%, respectively). Table 15 below presents the efficacy of BAC based on Effisayil 1 historical cohort data.[23]

Table 15 Efficacy of BAC based on Effisayil 1 historical cohort

Timepoint	Time to pustular clearance, n (%)			
	Typical past flare (N=28)	Most severe past flare (N=28)	Longest past flare (N=11)	Pooled (weights 0.45 for typical, 0.55 for most severe past flare)
< 1 week	5 (16.7%)	3 (10.7%)	0 (0.0%)	13.40%
1-2 weeks	11 (40.0%)	3 (10.7%)	1 (9.1%)	23.89%
3-4 weeks	6 (23.3%)	13 (46.4%)	3 (27.3%)	36.01%
5-8 weeks	3 (10.0%)	4 (14.3%)	4 (36.4%)	12.37%
9-12 weeks	0 (0.0%)	1 (3.6%)	2 (18.2%)	1.98%
>12 weeks	3 (10.0%)	4 (14.3%)	1 (9.1%)	12.37%

Source: Partly reproduced from CS Table 18 and EAG Table 1 of clarification response document (question B6)
BAC, best available care.

To adjust the Effisayil 1 historical cohort data from Table 15 to the timepoints of the model, the company made the following assumptions: responses for weeks 1 and 2 are informed by "1-2 weeks" by assuming that half of the proportion responds in week 1 and the other half in week 2; and responses for weeks 3 and 4 are informed by "3-4 weeks" by assuming the same as before. It was also assumed that all flares would be resolved by week 12 with a linear cumulative response occurring between week 4 and week 12.

The company's model inputs for the response to BAC are presented in Table 16.

Table 16 Efficacy of BAC based on Effisayil 1 trial and Effisayil 1 historical cohort (company's base case)

Timepoint	Assumption	Efficacy outcome
Day 2	No response	0.0%
Day 3	Effisayil 1 trial: 1/18 (1 new responder)	5.6%
Day 3-8	Effisayil 1 trial: 1/18 (1 new responder)	5.6%
Week 2	Effisayil 1 historical cohort 1-2 weeks/2	11.9%
Week 3	Effisayil 1 historical cohort 3-4 weeks/2	18.0%

Timepoint	Assumption	Efficacy outcome
Week 4	Effisayil 1 historical cohort 3-4 weeks/2	18.0%
Week 12	Remaining	40.9%

Source: Partly reproduced from company's model cells 'Data Library'!U36:U42

4.2.6.2.2 Structured Expert Elicitation (SEE) exercise

The SEE exercise is described in CS section B.2.9.3 and Appendix M. It was carried out by the company with the aim of identifying the treatments used in the UK to treat GPP flares and the efficacy and safety profiles of the current treatments.[14] It comprised two rounds of elicitation (one individual round and one group round), concluding in an expert consensus response to each question. [redacted] experts from the UK and Ireland participated in the elicitation exercise, [redacted] of whom worked in the NHS. [redacted] experts attended the consensus workshop. Analysis of results utilised the SHELF software, through R, to fit probabilistic distributions on absolute and multinomial probabilities.[14]

Table 17 shows the efficacy of BAC elicited by the group of experts participating in the SEE exercise for a GPPGA pustulation subscore of 0 and a GPPGA pustulation subscore of 0 or 1.[14] The experts elicited estimates for moderate and severe flares separately. We have applied the same weight as the company for moderate (45%) and severe flares (55%) and calculated the pooled efficacy of BAC for overall moderate-to-severe GPP flares.

Table 17 Efficacy of BAC for GPPGA pustulation subscore of 0 and 0 or 1, based on SEE exercise (consensus output)

Timepoints	GPPGA pustulation subscore 0			GPPGA pustulation subscore 0, 1		
	LL	Median	UL	LL	Median	UL
Moderate						
Day 1-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 2-3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 3-8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 2-4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe						
Day 1-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 2-3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 3-8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoints	GPPGA pustulation subscore 0			GPPGA pustulation subscore 0, 1		
	LL	Median	UL	LL	Median	UL
Week 2-4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled (45% moderate, 55% severe)						
Day 1-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 2-3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 3-8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 2-4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Boehringer Ingelheim. Structured Expert Elicitation, 2022[14]
BAC, best available care; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; LL, lower level; UL, upper level.

To adjust the SEE estimates from Table 17 to the timepoints of the Effisayil 1 trial, we made the following assumptions aligned with the previous company's approach: no patient responds on day 1; responses for day 2 are informed by "day 1-2"; responses for day 3 are informed by "day 2-3"; responses for day 8 are informed by "day 3-8"; responses for weeks 2, 3 and 4 are informed by "week 2-4" by assuming that a third of the proportion responds in week 2, a third responds in week 3 and the remaining third responds in week 4. It was assumed that all flares would be resolved by Week 12 with a linear cumulative response occurring between week 4 and week 12.

The model inputs for the response to BAC based on the SEE exercise are presented in Table 18.

Table 18 Efficacy of BAC based on SEE exercise to use in the model

Timepoint	GPPGA subscore 0	GPPGA subscore 0 or 1
Day 2	[redacted]	[redacted]
Day 3	[redacted]	[redacted]
Day 8	[redacted]	[redacted]
Week 2	[redacted]	[redacted]
Week 3	[redacted]	[redacted]
Week 4	[redacted]	[redacted]
Week 12	[redacted]	[redacted]

Source: EAG calculations
BAC, best available care; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment.

4.2.6.2.3 EAG view

Using data from Effisayil 1 trial to inform the efficacy of BAC for the first week of the model is appropriate, in the sense that it provides a direct comparison between the intervention and the comparator. However, it seems unrealistic that patients in the placebo arm of the Effisayil 1 trial do not receive any standard of care treatments. The EAG is uncertain on how the relative efficacy of spesolimab may change if patients receive any standard of care treatments. Therefore, using trial data to inform the efficacy of BAC does not seem to appropriately reflect UK reality. Consequently, we do not use the Effisayil 1 trial for BAC efficacy in the EAG base case, however we explore this assumption in alternative scenarios (see Table 19 below).

The Effisayil 1 historical cohort[23] uses the same cohort of patients as in the Effisayil 1 trial, however it is unclear how long in the past the flares have occurred and whether the standard of care at that time is similar to the standard of care currently used. It is also uncertain which treatments were included in standard of care for individual flares and how they align with the standard of care for the UK, and therefore how generalisable the results from Effisayil 1 historical cohort are to the current UK reality.

The SEE exercise[14] provides relevant data to inform the economic model for the efficacy of BAC, as the estimates elicited were in relation to the best available care as seen in the experts' practice, which would therefore be relevant to the NHS. Currently, the company's base case matches historical cohort efficacy with SEE best available care information. The EAG considers to be more appropriate and relevant to the NHS to match SEE estimates of BAC efficacy with SEE estimates of best available care treatments.

The limitations of the SEE exercise in relation to the estimation of the efficacy of BAC are:

- Lower quality source of evidence compared to clinical trials and RWE studies.
- Potential for lack of consistency in the definition of response to treatment – although clinicians had pictures and definitions of the GPPGA components to aid them, there could have been variation in how they interpreted treatment response. The EAG considers that other studies might have a similar problem in the interpretation of treatment response between different clinicians.
- Discrepancy in the estimates of efficacy between clinicians in the first round of elicitation – however, when the results were pooled, all the experts agreed with the outcomes obtained, which may provide some confidence on the results.

- Expert interpretation of best available care may have included more efficacious treatments than commonly used in UK or Ireland practice (for instance, other clinicians might use less aggressive treatment to reduce the possibility of adverse events).

As mentioned in section 4.2.6.1 for spesolimab, whether the use of a GPPGA pustulation subscore of 0 or 1 appropriately reflects the resolution of a flare is uncertain. We tested alternative scenarios assuming that treatment response is defined as a GPPGA pustulation subscore of 0 for the BAC arm (see Table 19 below).

Based on the discussion above, we use the SEE exercise estimates for a GPPGA pustulation subscore of 0 or 1 in the EAG base case from Day 1 until the end of the time horizon (Table 19). Nevertheless, we acknowledge the high uncertainty of this assumption and the limitations of each source; therefore, we tested all the alternatives presented in Table 19 in scenario analyses. We note that for each scenario not using the Effisayil 1 trial to inform the efficacy of BAC during the first week (including the EAG base case), we also changed the composition of the comparator arm to include active treatments during this week. The active treatments included are the ones from the SEE exercise (see Figure 1 above).

Table 19 Alternative scenarios for the efficacy of BAC

	GPPGA subscore of 0 or 1				GPPGA subscore of 0	
	Effisayil 1 trial (week 1) + Effisayil 1 historical cohort (company's base case)	**Effisayil 1 historical cohort (company's scenario)**	**SEE exercise (EAG base case)**	**Effisayil 1 trial (week 1) + SEE exercise**	**SEE exercise**	**Effisayil 1 trial (week 1) + SEE exercise**
Day 2	0.0%	0.0%	[redacted]	[redacted]	[redacted]	[redacted]
Day 3	5.6%	5.74%	[redacted]	[redacted]	[redacted]	[redacted]
Day 8	5.6%	19.60%	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	11.9%	11.9%	[redacted]	[redacted]	[redacted]	[redacted]
Week 3	18.0%	18.0%	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	18.0%	18.0%	[redacted]	[redacted]	[redacted]	[redacted]

EAG, External Assessment Group; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; SEE, structured expert elicitation.

4.2.6.3 Mortality

The mortality risk associated with a GPP flare is described in CS section B.3.3.4. The company applied a daily rate of death of 0.096% for patients in the ICU unit. This rate was derived from a French SNDS study in which 2.6% of patients (15 out of 569) died within four weeks after their last flare.[29]

The company stated that the French study was aligned with other European studies – Augey et al.[30] (reporting a rate of approximately 2%) and Kromer et al.[31] (reporting a rate of approximately 3%).

Experts participating in the SEE exercise were asked to predict the number of patients with a GPP flare lasting beyond four weeks who would die due to any reason. The final consensus output shows [redacted].[14] This results in a weighted average mortality of [redacted] for overall moderate-to-severe flares, based on the weights of 45% for moderate flares and 55% for severe flares, as above. We note that using this mortality rate has a low impact on the model results.

In response to clarification question B4, the company updated their model to add non-disease-specific general population mortality for patients resolved from a GPP flare in both the intervention and comparator arms. This were obtained from the UK Office of National Statistics National Life Tables for 2017-2019 in England (pre-COVID). The yearly rates have been converted to daily rates to fit the model's daily cycle. The EAG is unclear on why the company have not used the most recent version of the National Life Tables for 2020-2022, but we note that adding general population mortality to the model has a low impact on the model results.

4.2.6.4 Adverse event incidence

Adverse events are described in CS section B.3.3.3. The following adverse events were included in the company's base case: serious infection, tuberculosis reactivation and liver injury. Serious infection and tuberculosis reactivation were identified as important adverse events in a Cochrane review of biological side effects and a review of related NICE technology appraisals for psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis and Crohn's disease.[32-40] Liver injury was included based on clinical advice. The company applied a weekly probability of experiencing an adverse event while receiving treatment in the economic model.

The incidences of serious infection and tuberculosis for the BAC arm were obtained from previous NICE appraisals in other disease areas, TA375 (rheumatoid arthritis) and TA383 (ankylosing spondylitis and non-radiographic axial spondyloarthritis), for which similar types of treatment to the BAC arm are used.[37,38] The incidence of liver injury was based on the SEE exercise as no other source was identified by the company.[14] The company did not model any adverse events for patients receiving BAC during the first week of treatment since these patients were assumed not to receive any active treatments during this period.

The incidences of serious infection and liver injury for the spesolimab arm were obtained from the Effisayil 1 trial and it was assumed to be equal to the probability of experiencing an event over the first week of treatment (after the first dose of spesolimab).[16] Due to lack of evidence, rates of tuberculosis were assumed to be equal to the rates for BAC. CS Table 20 shows the incidence rates for each adverse event.

