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:

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NICE National Institute for Health and Care Excellence

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 6m on 14 February 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Boehringer Ingelheim

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	[Insert disclosure here]
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[Insert disclosure here]
Name of commentator person completing form:	[Insert name]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Thank you for the opportunity to respond to the Appraisal Consultation Document (ACD) on spesolimab for treating generalised pustular psoriasis (GPP) flares [ID3963] Boehringer Ingelheim are disappointed that the provisional recommendations do not recommend spesolimab, especially given the substantial impact of GPP flares on both physical and mental health along with the clear unmet need for effective treatments, as recognised by the committee (ACD Section 3.1) With the agreement of NICE, we have submitted additional cost-effectiveness estimates (as a separate document) to address the points raised by the Appraisal Committee (ACD Section 3.16). This incorporates the committees' preferred assumptions: • Structured Expert Elicitation (SEE) used to inform the composition and costs of treatments in the best available care (BAC) arm from Day 0. • Effisayil™ 1 historical cohort used for best-available care (BAC) response from Day 0. • Inclusion of a second flare within the modelled 12-week time horizon. • A spesolimab inpatient rate of 38.8%, derived from Wolf et al 2024.[1]

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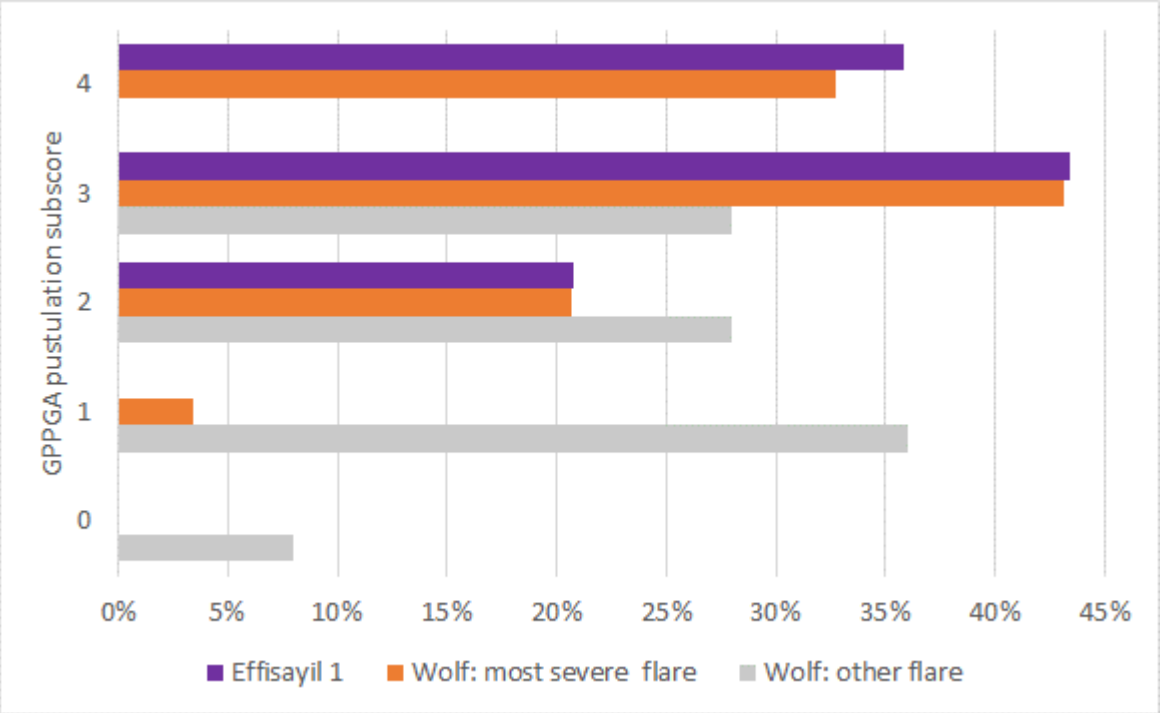
- Rate of intensive care unit (ICU) admissions with spesolimab equal to half that for BAC.

In addition, results of scenario analyses to capture the long-term mortality benefit of spesolimab are also incorporated as is a scenario analysis using the SEE exercise to inform BAC efficacy. Of note, this latter scenario uses SEE outcomes for 'severe' flares, as evidence from the Wolf et al 2024 study[1] – the only one to report on both clinician-assessed flare severity and Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscores – shows very close agreement in disease severity between the Effisayil™ 1 trial patients and the clinician-assessed 'severe' flare patients (see Figure 1 below, replicated from Figure 23 of the company submission).

Figure 1: GPPGA pustulation subscores by evidence source



Key: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment.
Source: Bachelez et al. 2021[2]; Wolf et al. 2024[1]

We hope that the additional cost-effectiveness analyses provided will enable the Committee to recommend spesolimab as a cost-effective option following the second Appraisal Committee meeting.

We would like to re-iterate that spesolimab is the only licensed treatment for GPP flares. Evidence for comparator treatments is typically obtained from small, open-label single-

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	arm studies. For the treatments currently used off-label to treat GPP in England (in the absence of spesolimab), a systematic literature review graded all of the available evidence as either 'low' or 'very low' quality, based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group criteria.[3] In addition, existing treatments are primarily those used for plaque psoriasis and so, unlike spesolimab, do not target the key pathogenic driver of GPP, Interleukin 36. This leads to slow effects with unpredictable results and safety concerns[3-5]. Hence, there is a clear unmet need that spesolimab addresses; as acknowledged by both the draft ACD and UK clinicians.

2	**Section 3.13: Evidence on inpatient and intensive care rates**
	
	From the ACD: "The committee concluded that it would prefer more UK clinical data on inpatient and intensive care admission rates and duration of stay for GPP flares treated with BAC and spesolimab, if available."
	
	Evidence from multiple sources in the UK were explored to ascertain if they could be used to inform rates of hospitalisations for BAC. A brief overview of these are provided below:
	
	• **Hospital episodes statistics (HES):** The International Classification of Diseases (ICD)-10 code, L40.1, can be employed to identify patients who have been admitted to the hospital with a primary diagnosis of GPP. However, it doesn't allow for the detection of GPP flare-ups, their severity, or the subsequent results. The information regarding the procedures undertaken and the pharmacological treatments administered is also scarce. Data from outpatient visits can only be linked to the specialty 'Dermatology' but cannot be linked to GPP admissions as less than 5% of all visits contain diagnostic information. [6] Furthermore, while there is some data on ICU stays, it's not feasible to ascertain if these are due to GPP flare-ups.
	
	  • As a result, HES cannot be utilised to accurately calculate hospitalisation rates since the ICD-10 cohort identification method, by its very nature, implies that 100% of patients are hospitalised. HES data was employed to support the estimates of recurring flare-ups incorporated in the model – as detailed in the separate document – and used in the company's submission to inform the percentage of admissions that are day cases.
	
	  • Following the ACD, Boehringer Ingelheim carried out an exploratory analysis for inpatient hospitalisation. Please see 'New evidence to support hospitalisation assumptions'.
	
	• **Primary care data:** A confined number of the data from Hospital Episode Statistics (HES) are linked to primary care data through the Clinical Practice Research Datalink (CPRD). To identify GPP flare-ups that did not result in hospitalisation, we explored the diagnoses for GPP based on SNOMED-CT codes in CPRD: ('1773605018', '1216579017', '1773604019', '1774891010', '1218069018', '1774890011', '357634011', '392053016', '357627014', '357630019', '1216578013',

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Draft guidance comments form

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	'490386015', '483991011', '392052014', '357628016', '357629012', '1218070017', '63431013', '48292011', '357633017', '357632010', '357626017'). However, the use of GPP-specific codes did not identify any patients. As a result, this linked dataset could not provide insights into hospitalisation rates. More information on this has been published. [7] This data source contributed to epidemiological estimates. • **BADBIR registry:** BADBIR, is a UK and Ireland observational study, that seeks to assess the long term safety of biologic treatments for psoriasis. The BADBIR registry can record patients with a diagnosis of GPP at baseline, and specific outcomes at follow up visits . After the ACD, we sought data from BADBIR to fulfill the request for UK data on BAC hospitalisation. Although the registry records the number of all-cause hospital admissions at follow up, it is not possible to attribute this to GPP/GPP flare, or determine the number of patients who avoided hospitalisation. Furthermore, BADBIR does not capture data on ICU admissions. Consequently, BADBIR cannot be used to address the hosptialisations of BAC, nor can it be used to collect this data prospectively (See comment 6 on Managed Access). • **Secure data environments:** The feasibility of using regional 'Secure data environments' such as 'Discover Now' was also explored. This uses a de-identified linked health and care dataset covering over 2.5 million people. Due to a lack of diagnostic codes, diagnosis of GPP was based on the 'Pustular Psoriasis' code M161D. However, this code could not differentiate GPP from other forms of pustular psoriasis (such as palmoplantar pustulosis) and was therefore not appropriate to address the healthcare resource utilisation of BAC. **New evidence to support hospitalisation assumptions:** • **Effisayil™ REP:** This ongoing, international, open-label, single-arm study involving patients with recurrent GPP flare provides additional data on GPP flares. For each flare in the trial, at the discretion of the investigator, a patient may be hospitalised prior to, during, or following first study drug administration. Limited, preliminary data on adverse events reported during the clinical trial is available for [redacted] patients. As of 1-Nov-2024, a total of [redacted] GPP flares were reported by the investigator that were treated with Spesolimab. [redacted] of these flares were classified by the investigator as a serious adverse event that required or prolonged hospitalisation. This translates to a preliminary GPP flare hospitalisation rate of [redacted] • **HES:** Following the ACD, Boehringer Ingelheim carried out an exploratory analysis to address hospitalisation rate for BAC. HES data was obtained for patients with a primary diagnosis of L40.1 who were admitted between April 2029 and July 2024; this identified [redacted] patients. Inpatient admissions for these patients were included if they occurred more than 14 days after a previous admission for GPP, in an attempt to remove admissions due to ongoing treatment for an existing flare. Outpatient admissions for these patients were included if there were two or more outpatient dermatology appointments within seven consecutive days, with the first appointment

