Spesolimab for treating generalised pustular psoriasis flares [ID3963]

Technology appraisal committee B [12 December 2024]

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Spesolimab for treating generalised pustular psoriasis flares

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on generalised pustular psoriasis and flares

Diagnosis and classification

- GPP is historically considered a variant of psoriasis but is phenotypically, genetically, immunologically and histopathologically distinct from plaque psoriasis

Epidemiology

- Incidence rates in England for GPP was 0.25 (95% CI 0.21–0.28) per 100 000 person-years
- Mortality rate due to GPP or associated treatment varies from 2%[a] to 16%[b]
- Estimated global prevalence of 1–9 cases per million persons

Symptoms and prognosis

- Fever, swelling, joint pain and fatigue
- Skin has pustules, pain, itching, scaling, redness, dryness and burning
- GPP has no cure and can be relapsing or persistent

GPP Flares

- can be life-threatening and requires emergency treatment 2%[a] to 16%[b]
- develops rapidly, affecting large areas of the body. Pus-filled blisters can merge and are associated with itching, pain and scaling

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Abbreviations: CI, confidence interval; GPP, generalised pustular psoriasis

Patient perspectives

Submissions from

- **British Association of Dermatologists**
- **Psoriasis Association**
- **Psoriatic Arthritis Alliance**

- There are no licensed therapeutic interventions with proven efficacy for GPP
- GPP flares are unpredictable, painful and incapacitating
- GPP flare is associated with severe systemic features, often requiring hospital admission and organ support in an intensive care setting
- The unpredictable nature of GPP further compounds the long-term psychological impact of the disease
- The appearance of GPP, which is very different to plaque psoriasis can lead to misdiagnosis, leaving people affected frustrated
- GPP impacts all aspects of people's lives including their relationships.

"I can't work, I can barely leave my house. I find it hard to cope outside my home environment ".

"It's demoralising and dictates your life down to how you feel with the pain, the clothes you wear, how people look at you, restricts everything you do"

"I'm in severe pain. I have to plan my days as to what work I can do. I wish I could reduce hours as there are days I feel I cannot get out of bed, but finances do not allow.

Abbreviations: BAD, British Association of Dermatologists; GPP, generalised pustular psoriasis; PAPAA, Psoriasis and Psoriatic Arthritis Alliance; PiP, personal independence payment

Clinical perspectives

Submissions from British Association of Dermatologists

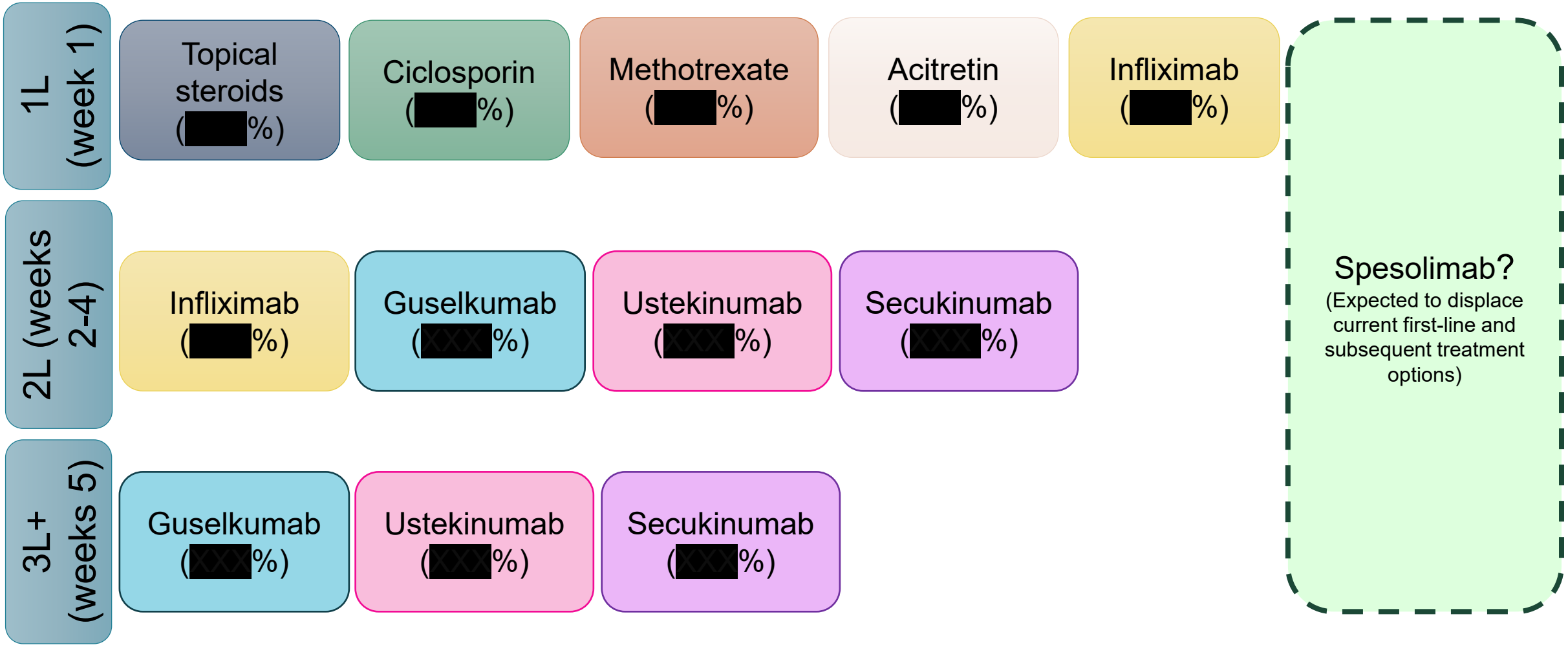
- Generalised pustular psoriasis is a rare disease associated with a substantial health and psychological burden
- Spesolimab is the first targeted and effective intervention specifically developed for managing acute GPP, addressing its key pathological drivers
- Clinically meaningful improvements in GPP include GPPGA/GPPASI scores of 0 or 1, resolution of skin pain, systemic symptoms, and fever, as well as a global assessment of at least mild.
- Adoption of spesolimab in NHS care is likely to reduce hospital stays, complications, flares, mortality, and follow-ups while alleviating the psychological burden of the disease

Abbreviations: GPP, generalised pustular psoriasis; GPPGA , Generalised Pustular Psoriasis Physician Global Assessment; GPPASI, Generalised Pustular Psoriasis Physician Global Assessment

Equality considerations

- No issues raised at scoping stage, or by patient or professional groups
- Previous technology appraisal (TA986) in skin conditions have noted that some disease measuring scores can underestimate severity in people with darker skin tones as ‘redness’ of skin is used to detect severity, and it was also used as part of the eligibility criteria

Treatment pathway for GPP flares



- Which treatments reasonably reflect the standard of care for moderate-to-severe GPP flares in the NHS?