In the SEE exercise, the incidence of adverse events elicited by the experts were [redacted] for serious infection and [redacted] for tuberculosis.[14] We note that changing these values has a negligible impact on the model results.

EAG comment on treatment effectiveness and extrapolation

In the company's base case, the efficacy of spesolimab is based on Effisayil 1 trial data while the efficacy of BAC is based on Effisayil 1 trial data for the first week and, beyond the first week, it is based on data from the Effisayil 1 historical cohort.

The standard of care treatments used to treat flares in the Effisayil 1 historical cohort are unknown for individual types of flares and therefore it is unclear how similar or different they might be from the best available care treatments currently used in UK practice. The EAG considers the SEE exercise estimates to reflect UK reality more closely and to be aligned with the modelled comparator treatments (which were elicited by the same experts). We use the SEE exercise estimates based on a GPPGA pustulation subscore of 0 or 1 from day 1 until the end of the time horizon in the EAG base case. We acknowledge, however, the uncertainty of this assumption and the limitations of each source and therefore we consider this to be a key issue (Key Issue 6). We tested several alternatives for the efficacy of BAC in scenario analyses.

The mortality and adverse event inputs seem reasonable, and we note that changing these input values has a low impact on the model results.

4.2.7 Health related quality of life

4.2.7.1 Systematic literature review for utilities

The company conducted a systematic literature review of HRQoL studies in patients with GPP. The methodology is described in CS Appendix I. The search date was 27 December 2022, with an update on 6 May 2024. CS Appendix I Table 46 presents the inclusion and exclusion criteria. We consider that the company searched an adequate range of sources, and the searches are adequately up to date. The searches identified 29 studies describing HRQoL in patients with GPP, but none of these reported health state utility or disutility values to be used in the model.

4.2.7.2 Study-based health-related quality of life

The health-related quality of life data used in the model is described in CS section B.3.4.5. EQ-5D-5L data were collected from the Effisayil 1 trial daily during the first week, then every week until week 4, and then in week 8 and 12.[16] The company mapped the EQ-5D-5L individual domain scores into a single utility index score using tariffs for the UK and mapped EQ-5D-5L to EQ-5D-3L using the approach described in Hernandez-Alava et al.[41]

The baseline utility in the Effisayil 1 trial was used as the utility of patients in the GPP flare health state in the economic model, regardless of treatment. The utility values for patients who recovered from a GPP flare (resolved flare health state) were based on data from the Effisayil 2 trial using a repeated-measures mixed effects model, which accounts for multiple measures per patient (clarification response B8). It is unclear why the company did not use data from the Effisayil 1 trial for patients with a GPPGA pustulation subscore of 0 or 1 to reflect a resolved flare. We note that the objective of Effisayil 2 trial was to assess the efficacy and safety of subcutaneous spesolimab for GPP flare prevention. The reason why the company used data from this trial for the utility of the resolved flare health state was because patients in Effisayil 2 trial spent most of their time in the trial without experiencing a GPP flare. In addition, the utility value for general population with a similar age and sex distribution is 0.85,[42] which is similar to the estimated utility for a resolved flare. Patients in the ICU had a utility of zero, as assumed in previous appraisals.[43] Table 20 presents the utility values used in the company's base case.

It seems reasonable to the EAG to assume that the quality of life of patients that have had resolved a flare for a while would be similar to the quality of life of patients not experiencing a flare. However, we would expect that the quality of life of patients immediately after resolving a flare is still slightly lower than if they have not had a flare for several months (or if their last flare was a mild one). This is mainly important for patients with moderate-to-severe

GPP flares that have required hospital stay and/or for patients that experienced some treatment adverse events. Although we were unable to check this assumption with clinical experts, we note that increasing or decreasing the utilities does not have a significant impact on the model results.

Table 20 Utility values used in the company's base case

State	Utility value, mean (standard error)	95% confidence interval
Active flare	[redacted]	[redacted]
Resolved flare	[redacted]	[redacted]
Hospitalisation ICU	0 (0)	0-0

Source: Partly reproduced from CS Table 21.
ICU, intensive care unit.

4.2.7.3 Adverse event disutilities

The adverse event disutilities were applied in the company's model and are described in CS section B.3.3.4.

The duration of each disutility was assumed to be 28 days. The disutility of serious infection was obtained from NICE TA375 (0.156),[44] and the company assumed a similar disutility for tuberculosis in the absence of any other evidence. For liver injury, a disutility of 0.0956 was obtained from a UK study by Sullivan et al.[45]

EAG comment on HRQoL

In the company's base case, utility values were informed by EQ-5D-5L data (mapped to EQ-5D-3L) derived from the Effisayil 1 and 2 trials. We agree with the company's approach to model health state utilities and adverse event disutilities. The EAG notes that no other sources reported utility values for GPP flares and also that changing the utility values do not have a significant impact on the model results.

4.2.8 Resources and costs

4.2.8.1 Literature review of cost and resource studies

The company's systematic literature review used to identify healthcare resource use studies is described in section 4.1 above. The results of the review are shown in CS Appendix H. The systematic literature review did not identify any UK-specific studies for patients with GPP with resource use data differentiated by whether patients experienced a flare or not.

The company assumed that European studies might also be applicable to the UK setting and therefore considered two European studies to be relevant: Viguier et al. 2024[46] and Wolf et al. 2024.[26] Viguier et al. is a retrospective study using the SNDS to identify healthcare resource use for patients who were hospitalised with GPP in France.[46] Wolf et al. is a retrospective study reporting rates of hospitalisation along with length of stay for patients with a GPP flare in Central and Eastern European countries.[26] CS Table 7 shows the healthcare resource use evidence from these studies.

In the company's base case, the study by Wolf et al. was used to inform the proportion of patients treated as inpatients. It was also used, as well as the Viguier et al. study, to inform company's sensitivity and scenario analyses (see Table 23).

4.2.8.2 Drug acquisition and administration costs

CS section B.3.5.1 presents the drug acquisition and administration costs. Acquisition costs were obtained from the British National Formulary (BNF)[47] and Drugs and Pharmaceutical Electronic Market Information Tool (eMIT).[48]

CS Table 22 shows the route of administration, pack cost, pack size and strength for each treatment used in the economic model. For all treatments, the company applied the minimum cost per mg. We note that the price for acitretin in CS Table 22 is incorrect and the company clarified that a price of £17.10, based on eMIT, should be considered for the economic model (clarification question B6). Similarly, the price for infliximab reported in CS Table 22 is incorrect and the company clarified that the price of £377.66 for a strength of 100mg (already used in the economic model) is correct (clarification question B7).

CS Table 23 shows the treatment dosing schedules for each treatment. Only spesolimab has a recommended treatment dosing regimen for GPP. The proportion of patients receiving a second dose of spesolimab was obtained from Effisayil 1 trial. For the patients eligible for a second dose of spesolimab who have not received it, the company assumed that this was because of previous adverse events and that these patients have ciclosporin on Day 8 instead (see section 4.2.4 above). For the BAC comparators, the dosing schedule was sourced from BNF assuming the same dosing as for severe psoriasis or plaque psoriasis, where available. If applicable, the company used the higher dosing regimens for each of the drugs to represent GPP treatment. In response to clarification question B7, the company explained that clobetasol propionate (a topical steroid) is only used in Week 1 of the economic model in a scenario where active treatment in the first week is modelled.

CS Table 24 shows the composition of the comparator arm in the company's base case. The weekly acquisition costs for spesolimab and the comparators are shown in Table 21.

Table 21 Weekly acquisition costs for spesolimab (PAS price) and the comparators (list price)

Treatment	Weekly cost	Source
Spesolimab	[redacted]	Company data on file
Immunosuppressant (ciclosporin)	£34.95	BNF[47]
TNF inhibitors (infliximab)	£1,360.14	eMIT[48]
Methotrexate	£14.55	
Retinoid (acitretin)	£5.98	
IL-23 inhibitors (guselkumab)	£2,250.00	
IL-17 inhibitors (secukinumab)	£1,218.78	
Ustekinumab	£2,147.00	
Topical steroids (clobetasol propionate)	£3.76	

Source: Partly reproduced from CS Table 25

In response to clarification question B13, the company provided an updated table with the correct administration costs to be considered in the model (Table 9 of the clarification response document). We reproduce these costs in Table 22 below.

Table 22 Administration costs used in the company revised base case model

Administration route	Cost in model	Source and justification
Oral	£0	Assumption: TA442, TA475, TA511, TA907
Subcutaneous (first dose)	£141.00	PSSRU 2023, unit costs of health and social care 2022/23, Nurse (Community-based band 5 without qualifications), wage cost per hour (3 hours); Cost incurred only once on the first use of subcutaneous therapy, as patients self-administer thereafter. As per TA935.[36,49]

Administration route	Cost in model	Source and justification
Subcutaneous (subsequent doses)	£0	See above.
Intravenous	£174.89	Assumed to be the total unit cost of a dermatology outpatient appointment (as per TA907) applied for each intravenous administration. National Schedule of NHS Costs 2021–2022. WF01A: Non-Admitted Face-to-Face Attendance, Follow-up. Dermatology (Service Code 330). Outpatient procedure[50]

Source: Reproduced from Table 9 of clarification response document
PSSRU, Personal Social Services Research Unit

4.2.8.3 Health state costs

The resource use and costs applied to each health state are described in CS section B.3.5.3, including outpatient and inpatient hospital visits, and ICU stay.

Resource use data were obtained from the two relevant European sources identified through the systematic literature review (see section 4.2.8.1) and the SEE exercise.[51] The company considered these sources more appropriate than the Effisayil 1 historical cohort because the location of treatment centres was mostly outside of Europe in the historical cohort study. CS Table 7 shows the healthcare resource use evidence for the two European studies while CS Table 27 shows the resource use elicited by the experts participating in the SEE exercise.

Table 23 presents the resource use modelled in the company's base case and scenario analyses.

Table 23 Modelled resource use implemented in the company revised base case model

Resource use during a flare	Value	Source
Proportion of patients treated as inpatients (spesolimab)	38.8%	Assumed 50% reduction in inpatient rates, based on the relative reduction of 48.4% in the proportion of patients with an active flare for spesolimab versus placebo in the Effisayil 1 trial.

Resource use during a flare	Value	Source
Proportion of patients treated as inpatients (BAC)	77.6%	Overall inpatient rate for a patient's last flare by Wolf et al.[26] Company scenarios: 93% (inpatient rate for a patient's most severe flare by Wolf et al.)[26] [redacted] (inpatient rate elicited for moderate/severe flares from the SEE exercise)[51]
Proportion of patients treated as outpatients (spesolimab)	61.2%	Assumption that all patients that did not have a hospitalisation would be treated as outpatients
Proportion of patients treated as outpatients (BAC)	22.4%	As above
Average weekly number of outpatient appointments: active flare	[redacted]	HCRU SEE[51]
Average annual number of outpatient appointments: resolved flare	[redacted]	HCRU SEE[51]
Proportion of inpatients treated in ICU (spesolimab)	0%	Assumption based on the fact that rapid resolution of flares as observed with spesolimab would alleviate the risk of the need for ICU care Company scenario: [redacted] based on HCRU SEE[51]
Proportion of inpatients treated in ICU (BAC)	[redacted]	HCRU SEE[51] Other sources: 25% (142/569) from Viguier et al.[46] 11.5% (3/26) from Wolf et al.[26] This uncertainty was explored via deterministic sensitivity analyses.

Resource use during a flare	Value	Source
Proportion of patients in ICU requiring mechanical ventilation	[redacted]	HCRU SEE[51]
Length of stay in ICU without mechanical ventilation, days	[redacted]	Maximum length of stay derived from the mean length of stay elicited in the SEE exercise and the response rates over time for BAC. SEE exercise: [redacted] days (mean length of stay) – not a company scenario.[51]
Length of stay in ICU with mechanical ventilation, days	[redacted]	Maximum length of stay derived from the mean length of stay elicited in the SEE exercise and the response rates over time for BAC. Company scenario: SEE exercise: [redacted] days (mean length of stay) [51]
Proportion of hospitalised patients treated in day care	[redacted]	Hospital Episodes Statistics data for GPP Non elective events, April 2016 – February 2022. Of [redacted] inpatient admissions where the primary patient diagnosis was GPP (ICD-10 code L401), [redacted] ([redacted]) were day cases (Clarification Response B9).