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 6m on 14 February 2025. Please submit via NICE Docs.

	starting more than 14 days after a previous flare-related admission (inpatient or outpatient). This resulted in [redacted] total flare-related admissions, of which 73%[redacted] were inpatients. Hence, given the caveats outlined above, this exploratory analysis supports the use of 77.6% admission rates for BAC used in the base case analysis. • **UK Consensus:** To further validate the assumptions on hospitalisations, Boehringer Ingelheim have obtained a UK consensus statement (provided separately) with 29 signatures from healthcare professionals, with experience treating GPP patients. This statement supports an estimate of 80% inpatient hospitalisation rate with current BAC and an expected reduction of 50% of inpatient hospitalisation for patients treated with spesolimab. For those who still require hospitalisation, clinicians endorsed an expected reduction in length of stay and decrease in need for high dependency care. • **Global Consensus:** Boehringer Ingelheim has investigated the available databases in countries where spesolimab is on the market and currently no data is being captured that can adddress the probability of hospitalisation or ICU for GPP flares. Following the ACD, Boehringer Ingelheim have sought a global consensus, from 20 healthcare professionals with experience of treating patients with spesolimab in Japan, US and China to validate the hosptialisations assumptions. Please see comment 4 for further clarification. We are not aware of any further evidence on hospitalisations – including inpatient or intensive care stays – that has been made available since the company submission. Given the new evidence above, we have used the committee preferred inputs for these, as per ACD Section 3.16.
3	**Section 3.3: Comparators** We agree with NICE that “there are no licensed treatments and no specific guidelines in the UK for GPP flares”. Because of this, we conducted an SEE exercise to obtain evidence on treatments for GPP flares. This exercise involved six participants and demonstrated heterogeneity in responses. A consensus output was reached and used by both Boehringer Ingelheim and the External Assessment Group (EAG) in their modelling. Whilst results are similar to those suggested by clinical experts to NICE, there are some differences such as the use of methotrexate or infliximab first line for a subset of flares. Given the noted heterogeneity in responses by individual, we believe that it is more appropriate to use the results of the SEE exercise as (i) these were elicited via a structured process and (ii) they are based on a larger sample of experts. This is also aligned with the committee’s preferred assumption that “SEE exercise used as the most appropriate source to inform the composition and costs of treatments in the BAC arm for week 1 and after week 1” (ACD Section 3.16)
4	**Section 3.17: Additional data requests** The ACD requested the following additional data: • any additional insights that can be provided from data on spesolimab use in Japan

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 6m on 14 February 2025. Please submit via NICE Docs.

	• data on the use or market share of the comparator treatments to verify the BAC cost estimates from the SEE exercise • data on the treatment distribution for BAC We have explored the feasibility of these requests but we have only been able to obtain the data shared below: **Data on spesolimab use in Japan:** To our knowledge, no data is available to address the probability of hospitalisation or ICU for GPP flares in Japan. Boehringer Ingelheim have obtained a statement (provided separately) with 5 signatures from Japanese healthcare professionals (HCP), with experience of treating GPP patients with spesolimab. Although spesolimab should be administrated while the patient is admitted into hospital as an inpatient in Japan, all HCPs have confirmed that spesolimab reduces the length of inpatient hospital stay compared with other treatments. Additionally, 4 HCPs agree that spesolimab reduces the need for escalation of care to high-dependency compared with other treatments. For further validation, Boehringer Ingelheim investigated the impact of spesolimab on hospitalisation and ICU in countries with extensive experience of spesolimab. Although this data is not being captured in several countries, 9 dermatologists in the US and 5 dermatologists from China agree that spesolimab reduces inpatient admissions by at least 50%, reduces the length of inpatient hospital stay, and the need for escalation of care to high dependency vs other treatments. **Market share of the comparator treatments**: Boehringer Ingelheim was unable to obtain market share data for the treatment of GPP flares, as the available data does not have the granularity to differentiate between GPP and plaque psoriasis usage. We believe that the SEE is a valid source for defining the BAC in UK clinical practice and this is aligned with the committee's preferred assumptions.
5	**Section 3.17: Acceptable incremental cost-effectiveness ratio (ICER)** As outlined in the company submission, spesolimab is the only licensed treatment for GPP, and there are no UK guidelines for the treatment of flares. Hence there is a paucity of studies for potential comparators, which are of unproven efficacy. In addition, GPP is a rare condition and the occurrence of flares is both unpredictable and highly heterogenous. This makes evidence generation inherently challenging, as is reflected by the uncertainty in the available evidence base. The situation is covered by the 'NICE process and methods [PMG36]' Section 6.2.34, for which "the committee may be able to make recommendations accepting a higher degree of uncertainty" (Section 6.2.34). We are disappointed that these considerations are not mentioned as part of the committee's deliberations about an acceptable ICER in the ACD Section 3.17.
6	**Section 3.3: Managed Access** From the ACD: 'Clinical expert opinion was that data collection is possible.'

NICE National Institute for Health and Care Excellence

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Draft guidance comments form

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	Boehringer Ingelheim, in discussion with the managed access team, has explored the potential for prospective data collection to mitigate the uncertainties in the model. Following the ACD, we have consulted clinical experts to reassess the feasibility of prospective data collection. The two primary data collection methods suggested by experts as possible data sources were the BADBIR registry and HES. **BADBIR:** The BADBIR registry collects baseline and follow up data for a limited group of GPP patients. The data gathered is not representative of BAC since the biological cohort is confined to treatments provided by the companies that fund the registry. The limited patient count also makes it unfeasible to establish a matched cohort for BAC and spesolimab comparison without significant confounding factors. **HES:** As previously detailed, The International Classification of Diseases (ICD)-10 code, L40.1, can be employed to identify patients that have been admitted to the hospital with a primary diagnosis of GPP. However, HES does not enable the identification of GPP flare-ups, their severity, treatments used or the resulting outcomes. It is also not viable to determine if ICU admissions are a result of GPP flare-ups. Clinical experts were in agreement with our assessment that the limitations of BADBIR and HES preclude prospective data collection to address the probability of hospitalisation and ICU admission with Spesolimab vs. BAC.
7	**Points for clarification:** Section 3.2: “There are no licensed treatments and no specific guidelines in the UK for GPP flares…” This should read “There are no licensed treatments <u>apart from spesolimab</u> and no specific guidelines in the UK for GPP flares…” Section 3.4: “Placebo response data from the Effisayil 1 trial was unavailable because over 80% of people who had placebo switched to spesolimab on day 8.” This should read “Placebo response data from the Effisayil 1 trial was unavailable <u>after Day 8</u> because over 80% of people who had placebo switched to spesolimab on day 8.” Section 3.9: “The EAG also raised issues about the lower-than-expected biologicals use in the historical cohort compared with the NHS.” There is no evidence available on use of biologicals to treat GPP flares in the NHS. In addition, as noted during the factual accuracy check, use of biologics in the historical cohort was similar to results of the first SEE exercise and greater than the subsequent workshop consensus output. Hence this statement should be amended to “The EAG also raised issues about the <u>potential</u> lower-than-expected biologicals use in the historical cohort compared with the NHS.”

Insert extra rows as needed

Checklist for submitting comments

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- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.

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NICE National Institute for Health and Care Excellence

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

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- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

References

1. Wolf P, Ceovic R, Conrad C, et al. Characteristics and management of generalized pustular psoriasis (GPP): Experience from the Central and Eastern Europe (CEE) GPP Expert Network. *Journal of the European Academy of Dermatology and Venereology*. 2024.
2. Bachelez H, Choon SE, Marrakchi S, et al. Trial of Spesolimab for Generalized Pustular Psoriasis. *N Engl J Med*. 2021; 385(26):2431-40.
3. Puig L, Choon SE, Gottlieb AB, et al. Generalized pustular psoriasis: A global Delphi consensus on clinical course, diagnosis, treatment goals and disease management. *Journal of the European Academy of Dermatology and Venereology*. 2023; 37(4):737-52.
4. Barker JN, Casanova E, Choon SE, et al. Global Delphi consensus on treatment goals for generalised pustular psoriasis. *British Journal of Dermatology*. 2025:ljae491.
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NICE National Institute for Health and Care Excellence

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 6m on 14 February 2025. Please submit via NICE Docs.

6. Agency MaHpR. Hospital Episode Statistics (HES) Outpatient Care and CPRD primary care data Documentation (November 2024). 2024.
7. 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.

Additional cost-effectiveness analyses following the NICE draft guidance

The draft appraisal committee document (ACD) requested two additional analyses that it was not possible to address in the submitted cost-effectiveness model (both Section 3.16 of the ACD):

- A second flare implemented within 12 weeks in the model
- The long-term benefit due to spesolimab reducing mortality

The implementation of these, and corresponding results, are discussed in turn.

Implementing a second flare within 12 weeks

Evidence on the rates of recurrent flares is available from the Effisayil™ 1 trial. As the comparator arm of this trial was placebo in the first week, followed by crossover to spesolimab, rates of recurrence are only informative for patients who were randomised to spesolimab. Amongst these 35 patients randomised to spesolimab, rescue treatment with spesolimab for a recurrent flare was received by four patients.

For the Effisayil™ 1 trial a patient was classified as having a recurrent flare if they experienced an initial response based on a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score of 0 or 1, followed by an increase of ≥2 points in both the GPPGA total score and the pustulation subscore. This response definition used to identify recurrent flares is different to the response definition used in the economic model, which is a GPPGA pustulation subscore of 0 or 1. Of the four patients who received rescue treatment with spesolimab, one did not respond based on the model definition (hence remained in the 'active flare' health state)

In addition, one of the four patients who received rescue treatment had previously received escape medication, defined as treatment with best available care (BAC) during the first week due to disease worsening that required immediate treatment. As such, this patient was also classified as a non-responder in the economic model.