Abbreviations: 1L, first-line; 2L, second-line; 3L+, third- or later-line; GPP, generalised pustular psoriasis

Spesolimab (Spevigo, Boehringer Ingelheim)

Marketing authorisation	• Spesolimab is indicated for the treatment of flares in adult patients with GPP as monotherapy • CMA from MHRA in July 2023 via the EC Decision Reliance Procedure. • Data on treatment of subsequent flares was not considered comprehensive. An additional open-label, single-arm post-authorisation study on the treatment of repeated flares with spesolimab is ongoing to comply with the CMA.
Mechanism of action	• Spesolimab is a humanised monoclonal IgG1 antibody that blocks IL-36R signalling. By binding to IL-36R, spesolimab prevents its activation by ligands (IL-36 α, β, γ) and stops downstream pro-inflammatory pathways.
Administration	• Intravenous infusion • Single dose of 900 mg (two vials of 450 mg) • If flare symptoms persist, an additional 900 mg dose may be administered 1 week after the initial dose.
Price	• £15,000 for 900 mg (two vials of 450 mg) • Average cost of a course of treatment: £20,265 • Confidential PAS discount in place

Abbreviations: CMA, conditional marketing authorisation; EC, European Commission; GPP, generalised pustular psoriasis; IL, interleukin; IL-36R, interleukin 36 receptor; MHRA, Medicines and Healthcare Products Regulatory Agency

Key issues

Issue	ICER impact
Clinical Effectiveness	
Trial evidence is from a narrower population	Unknown
Generalisability of Effisayil 1 trial to the NHS	Unknown
Use of Effisayil 1 historical to inform treatment response after week 1	Large
What is the right comparator?	Unknown
Cost Effectiveness	
Treatment response: the modelling of BAC efficacy in week 1	Large
Short time horizon and 2nd GPP flares not implemented	Large
Proportion of patients treated as inpatients in the spesolimab arm	Large

Abbreviations: BAC, best available care; GPP, generalised pustular psoriasis

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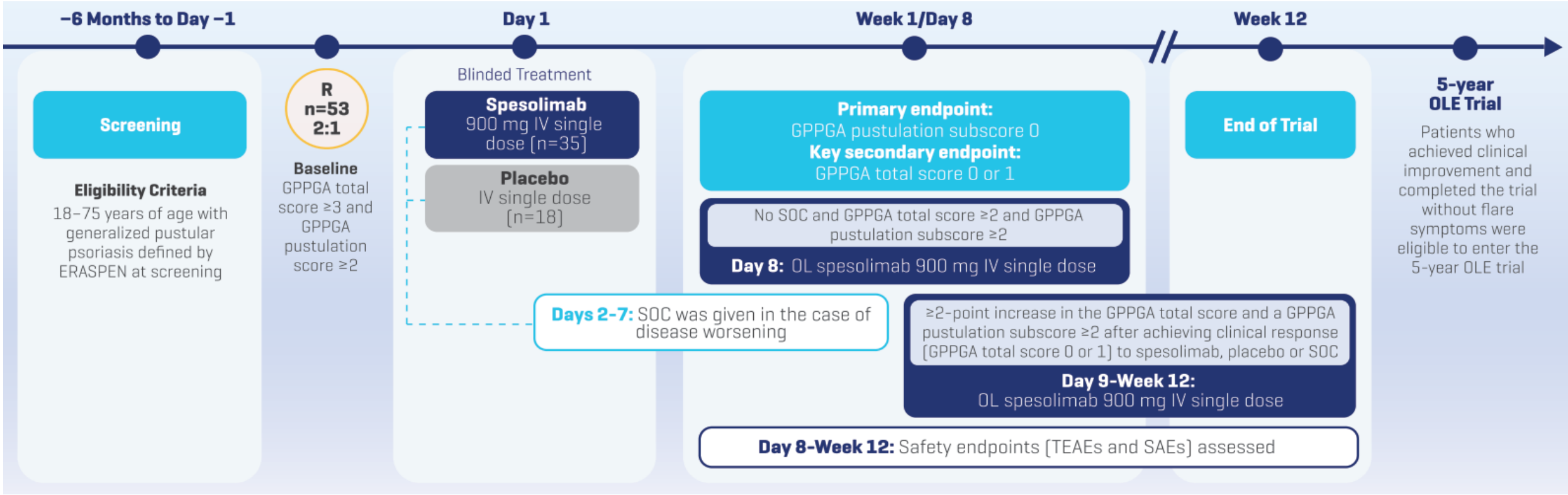
Key clinical trial Effisayil 1 (n=53)

Design	Multi-centre, randomised, double-blind phase II study
Population	• GPPGA score of at least 3 (moderate) • Presence of fresh pustules (new appearance or worsening of existing pustules) • GPPGA pustulation sub score of at least 2 (mild) • At least 5% of body surface area covered with erythema (redness of skin or mucous membranes) and presence of pustules
Intervention	Spesolimab
Comparator(s)	Placebo
Duration	12 weeks
Primary outcome	GPPGA pustulation subscore of 0 at week 1
Key secondary outcomes	GPPGA total score of 0 or 1 at week 1
Exploratory endpoints	GPPASI score, pain VAS, PSS and FACIT-Fatigue
Locations	Europe, North America, North Africa, and Asia
Outcome used in model	GPPGA pustular subscore of 0 or 1 (represents flare resolution)

More details on GPPGA scoring in appendix

Abbreviations: ERASPEN, European Rare And Severe Psoriasis Expert Network; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue Scale; GPP, GPP, generalised pustular psoriasis; GPPGA , Generalised Pustular Psoriasis Physician Global Assessment; GPPASI, Generalised Pustular Psoriasis Physician Global Assessment; PSS, Psoriasis Symptom Scale; VAS, Visual Analogue Scale

Effisayil 1 Trial design



Four post-hoc groups where the original randomised ITT set is split
Patients randomised to spesolimab who received,
• either 1 dose (day1) or 2 doses (day 1 and day 8), n=35
• 1 dose (day 1), n=23
• 2 doses (day 1 and day 8), n=12
Patients randomised to placebo who received
• spesolimab (day 8), n=15

Abbreviations: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; IV, intravenous infusion; OL, open-label; OLE, open-label extension; SD, single dose; SoC, standard of care.

Proportion who achieved GPPGA pustulation subscore of 0 or 1 at week 1

Spesolimab is more effective than placebo at all endpoints

- Spesolimab: GPPGA pustulation subscore of 0 or 1 observed at day 2 in n=13; at day 3 in n=19; day 8 in n= 22
- Proportion of patients who achieved a GPPGA subscore score of 0 or 1 (clear or almost clear skin) was higher in the spesolimab arm compared with the placebo arm

	Spesolimab (N=35)	Placebo (N=18)
GPPGA subscore score of 0 or 1, n/N (%) at week 1	20/35 (57.1%)	2/18 (11.1%)
Risk difference percentage points	46.0	

Risk difference percentage points: difference between the risk of an outcome in the exposed group and the unexposed group, expressed as a percentage.

This is the outcome that was used in economic model

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

Other key secondary outcomes

Time to first achievement of a GPPGA total score of 0 or 1

- Onset of skin clearance was rapid and started as early as day 3 in 2 patients and day 8 in 17 patients. 88% reached GPPGA total score of 0 to 1 (clear or almost clear skin) with a single dose of spesolimab achieved this by week 1 (day 8).

Median score change from baseline at week 1 (in pain VAS, FACIT-Fatigue, DLQI, PSS)

- **Using median score change** the spesolimab group [redacted] MCID for the pain VAS score (a [redacted] points, MCID is a decrease of =>30 points), and that the placebo group [redacted] MCID for the PSS score. Thus, the median score change from baseline is more conservative than the mean score change.
- **Using mean score change** spesolimab treatment resulted in improvements in PROs from baseline. The mean score change from baseline were all above the MCID thresholds for each PRO by week 1 in the spesolimab arm.

EQ-5D

- By week 1, the group initially randomised to spesolimab achieved an EQ-5D median score change from baseline [redacted], surpassing the [redacted]

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More details on total GPPGA score and EQ-5D

Abbreviations: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; ITT, intention-to-treat; PROs, patient reported outcomes.