Source: Partly reproduced from CS Table 29 and model sheet "Data Library", cells U62:U95.
BAC, best available care; GPP, generalised pustular psoriasis; HCRU, health care resource use; ICU, intensive care unit; SEE, structured expert elicitation.

The company assumed that inpatients will be discharged once their pustules have resolved, i.e., once they reached a GPPGA pustulation subscore of 0 or 1 in the model (see section 4.2.2.1 above).

For the BAC arm, the proportion of patients treated as inpatients (77.6%) was based on the overall inpatient rate for a patient's last flare reported in Wolf et al.[26] We consider that the company have conducted relevant scenarios to check this assumption (see Table 23). Spesolimab dominates BAC in both scenarios. The proportion of inpatients was modelled by assuming that all patients (77.6%) were hospitalised on Day 1 (day of treatment) and, after that, patients could only be discharged from hospital. We consider that this assumption lacks

face validity as patients are likely to be hospitalised beyond Day 1. However, there is no evidence on which proportion of patients were hospitalised at each day and this was modelled similarly for both arms, BAC and spesolimab. We consider therefore the company's approach to be reasonable.

The company assumed that the proportion of the spesolimab arm patients treated as inpatients was half that of the BAC arm (33.8%) (see Table 23). This assumption was based on the relative reduction of 48.4% in the proportion of patients with a GPPGA pustulation subscore ≥ 2 (active flare) for spesolimab versus placebo in the Effisayil 1 trial. As such, spesolimab increases the number of patients with resolved flares (by reducing the number of patients with active flares, see section 4.2.6.1) which, in practice, directly leads to a reduction in the number of patients that will be admitted to hospital. However, the EAG considers it to be very uncertain whether spesolimab has an additional residual benefit in reducing hospitalisation rates for patients not responding to treatment (patients with active flares) as there is no evidence showing that benefit or the size of that benefit. We consider the company's assumption of a 50% reduction is likely to be optimistic in the absence of data. The EAG considers this uncertainty to be a key issue (Key Issue 7) and we believe that further clinical expert opinion may be valuable. Although the company mentioned in the CS that alternative inpatient rates for spesolimab were explored in scenario analyses, these are not reported. We therefore tested alternative reductions in scenario analyses (30%, 20%, 10% and 0%) and further clinical expert opinion would help in reducing this uncertainty.

The proportion of patients hospitalised treated in ICU for the BAC arm was based on the SEE exercise ([redacted]). Viguier et al.[46] reported that 25% of hospitalised patients were treated in ICU while a 11.5% proportion was reported by Wolf et al.[26] The uncertainty around this assumption was tested in deterministic sensitivity analysis, by changing the base case value by ± 20%. We note that the results have not changed significantly and spesolimab dominates in both situations.

The company assumed that patients treated with spesolimab would not require treatment in the ICU. The company argued that spesolimab has demonstrated rapid and sustained control of disease, with skin clearance as early as day 3 and pustulation clearance as early as day 2. Spesolimab also demonstrated clinically meaningful improvements in patient reported outcomes and markers of inflammation. Therefore, the company assumed that spesolimab preventing patients from requiring admission to an ICU is not unreasonable (clarification question B12). In the company's scenario where the same proportion of patients in ICU for the BAC arm was used for spesolimab ([redacted]), spesolimab dominates the

comparator. Again, as above, we are uncertain whether spesolimab reduces the risk of being admitted to ICU for those patients with active flares in addition to the already modelled reduction of active flares. We would benefit from further clinical expert opinion, and we tested alternative proportions in scenario analyses: 5%, 10%, 15% and [redacted].

The company applied the maximum length of stay in ICU in the model and that was derived from the mean length of stay elicited by clinical experts in the SEE exercise[51] and the response rates over time for BAC. As time in hospital was modelled as the time needed for patients reaching a GPPGA pustulation subscore of 0 or 1, the purpose of this adjustment was to ensure that the modelled output mean length of stay for BAC was similar to the elicited values. We note that removing this adjustment has a very low impact on the model results.

Costs were mainly obtained from published literature, 2021/2022 NHS reference costs[50] and Unit Costs of Health and Social Care 2023;[49] these are summarised in CS Table 28.

4.2.8.4 Adverse event costs

CS section B.3.5.4 and CS Table 30 presents the unit costs applied to adverse events included in the model: serious infection, tuberculosis and liver injury. The costs were obtained from the NHS reference costs and were updated to 2021/2022 in response to clarification question B11. The updated costs are shown in Table 24 below.

Table 24 Unit costs for the treatment of adverse events (updated in response to clarification question B11)

Adverse event	Unit cost	Source
Serious infection	£2,718.58	National schedule of NHS costs 2021/2022. Total HRGs, weighted average of DZ11K-DZ11V and WJ06A-WJ06J (sepsis and pneumonia)
Tuberculosis	£4,253.13	National schedule of NHS costs 2021/2022. Total HRGs, weighted average of DZ14F-DZ14J (pulmonary, pleural or other tuberculosis)
Liver injury	£2,262.30	National schedule of NHS costs 2021/2022. Total HRGs, weighted average of GC01E-GC01F (liver failure disorders without interventions)

Source: Reproduced from Clarification Response B11 and partly reproduced from CS Table 30.
HRG, healthcare resource group; NHS, National Health Service.

4.2.8.5 Other costs

CS section B.3.5.5 reports an end-of-life cost of £5,877.88 (one-off cost) implemented by the company in the economic model. This cost was inflated from the original cost of £4,580 obtained from Georghiou et al.[52]

EAG comment on resources and costs

The costs for the administration and acquisition costs, adverse events and end-of-life are reasonable and based on relevant sources.

The health state costs were based on the SEE exercise estimates, two European prospective studies and some assumptions. We are unclear about two of the company's assumptions: the proportion of inpatients and proportion of patients admitted to ICU in the spesolimab arm. These assumptions are associated with a lot of uncertainty and therefore several scenarios were conducted by the EAG to test their impact on the model results (Key Issue 7).

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company's original base case results are shown in CS Table 34, with an incremental cost-effectiveness ratio (ICER) of -£194,860 per QALY for spesolimab versus best available care (spesolimab dominates). This and all other cost-effectiveness results presented in this report were conducted with a confidential Patient Access Scheme (PAS) price discount for spesolimab of [redacted] In response to the EAG's clarification questions, the company corrected the following input parameters in a company revised base case:

- Cost of acitretin: £17.10 instead of £17.92 (clarification question B6)
- Cost of ciclosporin: £41.59 instead of £68.28 (clarification question B7)
- Treatment dosing schedule for ustekinumab (clarification question B7)
- Weekly acquisition cost for clobetasol propionate: £3.76 instead of £0.04 (clarification question B7)
- Adverse event costs updated using the National Schedule of NHS costs 2021/22 (clarification question B11)
- Subcutaneous administration cost: £141 instead of £57 (clarification question B13)
- Inclusion of general population mortality (clarification question B4)

The company revised base case results using the PAS price for spesolimab are shown in Table 25. The ICER for spesolimab versus best available care is -£172,713 per QALY (spesolimab dominates).

Table 25 Company revised base case results after clarification responses using PAS price for spesolimab

Treatment	Total		Incremental		ICER (£/QALY)
	Cost (£)	QALYs	Cost (£)	QALYs	
BAC	[redacted]	[redacted]			-£172,713 (spesolimab dominates)
Spesolimab	[redacted]	[redacted]	[redacted]	[redacted]	

Source: Clarification response document Table 13, company revised economic model (Deterministic Results!F15)
BAC, best available care; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

The company submission reports the original deterministic sensitivity analyses (DSA) in section B.3.11.2. The results of the updated DSA conducted on the company revised model are provided in Figure 9 of the clarification response document. Parameters are varied by +/- 20% of the deterministic point estimate for each parameter. The top 10 most influential variables are presented in a tornado diagram (clarification response document Figure 9), which shows the DSA results including the PAS price for spesolimab. The three main drivers of the model are the percentage of patients treated as inpatients, the acquisition cost of spesolimab, and the daily cost of inpatient care. However, the ICER remained below -£50,000 per QALY in all cases (spesolimab still dominated the comparator).

5.2.2 Probabilistic sensitivity analyses

The company conducted a probabilistic sensitivity analysis (PSA) with input parameter uncertainty distributions as presented in CS Appendix O. The PSA was run for 1,000 iterations, and mean results for the PSA conducted on the company revised model were reported in Table 14 of the clarification response document using the PAS price for spesolimab. The cost-effectiveness plane and cost-effectiveness acceptability curve are presented in Figure 7 and Figure 8 of the clarification response, respectively. All required variables were included with appropriate distributions. The probabilistic results were in line with the deterministic results when run by the EAG.

5.2.3 Scenario analyses

The company reports the original results of nine scenario analyses in CS Table 38 (PAS price for spesolimab included), while the updated results of the same scenario analyses conducted on the company revised base case model are reported in Table 15 of the clarification response document (PAS price for spesolimab included). The scenario analyses explored the efficacy of BAC, inpatient proportions and costs, and length of stay in an ICU unit. Only one scenario, using the Effisayil 1 historical cohort data from day 0 to inform the efficacy of BAC, resulted in a positive ICER of £16,523 per QALY. For all other scenarios, spesolimab dominated best available care. The company reports in CS section B.3.5.3 that they would run scenario analyses on the proportion of patients receiving spesolimab that were hospitalised, however the EAG were unable to find these scenarios in the company submission or the clarification response document. The EAG will perform these as exploratory analyses in section 6.1 of this report.

5.3 Model validation and face validity check

We conducted a range of checks on the company model using an EAG checklist:

- Input checks: comparison of all parameter values in the model against the values stated in the company submission and cited sources.
- Output checks: replication of results reported in the company submission using the company model.
- 'White box' checks: manual checking of formulae working from the cohort-level Markov model, which includes reviewing the calculations across each cycle and working backwards to trace links to input parameters and forwards to the results.
- 'Black box' checks: working through a list of tests to assess whether changes to key model inputs or assumptions have the expected effects on the model results.

The model is well-implemented, and no coding errors were identified.

5.3.1 EAG corrections to the company model

The EAG corrected the application of the utility value for the ICU in the model. As described in section 4.2.7, the utility score for patients in the ICU is assumed to be zero. However, in the model the company have only applied this utility score to patients in the ICU on mechanical ventilation. The EAG have corrected the company model so that the utility score applies to all patients in the ICU, both on and off mechanical ventilation. The corrected model results are shown in Table 26. The corrected company revised model gives an ICER of -£167,783 per QALY for spesolimab versus best available care (i.e., spesolimab dominates best available care).

Table 26 EAG corrections to the company revised base case model using the PAS price for spesolimab

Treatment	Total		Incremental		ICER
	Cost (£)	QALYs	Cost (£)	QALYs	(£/QALY)
BAC	[redacted]	[redacted]			-£167,783 (spesolimab dominates)
Spesolimab	[redacted]	[redacted]	[redacted]	[redacted]	

BAC, best available care; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

5.3.2 EAG summary of key issues and additional analyses

A full summary of EAG observations on key aspects of the company's economic model is presented in Table 27.