Hence, for the economic model, there were only two recurrent flares amongst patients randomised to receive spesolimab. As there were 28 responders after week 2, the rate of recurrent flares is 7.14%. These two flares occurred between weeks 4 (at which time there was also 28 responders) and 12; hence for implementation in the economic model it was assumed that the rate of recurrence was constant between weeks 4 and 12. This is converted to daily rates to fit the model's daily cycle (see from row 191 column F, "Input calculation sheet").

Due to a lack of evidence on the rates of recurrent flares for BAC it was assumed that rates were the same for BAC and spesolimab. Note that as spesolimab leads to more patients responding sooner, it will result in a higher overall number of recurrent flares.

Some supportive information on rates of recurrent flares for BAC are available from an analysis of the English Hospital Episode Statistics (HES) data. This used the International Classification of Diseases (ICD)-10 code 'L401' to identify admissions for GPP; where this was the primary diagnosis it was assumed to represent an admission for a GPP flare. Between [redacted] and [redacted] this identified [redacted] patients with [redacted] spells, where a spell covers the period from

the patient's admission to hospital until their discharge. Of these spells, the proportions classified as non-elective, day case and elective were [redacted]%, [redacted] and [redacted]%, respectively. Of these [redacted] patients, [redacted] were re-admitted within 12 weeks and [redacted] of these had a primary diagnosis of generalised pustular psoriasis (GPP), so were assumed to be re-admitted for a GPP flare. This results in an estimate of [redacted]% for recurrent flares within 12 weeks. However, there are notable limitations with this estimate. First, it is restricted to patients for whom both their initial flare and subsequent flares required hospitalisation – it is unclear how representative this is of all GPP flares. Secondly, it is not possible to identify how many of the re-admissions were for the acute treatment of a recurrent GPP flare as opposed to planned management of the original flare – such as delivery of treatment, adverse event management or monitoring. It is likely that this accounts for some of the re-admissions, given that the proportion of day case spells increased from [redacted]% for the original admission to [redacted]% for the re-admission. The proportion of non-elective spells decreased from [redacted]% for the original admission to [redacted]% for the re-admission.

No special visits related to the administration of spesolimab rescue medication were planned; therefore, data on efficacy after rescue treatment with spesolimab are derived from the planned visits following administration of rescue treatment (mean follow up 23 days).

It is unclear whether recurrent flares would be treated the same or differently to the original flare. For the base case it was assumed that, for both spesolimab and BAC, recurrent flares would have the same treatments and outcomes as the original flare.

In the Effisayil™ 1 trial, only one rescue dose of spesolimab was allowed for the treatment of recurrent flares. This was explored in a scenario analysis, which also assumed that for patients whose flare does not respond after one week, subsequent flare treatment will be with ciclosporin. For BAC, clinical advice was that if patients experience a recurrent flare within a short period of time then this is an indication that the original BAC treatments were not effectively controlling the flare. In this situation biological treatments would be used. This was explored in a scenario that assumed that BAC treatment of recurrent flares would be with biologicals, based on the distribution of third line treatments outlined in the company submission (Figure 4; 40% guselkumab, 30% each secukinumab and ustekinumab). For these scenarios the drug cost of recurrence for the intervention and comparator arms is calculated in the "Treatment selection" sheet.

The incidence of recurrent flares per treatment arm is multiplied with the drug cost, total healthcare resource use costs, and total quality-adjusted life years (QALYs) of the initial flare to reflect the impact of recurrence (see cells D31, D32, D41 for the intervention arm, and E31, E32, and E41 for the comparator arm on the "Deterministic Results" sheet). Results with the committee's preferred assumptions, with and without incorporating recurrent flares are provided in Table 1 and Table 2, respectively. The committee's preferred assumptions that are different to the original company base-case are:

- Use of the Effisayil™ 1 historical cohort for BAC outcomes at all time points
- Rates of intensive care unit (ICU) admissions with spesolimab are not 0% but instead 50% reduced compared to BAC

Results also incorporate the updated confidential discount for spesolimab of [redacted]%. Results show that with and without the inclusion of recurrent flares, treatment with spesolimab dominates BAC.

Results of key scenarios (incorporating recurrent flares) are provided in Table 3. All results use the updated confidential discount for spesolimab. In addition to new scenarios for the treatment of recurrent flares, the following additional scenarios are included:

- For both treatments, 12.37% of patients have an active flare at the end of 12-weeks. This reflects scenarios introduced by the external assessment group (EAG) to assess the sensitivity of cost-effectiveness results to the assumption that all flares will have resolved by 12-weeks. As spesolimab results in faster flare resolution, use of the same proportion for both spesolimab and BAC is likely to conservative.
- A 30% reduction in either inpatient or ICU rates with spesolimab, compared to BAC. These are included to reflect uncertainty in the treatment effect of spesolimab. Given clinician input that the base case reduction of 50% may be an under-estimate, these scenarios are likely to be conservative.
- Use of the SEE for the efficacy of BAC from Day 0. As noted in the consultation response form, this uses estimates for 'severe' flares as there is evidence to suggest that these are more representative of the severity of flares observed in the Effisayil™ 1 trial.
- Two pertinent scenarios from the original company submission were also retained; use of BAC inpatient percentage from the literature[1] and not including a maximum length of stay for patients on ICU requiring mechanical ventilation.

For all of the scenarios considered spesolimab dominates BAC.

Table 1: Base case results, committee preferred assumptions incorporating the confidential spesolimab discount and recurrent flares

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	INHB at £20,000 / QALY	INHB at £30,000 / QALY
BAC	£24,082	[redacted]					
Spesolimab	[redacted]	[redacted]	[redacted]	0.020	Spesolimab dominates	0.243	0.169
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 2: Base case results, committee preferred assumptions incorporating the confidential spesolimab discount, no recurrent flares

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	INHB at £20,000 / QALY	INHB at £30,000 / QALY
BAC	£22,706	[redacted]					
Spesolimab	[redacted]	[redacted]	[redacted]	0.018	Spesolimab dominates	0.231	0.160
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 3: Base-case and scenario results including a recurrent flare

	Scenario	Justification	ICER versus BAC
	Base case		Spesolimab dominates
1	Treatment of recurrent flares different to initial flare: BAC	Explore uncertainty in the treatment of recurrent flares	Spesolimab dominates
2	Treatment of recurrent flares different to for initial flare: spesolimab	Explore uncertainty in the treatment of recurrent flares	Spesolimab dominates
3	Patients with active flare (both arms) at the end of the time horizon	Assess sensitivity of results to 12-week time horizon	Spesolimab dominates
4	30% reduction in inpatient admissions with spesolimab	Uncertainty in the effect of spesolimab in reducing inpatient admissions	Spesolimab dominates
5	30% reduction in ICU admissions with spesolimab	Uncertainty in the effect of spesolimab in reducing ICU admissions	Spesolimab dominates
6	BAC efficacy: SEE (severe patients)	Alternative approach to estimating BAC efficacy	Spesolimab dominates
7	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
8	LoS for ICU with MV not capped	Reflect uncertainty in how long patients stay in ICU	Spesolimab dominates
Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; SEE, structured expert elicitation			

The long-term mortality benefit of spesolimab

Based on the committee's preferred modelling assumptions, there are on average 0.015 and 0.025 deaths within the 12-week time horizon for patients receiving spesolimab and BAC, respectively. Patients receiving spesolimab accrue [redacted] QALYs across the 12 weeks; if there were no disutility due to a GPP flare they would have accrued [redacted] QALYs; hence the impact of a GPP flare is to reduce the QALYs accrued by [redacted]. If it is assumed that patients have a utility of [redacted] (the 'flare free' utility) when their flare is resolved, and also have on average one flare a year then the QALYs gained per year are ([redacted] – [redacted] =) [redacted].

Data from POLARIS shows that the average age of patients experiencing a GPP flare in England is 57 years, with 66% of these being female.[2] The average life-expectancy for a 57 year old male is 84 years, whilst for a female it is 87 years, hence the weighted general population life-expectancy for a GPP-flare patient is 29 years.[3] There is evidence that people with GPP have an elevated mortality risk compared to the general population, with a reported hazard ratio of 1.81 (95% confidence interval 1.58 to 2.08).[4] This results in an adjusted life expectancy of 16 years.

Hence the lifetime QALYs gained due to one avoided death = [redacted] = [redacted]. As spesolimab is estimated to avoid 0.01 deaths this corresponds to a lifetime QALY gain of [redacted] per recurrent flare.

Deterministic results and scenario analyses with the mortality benefit added are provided in Table 4. For base case and all the scenarios spesolimab dominates BAC.

Table 4: Base-case and scenario results including a recurrent flare and long-term mortality benefit

	Scenario	**Justification**	**ICER versus BAC**
	Base case		Spesolimab dominates
1	Treatment of recurrent flares different to for initial flare: BAC	Explore uncertainty in the treatment of recurrent flares	Spesolimab dominates
2	Treatment of recurrent flares different to for initial flare: spesolimab	Explore uncertainty in the treatment of recurrent flares	Spesolimab dominates
3	Patients with active flare (both arms) at the end of the time horizon	Assess sensitivity of results to 12-week time horizon	Spesolimab dominates
4	30% reduction in inpatient admissions with spesolimab	Uncertainty in the effect of spesolimab in reducing inpatient admissions	Spesolimab dominates
5	30% reduction in ICU admissions with spesolimab	Uncertainty in the effect of spesolimab in reducing ICU admissions	Spesolimab dominates
6	BAC efficacy: SEE (severe patients)	Alternative approach to estimating BAC efficacy	Spesolimab dominates
7	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
8	LoS for ICU with MV not capped	Reflect uncertainty in how long patients stay in ICU	Spesolimab dominates
Key: BAC, best available care; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; SEE, structured expert elicitation			

References

1. Wolf P, Ceovic R, Conrad C, et al. Characteristics and management of generalized pustular psoriasis (GPP): Experience from the Central and Eastern Europe (CEE) GPP Expert Network. *Journal of the European Academy of Dermatology and Venereology*. 2024.
2. 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.
3. Office for National Statistics. Life expectancy calculator. 2024.
4. Ericson O, Löfvendahl S, Norlin JM, et al. Mortality in generalized pustular psoriasis: a population-based national register study. *Journal of the American Academy of Dermatology*. 2023; 89(3):616-9.