Key issue: Trial evidence is from a narrower population

Background – more details appendix

- Effisayil 1 trial enrolled adult patients with GPP with flares of moderate-to-severe intensity
- Decision problem and NICE scope define the population for this appraisal as "*Adult patients with generalised pustular psoriasis presenting with flares*"
- GPPGA pustulation subscore of 0 or 1 is used in the model to represent flare resolution

Company

- Effisayil 1 trial provided evidence fully relevant to this technology appraisal and informed treatment effectiveness in the economic model

EAG comments

- Patient cohort that start in the economic model are in the moderate-to-severe flare health state
- Unclear whether the model results can be generalisable to patients experiencing mild flares as the population from studies informing the economic model is mainly a moderate-to-severe flare population

- Which patients are expected to receive spesolimab in clinical practice?
- Is there any potential for differences in spesolimab efficacy for mild flares in comparison to moderate-to-severe flares?
- Does the use of a GPPGA pustulation subscore of 0 or 1 appropriately reflect the resolution of a flare?
- Is the GPPGA pustulation score used and understood in the NHS?
- Is there potential for the GPPGA pustulation subscore to underestimate severity in people with darker skin?
- Would treatment be differentiated based on GPP flare intensity?

Abbreviations: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment

Key issue: Generalisability of Effisayil 1 Trial to NHS (1/2)

Background

- Trial included a high proportion (55%) who were Asian as 51% were at sites in Asia, compared to only 30% from Europe (France, Germany and Switzerland) with no sites in the UK
- Proportionally more Asian people in the placebo arm (72%) compared to the spesolimab arm (46%)
- Spesolimab arm showed slightly worse GPPASI and GPPGA pustulation scores, with a higher proportion of patients experiencing fever
- Limited data on prognostic factors for flare severity and duration make it unclear whether all relevant baseline factors were assessed
- Characteristics do not seem to be balanced between trial arms (baseline characteristics)

Abbreviations: GPP, Generalised Pustular Psoriasis; GPPASI, Psoriasis Area and Severity Index for Generalised Pustular Psoriasis, ; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment

Key issue: Generalisability of Effisayil 1 Trial to NHS (2/2)

Company

- Effisayil 1 is the only randomised trial for spesolimab
- Experts considered patient population of Effisayil 1 trial were representative, but noted some demographic differences in race and gender
- Differences are not reported prognostic factors
- Pre-planned sensitivity and subgroup analyses showed no difference in treatment effect based on race, gender or other demographic and clinical characteristics

EAG comments

- Effisayil 1 trial population may not be representative of UK patients
- Unable to obtain expert opinion to verify whether the baseline characteristics of the Effisayil 1 trial population are similar to GPP patients experiencing flares in England
- [redacted]

- Are the baseline characteristics of the Effisayil 1 trial population similar to GPP patients experiencing flares in the NHS?
- Are race and age prognostic characteristics?

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Abbreviations: GPP, Generalised Pustular Psoriasis; GPPASI, Psoriasis Area and Severity Index for Generalised Pustular Psoriasis, ; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment

Key issue: What is the right comparator?

Background

- Decision problem and NICE scope define comparator as established clinical management without spesolimab
- Comparator arm in Effisayil 1 received placebo only for first week of trial (prior to randomisation, patients discontinued biologic therapies, systemic non-biological therapies and other treatments such as phototherapy and topical treatments)
- No comparative evidence beyond week 1
- Comparator in economic model not fully aligned with NICE scope and company decision problem

Company

- No alternative source of comparative trial evidence for spesolimab where the comparator is established clinical management without spesolimab

EAG comments

- No direct comparative effectiveness evidence from the company's trial for spesolimab versus established clinical management without spesolimab
- Used active treatments from SEE exercise applied from day 1 until end of time horizon
- Active treatments included Topical steroids, Ciclosporin, Methotrexate, Acitretin, Infliximab, Guselkumab, Ustenkinumab and Secukinumab

- What is the appropriate comparator for Spesolimab?

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Abbreviations: BAC, best available care; SEE, structured expert elicitation

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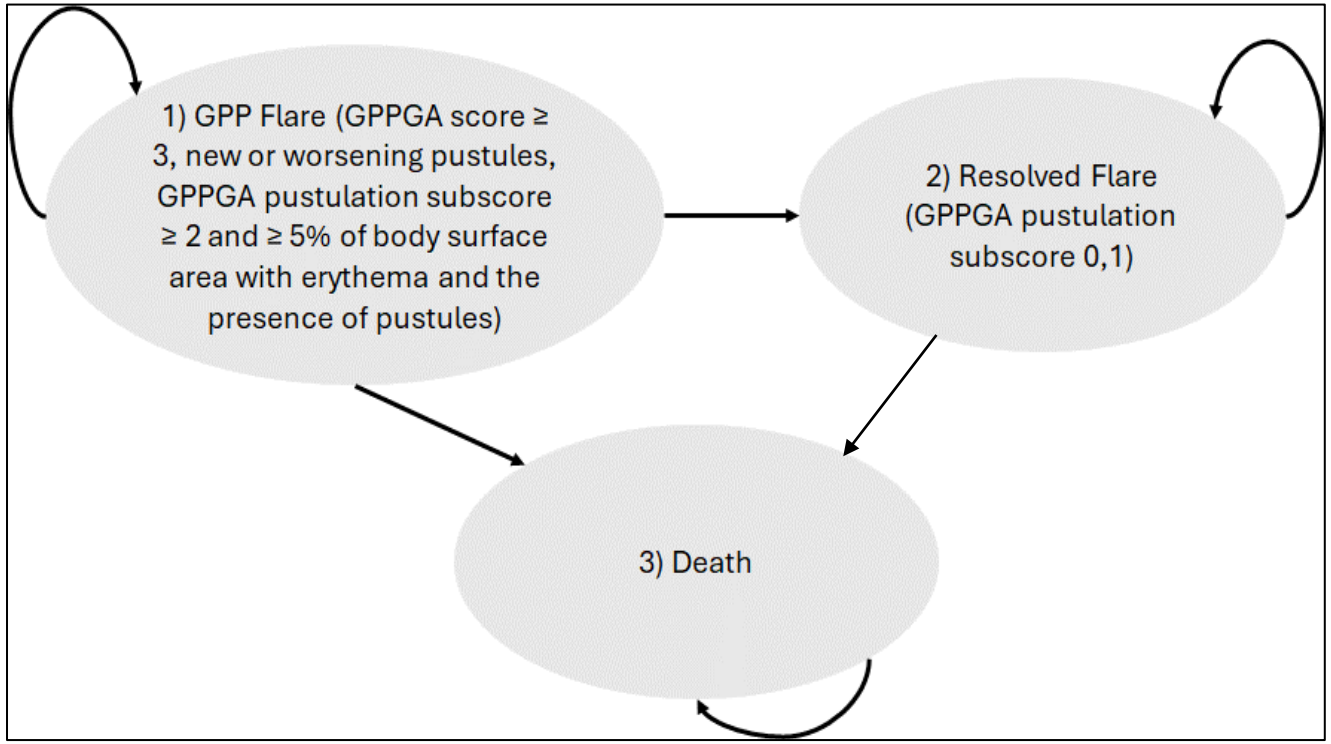
Company's model overview

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



Model features:
Time horizon: 12 weeks
Cycle length: daily

Note: No comparative evidence beyond week 1 and company uses data from Effisayil 1 historical cohort to inform cost-effectiveness modelling of comparator arm beyond week 1

Further details on variables applied in economic model and key model inputs

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Abbreviations: BAC, best available care; GPP, generalised pustular psoriasis; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment.