Table 27 EAG observations of the key aspects of the company's economic model

Parameter	Company base case	EAG comment	EAG base case/ EAG scenarios
Key model features			
Model structure	Section 4.2.2 Markov model	We agree	No change
Model assumptions (Relapse of a GPP flare is not considered in the model)	Section 4.2.2.2.1	11.3% of patients in the Effisayil 1 trial received rescue treatment with spesolimab to treat second/recurrent flares, and eight patients received a standard of care escape treatment, [redacted]. We consider this to be a key issue (Key Issue 3) as we believe this uncertainty can be resolved with further clinical data and further clinical input.	No change

Parameter	Company base case	EAG comment	EAG base case/ EAG scenarios
Model assumptions (Maximum flare duration is 12 weeks)	Section 4.2.2.2.3	Evidence from the studies informing the efficacy of spesolimab and BAC shows that a proportion of patients have not responded to treatment or that it is unknown whether they have responded to treatment by week 12.	EAG base case: no change EAG scenarios: • 12.37% of patients in the BAC arm with active flares by the end of the time horizon. • 20.0% of patients in the spesolimab arm with active flares by the end of the time horizon. • 12.37% of patients in the spesolimab arm with active flares by the end of the time horizon. • 5.7% of patients in the spesolimab arm with active flares by the end of the time horizon.
Model assumptions (others)	Section 4.2.2.2	We agree	No change
Population	Section 4.2.3	It is unclear whether the model results can be generalisable to patients experiencing mild flares as the population from the studies informing the economic	No change

Parameter	Company base case	EAG comment	EAG base case/ EAG scenarios
		model is mainly a moderate-to-severe flare population (Key Issue 1).	
Comparators	Section 4.2.4	The EAG is concerned that the composition of the comparator arm is not aligned with the UK clinical practice and/or the studies informing its efficacy (Key Issue 4).	EAG base case: active treatments from the SEE exercise applied from day 1 until the end of the time horizon (linked to change in efficacy of BAC)
Perspective	NHS and Personal Social Services	We agree	No change
Time horizon	85 days	It is unclear whether a 12-week time horizon is long enough to capture all the consequences of the treatment with spesolimab (Key Issue 5)	No change
Discounting	0%	We agree	No change
Model inputs			
Baseline characteristics	Section Population4.2.3	We agree	No change
Efficacy of spesolimab	Section 4.2.6.1	We are unclear whether the use of a GPPGA pustulation	EAG base case: no change

Parameter	Company base case	EAG comment	EAG base case/ EAG scenarios
	Effisayil 1 trial, based on a GPPGA pustulation subscore of 0 or 1	subscore of 0 or 1 appropriately reflects the resolution of a flare in UK practice.	EAG scenarios: • Effisayil 1 trial with treatment response defined as a GPPGA pustulation subscore of 0
Efficacy of BAC	Section 4.2.6.2 Effisayil 1 trial (week 1) plus Effisayil 1 historical cohort, based on a GPPGA pustulation subscore of 0 or 1	The standard of care treatments used to treat flares in the Effisayil 1 historical cohort are unknown for the individual types of flares and therefore it is unclear how similar or different they might be from the best available care treatments currently used in UK practice. The EAG considers the SEE exercise estimates to reflect UK reality more closely and to be aligned with the modelled comparator treatments (which were elicited by the same experts). We acknowledge however the uncertainty of this	EAG base case: SEE exercise estimates with treatment response defined as a GPPGA pustulation subscore of 0 or 1 from day 1 until the end of the time horizon. EAG scenarios: • Effisayil 1 trial (first week) + Effisayil 1 historical cohort (GPPGA pustulation subscore of 0 or 1, company's base case) • Effisayil 1 historical cohort (GPPGA pustulation subscore of 0 or 1, company's scenario) • Effisayil 1 trial (first week) + SEE exercise (GPPGA pustulation subscore of 0 or 1) • SEE exercise (GPPGA pustulation subscore of 0) • Effisayil 1 trial (first week) + SEE exercise (GPPGA pustulation subscore of 0)

Parameter	Company base case	EAG comment	EAG base case/ EAG scenarios
		assumption and the limitations of each source (Key Issue 6).	
Mortality	Section 4.2.6.3 Daily rate of death 0.096%	We agree	No change
Adverse event incidence	Section 4.2.6.4	We agree	No change
Utilities			
Health state utilities	Section 4.2.7.2	We agree	No change
Adverse event disutilities	Section 4.2.7.3	We agree	No change
Severity modifier	Not applied	We agree	No change
Resource use and costs			
Acquisition costs	Section 4.2.8.2	We agree	No change
Administration costs	Section 4.2.8.2	We agree	No change
Proportion of patients treated as inpatients (spesolimab)	Section 4.2.8.3 38.8% (reduction of 50%)	As there is no evidence, it is very uncertain whether patients not responding to treatment with spesolimab, and therefore with an active flare, will have any reduction in hospitalisation rates compared with patients in a	EAG base case: no change EAG scenarios: • 77.6% (no reduction) • 69.84% (reduction of 10%) • 62.08% (reduction of 20%) • 54.32% (reduction of 30%)

Parameter	Company base case	EAG comment	EAG base case/ EAG scenarios
		similar situation in the BAC arm. We consider the company's assumption is likely to be optimistic in the absence of data (Key Issue 7).	
Proportion of patients treated as inpatients (BAC)	Section 4.2.8.3 77.6%	We agree	No change
Proportion of inpatients treated in ICU (spesolimab)	Section 4.2.8.3 0%	We are uncertain whether spesolimab reduces the risk of being admitted to ICU for those patients with active flares in addition to the already modelled reduction of active flares.	EAG base case: no change EAG scenarios: • 5% • 10% • 15% • [redacted] (company's scenario)
Proportion of inpatients treated in ICU (BAC)	Section 4.2.8.3 [redacted]	We agree	No change
Proportion of patients in ICU requiring mechanical ventilation	Section 4.2.8.3 [redacted]	We agree	No change

Parameter	Company base case	EAG comment	EAG base case/ EAG scenarios
Other health state costs	Section 4.2.8.3	We agree	No change
Adverse event costs	Section 4.2.8.4	We agree	No change
End of life costs	Section 4.2.8.5	We agree	No change
NHS, National Health Service; BAC, best available care.			

6 EAG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG performed scenario analyses based upon the uncertainties discussed in section 4 using the EAG corrected company base case. The results of these scenario analyses are presented in Table 28. The EAG have made the following additional changes to the model when altering the efficacy of BAC:

- For scenarios using a GPPGA pustulation subscore of 0, the corresponding efficacy of spesolimab from the Effisayil 1 trial also uses a GPPGA pustulation subscore of 0.
- For the scenarios using the Effisayil 1 historical cohort from Day 1 or the SEE exercise from Day 1, comparator treatments are also included from Day 1.

Spesolimab dominates the comparator (i.e., is more effective and less expensive) in all but two scenarios: using the Effisayil 1 historical cohort from Day 1 with a GPPGA pustulation subscore of 0 or 1, where spesolimab remains cost-effective; and using the SEE exercise from Day 1 with a GPPGA pustulation subscore of 0 or 1, where spesolimab is no longer cost-effective at a willingness-to-pay (WTP) threshold of £30,000.

Table 28 EAG scenario analyses on the EAG corrected company base case using the PAS price for spesolimab

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
EAG corrected company base case	[redacted]	[redacted]	-£167,783 (spesolimab dominates)
Model assumptions			
12.37% of patients in BAC arm with active flare by end of time horizon	[redacted]	[redacted]	-£214,995 (spesolimab dominates)
5.7% of patients in spesolimab arm with active flare by end of time horizon	[redacted]	[redacted]	-£160,012 (spesolimab dominates)
12.37% of patients in spesolimab arm with active flare by end of time horizon	[redacted]	[redacted]	-£149,083 (spesolimab dominates)

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
20% of patients in spesolimab arm with active flare by end of time horizon	[redacted]	[redacted]	-£133,250 (spesolimab dominates)
Comparator costs			
Cost of ciclosporin: £48.50 (NICE requested scenario)	[redacted]	[redacted]	-£167,783 (spesolimab dominates)
Efficacy of BAC: GPPGA pustulation subscore of 0 or 1			
Effisayil 1 historical cohort	[redacted]	[redacted]	£15,680
SEE exercise	[redacted]	[redacted]	£143,574
Effisayil 1 trial (first week) + SEE exercise	[redacted]	[redacted]	-£143,513 (spesolimab dominates)
Efficacy of BAC: GPPGA pustulation subscore of 0			
SEE exercise	[redacted]	[redacted]	-£118,683 (spesolimab dominates)
Effisayil 1 trial (first week) + SEE exercise	[redacted]	[redacted]	-£167,597 (spesolimab dominates)
Proportion of inpatients on spesolimab			
77.6% (0% reduction)	[redacted]	[redacted]	-£5,009 (spesolimab dominates)
69.84% (10% reduction)	[redacted]	[redacted]	-£37,564 (spesolimab dominates)
62.08% (20% reduction)	[redacted]	[redacted]	-£70,119 (spesolimab dominates)
54.32% (30% reduction)	[redacted]	[redacted]	-£102,674 (spesolimab dominates)

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
Proportion of inpatients treated in the ICU on spesolimab			
5%	[redacted]	[redacted]	-£166,247 (spesolimab dominates)
10%	[redacted]	[redacted]	-£164,703 (spesolimab dominates)
15%	[redacted]	[redacted]	-£163,151 (spesolimab dominates)
[redacted]	[redacted]	[redacted]	-£161,151 (spesolimab dominates)

Source: EAG corrected company base case model.
QALY, quality adjusted life-year; ICER, incremental cost-effectiveness ratio.

6.2 EAG's preferred assumptions

Based on the EAG critique of the company's model discussed in section 4, we have identified one significant aspect of the company base case with which we disagree. Our preferred model assumption is to use the SEE exercise with a GPPGA pustulation subscore of 0 or 1 from Day 1 for the efficacy of BAC rather than the Effisayil 1 trial (first week) plus the Effisayil 1 historical cohort. As noted above, this also includes using comparator treatments from Day 1. Although the EAG has concerns with other assumptions made by the company (see Key Issues in section 1.5), we do not have the required data to make an informed decision on what the correct assumptions should be. The EAG base case results are reported in Table 29 below. When making this sole change, the ICER increases to £143,574 per QALY for spesolimab versus best available care.

Table 29 EAG preferred base case results using PAS price for spesolimab

Treatment	Total		Incremental		ICER (£/QALY)
	Cost (£)	QALYs	Cost (£)	QALYs	
BAC	[redacted]	[redacted]			£143,574
Spesolimab	[redacted]	[redacted]	[redacted]	[redacted]	

6.2.1 EAG scenario analyses

For consistency, we performed the same scenarios on our EAG base case model as previously run on the EAG corrected company base case model. Table 30 summarises these results. The ICERs varied between -£167,783 (the EAG corrected company base case model using the Effisayil 1 trial and the Effisayil 1 historical cohort for the efficacy of BAC) and £581,059 (20% of patients in the spesolimab arm with active flare by the end of the 12-week time horizon).

Table 30 EAG scenario analyses on the EAG preferred base case using the PAS price for spesolimab

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
EAG base case	[redacted]	[redacted]	£143,574
Model assumptions			
12.37% of patients in BAC arm with active flare by end of time horizon	[redacted]	[redacted]	-£12,812 (spesolimab dominates)
5.7% of patients in spesolimab arm with active flare by end of time horizon	[redacted]	[redacted]	£213,829
12.37% of patients in spesolimab arm with active flare by end of time horizon	[redacted]	[redacted]	£335,032
20% of patients in spesolimab arm with active flare by end of time horizon	[redacted]	[redacted]	£581,059
Comparator costs			
Cost of ciclosporin: £48.50 (NICE requested scenario)	[redacted]	[redacted]	£143,351
Efficacy of BAC: GPPGA pustulation subscore of 0 or 1			
Effisayil 1 trial (first week) + Effisayil 1 historical cohort (company base case)	[redacted]	[redacted]	-£167,783 (spesolimab dominates)
Effisayil 1 historical cohort	[redacted]	[redacted]	£15,680
Effisayil 1 trial (first week) + SEE exercise	[redacted]	[redacted]	-£143,513 (spesolimab dominates)

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
Efficacy of BAC: GPPGA pustulation subscore of 0			
SEE exercise	[redacted]	[redacted]	-£118,683 (spesolimab dominates)
Effisayil 1 trial (first week) + SEE exercise	[redacted]	[redacted]	-£167,597 (spesolimab dominates)
Proportion of inpatients on spesolimab			
77.6% (0% reduction)	[redacted]	[redacted]	£455,571
69.84% (10% reduction)	[redacted]	[redacted]	£393,172
62.08% (20% reduction)	[redacted]	[redacted]	£330,772
54.32% (30% reduction)	[redacted]	[redacted]	£268,373
Proportion of inpatients treated in the ICU on spesolimab			
5%	[redacted]	[redacted]	£148,852
10%	[redacted]	[redacted]	£154,190
15%	[redacted]	[redacted]	£159,590
[redacted]	[redacted]	[redacted]	£166,593

6.3 Conclusions on the cost effectiveness evidence

The company developed a three-state Markov model to estimate the cost-effectiveness of spesolimab compared to best available care for patients with generalised pustular psoriasis flares. Response to treatment was obtained from the Effisayil 1 trial for the spesolimab arm and from the Effisayil 1 trial (Week 1) combined with the Effisayil 1 historical cohort (beyond Week 1) for the best available care arm. The EAG considers the overall structure of the model to be appropriate, however there are concerns with the length of the time horizon (12 weeks), the lack of implementation of second/recurrent GPP flares and the assumption that all patients have a resolved flare by Week 12 (see section 4.2.2). The company made some minor changes to the model in response to clarification questions. The company's revised base case produced an ICER of -£172,713 per QALY, using a confidential PAS discount of [redacted] for spesolimab (spesolimab dominates best available care). The EAG identified an inconsistency regarding the application of utility scores for patients in the ICU in the model; this was corrected and resulted in an ICER of -£167,783 per QALY (see section 5.3.1).