Boehringer Ingelheim

UK Clinician statement

As healthcare professionals with experience treating Generalised Pustular Psoriasis (GPP) patients in the UK, we collectively endorse the integration of spesolimab into the patient care pathway. Spesolimab represents a significant advancement in the treatment of GPP flares. The Effisayil-1 clinical trial has demonstrated rapid and complete clearance of pustules, and feedback from countries where the drug is available supports this efficacy in the real-world setting. We are confident that it will transform our approach to patient care in the UK.

Genetic and immunological research demonstrates unequivocally that the IL-36 pathway is the primary biological driver for GPP. Spesolimab is the only licensed treatment specifically targeting the interleukin 36 (IL-36) pathway. Treatments currently used in the NHS are not licensed for GPP; they were developed for plaque psoriasis which has different biological drivers to GPP. There is also a lack of clinical evidence supporting their effectiveness in resolving GPP flares. The limited evidence, from case reports and open label studies, demonstrate unpredictable results, slow effect, and incomplete response. This is consistent with our clinical experience, leaving patients vulnerable to infections and complications, needing inpatient care for approximately 80% of our patients, with long durations of stay.

Our discussions with dermatologists in other countries who have treated GPP patients with spesolimab, and our understanding of the clinical trial, lead us to believe that spesolimab will not only provide rapid relief to our patients but also significantly decrease the level of inpatient care needed to successfully resolve a flare. Unlike existing treatments, spesolimab rapidly and completely resolves flares, often within 2-3 days, as evidenced in the Effisayil-1 trial (Bachelez et al. 2021). Given these treatment effects, it is reasonable to anticipate that introducing spesolimab into the treatment pathway could reduce hospital admissions by at least 50%. For those who still require hospital admission, we anticipate spesolimab would shorten their stay and decrease the need for high-dependency care escalation compared to current treatments. Spesolimab could also reduce or prevent systemic complications, such as fever and malaise, as well as drug-related toxicity, and decrease the use of treatments with unproven and unpredictable benefits.

Our patients, individuals with a rare disease associated with severe pain, high risk of infection, and other potentially life-threatening complications, deserve the best care possible. As clinicians, we strongly advocate for the adoption of this technology into NHS care, which will not only provide a much-needed treatment option for these individuals but also reduce the need for hospital care.

Professor Jonathan Barker
Consultant Dermatologist
St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust

Supported by [redacted], BDNG President and Nurse Consultant, and the BDNG Executive Committee on behalf of the BDNG organisation.

Supported by [redacted], Chair of the Psoriasis Association and Consultant Dermatologist, United Lincolnshire Teaching Hospitals NHS Trust.

Name	Role	Hospital	Trust
Prof. Jonathan Barker	Consultant Dermatologist	St John's Institute of Dermatology, Guy's Hospital	Guy's and St Thomas' NHS Foundation Trust
[redacted]	Consultant Dermatologist	St John's Institute of Dermatology, Guy's Hospital	Guy's and St Thomas' NHS Foundation Trust
[redacted]	Consultant Dermatologist	Royal London Hospital	Barts Health NHS Trust
[redacted]	Consultant Dermatologist	Salford Royal Hospital	Northern Care Alliance NHS Foundation Trust

Boehringer Ingelheim

[redacted]	Consultant Dermatologist	King's College Hospital	King's College Hospital NHS Foundation Trust
[redacted]	Consultant Dermatologist	Salford Royal Hospital	Northern Care Alliance NHS Foundation Trust
[redacted]	Consultant Dermatologist	Salford Royal Hospital	Northern Care Alliance NHS Foundation Trust
[redacted]	Consultant Dermatologist	Royal Victoria Infirmary	The Newcastle Upon Tyne Hospitals NHS Foundation Trust
[redacted]	Consultant Dermatologist	Bristol Royal Infirmary	University Hospitals Bristol NHS Foundation Trust
[redacted]	Consultant Dermatologist	Churchill Hospital	Oxford University Hospitals NHS Foundation Trust
[redacted]	Consultant Dermatologist	Glamorgan House	Cardiff and Vale University Health Board
[redacted]	Consultant Dermatologist	Royal Hallamshire Hospital	Sheffield Teaching Hospitals NHS Foundation Trust
[redacted]	Consultant Dermatologist	Chapel Allerton Hospital	Leeds Teaching Hospitals NHS Foundation Trust
[redacted]	Associate Specialist in Dermatology	West Glasgow Ambulatory Care Hospital	NHS Greater Glasgow and Clyde
[redacted]	Consultant Dermatologist	West Glasgow Ambulatory Care Hospital	NHS Greater Glasgow and Clyde
[redacted]	Consultant Dermatologist	Queen Elizabeth Hospital	University Hospitals Birmingham NHS Foundation Trust
[redacted]	Consultant Dermatologist	Queen Elizabeth Hospital	University Hospitals Birmingham NHS Foundation Trust
[redacted]	Consultant Dermatologist	Queen Elizabeth Hospital	University Hospitals Birmingham NHS Foundation Trust
[redacted]	Consultant Dermatologist	Queen Elizabeth Hospital	University Hospitals Birmingham NHS Foundation Trust
[redacted]	Consultant Dermatologist	Queen Elizabeth Hospital	University Hospitals Birmingham NHS Foundation Trust
[redacted]	Consultant Dermatologist	Queen Elizabeth Hospital	University Hospitals Birmingham NHS Foundation Trust
[redacted]	Consultant Dermatologist	Queen Elizabeth Hospital	University Hospitals Birmingham NHS Foundation Trust
[redacted]	Consultant Dermatologist	Lincoln County Hospital	United Lincolnshire Teaching Hospitals NHS Trust
[redacted]	Nurse Consultant	St John's Institute of Dermatology, Guy's Hospital	Guy's and St Thomas' NHS Foundation Trust
[redacted]	Nurse Consultant	Royal Berkshire Hospital	Royal Berkshire NHS Foundation Trust
[redacted]	Advanced Nurse Practitioner	Belfast City Hospital	Belfast Health and Social Care Trust
[redacted]	Nurse Consultant	St Woolos Hospital	Aneurin Bevan University Health Board
[redacted]	Senior ANP in Dermatology	Walsall Manor Hospital	Walsall Healthcare NHS Trust
[redacted]	Consultant Dermatologist	St George's Hospital	St George's University Hospitals NHS Foundation Trust

Boehringer Ingelheim is working towards getting spesolimab intravenous (IV) infusion for treating patients with Generalised Pustular Psoriasis (GPP) covered by the public health system in England. In the UK, there is an organisation called the National Institute for Health and Care Excellence (NICE). They evaluate new medications the effectiveness and cost-efficiency of medical treatments and drugs.

Spesolimab has received approval for sale in the UK, a process known as "marketing authorisation". However, it's not yet covered by the public health system, meaning it's not automatically paid for by public health insurance.

We are asking for your help, based on your knowledge and experience with spesolimab, to support our efforts. This way, patients in England who need this medication can have easier access to it.

With your consent, we would use this statement as supporting information to our response to NICE.

I confirm that I have experience with spesolimab IV for treating GPP flares and from my experience, the usage of spesolimab IV:

- *Reduces inpatient admissions (overnight stay in a hospital bed) vs other treatments by at least 50%.*
- *Reduces the length of inpatient hospital stay compared with other treatments.*
- *Reduces the need for escalation of care to high dependency (e.g. ICU admission) compared with other treatments.*

Supported by:

Name	Role	Hospital
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Boehringer Ingelheim is working towards getting Spesolimab intravenous (IV) infusion for treating patients with Generalised Pustular Psoriasis (GPP) covered by the public health system in England. In the UK, there is an organisation called the National Institute for Health and Care Excellence (NICE). They evaluate new medications the effectiveness and cost-efficiency of medical treatments and drugs.

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With your consent, we would use this statement as supporting information to our response to NICE.

I confirm that I have experience with spesolimab IV for treating GPP flares and from my experience, spesolimab IV:

- *Must be administered while patient is admitted into hospital as an inpatient*
- *Reduces the length of inpatient hospital stay compared with other treatments.*
- *Reduces the need for escalation of care to high dependency (e.g. ICU admission) compared with other treatments.*

Name	Hospital
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

**This expert agreed on the first and second bullet point only*

Boehringer Ingelheim is working towards getting spesolimab intravenous (IV) infusion for treating patients with Generalised Pustular Psoriasis (GPP) covered by the public health system in England. In the UK, there is an organisation called the National Institute for Health and Care Excellence (NICE). They evaluate new medications the effectiveness and cost-efficiency of medical treatments and drugs.

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I confirm that I have experience with spesolimab IV for treating GPP flares and from my experience, the usage of spesolimab IV:

- *Reduces inpatient admissions (overnight stay in a hospital bed) vs other treatments by at least 50%.*
- *Reduces the length of inpatient hospital stay compared with other treatments.*
- *Reduces the need for escalation of care to high dependency (e.g. ICU admission) compared with other treatments.*

Name	**Hospital**
Prof. Mark Lebwohl, MD	Icahn School of Medicine at Mount Sinai, Waldman Department of Dermatology
[redacted]	[redacted]
Dr Oanh Lauring, MD	Lauring Dermatology
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Dr Marshall Shuler, MD	Carolina Dermatology
Dr Raj Chovatiya, MD	Rosalind Franklin University of Medicine and Science
Douglas DiRuggiero, PA-C	Skin Cancer & Cosmetic Dermatology Center, Georgia

NICE National Institute for Health and Care Excellence

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of 20 February 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Psoriasis Association

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

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Disclosure
Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]
Please state:

- the name of the company
- the amount
- the purpose of funding including whether it related to a product mentioned in the stakeholder list
- whether it is ongoing or has ceased.