Key issue: Use of Effisayil 1 historical cohort to inform treatment response after week 1 (1/2)

Background

- Beyond week 1 the historical cohort (n=53) was used to inform the model
- Effisayil 1 historical cohort uses same cohort of as Effisayil 1 trial and provides data on the characteristics and clinical course of past GPP flares
- Treatments in BAC arm of company's model beyond week 1 obtained from SEE exercise
- Historical cohort lacked GPPGA pustulation subscore data (0 or 1), using time to pustular clearance as a proxy, raising concerns about appropriateness
- No standard definition for typical, most severe and longest flares, based on investigator interpretation
- Company used patient demographic and flare data from POLARIS and SCRIPTOR RWE to assess representativeness of historical cohort for GPP population in England, cautioning against cross-source comparisons due to differing definitions and methods
- Patients with incident GPP in POLARIS study (mean age 57.3, SD 19.0) and [redacted]
- Ethnic distributions varied between POLARIS, SCRIPTOR and Effisayil 1 trial due to locations
- Comparisons for other characteristics were limited by missing or inconsistently reported data

Abbreviations: GPP, Generalised Pustular Psoriasis; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; RWE, real-world evidence; SEE, structured expert elicitation

Key issue: Use of Effisayil 1 historical cohort to inform treatment response after week 1 (2/2)

Company

- Response to BAC not obtained from Effisayil 1 trial because crossover occurred for more than 80% of patients in placebo arm, who received spesolimab on day 8
- SEE appropriate proxy as provides relevant data to inform model for efficacy of BAC since estimates elicited related to the BAC as seen in experts' practice, therefore relevant to NHS
- Details on company base case and scenario analysis

EAG comments

- Do not use Effisayil 1 historical cohort for BAC efficacy in base case and use SEE exercise
- SEE is lower quality evidence source compared to RWE for estimating BAC efficacy
- Explore assumption of using SEE exercise and Effisayil 1 trial for GPPGA subscore of 0 or 1 in alternative scenarios
- Use of biologic treatments in Effisayil 1 historical cohort, seems lower than might be expected in NHS
- Concerns about how well flares and treatments received for flares represent current BAC in England

- What is the best source for efficacy after week 1?
- Are the baseline characteristics of the Effisayil 1 historical cohort population similar to GPP patients experiencing flares in England?

Abbreviations: BAC, best available care; GPP, Generalised Pustular Psoriasis; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; RWE, real-world evidence

Key issue: Treatment response: the modelling of BAC efficacy in week 1

Background

- For first week of model, treatment response to BAC obtained from the Effisayil 1 trial
- Patients in placebo arm of Effisayil 1 trial do not receive any SoC treatments
- Economic model assumes patients in comparator arm receive no treatment during first week
- Clinical effectiveness evidence for comparator arm in first week of trial and model may not align with clinical practice

Company

- Effisayil 1 trial provides direct intervention vs. comparator comparison
- Effisayil 1 is only randomised trial for spesolimab, patients could receive OL spesolimab day 8, so comparative data is only available for first week
- First week of economic model mirrors Effisayil 1, using placebo arm data to inform BAC

EAG comments – more detail appendix

- Using data from Effisayil 1 trial to inform efficacy of BAC for week 1 of model is appropriate, as it provides a direct comparison between intervention and comparator, but may not reflect UK reality
- Prefers to model using SEE instead of trial
- Uncertain on how relative efficacy of spesolimab may change if patients receive any SoC treatments

- What is the likely impact on flare symptoms when a patient does not receive any pharmacological treatment for a week?
- What is the best source to inform the efficacy of the comparator arm in week 1?

Abbreviations: BAC, best available care; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; OL, open-label; SEE, Structured expert elicitation; SoC, standard of care

Key issue: Short time horizon and 2nd GPP flares not implemented

Background

- In company model, all patients assumed to respond (spesolimab or BAC) by week 12, (follow up period in trial) and company did not include second flares
- Effisayil 1 historical cohort: 12% of patients have not responded in 12 weeks
- Effisayil 1 trial: 25 people at week 12 had a GPPGA pustulation subscore of either 0 (n=21) or 1 (n=4) and remaining 10 had received escape therapy so no information on their week 12 GPPGA pustulation subscore
- Effisayil 1: 11.3% of patients received rescue treatment with spesolimab to treat 2nd flares, and 8 received a SoC escape treatment after day 8 (more detail appendix)

Company

- Clinicians validated assumption that patients are assumed to respond by week 12
- Evidence on flare frequency shows patients are unlikely to have more than two flares per year
- Currently no early results available from Effisayil ON to inform a scenario analysis for a longer time horizon

EAG comments

- Relevant evidence for model is only available for 12 weeks, making a longer time horizon difficult to model
- Treating one flare with spesolimab may impact the efficacy and safety of later treatments, beyond 12 weeks
- Evidence shows it is unlikely patients have more than two flares per year, that does not mean that patients cannot have two flares in a 12-week period

- Is it clinically reasonable to assume that all patients have responded to treatment (both to spesolimab and to BAC) by week 12, in the model?
- How likely is a second GPP flare to occur and is a second flare the same as a recurrent flare?

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Abbreviations: BAC, best available care; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; SoC, standard of care

Key issue: Proportion of patients treated as inpatients in the spesolimab arm

Background

- Reduction in active flares in spesolimab arm decreases hospitalisation rates, as model assumes resolved flares eliminate hospitalisation risk
- BAC arm inpatient rate was based on Wolf et al., with 77.6% of patients treated as inpatients

Company

- Assumed a reduced inpatient rate of 38.8%, based on a 48.4% relative reduction in active flare rates (GPPGA pustulation subscore >1) for spesolimab vs. placebo in Effisayil 1 trial
- Clinical advice: due to rapid onset of action, use of spesolimab would lead to a significant reduction in inpatient admissions
- Patients receiving spesolimab will not require ICU admission due to spesolimab's rapid onset of action

EAG comments

- Inpatient rate significantly impact the ICER
- Company's assumption of reduced hospitalisation rate may be optimistic given current lack of data
- Uncertain if spesolimab has additional benefits in reducing hospitalisation for patients who do not respond and continue to have active flares; there is no supporting evidence for such an effect
- Explored the uncertainty around this assumption by conducting alternative scenario analyses

- Has a benefit of reduced inpatient admissions from the use of spesolimab on active flares been observed in clinical practice?