The EAG's preferred base case comprises a singular change to the EAG corrected base case: the efficacy of BAC using the SEE exercise from Day 1 (based upon a GPPGA pustulation subscore of 0 or 1). This also includes comparator treatments from Day 1. Although the EAG has concerns with other assumptions made by the company (see Key Issues in section 1.5), no data was available to make informed decisions about alternative assumptions for the EAG base case. The EAG preferred base case increases the ICER to £143,574 per QALY gained for spesolimab compared to best available care. Both the company and EAG base cases are most sensitive to changes in the source of efficacy for the BAC arm, the proportion of patients in the spesolimab arm with active flares by the end of the 12-week time horizon, and the proportion of patients in the spesolimab arm admitted into hospital.

7 SEVERITY

Severity is described in CS section B.3.6. The company used the QALY shortfall calculator[53] to calculate the expected total QALYs for the general population, using the baseline characteristics of the Effisayil 1 trial (age: 43, 68% female). This results in a remaining discounted QALYs of 17.91.

UK evidence suggests that patients with GPP experience between 0.9 to 1.79 flares per year. However, the company concluded that a patient would have to experience more than 1.79 flares per year over 100 years to be eligible for a severity modifier. Therefore, a severity modifier was not applied for this appraisal. The EAG agrees with the company's conclusion.

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9 APPENDICES

Appendix 1 EAG summary appraisal of the company's systematic review methods

Table 31 EAG appraisal of systematic review methods

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The SLR sought to identify all relevant evidence of clinical efficacy and safety associated with spesolimab and current available treatment options for GPP (CS Appendix D.1.1) and the eligibility criteria are defined according to a PICOS framework in CS Appendix Table 10.
Were appropriate sources of literature searched?	Yes	Core healthcare databases, MEDLINE, Embase, CDSR and CENTRAL were searched, alongside hand searches of several dermatology and psoriasis conferences and ISPOR, three clinical trials platforms and reference lists of relevant systematic reviews and meta-analyses.
What time period did the searches span and was this appropriate?	Yes	The time period was database inception to 14th December 2022, with an update search on 6th May 2024. Conference abstracts were restricted to the preceding two years, i.e. since 2022. The searches are recent and the EAG has not carried out any updates.
Were appropriate search terms used and combined correctly?	Yes	Search strings included both relevant subject headings and appropriate free text terms. Relevant published search filters were used.
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes, (clarity issue resolved in clarification response A4)	A broad set of eligibility criteria is reported in CS Appendix Table 10, however, eligibility criteria to align with the decision problem were not clear (whether data specific to GPP flares was relevant to population, or outcomes, or both – resolved in Clarification Response A4) and appeared to have been conflated with a

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
		feasibility assessment for the indirect treatment comparison that included evidence not eligible for this appraisal. Eligibility criteria for the evidence included in this appraisal are not clearly distinguished from the eligibility criteria and feasibility assessment aligned with the broader scope of the SLR (see Clarification Response A5).
Were study selection criteria applied by two or more reviewers independently?	Yes	Two independent researchers performed title and abstract screening and full-text screening; a third independent researcher was invited to resolve any discrepancies (CS Appendix D.1.1.4).
Was data extraction performed by two or more reviewers independently?	No, but methods are adequate	One researcher performed data extraction with a second researcher checking to ensure accuracy, with any discrepancies resolved by mutual discussion (CS Appendix D.1.1.5).
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	RCTs were assessed using the quality assessment checklist adapted from CRD, University of York guidance (CS Appendix D. 1.3.1). Non-randomised and observational studies were assessed using the Downs and Black checklist (CS Appendix D.1.3.2).
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Yes	Each reviewer performed the quality assessment independently (CS Appendix D.1.3.1).
Is sufficient detail on the individual studies presented?	Yes	Effisayil 1 – yes, the entire CSR and all trial publications Effisayil 1 historical cohort – study publication (no company study report)

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
		CEE cohort study – study publication and extracted data alongside other studies in Appendix M. SEE study – yes, technical report with methods and results supplied with CS (copies of training and preparation material not included), summary in CS Appendix M.1.1.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Not applicable.	Statistical analysis of treatment comparisons was not carried out. The company used historical chart review of participants in their pivotal RCT, supplemented with data from a case series study of patients with GPP in CEE countries and a company SEE study to provide a descriptive comparison. This is discussed in section 3.3.

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CEE, Central Eastern European; CENTRAL, Cochrane Central Register of Controlled Trials; CRD, Centre for Reviews and Dissemination; GPP, generalised pustular psoriasis; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; ITC, indirect treatment comparison; MEDLINE, Medical Literature Analysis and Retrieval System Online; NMA, network meta-analysis; PICOD/PICOS, Population Intervention Comparator Outcome Study Design framework; RCT, randomised controlled trial; SEE, structured expert elicitation.

Appendix 2 Company and EAG risk of bias assessment for Effisayil 1

Table 32 Risk of bias assessment for Effisayil 1

Question	Company conclusion	Company comments	EAG assessment
Was randomisation carried out appropriately?	Yes	Patients were randomised to receive spesolimab or placebo in a ratio of 2:1 with stratification for Japanese vs non-Japanese ethnic group	Low risk of bias. An interactive response technology system was used to implement randomisation. Participants were stratified according to ethnicity (Japanese/not Japanese).
Was concealment of treatment allocation adequate?	Yes	Interactive response technology was used to perform treatment allocation and manage ordering of drug supplies. Clinicians were provided with a solution for infusion which could be spesolimab or a placebo solution.	Agree. Low risk of bias. The study drug was allocated using computerised interactive response technology (Study protocol, Choon et al. 2021). [54]
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	There were some differences observed in some demographic and clinical characteristics at baseline, namely gender, race, GPPASI score, and GPPGA pustulation subscore. Clinical characteristics representative of more severe disease were observed in the spesolimab arm so any resulting bias would be in	Not enough information. Unclear risk of bias. Without clinical expertise we have been unable to determine which characteristics are prognostic factors for flares (sections 2.2.1 and 3.2.1.2). We agree that there were some differences in demographic and clinical characteristics at baseline, for example, disease severity according to GPPASI and GPPGA was slightly greater in the spesolimab arm,

Question	Company conclusion	Company comments	EAG assessment
		favour of the placebo arm.	systemic symptoms, e.g. fever (Suppl. Table 1) was higher in the spesolimab arm, but having the IL36RN mutation was similar between arms. We observe a slight bias in favour of the placebo arm, however, disease severity is not a confirmed prognostic factor.
Were the care providers, participants and outcome assessors blinded to treatment allocation?	Yes	Patients and clinicians were blinded to randomised treatment allocation until after the database lock for final analysis.	Agree. Low risk of bias. [redacted]
Were outcome assessors blind to treatment allocation?	Unclear (CS Appendix Table 12)	[CS Appendix Table 12 does not include supporting statements]	Agree. Unclear risk of bias. It is not clear to the EAG whether the outcome assessors were the same people as the care providers, if so then they probably were blinded, but we cannot be sure if they were the same people.
Were there any unexpected imbalances in dropouts between groups?	No	91% of patients to the spesolimab arm and 94% of patients randomised to the placebo arm completed the 12-week trial period.	Agree. Low risk of bias. The patient flow diagram in CS Figure 6 shows that early discontinuations were few and roughly proportional to the 2:1 randomisation. During the follow-up period

Question	Company conclusion	Company comments	EAG assessment
			proportionally more participants in the placebo group received open label spesolimab or rescue treatment with spesolimab, but this would be expected.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	[No company justification made]	Unclear risk of bias. The published study protocol, Choon et al. 2021,[54] and CS Appendix N, Table 62 have GPPASI-related secondary outcomes but the results for the GPPASI outcomes are not reported in the CS, and limited results in Supplementary Figure 6 of the trial publication (Bachelez et al. 2021)[16]. All other planned outcomes are reported.
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Primary endpoint and key secondary endpoint analysis at Week 1 was based on an ITT analysis with patients withdrawing or receiving escape medication assumed not to have responded. Due to high levels of open-label spesolimab use in the placebo arm after Week 1, changes at Week 4 for secondary endpoints and further	Agree. Low risk of bias. An ITT analysis was carried out. Methods to account for missing data were to impute non-response for the binary outcomes and to use the last observation carried forward for the continuous outcomes. These methods appear appropriate, but the amount of missing data is unclear. See also section 3.2.4 for EAG discussion of statistical

Question	Company conclusion	Company comments	EAG assessment
		endpoints were reported descriptively. The ITT principle was still adopted with appropriate methods used to account for missing data.	methods around missing data.
Does the study reflect routine clinical practice in England?	Yes	The study population, intervention, comparator and outcomes are applicable to routine clinical practice as discussed in Section B.2.12.3, despite not being directly reflective due to a lack of active treatment for the control arm and a high Asian cohort in the study population.	This question, not in the original CRD checklist, is about generalisability rather than risk of bias. No EAG risk of bias statement made; generalisability of the trial to the UK/England is discussed in sections 3.2.1.1 and 3.2.1.2.

Source: Reproduced from CS Table 11 and CS Appendix Table 12; with EAG additional comments.
Abbreviations: CRD, Centre for Reviews and Dissemination; CSR, clinical study report; GPP, generalised pustular psoriasis; GPPASI, Psoriasis Area and Severity Index for Generalized Pustular Psoriasis; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; IL36RN, interleukin-36 receptor antagonist protein; ITT, intention to treat.

Appendix 3 Outcomes assessment: Pain VAS, FACIT-Fatigue, DLQI, and PSS

The following patient reported outcome measures (PROs) used in Effisayil 1 are not specific to GPP. Two are specific to psoriasis (Psoriasis Symptom Scale) or skin conditions (Dermatological Quality of Life Index) and the others are generic PROs (pain VAS, Functional Assessment of Chronic Illness Therapy – Fatigue scale, and EQ-5D). The EAG has found no scientific literature reporting validation of these outcome measures or consensus on minimum clinically important difference (MCID) in GPP. A recent paper states the need for validation and international consensus for the consistent use of these measures (and efficacy measures) in GPP.[55] The EAG agree this would be useful as we have been unable to verify the use of these measures in clinical practice and what might constitute a valid response due to lack of clinical expertise available to us. All PROs, except EQ-5D, were secondary outcomes, measuring change from baseline at Week 4, that were included in the planned hierarchy for statistical testing. Measurements at other timepoints, and for EQ-5D, were exploratory outcomes. EQ-5D is the only PRO that informs the economic model.