Company	? related to a product	?ongoing or ceased	Membership	Conference costs	Honorarium	Core funding	Total
Boehringer Ingelheim	**No**	**ceased**	**2000**	**2500**	**138**	**2500**	**7138**
Abbvie	No	ceased	2000		78	6000	8078
UCB	No	Ceased	2000	2500	660		5160
Janssen	No	Ceased	2000	2500		8000	12500
Novartis	No	Ceased	1500	2500			4000
BMS	No	Ceased		2500			2500
Medac Pharma	No	ceased		2500			2500
Almirall	No	Ceased		2500			2500
Total							**41,876**

The Psoriasis Association has a policy that no more than 15% of total income can come from the pharmaceutical industry. This figure represented 8.9% of total income in 2024.
Income from Boehringer Ingelheim in 2024 represented 1.5% of total income.

Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.

None

Name of commentator person completing form:

[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..

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NICE National Institute for Health and Care Excellence

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Draft guidance comments form

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1	Generalised Pustular Psoriasis (GPP) is rare and life-threatening. A diagnosis of GPP always has a massive impact on a patient's quality of life and mental health. We are concerned that this recommendation will mean that people with GPP are denied access to the only treatment that is licensed to specifically target their condition.
2	We are concerned that the seriousness of GPP has been overlooked owing to the rareness of the condition, and that some references to defining the much more common plaque psoriasis may have been drawn unintentionally. GPP is always severe – never mild or moderate. NICE CKS states - If a person presents with suspected generalized pustular psoriasis or erythrodermic psoriasis, this should be managed as a medical emergency: Arrange for immediate same-day specialist dermatology assessment and ongoing management.
3	The worry and anxiety around where patients will receive treatment for GPP and how they will access this treatment is a huge concern particularly with there now being very few (if any) dedicated dermatology beds (even in tertiary centres). Therefore a quick and effective targeted treatment such as Spesolimab will decrease the need for in-patient hospital treatment which will in turn improve the quality of life for people with GPP and relieve pressure on the need for a hospital bed.
4	Given how quickly this treatment can work, we are concerned that the decision has not taken into account the best needs of patients – with the alternative being long stays in hospital (away from family / friends / support network) which in turn puts extra pressure on work and family-life, and / or treatments that are not targeted for this specific disease (continuing the trial and error approach). This will add to the stress and distress of an already difficult and worrying time. Patients fear they will die from a GPP flare and so they should have access to a treatment that can effectively get the condition under control quickly, preferably without the need for a hospital stay.
5	As there are very few dedicated dermatology beds in England and Wales, GPP patients are already receiving a substandard treatment experience as they do not have access to dermatology specialist nurses to help with their care. As such there is an unmet need for patients to have access to the right treatment, first time – it is our view that Spesolimab should be available for clinicians to prescribe when appropriate.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.

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Spesolimab for treating generalised pustular psoriasis flares [ID3963]

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- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

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Spesolimab for treating generalised pustular psoriasis flares [ID3963]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Association of Dermatologist (BAD)

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NICE National Institute for Health and Care Excellence

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	None.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted] and [redacted] on behalf of the British Association of Dermatologists' Therapy & Guidelines Sub-committee, and [redacted] on behalf of the British Association of Dermatologists' guideline development group on biologics for psoriasis

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are very disappointed with NICE's decision not to recommend spesolimab for generalised pustular psoriasis (GPP) flares and we have outlined our arguments below. The key issues raised by the EAG include: 1. No / little UK data.

Please return to: **NICE DOCS**

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

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2. Trial participants might not be representative of the UK population due to few / no participants from the UK.
3. Trials are placebo-controlled and there are no head-to-head comparisons with current standard of care or best available care (BAC) in the draft guidance document, therefore the efficacy of the intervention might be over-estimated.

Spesolimab was not available for use in the UK in normal NHS practice or in research (none of the Effisayil 1 trial participants were from the UK). It would be unfair to deny UK patients access to this intervention for the reasons outlined above. UK real-world data could be collected by giving UK clinicians access to the treatment, acknowledging that such data might take some time to accrue. However, we note that in the draft guidance document, it was stated that the company has not made a proposal for managed access after carrying out a feasibility assessment.

Given the ethnic diversity across the UK, it is unlikely that the UK population with GPP would differ significantly from that in the clinical trial cohort. Please also refer to https://doi.org/10.1016/j.jaci.2018.06.038, including the supporting information document which suggests that the clinical features across the different ethnicities are similar (acknowledging that the study did have a greater proportion of Asian participants that might be expected in the UK; demographics of the UK cohort from this paper, collected under the PLUM study to identify genetic determinants of GPP, is pasted below.

	n	%age		Ever exposed to..					
With GPP	110			**Ethnicity**	All				
Age (recruitment)		56.3	Average	**Any Biologic**	**n**	**%age**	**n biologics**	**n**	**%age**
Gender (Female)	73	66%	Female	Secukinumab	8	7.3%	0	62	56.4%
Ethnicity	92	84%	White	Ixekizumab	5	4.5%	1	25	22.7%
Ethnicity	16	15%	Asian	Ustekinumab	12	10.9%	2	12	10.9%
PGA		3.7	Average	Infliximab	15	13.6%	3	8	7.3%
ppPASI		8.9	Average	Adalimumab	27	24.5%	4	2	1.8%
DLQI		11	Average	Risankizumab	3	2.7%	5	0	0.0%
Current Smoker	14	13%		Etanercept	8	7.3%	6	1	0.9%
Ex Smoker	41	37%		Guselkumab	3	2.7%			
Biologic	48	44%	Ever had	Certolizumab	4	3.6%			
Systemic	79	72%	Ever had	Efalizumab	1	0.9%			
UVTherapy	12	11%	Ever had	Golimumab	1	0.9%			
Age of Onset		42.1	Average						
BMI		29.7	Average	**Any Systemic**			**n systemics**	**n**	**%age**
				Acitretin	35	31.8%	0	31	28.2%
				Methotrexate	47	42.7%	1	40	36.4%
				Ciclosporin	37	33.6%	2	25	22.7%
				Oral PUVA	8	7.3%	3	13	11.8%
				Fumaric acid esters	2	1.8%	4	1	0.9%
				Mycophenolate	2	1.8%			
				Azathioprine	1	0.9%			
				Apremilast	1	0.9%			
				Fumaric acid esters	2	1.8%			

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

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	Although we acknowledge that, inevitably, there will be some uncertainty about the model, however, as evidenced by the PLUM data, patients are being exposed to multiple biologics and data from our psoriasis registry, BADBIR, indicate that stopping therapy is mostly due to ineffectiveness, which is likely to be the case here.
2	The evidence presented on the pathway of care for people with GPP, particularly the burden of disease on the patient, clinicians, and healthcare system more generally, is incomplete. Related to this, the cost-effectiveness modelling is likely to underestimate the benefit of this targeted (albeit high-cost) intervention. GPP has a profound psychological/psychosocial impact on patients, which is very difficult to quantify accurately. Anecdotally, one patient was treated with spesolimab on compassionate grounds, *likely* to be the only case in the UK, and the knowledge that an effective treatment was available had a profound impact on the patient's well-being.
3	Specifically, routinely collected primary healthcare data, and hospital episodes statistics (HES) data, do not capture the course of GPP adequately. We know that coding hospital admissions is poor, so likely to under-represent admissions for GPP. Further, whilst acute, severe generalised flares will be managed with inpatient admissions, less severe but still very significant disease flares with major patient impact will be managed through day centres and repeated attendances to outpatient departments for systemic treatment monitoring and topicals/supportive care. Finally, because high-cost drugs are not captured in primary healthcare records or HES data, the cost of ineffective, targeted high-cost drugs is captured incompletely.
4	Therefore, the cost-effectiveness of spesolimab is very difficult (impossible) to estimate accurately, given the underpinning data is so poor. We would strongly recommend that this intervention is approved for use OR approved through the managed access route with prospective data collection to better understand the cost-effectiveness of the intervention.
5	The development of this drug was driven by science from the UK. It is profoundly disappointing that the UK is not able to benefit from this intervention for patients with GPP. In the long term, short-sighted decisions like this may influence industries' appetite for investing in drug development in the UK, especially for rare diseases which, when considered collectively, are a major source of burden and expenditure to the UK's healthcare systems.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your

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NICE National Institute for Health and Care Excellence

Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of 20 February 2025. Please submit via NICE Docs.

comments form with that information replaced with asterixis and highlighted in black.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Understanding the Lived Experience of Generalised Pustular Psoriasis (GPP): Survey Summary

Background

Generalised Pustular Psoriasis (GPP) is a rare and severe form of psoriasis characterised by widespread pustules on an inflamed background. In July 2024, an online survey was conducted by the Psoriasis Association to gather insights from individuals living with GPP or their loved ones / carers, aiming to better understand the disease burden, treatment experiences and unmet needs.

Methods

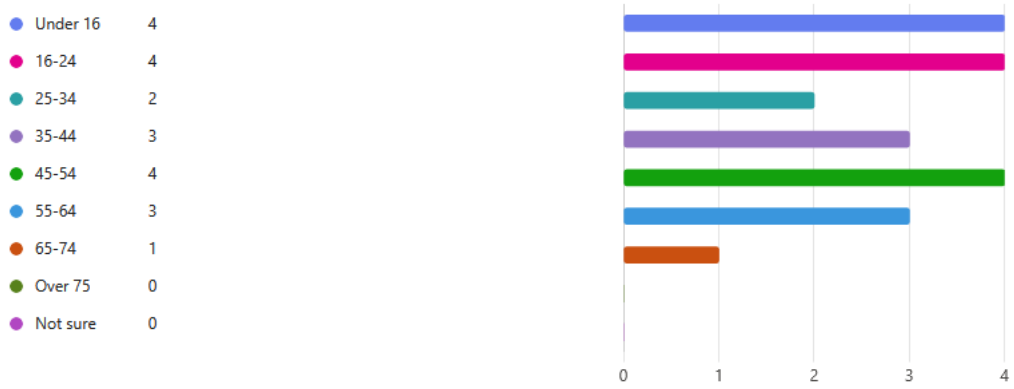
The Psoriasis Association hosted a 14-question survey on their website, featuring a mix of fixed-choice and open-ended responses. The survey was promoted through the Psoriasis Association's website and social media platforms. The survey was open for 4 weeks in July 2024. A total of 21 survey responses were received and analysed. All respondents were either individuals diagnosed with GPP or close carers. Participants provided open-ended responses regarding their diagnosis, symptoms, treatment experiences and views on healthcare services.