Abbreviations: BAC, best available care; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment

Company and EAG base case assumptions/scenario analyses

Assumption	Company base case and scenarios	EAG base case and scenarios
Comparators (week 1)	• **Base case**: Effisayil 1 trial	• **Base case**: SEE exercise (GPPGA subscore of 0 or 1), active treatments from SEE exercise applied from day 1 until the end of the time horizon • **Scenario 1**: Effisayil 1 trial
Comparators (after week 1)	• **Base case**: SEE exercise	
Efficacy of BAC (week 1)	• **Base case**: Effisayil 1 trial (GPPGA subscore of 0 or 1) • **Scenario 1**: Effisayil 1 historical cohort (GPPGA subscore of 0 or 1)	• **Base case**: SEE exercise (GPPGA subscore of 0 or 1), estimates with treatment response from day 1 until the end of the time horizon • **Scenario 1**: Effisayil 1 trial (GPPGA subscore of 0 or 1) • **Scenario 2**: SEE exercise (GPPGA subscore of 0) • **Scenario 3**: Effisayil 1 trial (GPPGA subscore of 0)
Efficacy of BAC (after week 1)	• **Base case**: Effisayil 1 historical cohort (GPPGA subscore of 0 or 1) • **Scenario 1**: Effisayil 1 historical cohort (GPPGA subscore of 0 or 1)	• **Base case**: SEE exercise (GPPGA subscore of 0 or 1) • **Scenario 1**: SEE exercise (GPPGA subscore of 0 or 1) • **Scenario 2**: SEE exercise (GPPGA subscore of 0) • **Scenario 3**: SEE exercise (GPPGA subscore of 0)

Link to details of alternative scenarios

Abbreviations: BAC, best available care; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; SEE, Structured Expert Elicitation

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

EAG scenarios on EAG corrected company base case using PAS for spesolimab (1/2)

No.	Scenario (applied to company base case)	Impact on ICER
1	**Company base case**	See part 2
2	12.37% of patients in BAC arm with active flare by end of time horizon	↓ Decrease
3	5.7% of patients in spesolimab arm with active flare by end of time horizon	↑ Increase
4	12.37% of patients in spesolimab arm with active flare by end of time horizon	↑ Increase
5	20% of patients in spesolimab arm with active flare by end of time horizon	↑ Increase
	Comparator costs	
6	Cost of ciclosporin: £48.50 (NICE requested scenario)	↔ Equal
	Efficacy of BAC: GPPGA pustulation subscore of 0 or 1	
7	Effisayil 1 historical cohort	↑ Increase
8	Effisayil 1 trial (first week) + SEE exercise	↑ Increase

Results do not include confidential commercial discounts for comparators

Abbreviations: BAC, best available care; GPPGA, generalised pustular psoriasis global assessment; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life-year; SEE, Structured Expert Elicitation

EAG scenarios on EAG corrected company base case using PAS for spesolimab (2/2)

No.	Scenario (applied to company base case)	Impact on ICER
	Company base case	See part 2
	Efficacy of BAC: GPPGA pustulation subscore of 0	
9	SEE exercise	↑ Increase
10	Effisayil 1 trial (first week) + SEE exercise	↑ Increase
	Proportion of inpatients on spesolimab	
11	77.6% (0% reduction)	↑ Increase
12	69.84% (10% reduction)	↑ Increase
13	62.08% (20% reduction)	↑ Increase
14	54.32% (30% reduction)	↑ Increase
	Proportion of inpatients treated in the ICU on spesolimab	
15	**5%**	↑ Increase
16	10%	↑ Increase
17	15%	↑ Increase
18	[redacted]	↑ Increase

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Results do not include confidential commercial discounts for comparators

Abbreviations: BAC, best available care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme, QALY, quality adjusted life-year; SEE, Structured Expert Elicitation

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Managed access and innovation

- Company has not made a proposal for managed access but have carried out a feasibility assessment which concluded that current UK data sources do not allow use of routinely collected data to reduce uncertainties and do not have appropriate processes in place to establish new data collection based on existing procedures

- Uncaptured benefits or innovation considerations

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Key issues

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What is the right comparator?	Unknown
Cost Effectiveness	
Treatment response: the modelling of BAC efficacy in week 1	Large
Short time horizon and 2nd GPP flares not implemented	Large
Proportion of patients treated as inpatients in the spesolimab arm	Large

Abbreviations: BAC, best available care; GPP, generalised pustular psoriasis

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Supplementary appendix

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Decision problem (1/2)

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	Adult patients with generalised pustular psoriasis presenting with flares	Adult patients with generalised pustular psoriasis presenting with flares	Clinical evidence is therefore drawn from a narrower population than defined in the NICE scope and the company's decision problem as the company's pivotal trial, Effisayil 1, only included adult patients with GPP experiencing moderate-to-severe intensity flares
Intervention	Spesolimab	Spesolimab	The intervention matches the NICE scope and in the pivotal Effisayil 1 trial, the licensed dose of spesolimab was used.

Decision problem (2/2)

	Final scope	Company	EAG comments
Comparators	Established clinical management without spesolimab which may include: Systemic non-biological therapies such as ciclosporin Biological therapies (such as TNF-alpha inhibitors, IL-17 and IL-23 family inhibitors)	Established clinical management without spesolimab	EAG note that the comparator in the economic model is not fully aligned with the NICE scope and company definition of the decision problem
Outcomes	The outcome measures to be considered include: • Symptoms specific to GPP including pain • Severity of flares • Mortality • Response rate • Duration of response • Relapse rate • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Symptoms specific to GPP including pain • Severity of flares • Mortality • Response rate • Duration of response • Relapse rate • Adverse effects of treatment • Health-related quality of life	The outcomes listed by the company match those in the NICE scope and the majority are clearly reported in the CS. An exception is duration of response for which there is limited data due to the length of the Effisayil 1 trial (response was still ongoing for a proportion of patients at the end of this 12-week study).

Abbreviations: CS, company submission; GPP, Generalised Pustular Psoriasis; IL-17, interleukin-17; IL-23, interleukin-23; TNF, tumour necrosis factor.

Scoring for the GPPGA

Score	Erythema	Pustules	Scaling
0 (clear)	Normal or post-inflammatory hyperpigmentation	No visible pustules	No scaling or crusting
1 (almost clear)	Faint, diffuse pink, or slight red	Low-density occasional small discrete pustules (noncoalescent)	Superficial focal scaling or crusting restricted to periphery of lesions
2 (mild)	Light red	Moderate-density groups discrete small pustules (noncoalescent)	Predominantly fine scaling or crusting
3 (moderate)	Bright red	High-density pustules with some coalescence	Moderate scaling or crusting covering most or all lesions
4 (severe)	Deep fiery red	Very-high-density pustules with pustular lakes	Severe scaling or crusting covering most or all lesions

Each component is graded separately and then the average composite mean score is used to produce a total GPPGA score

Mean composite score	Total GPPGA score	Description
0	0	Clear
> 0 to < 1.5	1	Almost clear
≥ 1.5 to 2.5	2	Mild
≥ 2.5 to 3.5	3	Moderate
≥ 3.5	4	Severe

NICE

Link to Key clinical trial slide

Abbreviations: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; GPPASI, Generalised Pustular Psoriasis Area and Severity Index.

Key secondary outcome: GPPGA total score 0 or 1 at week 1 and results of post-hoc sensitivity analysis

Proportion of patients who achieved a GPPGA total score of 0 or 1 (clear or almost clear skin) was higher in the spesolimab arm compared with the placebo arm, leading to a risk difference of 31.7 percentage points (95% CI: 2, 53; p-value=0.02)

Key secondary outcome	Spesolimab (N=35)	Placebo (N=18)
GPPGA total score of 0 or 1, n/N (%) at week 1	15/35 (42.9%)	2/18 (11.1%)
Risk difference percentage points (95% CI), p-value	31.7 (2.2 to 52.7), p<0.02	
Post-hoc sensitivity analyses of key secondary outcome[a]		

	Spesolimab	**Placebo**	**Spesolimab**	**Placebo**
Sex	**Female**		**Male**	
Responders/total patients	10/21	2/15	5/14	0/3
Adjusted risk difference percentage points (95% CI), p-value for treatment difference	34.6 (11.3 to 57.9), p=0.005			
Race	**Asian**		**White**	
Responders/total patients	8/16	2/13	7/19	0/5
Adjusted risk difference percentage points (95% CI), p-value for treatment difference	35.4 (12.5 to 58.3), p=0.004			

Baseline GPPASI value	
Adjusted risk difference percentage points (95% CI), p-value for treatment difference	29.7 (5.8, 53.5), p=0.018

NICE

Link to Other key secondary outcomes slide

Abbreviations: CI, confidence interval; GPPASI, Generalised Pustular Psoriasis Area and Severity Index; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment

EQ-5D

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

- By week 1, the group initially randomised to spesolimab achieved an EQ-5D median score change from baseline [redacted], surpassing the [redacted]
- Exploratory analyses of the EQ-5D health index indicated a general trend of improved quality of life in the week following spesolimab treatment, as shown in the figure; however, these improvements were inconsistent following week 1 throughout the 12-week period.