Table 33 Summary of PRO outcomes assessed in Effisayil 1

Outcome	Description / Validation / MCID
Pain VAS	• Generic scale to record current pain intensity by marking a point on a single line 100mm in length representing 0 (no pain) to 100 (very severe pain) • Score can be influenced by other comorbid conditions,[55] and another study warns it does not behave linearly with raw change scores either under- or over-estimating true change. [56] • Wide range of MCIDs reported (9 to 30 mm) but none for GPP[56] • Effisayil 1 used an MCID of a 30-point decrease from baseline (CS Appendix N Table 63) which is at the more conservative end of that range requiring a larger decrease in pain to show meaningful response.
FACIT-Fatigue	• 13-item questionnaire to assess fatigue and its impact on daily activities and functioning over a 1-week recall period. • Each question is scored 0 to 4 total score 0 to 52, higher scores indicate a lower impact on fatigue/function. • Validated in several chronic diseases, but not for GPP.[55] • Effisayil 1 used an MCID of a 4-point increase from baseline (CS Appendix N Table 63)

Outcome	Description / Validation / MCID
PSS	• 4-item scale (symptoms: pain, redness, itching, and burning) to assess skin condition over a 1-day recall period. • Each symptom scored 0 to 4, total score 0 to 16, higher scores indicate increased severity. • Validated in plaque psoriasis patients,[57] but not for GPP.[55] • Effisayil 1 used an MCID of a 2-point decrease in score from baseline (CS Appendix N Table 63)
DLQI	• 10-item questionnaire to assess symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment, over a 1-week recall period. • Each question is scored 0 to 3, total score 0 to 30, higher scores indicate worse quality of life. • Validated for use in psoriasis generally,[58] but not for GPP specifically.[55] It does not assess any of the systemic symptoms associated with GPP. • Effisayil 1 used an MCID of a 4-point decrease from baseline (CS Appendix N Table 63)
EQ-5D-5L	• A 5-item questionnaire to assess current mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; and a visual analogue scale (EQ-VAS, a vertical scale for patients to provide a global assessment of their health that takes values between 100 (best imaginable health) and 0 (worst imaginable health)). • Each question is scored 1 to 5, a summary score is calculated from a regional value set, higher scores indicate worse quality of life. • Evaluated for psoriasis generally;[59] bolt-ons for skin irritability and self-confidence contribute to improved content validity for patients with psoriasis;[60] but it still does not assess pustular or systemic symptoms specific to GPP and the bolt-ons were not used in Effisayil 1. • Mapped to EQ-5D-3L using the NICE preferred mapping function (CS section B.3.4.2)

Sources: CS Table 8, CS Appendix N Table 63,
Abbreviations: DLQI, Dermatology Life Quality Index; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue scale; GPP, generalised pustular psoriasis; MCID, minimum clinically important difference; PSS, Psoriasis Symptoms Scale; VAS, visual analogue scale.

Appendix 4 Mean composite GPPGA score in relation to the total GPPGA score

Table 34 Components of the mean composite GPPGA score (erythema, pustules and scaling) and how this relates to total GPPGA score

Erythema Score component	Pustules score component					Scaling Score component
	0	1	2	3	4	
0	0.00	0.33	0.67	1.00	1.33	0
0	0.33	0.67	1.00	1.33	1.67	1
0	0.67	1.00	1.33	1.67	2.00	2
0	1.00	1.33	1.67	2.00	2.33	3
0	1.33	1.67	2.00	2.33	2.67	4
1	0.33	0.67	1.00	1.33	1.67	0
1	0.67	1.00	1.33	1.67	2.00	1
1	1.00	1.33	1.67	2.00	2.33	2
1	1.33	1.67	2.00	2.33	2.67	3
1	1.67	2.00	2.33	2.67	3.00	4
2	0.67	1.00	1.33	1.67	2.00	0
2	1.00	1.33	1.67	2.00	2.33	1
2	1.33	1.67	2.00	2.33	2.67	2
2	1.67	2.00	2.33	2.67	3.00	3
2	2.00	2.33	2.67	3.00	3.33	4
3	1.00	1.33	1.67	2.00	2.33	0
3	1.33	1.67	2.00	2.33	2.67	1
3	1.67	2.00	2.33	2.67	3.00	2
3	2.00	2.33	2.67	3.00	3.33	3
3	2.33	2.67	3.00	3.33	3.67	4
4	1.33	1.67	2.00	2.33	2.67	0
4	1.67	2.00	2.33	2.67	3.00	1
4	2.00	2.33	2.67	3.00	3.33	2
4	2.33	2.67	3.00	3.33	3.67	3
4	2.67[a]	3.00	3.33	3.67	4.00	4
	Cells above show mean composite scores					

Source: EAG table

KEY:

Mean composite score	0	> 0 to < 1.5	≥ 1.5 to 2.5	≥ 2.5 to 3.5	≥ 3.5
Total GPPGA score	0	1	2	3	4
Description	Clear	Almost clear	Mild	Moderate	Severe

GPPGA, Generalised Pustular Psoriasis Physician Global Assessment

[a] A patient with a GPPGA pustulation subscore of 0 could still be assessed as having moderate GPP, if their erythema and scaling scores were both 4 because the mean composite score would be 2.67.

Appendix 5 Location and sources of evidence identified by the company for their indirect treatment comparison feasibility assessment

Appendix D.1.5 (Relevance of evidence base and heterogeneity assessment findings) provides some information on the company's systematic review which would have been expected to identify comparator data. The company's systematic review identified 79 unique studies from which the company identified a sub-set of 15 studies that they stated were relevant to their decision problem because they reported data specific to GPP flares (these 15 studies are listed in CS Appendix D Table 11).

It was not clear to us whether the feasibility assessment for indirect treatment comparison was performed on the broader set of 79 studies identified by the company's systematic literature review described in CS Appendix D or the sub-set of 15 studies the company stated were relevant to the decision problem. In response to clarification question A5 the company confirmed all studies identified in the clinical systematic literature review were assessed.

The evidence identified by the company's systematic review that the company stated was relevant to the decision problem (i.e. the 15 studies listed in CS Appendix D Table 11), comprised:

- Four studies related to the Effisayil trial program[16,19,21,61]
- Two small (10 patients or fewer) prospective studies of currently unlicensed products for the treatment of GPP flare (imsidolimab[62] and HB0034[63])
- Nine retrospective studies:
  - One was conducted in Taiwan[64]
  - One was conducted in China[65]
  - Three were conducted in North America (two in the USA[66,67] and one in Canada[68]
  - Three were conducted in Europe (France[46], Italy[69] and Central and Eastern Europe[26]
  - One was a retrospective analysis of the Effisayil 1 trial cohort. This is described as the Effisayil 1 historical cohort[23]

Although not explicitly stated, it seems that the company have assessed the 11 studies that were not part of the Effisayil trial program for their suitability to provide comparator data in an indirect treatment comparison. From the information provided in CS Appendix D.1.5 it appears that the two prospective studies on unlicensed products were excluded as they

were not part of the clinical pathway of care in the UK, the studies conducted in China, Taiwan and North America were excluded on the grounds that they lacked generalisability to the UK and the remaining four studies (the three conducted in Europe[26,46,69]) and the Effisayil 1 historical cohort[23] were reviewed to discern whether they could inform the efficacy and safety of BAC in formal evidence synthesis. The company presents the data from these three European studies in CS Appendix M (the Effisayil 1 historical cohort is not included in Appendix M). In addition to the three European studies identified by the company's systematic review, CS Appendix M Table 57 provides data for another three real-world evidence sources and two Structured Expert Elicitation sources. The three real-world evidence sources are:

- HES (Health Episode Statistics data[70]);
- POLARIS[8] and
- SCRIPTOR[24]

It is not clear to us how the POLARIS study was identified and included as it does not appear within the clinical SLR tables (CS Appendix D.1.2).

The two Structured Expert Elicitation (SEE) sources are:

- SEE – Best Available Care (BAC) efficacy and safety[14] and
- SEE – Health Care Resource Use (HCRU)[51].

Appendix 6 EAG review of studies identified in the CS to ascertain if any could contribute data in an indirect treatment comparison

Table 35 EAG review of studies identified in the CS

Study ID & design	GPP Population	Intervention	EAG comments
Tseng et al. 2023[64] Retrospective cohort	243 patients in Taiwan with data on 1,151 flares between January 2017 and September 2020.	Systemic treatment (not specified)	No treatment or efficacy data reported.
Hu et al. 2024[65] Retrospecti	18 patients in China with flares between June 2019 and October 2023.	Secukinumab (n=13) or ixekizumab (n=5)	Reports response at 4 weeks over time to 96 weeks.

Study ID & design	GPP Population	Intervention	EAG comments
ve case series			
Zema et al. 2022[66] Retrospective cohort	271 patients in the US with data on 513 flares between July 2015 and June 2020.	Topical corticosteroids (35% of flares), opioids (21%), other oral treatments[a] (13%), oral corticosteroids (11%)	No efficacy data reported.
SNDS Viguier et al.	569 hospitalized patients in France with flares between 2012 and 2015.	Not reported.	Reports duration of hospital stay.

Study ID & design	GPP Population	Intervention	EAG comments
2024[46] Retrospective cohort			
CAPPS Milan et al. 2023[68] Retrospective cohort	15 patients in Canada 66.7% of whom had a least one flare between January 2011 and December 2020.	Topical corticosteroids (73.3%), oral corticosteroids (46.7%), biologics (13.3%)	No detailed efficacy data reported.

Study ID & design	GPP Population	Intervention	EAG comments
Effisayil™ 1 historical cohort Choon et al. 2023[23] Retrospective cohort	53 patients, 29 patients with data for flares per year (time period of study not defined).	For 46 patients with at least one historical medication for past flare. At least one biologic (24.5%)[b], acitretin (45.3%), methotrexate (43.4%), cyclosporine (30.2%), Other systemic and topical therapies[c].	Reports typical time to pustular clearance for each flare category but flare resolution not linked to a set of particular treatments for a category of flare.

Study ID & design	GPP Population	Intervention	EAG comments
Bellinato et al. 2023[69] Retrospective cohort	66 patients in Italy with a history of flares between 2018 and 2022.	Reported as proportion of patients: corticosteroids alone (69.7%) or in combination with systemic retinoids (36.4%), biologics[d], other treatments[e]	No efficacy data reported.
Reisner et al. 2022[67] Online surve	66 patients in the US, all had experienced at least one flare in the past 12 months (survey took place 4-14th August 2020).	Treatments added during a flare (n=21 patients): topicals (38%); oral corticosteroids (38%), biologics (IL-12/23 inhibitors 14%, IL-17 inhibitors 5%), other (14%).	No efficacy data reported.

Study ID & design	GPP Population	Intervention	EAG comments
y of people living with GPP			
CEE GPP Expert Network Wolf et al. 2024[26] Retrospecti	58 patients in Central and Eastern Europe. Captured characteristics of most recent flare and most severe flare within the past 10 years up to December 2022.	For historical most severe flare (n=26); retinoids (53.8%), methotrexate (23.1%), systemic steroids (23.1%), PUVA (19.2%), biologics (15.4%), anti-TNF-α (7.7%), Anti-IL-12/23 (3.8%), Anti-IL-36R (7.7%), UVB (15.4%).[f]	Reports time from initiation of treatment to flare resolution for subgroups by flare type.

Study ID & design	GPP Population	Intervention	EAG comments
ve case series			
HES[70] Retrospective cohort	[redacted] patients in England with a GPP diagnosis ([redacted])	Not reported	Relevant population but no data on treatment received for flares or its efficacy.
POLARIS[8] Retrospective	373 patients in England with a GPP diagnosis (registered in CPRD Aurum database between 1 January 2008 and 31 December 2019)	Not reported but likely to have been best available care in England	Relevant population and a subgroup analysis of patients with GPP flares but no data on treatment efficacy.

Study ID & design	GPP Population	Intervention	EAG comments
cohort			
SCRIPTOR[24] Retrospective chart review	27 patients [redacted] in the UK with a confirmed diagnosis of GPP [redacted]. A total of [redacted] flare episodes amongst [redacted] patients.	Reported for patients with at least one drug-based treatment for flare [redacted]	Relevant population and includes [redacted] flare episodes [redacted] does not provide what would be needed for the economic model.
SEE – BAC efficacy and	[redacted] clinical experts ([redacted])	Best available care [redacted]	Expert predictions for BAC efficacy and safety based on their experience of treating GPP patients at specialist centres.