Key Findings

Diagnosis and Flares

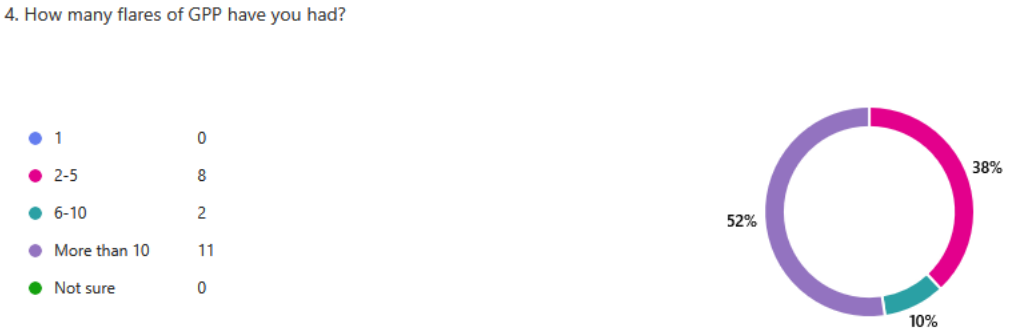
- Respondents reported being diagnosed across a wide age range, with many diagnoses occurring either under 25 years of age or between 45-64 years.

3. How old were you when you were diagnosed with GPP?



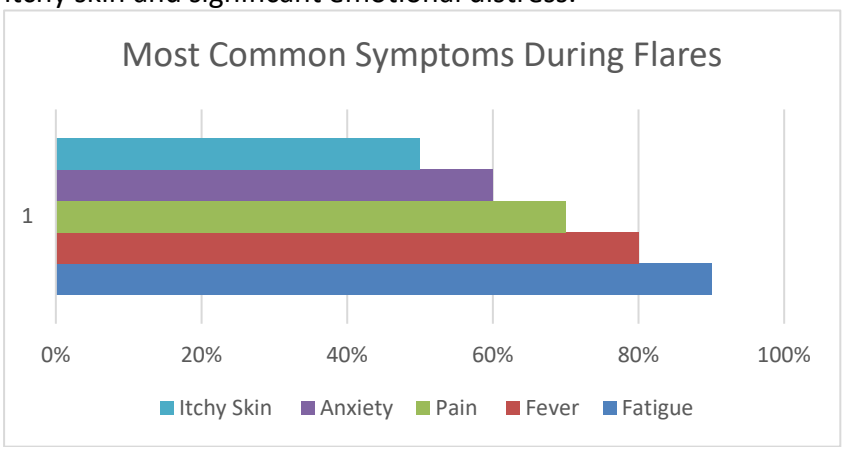
The Psoriasis Association, Dick Coles House, 2 Queensbridge, Northampton, NN4 7BF
Telephone: 01604 251620 **Email:** mail@psoriasis-association.org.uk **Website:** www.psoriasis-association.org.uk
Charity Numbers 1180666 and SC049563
Survey carried out 10/7/24 – 7/8/24

- Flares were frequent: the majority experienced more than 10 flares over the course of living with GPP.



Symptom Burden

- Commonly reported symptoms during flares included severe fatigue, fever, pain, dry and itchy skin and significant emotional distress.



- Several respondents described the flares as “life threatening” or “debilitating” illustrating the severity of episodes.

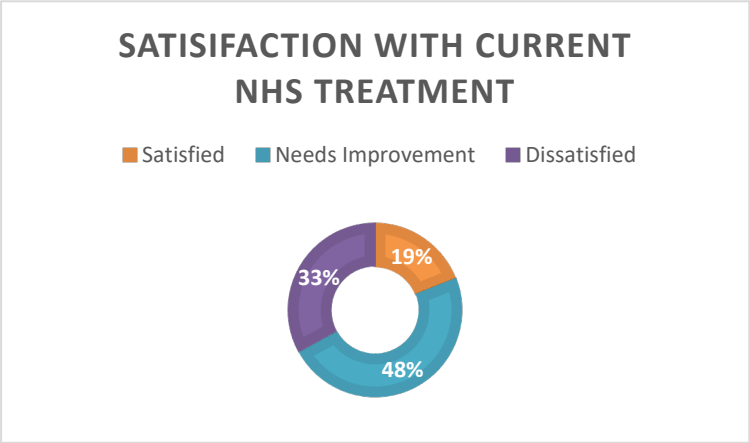
Impact on Life

- Flares led to major disruptions in home life, work, education, social activities and mental health.
- Between flares, many participants lived with ongoing anxiety about potential recurrences.
- GPP made everyday activities significantly more difficult, or, at times, impossible.

Treatment Experiences

- Frequently used treatments included topical therapies, systemic medications and hospital interventions.
- Patient satisfaction with treatment was mixed, with issues cited including long waiting times to see dermatologists, lack of healthcare professional understanding, and difficulty

accessing appropriate support.



Views on New Treatments

- There was strong support for treatments aimed at preventing flares.
- Respondents believed early access to preventive treatment would have significantly improved their quality of life, including enabling them to continue education, maintain employment and preserve mental wellbeing.

Discussion

These findings underscore the significant physical, emotional and social burden of living with GPP. The unpredictable, severe nature of flares not only disrupts life during episodes but creates constant fear between them. There is considerable dissatisfaction with current healthcare access and support. This highlights an urgent need for both improved treatments and better healthcare infrastructure to support GPP patients.

Nearly 100% of respondents strongly support the development of preventive treatments for GPP – "living with the fear of the next flare is almost worse than the flare itself".

Conclusions and Recommendations

- Accelerate access to treatments that both treat and prevent GPP flares to improve patients' quality of life.
- Enhance healthcare professional education regarding GPP, emphasising empathy and rapid intervention.
- Expand research into new therapies, including the long-term psychosocial effects of GPP.
- Implement streamlined referral pathways ensuring quicker access to specialist dermatology services and treatments.

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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 [ID3963]

EAG's critique of the company's response to the Draft Guidance document.

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

BAC	Best available care
CS	Company submission
EAG	External Assessment Group
GPP	Generalised pustular psoriasis
GPPGA	Generalised Pustular Psoriasis Physician Global Assessment
HCRU	Health care resource use
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
INHB	Incremental net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PAS	Patient Access Scheme
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
SEE	Structured expert elicitation
TA	Technology appraisal
UK	United Kingdom
USA	United States of America

1 INTRODUCTION

This document is the External Assessment Group's (EAG's) critique of the response by the company, Boehringer Ingelheim, to the NICE Draft Guidance Document (issue date 24 January 2025) for the technology appraisal on spesolimab for treating generalised pustular psoriasis flares [ID3963]. The EAG received the company's Draft Guidance stakeholder comments form, associated documents and post-draft guidance model on 18th February 2024.

The company's draft guidance response contains the following:

- The Draft Guidance stakeholder comments form and cited documents:
  - Three documents (one for China, one for Japan and one for the USA) provided in support of the company assumptions on hospitalisations (including inpatient or intensive care stays).
  - A UK consensus statement supported by 29 healthcare professionals with experience in treating GPP patients to validate the assumptions on hospitalisations.
  - A document containing additional cost-effectiveness estimates which incorporate the committee's preferred assumptions as set out in section 3.16 of the Draft Guidance document.
- A post-draft guidance version of the company economic model

In this report we present the following:

- Our critique of the company's response to NICE's draft guidance on spesolimab for treating generalised pustular psoriasis flares and the company's supporting evidence (Section 2)
- A validation of the results of the company's updated cost-effectiveness analysis (Section 3)
- The results of the EAG scenario analyses (Section 4)

2 CRITIQUE OF THE COMPANY'S RESPONSE TO NICE DRAFT GUIDANCE

The NICE Draft Guidance document listed the committee's preferred assumptions and requested additional analyses in section 3.16. We summarise these below (Table 1) and, where necessary, sign post the reader to sections of our critique where the company response is considered in more detail.

Table 1 Summary of Committee preferred assumptions

Committee preferred assumptions	EAG comment
Current BAC being ciclosporin and acitretin at first line (week 1). − SEE exercise used as the most appropriate source to inform the composition and costs of treatments in the BAC arm for week 1 and after week 1.	Implemented in the company post-draft guidance model. No additional discussion required.
Effisayil 1 historical cohort used to inform treatment response in the BAC arm for week 1 and after week 1.	Implemented in the company post-draft guidance model. No additional discussion required.
A second flare implemented within 12 weeks in the model to align with clinical practice based on recurrence from Effisayil 1 trial.	The company describe how a second flare is implemented in the post-draft guidance model in the company document that contains their additional cost-effectiveness estimates. However, the implementation was not correct (see section 3.1.1 of this document).
Wolf et al. (2024)[1] used to estimate spesolimab inpatient rate at 38.8%.	Implemented in the company base case and post-draft guidance model. No additional discussion required.
Use of spesolimab does not lead to no (0%) intensive care admissions.	The company sought data on intensive care admissions, but no suitable data were

Committee preferred assumptions	EAG comment
	identified. See section 2.1 of this document.
If no suitable data is found on the reduction in intensive care from spesolimab use, then a 50% relative reduction can be used as an upper bound.	As no suitable data were found, the company have used a 50% reduction of the proportion of BAC patients in ICU. No additional discussion required.
Committee requested additional analyses	
Clinical data on the inpatient and intensive care admission rates for BAC and spesolimab, ideally from UK registry data or UK real-world evidence.	The company sought data on inpatient and intensive care admissions, but no suitable data were identified. See section 2.1 of this document. Data was also sought from other countries (section 2.2).
Scenario analyses of SEE exercise to inform BAC efficacy.	The company have conducted an analysis using the SEE outcomes for 'severe' flares. See section 2.3.

Source: EAG compiled table.
BAC, best available care; ICU, intensive care unit; SEE, structured expert elicitation.