Link to Other key secondary outcomes slide

Abbreviations: IV, intravenous; MCID, minimal clinically important difference; NR, non-response; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Key issue: Trial evidence is from a narrower population

Background

- The clinical threshold for moderate-to-severe intensity flare was defined as:
  - A GPPGA score of at least 3 (moderate), and
  - Presence of fresh pustules (new appearance or worsening of existing pustules), and
  - A GPPGA pustulation subscore of at least 2 (mild), and
  - At least 5% of body surface area covered with erythema (abnormal redness of the skin or mucous membranes) and the presence of pustules

Link to original slide

Abbreviations: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment

Effisayil 1 baseline characteristics

Characteristic	Spesolimab (n = 35)	Placebo (n = 18)
Age, mean years (SD)	43.2 (12.1)	42.6 (8.4)
Female, n (%)	21 (60)	15 (83)
GPPGA total score, n (%)		
3 (moderate)	28 (80)	15 (83)
4 (severe)	7 (20)	3 (17)
GPPGA pustulation subscore — n (%)		
2 (mild)	6 (17)	5 (28)
3 (moderate)	16 (46)	7 (39)
4 (severe)	13 (37)	6 (33)
Median GPPASI total score (IQR)	27.4 (15.5–36.8)	20.9 (12.0–32.0)
Median DLQI score (IQR)	19.5 (16–25)	19.5 (14–24)
Median pain VAS score (IQR)	79.8 (70.5–87.8)	70.0 (50.0–89.4)
Median PSS score (IQR)	11.0 (9–12)	10.5 (9–11)

Link to Key issue: Generalisability of Effisayil 1 Trial

Link to Key issue: Use of Effisayil 1 historical

Abbreviations: DLQI, Dermatology Life Quality Index; GPPASI, Psoriasis Area and Severity Index for Generalised Pustular Psoriasis; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; IQR, interquartile range; n, number; PSS, Psoriasis Symptom Scale; SD, standard deviation; VAS, Visual Analogue Scale.

Sources of evidence

Source	Details
Effisayil 1 trial	• Company-sponsored, multi-centre, randomised, double-blind phase II study of spesolimab versus placebo for the treatment of adult patients with GPP flares of moderate-to-severe intensity • Provides evidence fully relevant to this appraisal and informs the economic model • provides a direct comparison between the intervention and the comparator
Effisayil 1 historical cohort	• In the absence of an indirect treatment comparison to inform the economic model the company used data from the Effisayil 1 historical cohort • Retrospective study that provides data on the characteristics and clinical course of past GPP flares • Study did not report on which medications were received for the three categories of flare or the treatment composition for individual flares
SEE	• Carried out by the company to identify treatments used in the UK to treat GPP flares and the efficacy and safety profiles of the current treatments • Two rounds of elicitation (one individual round and one group round) • Modelling the treatments indicated by the UK experts as part of the SEE exercise is a reasonable approach • EAG considers the SEE exercise estimates to reflect UK reality more closely and to be aligned with the modelled comparator treatments (which were elicited by the same experts)

NICE Link to Key issue: Use of Effisayil 1 historical (1/2), (2/2)

Abbreviations: GPP, Generalised Pustular Psoriasis; SEE, Structured expert elicitation

Demographic and flare characteristics of patients enrolled to Effisayil 1 trial, POLARIS and SCRIPTOR (1/2)

	Effisayil™ 1 trial historical cohort	POLARIS[9]				SCRIPTOR
		Incident GPP patients from 2008-2019 (n = 206)				
	GPP patients experiencing flare (n = 53)[5]	Hospital admission with any GPP code and ≥3 days hospitalisation	Hospital admission with primary GPP code and ≥3 days hospitalisation	Hospital admission with primary GPP code of any duration	Emergency (non-elective) hospital admission with primary GPP code of any duration	GPP diagnosis after 2011 (n = 27)[10]
Age, years	At Effisayil™ 1 trial baseline:	At index date:				[redacted]
Mean (SD)	43.0 (10.9)	57.3 (19.0)				[redacted]
Female, n (%)	36 (67.9)	136 (66.0)				[redacted]
Ethnicity, n (%)		All GPP patients (n = 373)				
Asian	29 (54.7)	32 (8.6)				[redacted]
White	24 (45.3)	172 (46.1)				[redacted]
BMI kg/m², n (%)	At Effisayil™ 1 trial baseline:	All GPP patients (n = 373)				
<18.5	<25: 24 (45.3)	10 (2.7)				[redacted]
18.5–<25	16 (30.2)	93 (24.9)				[redacted]
25–<30	13 (24.5)	83 (22.3)				[redacted]
≥30	0	98 (26.3)				[redacted]
Missing		89 (23.9)				
Comorbidities, n (%)		All GPP patients (n = 373)				
≥1 comorbidity	NR	285 (76.4)				[redacted]

Abbreviations: GPP, generalised pustular psoriasis; ID, identification; RWE, real-world evidence; SD, standard deviation.

Demographic and flare characteristics of patients enrolled to Effisayil 1 trial, POLARIS and SCRIPTOR (2/2)

	Effisayil™ 1 trial historical cohort	POLARIS[9] Incident GPP patients from 2008-2019 (n = 206)				SCRIPTOR
	GPP patients experiencing flare (n = 53)[5]	Hospital admission with any GPP code and ≥3 days hospitalisation	Hospital admission with primary GPP code and ≥3 days hospitalisation	Hospital admission with primary GPP code of any duration	Emergency (non-elective) hospital admission with primary GPP code of any duration	GPP diagnosis after 2011 (n = 27)[10]
GPP flare duration						
Mean days (SD) Median days (range)	NR	NR	NR	NR	NR	[redacted]
<1 week, % 1–2 weeks, % 3–4 weeks, % 5–8 weeks, % 9–12 weeks, % >12 weeks, %	11.4^ 31.4^ 34.3^ 11.4^ 0^ 11.4^	NR	NR	NR	NR	NR

Notes: *data available for 29 patients; of patients who did not provide the number of flares per year, six had constant flares with persistent pustules; ^data presented for the 'typical past flare'; $White, Caucasian and/or of European descent.

Link to Key issue: Use of Effisayil 1 historical to inform treatment response slide

Abbreviations: GPP, generalised pustular psoriasis; ID, identification; RWE, real-world evidence; SD, standard deviation.

Effisayil 1 Primary outcome: % who achieved no visible pustules at week 1

Patients who achieved a GPPGA pustulation sub score of 0 (no visible pustules) at week 1 significantly higher for patients who received spesolimab vs. placebo

Primary outcome	Spesolimab (N=35)	Placebo (N=18)
GPPGA pustulation subscore of 0 at week 1, n/N (%)	19/35 (54.3%)	1/18 (5.6%)
Risk difference percentage points (95% CI), p-value	48.7 (21.5 to 67.2), p<0.001	

Risk difference percentage points: difference between the risk of an outcome in the exposed group and the unexposed group, expressed as a percentage.