Study ID & design	GPP Population	Intervention	EAG comments
safety[14] Expert opinion (note it is not clear if these experts were the same exper			

Study ID & design	GPP Population	Intervention	EAG comments
ts who contributed to the SEE – HCRU)			
SEE – HCRU[51] Expert opinion (note	[redacted]	[redacted]	Expert predictions for healthcare resource use.

Study ID & design	GPP Population	Intervention	EAG comments
it is not clear if these experts were the same experts who contributed to the SEE –			

Study ID & design	GPP Population	Intervention	EAG comments
BAC efficacy and safety).			

Source: EAG created table with information drawn from cited sources and CS Table 11
BAC, best available care; CAPPS, Canadian Pustular Psoriasis Study; CEE GPP, Central and Eastern Europe generalised pustular psoriasis; CPRD, Clinical Practice Research Datalink; GPP, generalised pustular psoriasis; GPPGA, generalised pustular psoriasis global assessment; HCRU, health care resource utilisation; HES, Hospital Episode Statistics; IL, interleukin; PUVA, psoralen plus ultraviolet A; SEE, structured expert elicitation; SNDS, Système National des Données de Santé; TNF, tumour necrosis factor; [redacted] US, United States; UVB, ultraviolet B

[a] Other oral treatments e.g. methotrexate, cyclosporine, tacrolimus
[b] Ustekinumab (13.2%), Adalimumab (9.4%), Infliximab (7.5%), Ixekizumab (5.7%) or Secukinumab (5.7%)
[c] **Systemic:** Acitretin (45.3%), Methotrexate (43.4%), Cyclosporine (30.2%), Cefuroxime axetil (11.3%), Prednisolone (11.3%), Etanercept (9.4%), Cetirizine hydrochloride (7.5%), Hydroxyzine hydrochloride (7.5%), Amoxicillin; clavulanic acid (5.7%), Ampicillin sodium; sulbactam sodium (5.7%), Azithromycin (5.7%), Cefuroxime (5.7%), Cetirizine (5.7%), Dexchlorpheniramine maleate (5.7%), Etretinate (5.7%), Isotretinoin (5.7%), Loratadine (5.7%). **Topical:** Clobetasol propionate (20.8%), Potassium permanganate (17.0%), Betamethasone (15.1%), Betamethasone; calcipotriol (15.1%), Betamethasone valerate (11.3%), Clobetasone butyrate (11.3%), Mometasone furoate (11.3%), Calcipotriol (9.4%), Camphor; coal tar; salicylic acid; sulfur (9.4%), Coal tar; Pinus spp. tar; salicylic acid (9.4%), Antipsoriatics for topical use (7.5%), Betamethasone valerate; fusidic acid (7.5%), Clobetasol (7.5%), Emulsifying wax; liquid paraffin; white soft paraffin (7.5%), Hydrocortisone (7.5%), Betamethasone; salicylic acid (5.7%), Coal tar; salicylic acid (5.7%)
[d] ixekizumab (22.7%), risankizumab (16.6%), secukinumab (19.7%), adalimumab (9.1%), guselkumab (3%), tildrakizumab (3%), and brodalumab (3%)
[e] non-biologic treatments (cyclosporine and methotrexate), NB-UVB and PUVA phototherapy.
[f] Also reported summary of treatments used for 'Last flare: other' and 'Last flare = most severe'.

Appendix 7 Company and EAG risk of bias assessment for the Effisayil 1 historical cohort study

Table 36 Summary of company and EAG risk of bias assessment of the Effisayil 1 historical cohort study[23] using the ROBINS-I tool

	Effisayil 1 historical cohort, Choon et al. 2023[23]	
	Company	**EAG**
Bias due to confounding	Moderate	Serious
	The study acknowledges various confounding factors such as stress, infections, and treatment withdrawal that can trigger GPP flares. However, no adjustment has been made; retrospective nature of data collection and lack of control for these confounders may introduce bias.	Confounding expected (pre-intervention prognostic factors may have influenced receipt of particular interventions for GPP flare) but prognostic factors for flare resolution not discussed. No control for potential confounders described.
Bias in selection of participants into the study	Low	Low
	53 participants were selected based on specific inclusion criteria related to their history of GPP and systemic inflammation, which were clearly defined. This reduces the risk of selection bias.	All the patients eligible for the Effisayil1 RCT were included in the Effisayil1 historical cohort.
Bias in classification of interventions	Low	Low
	The classification of interventions was based on historical medical data and standardized questionnaires, reducing the risk of misclassification.	Interventions received were identified from retrospective chart review. Presume charts would have been completed at the time of the intervention.
Bias due to deviations from the intended intervention	Moderate	Moderate
	The study relies on retrospective data, and deviations from intended interventions were not systematically recorded or controlled.	There was potential for deviations from the intended interventions.

	Effisayil 1 historical cohort, Choon et al. 2023[23]	
	Company	**EAG**
Bias due to missing data	Moderate	Moderate
	There were instances of missing data for several parameters. No analysis was done to assess the effect of missing data, which could affect the study's conclusions.	Patients with no historical flare could not be included. Patients with constant flare could not contribute flare frequency data. Not all patients contributed treatment data.
Bias in measurement of outcomes	Moderate	Serious
	Outcome measurements were based on patient recall, chart review and investigator interpretation, which could introduce measurement bias.	Outcomes were assessed for three categories of flare, but there was no standard definition of these three flare categories. Flare clinical course obtained from patients (potential for recall bias) and from chart review.
Bias in selection of the reported result	Low	Low
	The study appears to report relevant outcomes related to GPP flares comprehensively.	For the outcome of interest (duration of past flares) reporting appears comprehensive.
Overall risk of bias	Low	Serious
	The study provides valuable insights into GPP flares, but the retrospective design introduces some bias. The overall risk of bias is assessed as Low.	Study judged to be at a serious risk of bias in two domains, a moderate risk of bias in two domains, a low risk of bias in three domains.

Source: Part reproduction on company response to clarification question A23 Table 5 with EAG decisions and comments added.
GPP, generalised pustular psoriasis; RCT, randomised controlled trial.

FACSingle Technology Appraisal

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 29 October 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Comparator in the Effisayil 1 trial is used in the first week of the economic model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Potentially misleading statements: EAG report page 3: *"The model is likely to over-estimate the treatment difference between spesolimab and best available care in the first week because it is based on data from spesolimab and placebo treated trial participants"* EAG report page 6: *"Effisayil 1 trial provides a direct comparison between the intervention and the comparator. However, patients in the placebo arm of the Effisayil 1 trial do not receive any standard of care treatments. Therefore, using trial data to inform the efficacy of BAC does not seem to appropriately reflect UK reality."*	Reword to reflect the unknown effectiveness of best available care: *"It is unknown if best available care is more effective than placebo (with inpatient monitoring where required)."* And *"Effisayil 1 trial provides a direct comparison between the intervention and the comparator. Patients in the placebo arm of the Effisayil 1 trial may be admitted to hospital but do not receive active treatments. It is unknown if receiving active treatments would have led to different effectiveness outcomes."*	As outlined in the company submission (Sections B.1.3.3. and B.1.3.4.) spesolimab is the only licensed treatment for GPP; it is unknown if best available care without spesolimab is more effective than placebo as the evidence for these treatments is typically based on small, open-label, uncontrolled studies. It should also be acknowledged that the Effisayil 1 trial included hospital admissions to monitor patients, where required. Use of effectiveness data from the Effisayil 1 trial during the first week represents the most suitable evidence source based on the hierarchy of evidence, as this	We should have been clear that it is the EAG's opinion that the model may over-estimate the treatment difference between spesolimab and best available care in the first week. We agree that there are no reliable data to quantify any differences in effectiveness between placebo and best available care. We have therefore amended the text for Issue 2 on page 3 of the EAG report to read: "*In the EAG's opinion the model may over-estimate the treatment difference between spesolimab and best available care in the first week because it is based on data from*

		represents an estimate of relative effectiveness derived from a randomised, double-blind trial. Estimates of best available care (BAC) from the structured expert elicitation (SEE) exercise, while robustly generated, are at risk of bias considering the specialist nature of the experts included and the small sample size, and may not reflect the experience of patients presenting in the emergency care setting where there will be less experienced dermatologists not as familiar with treating GPP flares.	*spesolimab and placebo treated trial participants. However, we acknowledge the absence of any reliable data to show whether there is a difference in effectiveness between best available care and placebo.*" EAG report Issue 6, page 6 text has been amended to: "*Effisayil 1 trial provides a direct comparison between the intervention and the comparator. However, patients in the placebo arm of the Effisayil 1 trial do not receive any standard of care treatments although they may be admitted to hospital. It is unknown if receiving active treatments would have led to different*

			effectiveness outcomes. Therefore, using trial data to inform the efficacy of BAC does not seem to appropriately reflect UK reality."

Issue 2 Comparator treatments in UK clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 5, potentially misleading statement: *"However, we are concerned that these treatments do not match the treatments used to treat GPP flares in the Effisayil 1 historical cohort study"* AND EAG report page 45: *"In comparison to the composition of comparator treatments identified by the company's SEE (CS Table 24) the use of biologic treatments*	Reword to better reflect the uncertainties in the elicited comparator treatments: *"It is unclear if the treatments used to treat GPP flares in the Effisayil 1 historical cohort study represent current UK practice but clinical experts consulted by the manufacturer confirmed the basket of treatments were similar."*	We agree there are limited details on treatments received in the Effisayil 1 historical cohort, including the timings of past flares which would help consider how reflective they may be of current real world practice. There was also variability in the treatment estimates obtained in the SEE exercise, further reflecting the lack of established standard of care. We do know that in the Effisayil 1 historical cohort study, 25% of patients received biologics for their	We agree with the company that it is unclear if the treatments used to treat GPP flares in the Effisayil 1 historical cohort study represent current UK practice, and we state that as part of Key Issue 6 and section 4.2.6.2 in the EAG report. We agree that CS ref 46 shows [redacted] clinical experts confirming the basket of treatments derived from the SEE exercise were reflective of UK clinical practice. These experts also noted

in the Effisayil 1 *historical cohort seems lower than might be expected with current treatment in England."*		flares. This closely aligns with the results of the first SEE exercise, for which the pooled average response (round 1) was [redacted] of patients receiving a biologic. It is also greater than the subsequent workshop consensus output, which estimated [redacted] of patients receiving a biologic. Clinical experts consulted by the manufacturer confirmed that the basket of treatments defined in the SEE exercise and the Effisayil 1 historical cohort were similar, including the usage of biologics. Reference 33 (SEE report) and reference 46 (clinical validation report) of the company submission provide more details.	that the basket of treatments defined in the SEE exercise and the Effisayil 1 historical cohort were similar, including in the use of biologics. However, we are unclear how closely the treatments from the SEE exercise align with the treatments used in the Effisayil 1 historical cohort for patients with moderate-to-severe flares. In EAG report page 5 (Key Issue 4), our intention was to highlight the potential mismatch between the basket of comparator treatments costed in the model and the basket of comparator treatments used to treat GPP flares in the Effisayil 1 historical cohort study and therefore informing its efficacy. We have

			slightly reworded the statement in EAG report page 5 to "*However, it is unclear how closely these treatments match the treatments used to treat moderate-to-severe GPP flares in the Effisayil 1 historical cohort study*" With regard to the statement on page 45, section 3.3.1.3, the EAG, as stated above note that the use of prior treatments for past GPP flares in the historical cohort is not specific for moderate-to-severe flares experienced by this cohort. Therefore, the EAG's opinion remains that the use of biologic treatments in the Effisayil 1 historical cohort could be lower than might be expected with current treatment for moderate-to-severe flares in

			England. To improve clarity on our view we have updated the text in EAG report section 3.3.1.3: "*We note that the use of prior treatments for past GPP flares in the historical cohort is not specific for moderate-to-severe flares as data were not reported in this way in the publication. In the EAG's opinion the use of biologic treatments in the Effisayil 1 historical cohort (24.5%),23 seems lower than might be expected with current treatment in England [CS Figure 4 shows [redacted] at first-line (Week 1) and [redacted] at second-line (weeks 2-4) and [redacted] at third and later lines of therapy (Weeks 5+)] but the EAG acknowledges that [redacted] clinical experts consulted*

			by the company confirmed the prior treatments for past GPP flares in the historical cohort was similar to the basket of treatments defined in the SEE."