2.1 Evidence on inpatient and intensive care rates in the UK

Comment 2 of the company's Draft Guidance stakeholder comments form provides a brief overview of existing sources of evidence the company explored to ascertain whether they would provide evidence on inpatient and intensive care rates. Unfortunately, none of the sources explored by the company provide the required information. A key difficulty is an inability to identify data specifically for patients experiencing a GPP flare.

The company also presents new evidence from three other sources briefly summarised below:

- For a spesolimab GPP flare hospitalisation rate: Data as of 1 November 2024 from the ongoing open-label Effisayil REP single arm study provides some preliminary data for [redacted] patients. Of [redacted] flares experienced and treated with spesolimab, [redacted] ([redacted]

%) were classified as a serious adverse event that required or prolonged hospitalisation.

- For a BAC hospital admission rate: The company conducted their own exploratory analysis of HES data. Between April 2019 and July 2024 there were [redacted] patients admitted with a primary diagnosis of GPP. As described in the company response they aimed to remove admissions due to ongoing treatment for an existing flare. A total of [redacted] flare-related admissions were identified and of these, 73% (n=[redacted]) were inpatients.
- For BAC and spesolimab hospital admission rates: A UK consensus statement on hospital admissions is provided as a separate document. In the experience of the 29 healthcare professionals who supported the statement, approximately 80% of UK patients need inpatient care for the BAC treatment of GPP flares and have long durations of stay. The statement does not specify 'long duration' any further, in terms of numbers of days or weeks of care. The clinicians consider it reasonable to anticipate that there will be a reduction in hospital admissions with spesolimab use of at least 50%. When people treated for a GPP flare with spesolimab do require a hospital admission it is anticipated that their stay will be shorter and there will be a decreased need for high-dependency care compared to BAC. The statement does not estimate the length of stay for admitted patients in treated with spesolimab for GPP flare or the proportion of admitted patients in receipt of spesolimab for GPP flare who might need high-dependency care.

In the company's post-draft guidance model, the proportion of BAC patients treated as inpatients (77.6%) is unchanged from the company and EAG base cases because the company's exploratory analysis of HES data, which identified 73% of flare-related admissions were treated as inpatients, supports this value The proportion of spesolimab patients treated as inpatients (38.8%) which is a 50% reduction in comparison to BAC treated patients is also unchanged from the company and EAG base cases. This may be a conservative estimate because the preliminary data from the ongoing open-label single-arm Effisayil REP study found [redacted] % of [redacted] flares treated with spesolimab required or prolonged hospitalisation. The company have included a scenario for a 30% reduction in inpatient admissions with spesolimab.

In the company's post-draft guidance model, the proportion of BAC patients who require treatment in ICU has been changed to align with the value provided in section 3.13 of the draft guidance document ([redacted] %). The proportion of spesolimab patients who require

treatment in the ICU has also been changed from 0% and is now 50% reduced compared to BAC (i.e. [redacted] %). The reduction of 50% in comparison to the BAC proportion may be an underestimate as the UK consensus statement indicates that clinicians believe at least a 50% reduction is reasonable (i.e. the reduction could be greater) however we acknowledge that there is no evidence for this.

2.2 Evidence on inpatient and intensive care rates from other countries

Comment 2 and Comment 4 of the company's Draft Guidance stakeholder comments form show that the company has explored whether evidence on inpatient and intensive care rates can be obtained from databases in countries where spesolimab is in use for GPP flares. They found that no data is being captured to help inform the probability of hospitalisation or need for ICU treatment of GPP flares. The EAG is not clear how many countries have such databases.

The NICE Appraisal Committee specifically requested information on any additional insights that can be provided from data on spesolimab use in Japan. In the absence of data on hospitalisation or need for ICU treatment of GPP flares in Japan, the company have provided as a separate document a statement signed by five Japanese healthcare professionals. They all confirm that in their experience spesolimab reduces the length of inpatient hospital stay compared with other treatments and four of the five confirm that spesolimab treatment of GPP flares reduces the need for escalation of care to high dependency (e.g. ICU admission) compared with other treatments. We note that in Japan spesolimab must be administered when the patient has been admitted to hospital. No estimates of the degree to which length of stay or need for ICU admission is reduced is included in the statement.

Two other documents provide similar information from clinicians in the USA (9 dermatologists) and China (5 dermatologists, although we note that one of these is the [redacted] of the [redacted] so it is not clear if they have experience of treating adults with GPP flare). The 14 dermatologists all confirm that use of spesolimab for treating GPP flares reduces inpatient admissions by at least 50%, reduces the length of inpatient stay and reduces the need for escalation to high dependency care compared with other treatments. No estimates of the degree to which length of stay or need for ICU admission is reduced are included in the statements.

2.3 Company scenario analyses of SEE exercise to inform BAC efficacy

The company's scenario analysis using the SEE exercise to inform BAC efficacy uses the estimates from the SEE exercise for a GPPGA pustulation subscore of 0 or 1 for severe

flares only for the duration of the time horizon. Comment number 1 in the company's Draft Guidance stakeholder comments form, states that the SEE outcomes for 'severe' flares has been used for the company's scenario because of the very close agreement in disease severity between the Effisayil 1 trial patients and the clinician-assessed 'severe' flare patients in the Wolf et al. 2024 study.[1] We do not think this is appropriate. In the SEE exercise, experts elicited values for severe flares and moderate flares separately. We do not know what definition of moderate (or severe) flare the experts were working to in the SEE exercise, but we know from Figure 4 in the Structured Expert Elicitation in Generalised Pustular Psoriasis Report[2] that [redacted]. The Effisayil 1 RCT baseline data shows that for the whole trial population 81% of the 53 participants had a GPPGA total score of 3 (moderate) and 19% a score of 4 (severe). Therefore, in the post-draft guidance EAG scenario analyses we have calculated a pooled efficacy for BAC for moderate-to-severe GPP flares by weighting the SEE estimates in line with the Effisayil 1 RCT baseline GPPGA total scores (i.e. 81% moderate, 19% severe). Because we do not know what definitions the experts had for moderate and severe flares in the SEE exercise, we include the scenario analysis using the SEE outcome for severe flares only (as the company has done) and using the 45% moderate, 55% severe weighting as used in the EAG base case for ACM1.

A comparison of the company and EAG values for the efficacy of BAC is provided in Table 2.

Table 2 SEE exercise values for the efficacy of BAC

	Company response to NICE draft guidance SEE exercise, GPPGA subscore of 0 or 1, (100% severe)	ACM 1 EAG base case SEE exercise, GPPGA subscore of 0 or 1, pooled (45% moderate, 55% severe)	ACM 1 EAG Scenario SEE exercise, GPPGA subscore of 0, pooled (45% moderate, 55% severe)	Post-draft guidance EAG base case SEE exercise, GPPGA subscore of 0 or 1, Pooled (81% moderate, 19% severe)
Day 2	[redacted]	[redacted]	[redacted]	[redacted]
Day 3	[redacted]	[redacted]	[redacted]	[redacted]
Day 8	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 3	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week12	[redacted]	[redacted]	[redacted]	[redacted]

Source: EAG compiled table
EAG, External Assessment Group; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; SEE, structured expert elicitation.

2.4 Implementation of long-term mortality benefit of spesolimab

The company include calculations to estimate the long-term mortality benefit of spesolimab in an additional results document provided with the draft guidance form as follows:

- Across the 12-week time horizon, patients on spesolimab accrue [redacted] QALYs. If there were no disutility due to a GPP flare, i.e. the utility in the GPP flare health state and the resolved flare health state were equal, then the total QALYs accrued by patients in the spesolimab arm would be [redacted] QALYs. Therefore, experiencing a GPP flare reduces QALYs by [redacted].
- Patients in the resolved flare health state have a utility of [redacted]. The company assume patients experience, on average, one flare per year; thus the mean QALYs per year are estimated at [redacted] – [redacted] = [redacted].
- The company use POLARIS, a cohort study analysing longitudinal health record data, to obtain an average age and sex of patients experiencing a GPP flare in England (57 years, 66% female).[3] Based on the average general population life expectancy (ONS life expectancy calculator)[4] of a 57-year-old (84 years for males and 87 years for females), the company calculates a weighted general population life-expectancy of 29 years.
- The company then adjust for elevated mortality risk for people with a GPP flare compared with the general population. They use a hazard ratio of 1.81 (95% CI: 1.58-2.08) for all-cause mortality in GPP compared with general population controls from a Swedish case-control study reported by Ericson et al. (2023)[5] to estimate a 16-year life expectancy for people with GPP (29 / 1.81).
- The company multiplied the 16-year life expectancy by the average [redacted] QALYs per year for a GPP patient to estimate a lifetime quality adjusted life expectancy (QALE), or QALY gain per death avoided, of [redacted].
- In the company's economic model with the committee's preferred assumptions, there are an average of [redacted] and [redacted] deaths in the spesolimab and BAC arms, respectively, across the 12-week time horizon – therefore, use of spesolimab is estimated to avoid 0.01 deaths per patient treated over this time horizon. The company therefore estimated an additional long-term QALY gain for spesolimab due to avoided mortality of [redacted] (0.01 x [redacted]).
- The company report results for the scenario analyses (but not the base case) including recurrent flare and long-term mortality benefit in Table 5 of the additional results document (dated 20 February). For Scenario 1, this includes an incremental

QALY of [redacted], compared to 0.0200 in the equivalent analysis excluding the long-term mortality benefit (Table 4).