Abbreviations: CI, confidence interval; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; GPPASI, Generalised Pustular Psoriasis Area and Severity Index.

Effisayil 1 secondary outcome: % who achieved GPPGA total score of 0 or 1 at week 1

Proportion of patients who achieved a GPPGA total score of 0 or 1 (clear or almost clear skin) was higher in the spesolimab arm compared with the placebo arm

GPPGA total score 0 or 1 at week 1 and results of post-hoc sensitivity analysis

	Spesolimab (N=35)	Placebo (N=18)
GPPGA total score of 0 or 1, n/N (%) at week 1	15/35 (42.9%)	2/18 (11.1%)
Risk difference percentage points (95% CI), p-value	31.7 (2.2 to 52.7), p<0.02	

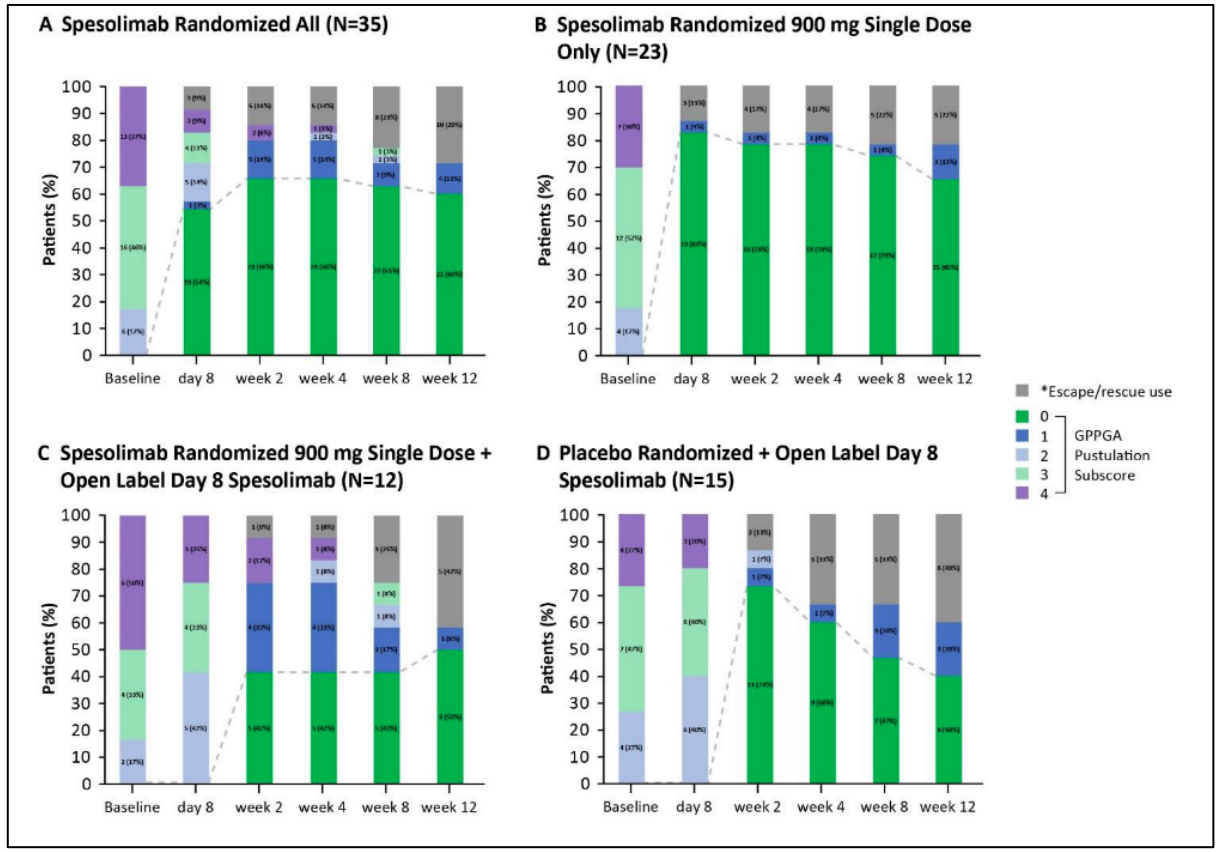
A linear regression that adjusted for sex, race, and baseline GPPASI value because these were imbalanced covariates at baseline was also conducted for this key secondary outcome as a post-hoc sensitivity analysis.

Abbreviations: CI, confidence interval; GPPASI, Generalised Pustular Psoriasis Area and Severity Index; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment

Effisayil 1 Secondary outcome: Time to first GPPGA pustulation subscore of 0

Spesolimab is more effective than placebo at all endpoints

- Spesolimab: complete pustular clearance observed at day 2 in n=4; at day 3 in n=11; day 8 in n= 21
- All patients who reached GPPGA pustulation sub score 0 (n = 19/35) achieved by week 1 (day 8)



GPPGA Pustulation Sub Score Over Time by Randomised Treatment at day 1 and Open-Label Spesolimab Treatment at day 8

Patients randomised to spesolimab who received,

- **Group A**: either 1 dose (day 1) or 2 doses (day 1 and day 8), n=35
- **Group B**: 1 dose (day 1), n=23
- **Group C**: 2 doses (day 1 and day 8), n=12

Patients randomised to placebo who received

- **Group D**: spesolimab (day 8), n=15

NICE

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

Company's model overview: variables applied in the economic model (1/2)

Variable	Value	Standard error	Measurement of uncertainty and distribution
Model parameters			
Time horizon (days)	85	Fixed	No sampling
Discount rate (costs and effects)	0.00%	Fixed	No sampling
Efficacy			
Intervention: % people whose GPP flare responds at day 2	37.1%	1.9%	Beta
Comparator: % people whose GPP flare responds at day 2	0.0%	0.0%	Beta
Intervention: % people whose GPP flare responds at day 3	17.1%	0.9%	Beta
Comparator: % people whose GPP flare responds at day 3	5.6%	0.3%	Beta
Intervention: % people whose GPP flare responds at day 8	8.6%	0.4%	Beta
Comparator: % people whose GPP flare responds at day 8	11.1%	0.6%	Beta
Intervention: % people whose GPP flare responds by Week 2	22.9%	1.1%	Beta
Comparator: % people whose GPP flare responds by Week 2	34.1%	1.7%	Beta
Intervention: % people whose GPP flare responds by Week 3	0.0%	0.0%	Beta
Comparator: % people whose GPP flare responds by Week 3	14.0%	0.7%	Beta
Intervention: % people whose GPP flare responds by Week 4	0.0%	0.0%	Beta
Comparator: % people whose GPP flare responds by Week 4	14.0%	0.7%	Beta
Intervention: % people whose GPP flare responds by Week 12	14.3%	0.7%	Beta
Comparator: % people whose GPP flare responds by Week 12	21.3%	1.1%	Beta
Utilities			
Active flare	[redacted]	0.0148	Beta
Resolved flare	[redacted]	0.0418	Beta

Abbreviations: GPP, generalised pustular psoriasis

Company's model overview: variables applied in the economic model (2/2)