Issue 3 Lack of available evidence

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Potentially misleading statements: EAG report page 4: *"The EAG is unable to model second or recurrent flares because we do not have access to the relevant data (efficacy, safety, and costs) needed to incorporate this in the model"* EAG report page 5: *"The EAG is unable to model a longer time horizon as we do not have access to long-term data."*	Reword to reflect that this data does not exist: *"The EAG is unable to model second or recurrent flares as there is currently insufficient evidence (efficacy, safety, and costs) available to incorporate this in the model"* And *"The EAG is unable to model a longer time horizon as evidence on outcomes beyond 12 weeks are not currently available."*	The current wording may be misinterpreted as implying that the relevant data exists but has not been made available to the EAG. These data are being collected as part of the on-going Effisayil REP trial (NCT06013969), for which estimated study completion is November 2026.	We have amended the text in EAG report page 4 (Key Issue 3) to: "*The EAG don't have data to model second or recurrent flares. It is unclear whether there is currently sufficient evidence (efficacy, safety, and costs) available to incorporate this in the model.*"

			We have amended the text in EAG report page 5 (Key Issue 5) to: "*The EAG is unable to model a longer time horizon as long-term data does not seem to be currently available*"

Issue 4 Requirement for clinical validation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Statements do not acknowledge clinical validation undertaken by company: EAG report page 26: *"The EAG was unable to obtain expert opinion to verify the whether the baseline characteristics of the Effisayil 1 trial population are similar to GPP patients experiencing flares in England."* EAG report page 47:	Re-word sentences to acknowledge that these have been validated by the company as part of their submission.	We assume that the statements on pages 47-48 are referring to the EAG not being able to obtain clinical validation. However, this was obtained for the company submission, which should be acknowledged.	Thank you for your comment. To add clarity, we have edited the EAG report, in sections 3.2.1.2 and 3.4 for the highlighted sentences, to clarify that we could not obtain clinical expertise to independently verify the company's clinical experts' validation. EAG report section 3.2.1.2 page 27 now reads:

"Expert opinion would help to determine whether this affects the generalisability of the trial evidence to NHS practice." EAG report page 48: *"Expert clinical opinion on the appropriateness of this definition of flare resolution would be welcome."*			"The company's clinical experts validated the evidence from Effisayil 1 as relevant (CS section B.2.12.3), however, the EAG was unable to obtain expert opinion to independently verify whether the baseline characteristics of the Effisayil 1 trial population are similar to GPP patients experiencing flares in England." EAG report section 3.4 page 48 now reads: "The company assessed the Effisayil 1 population as applicable to routine clinical practice [in the NHS] despite the high proportion of Asian people in the cohort (CS Table 11; CS section B.2.12.3), however, the EAG was unable to independently recruit

			clinical experts to verify this." And "Independent expert clinical opinion to verify the company's validation of the appropriateness of this definition of flare resolution would be welcome."

Issue 5 Incorrect statements

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 7 and page 76: *"We note that no patients had resolved their flares on Day 1 (day of spesolimab treatment)."*	Update both sentences: *"We note that the impact of spesolimab treatment on flare outcomes was not collected on Day 1 (day of spesolimab treatment)."*	The impact of spesolimab treatment on flare outcomes was not collected on Day 1.	We agree with the company, however we have amended the text in page 7 and page 76 to reflect the factual inaccuracy raised by the company below (in the third row of the current table) and therefore this statement was deleted.
EAG report page 7:	Update sentence:	Acknowledge that the impact of different inpatient rates will	This is not a factual inaccuracy as we

"Different inpatient rates for spesolimab changes the ICER considerably"	*"For the company base case, spesolimab remained dominant when assessing different inpatient rates. For the EAG base case different inpatient rates for spesolimab changes the ICER considerably"*	depend on the chosen base case.	consider our statement is correct: different inpatient rates for spesolimab changes the absolute values of the ICER considerably. This input is therefore a source of model uncertainty which could affect the model conclusions (whether spesolimab is or is not cost-effective). This depends on the other chosen inputs (namely the source of efficacy of the comparator). In section 6.1 of the EAG report, we show that spesolimab remained dominant when assessing different inpatient rates.
EAG report page 7: *"After Day 2, we note that the reduction of patients with an active flare directly leads to a reduction in the number of*	Remove sentence	Within the economic model all hospitalisations are assumed to occur on Day 1 (model start), hence whilst the effectiveness of spesolimab	We have misinterpreted this aspect of the model, but we note that this was not clearly explained in the original company

hospitalisations for the spesolimab arm, as in the model if patients have a resolved flare, they are not at risk of being hospitalised"		leads to a reduction in length of stay after Day 1 it does not lead to further reductions in hospitalisations.	submission; the EAG was not aware that all hospitalisations occurred on Day 1 and that the company assumed no further hospitalisations throughout the remainder of the time horizon. The EAG have amended Key Issue 7 on page 7 of the EAG report accordingly; and also added new text and amended existing text in pages 76 and 77 of the EAG report. The second paragraph for Key Issue 7 on page 7 now reads: "*We note that the reduction of patients with an active flare directly leads to a reduction in the number of hospitalisations, as the clinical experts advising the company stated that patients with a resolved flare defined by a*

			GPPGA pustulation subscore of 0 or 1 are discharged from hospital, and therefore we assume that they are not at risk of being hospitalised." New text has been added to page 76-77: "*The proportion of inpatients was modelled by assuming that all patients (77.6%) were hospitalised on Day 1 (day of treatment) and, after that, patients could only be discharged from hospital. We consider that this assumption lacks face validity as patients are likely to be hospitalised beyond Day 1. However, there is no evidence on which proportion of patients were hospitalised at each day and this was*

			modelled similarly for both arms, BAC and spesolimab. We consider therefore the company's approach to be reasonable." Text has been deleted from page 77, so this now reads: "*The company assumed that the proportion of the spesolimab arm patients treated as inpatients was half that of the BAC arm (33.8%) (see Table 23). This assumption was based on the relative reduction of 48.4% in the proportion of patients with a GPPGA pustulation subscore ≥ 2 (active flare) for spesolimab versus placebo in the Effisayil 1 trial. As such, spesolimab increases the number of patients*

			with resolved flares (by reducing the number of patients with active flares, see section 4.2.6.1) which, in practice, directly leads to a reduction in the number of patients that will be admitted to hospital. However, the EAG considers it to be very uncertain whether spesolimab has an additional residual benefit in reducing hospitalisation rates for patients not responding to treatment (patients with active flares) as there is no evidence showing that benefit or the size of that benefit."
EAG report page 8 *"The Effisayil 1 trial had a duration of 12 weeks and 60% of spesolimab treated participants had a GPPGA*	Update sentence: *"The Effisayil 1 trial had a duration of 12 weeks and 60% of patients originally randomised to spesolimab had a GPPGA pustulation subscore of 0 (clear) at Week 12"*	The denominator for the % quoted are patients originally randomised to spesolimab and not all spesolimab treated patients	Thank you, this is corrected as requested.

pustulation subscore of 0 (clear) at Week 12"			
EAG report page 13: *"…states that spesolimab is expected to be used in first-line treatment of GPP flares, confirmed in Clarification Response A2ii, which further elaborates that it is expected to displace the current first-line treatment options."*	Update sentence: *"…states that spesolimab is expected to be used in first-line treatment of GPP flares, confirmed in Clarification Response A2ii, which further elaborates that it is expected to displace the current first-line and subsequent-line treatments, providing an alternative option to the multiple lines of treatment approach."*	Current sentence is incomplete and does not reflect the company statements in Clarification Response A2ii	Thank you, this is updated as requested.
EAG report page 18: *"The studies cited in CS section B.1.3.2.1.2, for example, the POLARIS and SCRIPTOR studies which are specifically stated as including GPP flare patients in CS Table 4, are not included in the set of 15 studies because they include a broader GPP population and not just those patients experiencing a GPP flare (Clarification Response A4)."*	Remove sentence	CS Table 4 provides GPP patient demographics and the table title is aligned with this. Demographic data are included for a subgroup of GPP flare patients for whom such data were available but the statement that these studies are *"specifically stated as including GPP flare patients"* in the context of the current statement in the EAG report is not true.	Agree. Our statement was confused and misleading, it is now deleted.
EAG report page 36:	Update sentence:	Second mention of outcome is incorrectly detailed as having	Thank you, this is updated as requested.

"At Day 8, 57% (n=20/35) of participants had a GPPGA pustulation score of 0 or 1, rising to 80% (n=28/35) had a GPPGA pustulation subscore of 0 at week 2…"	*"At Day 8, 57% (n=20/35) of participants had a GPPGA pustulation score of 0 or 1, rising to 80% (n=28/35) had a GPPGA pustulation subscore of 0 or 1 at week 2…"*	a GPPGA pustulation subscore of 0 in current sentence	
EAG report page 44: *".We note that patients in the POLARIS study with incident GPP (n=373 who were in England, 206 of whom experienced a flare)…"*	Update sentence: *"We note that patients in the POLARIS study with incident GPP (n=206 who were in England, 129 of whom experienced a flare)"*	Current data are reporting 'n' of the GPP population as incident GPP patients and incident GPP patients as those who experienced a flare in error	Thank you, this is now corrected.

Issue 6 Typographical errors

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
EAG report page 1, incorrect section reference: *"Sections 0 to 1.6 explain the key issues in more detail."*	Update reference to 'Section 0' to the correct section	Fix typographical error	Thank you, this is now corrected.
EAG report page 50 and page 57, abbreviation already defined: *"best available care (BAC)"*	Change both occurrences to "BAC"	Fix typographical error	Thank you for highlighting this, we have replaced both by "BAC"

EAG report page 58, unclear wording (occurs twice): *"No discounting rate"*	Re-word both instances to: *"No discounting"*	Fix typographical error	Thank you for highlighting this, we have amended this.
EAG report page 72 Table 21 Values for ciclosporin, infliximab and acitretin should use the updated values post clarification. Also typo *"acitrenin"*	Values are: £34.95 (ciclosporin), £1,360.14 (infliximab) and £5.98 (acitretin) Also change *"acitrenin"* to *"acitretin""*	Fix typographical errors	Thank you for highlighting this, we have amended Table 21 of the EAG report to reflect this.

Errors in CIC markings

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG response**
EAG report: Page 2, Table 2 Page 2, text reporting numerical ICER Page 5, text reporting numerical ICERs	For consistency with the company submission, please mark all numerical ICERs as CIC	Corresponding ICER values should be marked CIC	This is not a factual inaccuracy. It is customary to leave ICERs unmarked, since the QALYs and costs for all results are marked as CIC. Therefore, there is no possibility of determining any PAS

Page 7, text reporting numerical ICERs Page 8, text reporting numerical ICERs Page 9, Table 3 Page 9, text reporting numerical ICER Page 79, Table 25 Page 79, text reporting numerical ICER Page 80, text reporting ICER for scenario using the Effisayil 1 historical cohort data Page 81, Table 26 and discussion in text Page 89-91, Table 28 Page 91, Table 29 and discussion in text Page 92-94, Table 30 and discussion in text			discounts for spesolimab or other CIC inputs using the ICER value alone.
Page 13, Figure 1 Page 63, Table 18	For consistency with the company submission, please mark all SEE estimates as CIC	Corresponding SEE values should be marked CIC	We apologise for this missing CIC marking and have rectified this.

Page 66, Table 19 Page 68, text reporting AE rates from SEE exercise			