The EAG notes several problems with the above calculations:

- The adjusted life expectancy of 16 years is derived using an average age and proportion of female patients experiencing a GPP flare in England from the POLARIS study (57 years, 66% female). However, the QALYs are taken from the model, which uses the mean age and proportion female from the Effisayil 1 trial (43 years, 67.9% female). As the utilities in the model for the GPP flare and resolved flare health states are hardcoded, the EAG are unable to adjust these for different baseline characteristics.
- The company use a hazard ratio of 1.81 reported by Ericson et al. (2023). This study was not included in the original company submission, and the EAG have not critiqued this study.
- The method used to calculate life expectancy for the GPP flare population is crude, as the general population life expectancy is simply divided by a hazard ratio for mortality. The analysis also does not account for differences in the mortality hazard ratio by age, as reported by Ericson et al.
- The company have not discounted the 16-year life expectancy. Discounting is not used in the model, as the time horizon is only 12 weeks. However, extrapolating over a longer time period requires discounting at the NICE preferred rates.
- There is no age-adjustment of utilities over the life expectancy period to account for decline in quality of life due to comorbidities, as observed in the general population.
- The EAG are unable to replicate the scenario analyses results in Table 5 of the additional results document provided by the company (dated 20 February). The company has not provided a version of the model including the long-term mortality benefit calculations. It is therefore not clear how the company have used the estimated gain of [redacted] QALYs per death avoided to estimate the scenario results in Table 5.

Despite these concerns, the implementation of a long-term mortality benefit of spesolimab will only increase the QALYs for spesolimab, making spesolimab more cost-effective. The cost-effectiveness results will therefore not be sensitive to inclusion of this additional benefit.

3 VALIDATION OF THE COMPANY'S REVISED COST EFFECTIVENESS RESULTS

3.1 Company's revised base case cost-effectiveness results

The EAG reviewed the company's post-draft guidance model and have noted an issue with the implementation of recurrent flares and the proportion of patients on spesolimab in the ICU on mechanical ventilation which we describe in section 3.1.1 and section 3.1.2.

The changes from the original company base case to the company revised base case following committee draft guidance are shown in Table 3.

Table 3 Comparison of parameters that have changed from the original company model to the post-draft guidance company model

Parameter	Original company model	Post-draft guidance company model	Section in committee draft guidance
Efficacy of BAC	Effisayil 1 + Effisayil 1 historical cohort for GPPGA subscore of 0-1	Effisayil 1 historical cohort for GPPGA subscore of 0-1	Section 3.9
Proportion of patients on BAC in ICU	[redacted]	11.54%	Section 3.13
Proportion of patients on spesolimab in ICU	0%	5.77% (50% reduction of proportion of patients on BAC in ICU)	Section 3.13
Proportion of patients on spesolimab in ICU on MV	0%	[redacted]	See 3.1.2 below
Recurrent flares	Excluded	Included	Section 3.11
PAS price for spesolimab	[redacted]	[redacted]	Not applicable

Source: EAG compiled table
BAC, best available care; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; ICU, intensive care unit; MV, mechanical ventilation; PAS, Patient Access Scheme.

3.1.1 Implementation of recurrent flares

As requested by the committee, the company implemented a second flare within the 12-week time horizon to align with clinical practice based on recurrence from the Effisayil 1 trial (see draft guidance section 3.11). The company included recurrent flare QALYs in both arms by multiplying the QALYs excluding flares by the total incidence of recurrence. However, this gives rise to a higher total QALY including flares than when flares are excluded, which is not plausible. The EAG have rectified this by taking the difference in daily QALYs between a resolved health state and a GPP flare health state and considering this as a daily QALY loss when experiencing a recurrent flare. This daily QALY loss is multiplied by the total time in a GPP flare health state for both the spesolimab arm and the BAC arm to provide the total QALYs across the time horizon. We then deduct this QALY loss from the total QALYs excluding flares, to calculate total QALYs including recurrent flares. This approach is conservative, as it includes the total estimated QALY loss associated with incident recurrent flares that occur within the 12 week time horizon, including QALY loss beyond after 12 weeks for those recurrent flares that have not resolved by that time. The EAG has included a toggle in the model to switch between including/excluding flares.

3.1.2 Proportion of patients on spesolimab in the ICU on mechanical ventilation

CS Table 29 reports that for both the spesolimab and BAC arms, the proportion of patients in the ICU requiring mechanical ventilation (MV) is [redacted]. However, in the model this proportion was only applied to the BAC arm; the spesolimab arm had corresponding proportion of 0%. The EAG have updated the model to include the corrected proportion for spesolimab.

3.1.3 Results of EAG-corrected post-draft guidance company base case

The results from the EAG-corrected company post-draft guidance base case either excluding recurrent flares or including recurrent flares are shown in Table 4 and Table 5 respectively. In both cases the results include the updated PAS for spesolimab. The results from the company scenarios using the EAG-corrected company post-draft guidance base case including recurrent flares and use of MV in ICU in both arms, and using an updated PAS for spesolimab are shown in Table 6. As the majority of incremental cost-effectiveness ratios are negative (spesolimab dominates BAC), we report results using Incremental Net Health Benefits (INHB) at thresholds of £20,000 and £30,000 per QALY gained, as noted in the NICE reference manual.

Table 4 EAG-corrected company post-draft guidance base case excluding recurrent flares using updated PAS for spesolimab

Treatment	Total		Incremental		ICER (£/QALY)	INHB	
	Cost (£)	QALYs	Cost (£)	QALYs		£20,000	£30,000
BAC	[redacted]	[redacted]			Spesolimab dominates	[redacted]	[redacted]
Spesolimab	[redacted]	[redacted]	[redacted]	[redacted]			

BAC, best available care; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit.

Table 5 EAG-corrected company post-draft guidance base case including recurrent flares using updated PAS for spesolimab

Treatment	Total		Incremental		ICER (£/QALY)	INHB	
	Cost (£)	QALYs	Cost (£)	QALYs		£20,000	£30,000
BAC	[redacted]	[redacted]			Spesolimab dominates	[redacted]	[redacted]
Spesolimab	[redacted]	[redacted]	[redacted]	[redacted]			

BAC, best available care; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit.

Table 6 Company scenarios on EAG-corrected company post-draft guidance base case including recurrent flares and using updated PAS for spesolimab

Scenario	Incremental		ICER (£/QALY)	INHB	
	Costs	QALYs		£20k	£30k
Treatment of recurrent flares different to initial flare: BAC	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
Treatment of recurrent flares different to initial flare: spesolimab	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
12.37% of patients in both arms with active flare at end of time horizon	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
30% reduction in inpatients admissions: spesolimab	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
30% reduction in ICU admissions: spesolimab	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]

Scenario	Incremental		ICER (£/QALY)	INHB	
	Costs	QALYs		£20k	£30k
Efficacy of BAC: SEE exercise (severe flares)	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
Proportion of inpatients on BAC based on literature (most severe flares)	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
Length of stay for ICU with mechanical ventilation: not capped	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]

BAC, best available care; ICU, intensive care unit; INHB, incremental net health benefit; QALY, quality adjusted life year; SEE, structured expert elicitation.

4 EAG ANALYSES

4.1 EAG scenarios on the EAG-corrected post-draft guidance company base case

The EAG have no preferred changes to the EAG corrected post-draft guidance company base case. To test the uncertainties in the model, we have conducted further scenario analyses, presented in Table 7 below. Spesolimab dominates best available care in all but two scenarios: using a 0% reduction in the proportion of inpatients on spesolimab, which results in an ICER of [redacted] per QALY, and using a 5% reduction in the proportion of inpatients on spesolimab, which results in an ICER of [redacted] per QALY.

Table 7 EAG scenarios on EAG-corrected post-draft guidance company base case

Scenario	Incremental		ICER (£/QALY)	INHB	
	Costs	QALYs		£20k	£30k
EAG corrected post-DG company base case	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
Model assumptions					
12.37% of patients in BAC arm with active flare by end of time horizon	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
5.7% of patients in spesolimab arm with active flare by end of time horizon	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
12.37% of patients in spesolimab arm with active flare by end of time horizon	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
20% of patients in spesolimab arm with active flare by end of time horizon	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
Comparator costs					
Cost of ciclosporin: £48.50 (NICE requested scenario)	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
Efficacy of BAC: GPPGA pustulation subscore of 0 or 1					
Effisayil 1 trial (first week) + Effisayil 1 historical cohort	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
Effisayil 1 trial (first week) + SEE exercise (81%/19%)	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]

Scenario	Incremental		ICER (£/QALY)	INHB	
	Costs	QALYs		£20k	£30k
SEE exercise (45% moderate/55% severe)	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
SEE exercise (81% moderate/19% severe)	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
Efficacy of BAC: GPPGA pustulation subscore of 0					
SEE exercise (81% moderate/19% severe)	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
Effisayil 1 trial (first week) + SEE exercise (81%/19%)	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
Proportion of inpatients on spesolimab					
77.6% (0% reduction)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
73.7% (5% reduction)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
69.84% (10% reduction)	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
62.08% (20% reduction)	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
54.32% (30% reduction)	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
Proportion of inpatients treated in the ICU on spesolimab					
0%	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
5%	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
10%	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
15%	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	Spesolimab dominates	[redacted]	[redacted]

BAC, best available care; DG, draft guidance; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; INHB, incremental net health benefit; QALY, quality adjusted life year; SEE, structured expert elicitation.

5 EAG CONCLUSION

The committee's preferred assumptions for this topic were set out in the NICE Draft Guidance document as summarised in Table 1. The company revised their base case following draft guidance as discussed in section 2. We identified issues with the implementation of recurrent flares and the proportion of ICU patients in the spesolimab arm on mechanical ventilation in the company's post-draft guidance model, which we have corrected. Using the EAG-corrected post-draft guidance company base case model and the company's updated PAS, spesolimab dominates best available care when both including and excluding recurrent flares. Spesolimab dominated in all the company scenarios when run on the EAG-corrected company post-draft guidance model.

Spesolimab continued to dominate best available care in all but two of the EAG scenarios run on the EAG-corrected post-draft guidance company base: when there is a 0% reduction in the proportion of inpatients on spesolimab, the ICER is [redacted] per QALY; and with a 5% reduction in the proportion of inpatients on spesolimab, the ICER is [redacted] per QALY.

We note that the company reported an analysis including long-term benefits of the lower modelled mortality in the spesolimab arm. The EAG consider that there are serious flaws in the implementation of this analysis and we could not replicate the results. However, inclusion of a long-term mortality benefit will increase estimated QALYs for spesolimab, so will not change the cost-effectiveness conclusions.

6 REFERENCES

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