Variable	Value	Standard error	Measurement of uncertainty and distribution
Drug costs (£)			
Cost of spesolimab (IV infusion, simple)	15,000	Fixed	No sampling
Cost of acitretin	17.92	Fixed	No sampling
Cost of ciclosporin	41.59	Fixed	No sampling
Cost of clobetasol propionate	7.51	Fixed	No sampling
Cost of guselkumab	2,250.00	Fixed	No sampling
Cost of infliximab	755.32	Fixed	No sampling
Cost of methotrexate	14.55	Fixed	No sampling
Cost of secukinumab	1218.78	Fixed	No sampling
Cost of ustekinumab	2147.00	Fixed	No sampling
Resource use unit costs (£)			
Outpatient appointment	174.89	16.34	Gamma
Daily care of inpatient care	857.00	85.70	Gamma
Daily cost of ICU care	1,704.84	159.29	Gamma
Daily cost of MV care	2,685.24	250.89	Gamma
Terminal care	5,877.88	4.33	Gamma
Cost of day care	1,110.00	111.10	Gamma
Resource use			
Outpatient appointments per week, GPP flare	[redacted]	0.52	Log-normal
Outpatient appointments per year, resolved flare	[redacted]	0.56	Log-normal
% patients treated as inpatients, GPP flare, BAC	77%	3.9%	Beta
% reduction in patients treated as inpatients, GPP flare, spesolimab	50%	2.5%	Beta
% of inpatients treated in ICU: spesolimab	0%	Fixed	No sampling
% of inpatients treated in ICU: BAC	[redacted]	1.1%	Beta
% of ICU patients requiring MV	[redacted]	1.5%	Beta

Link to Company's model overview slide

Abbreviations: BAC, best available care; GPP, generalised pustular psoriasis; ICU, intensive care unit; IV, intravenous; MV, mechanical ventilation

Company's model overview: Key model inputs

Model parameters	Source
Clinical parameters and variables:	
• Response to treatment: spesolimab • Response to treatment: BAC • AE incidence	Effisayil 1
Mortality	French SNDS study (Viguier et al., 2024)
Cost and healthcare resource use identification, measurement and valuation:	
Intervention and comparators' costs and resource use	BNF (generalised pustular psoriasis, severe extensive psoriasis, severe psoriasis, moderate-to-severe plaque psoriasis, plaque psoriasis and short-term treatment only of severe resistant inflammatory skin disorders)
Structured expert elicitation – HCRU for a GPP flare	[redacted] English dermatologists, with experience treating GPP patients at specialist centres
Health state unit costs and resource use	Unit Costs of Health and Social Care, 2023,
Adverse reaction unit costs and resource use	National schedule of NHS costs 2020/2021.
Miscellaneous unit costs and resource use	Georghiou et al. 2014.

Link to Company's model overview slide

Abbreviations: GPP, generalised pustular psoriasis; HCRU, health care resource use; SNDS, French National Health System database

Key issue: Treatment response: the modelling of BAC efficacy in week 1

Background

- Treatment effect for the first week for a comparison of spesolimab versus best available care is unknown in the trial
- Unknown if receiving active treatments would lead to different effectiveness outcomes during the first week
- Unlikely that patients in UK clinical practice would not receive any active drugs to treat GPP flares for a whole week

EAG comments

- Included active treatments in the comparator arm in the first week of the model in its base case, obtained from the SEE exercise
- Active treatments included Topical steroids, Ciclosporin, Methotrexate, Acitretin, Infliximab, Guselkumab, Ustenkinumab and Secukinumab
- Concerned that beyond week 1, the treatments obtained from the SEE exercise do not match the treatments used to treat GPP flares in the Effisayil 1 historical cohort study, as the treatments used to treat each flare in this study are not possible to derive

Link to Key issue: Treatment response: modelling BAC efficacy in week 1

Abbreviations: BAC, best available care; GPP, generalised pustular psoriasis

Key issue: Short time horizon and 2nd GPP flares not implemented

Background

- Patients who respond to treatment (have a GPPGA pustulation subscore of 0 or 1) were assumed to remain responders for the remainder of the modelled time horizon
- No information on how many [redacted] of the eight patients received a standard of care escape treatment after day 8
  - Within the 12-week Effisayil 1 trial period:
    - Two patients in spesolimab arm received single dose of spesolimab (at baseline) for their first flare and then rescue dose for a second flare
    - Two patients in spesolimab arm received two doses of spesolimab (at baseline and at day 8) for the first flare and then rescue dose for a second flare
    - Two patients in placebo arm received a single dose of spesolimab at day 8 and then rescue dose for a second flare

EAG comments

- Different numbers of patients achieving a GPPGA pustulation subscore of 0 or 1 by week 12 were tested in scenario analysis which decreased the ICER:
  1. In the worst-case scenario, 20.0% (7 out of 35) did not respond by week 12. Modelling limitations capped this at 7 patients, despite a theoretical 28.6% (10/35).
  2. The same proportion of patients as for the comparator arm have not responded to treatment by week 12: 12.37%.
  3. For those receiving escape therapy between weeks 8–12, 5.7% did not respond, assuming insufficient recovery time after therapy.

Link to Key issue: Short time horizon and 2nd GPP flares slide

Abbreviations: GPPGA, Generalised Pustular Psoriasis Physician Global Assessment

Scenarios for the efficacy of BAC

	GPPGA subscore of 0 or 1				GPPGA subscore of 0	
	Effisayil 1 trial (week 1) + Effisayil 1 historical cohort (company's base case)	Effisayil 1 historical cohort (company's scenario)	SEE exercise (EAG base case)	Effisayil 1 trial (week 1) + SEE exercise	SEE exercise	Effisayil 1 trial (week 1) + SEE exercise
Day 2	0.0%	0.0%	[redacted]	[redacted]	[redacted]	[redacted]
Day 3	5.6%	5.74%	[redacted]	[redacted]	[redacted]	[redacted]
Day 8	5.6%	19.60%	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	11.9%	11.9%	[redacted]	[redacted]	[redacted]	[redacted]
Week 3	18.0%	18.0%	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	18.0%	18.0%	[redacted]	[redacted]	[redacted]	[redacted]

Link back to Company and EAG assumptions/ scenarios

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

Overview of key model

How the technology is modelled to affect QALYs and Costs

Effect on QALYs	• The number of patients achieving a GPPGA pustulation subscore of 0 or 1 is different between spesolimab and BAC, which determines the proportion moving into the resolved flare health state and results in considerable QALY differences. • The number of patients hospitalised in each arm. As the number of patients hospitalised on spesolimab is half that of the comparator arm, the QALY difference is significant. • The number of patients admitted to ICU in the spesolimab arm, which further increases the QALY difference between the two arms. • The rate of adverse events, which is different between the arms although the impact in QALYs is minor.
Effect on costs	• The number of patients achieving a pustulation subscore of 0 or 1, hospitalised and admitted to the ICU in each arm. • The different adverse events that arise with the different medications in each arm, although the impact on costs is minor. • The different acquisition and administration costs for spesolimab and the medications in best available care.

Abbreviations: BAC, best available care; GPPGA, Generalised Pustular Psoriasis Physician Global Assessment; ICE, intensive care unit; QALY, quality adjusted life-year

Model inputs and evidence sources

Input	Assumption and evidence source
Baseline characteristics	• Patients with mean age 43 years in both groups; 67.90% females – Effisayil 1 trial
Model structure	• Cohort Markov state transition
Intervention and comparator efficacy	• Efficacy and safety of spesolimab: Effisayil 1 trial • Efficacy and safety of comparator: Effisayil 1 trial and historical cohort
Utilities	• Health state utilities: Effisayil 1 trial • AE disutilities: literature (Sullivan et al., 2011 and Stevenson et al., 2016)
Costs	• Drug costs: Monthly Index of Medical Specialties and the electronic Market Information Tool • Resource use: NHS reference costs 2020/21 (published 2022)