Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende spesolimab til behandling af generaliseret pustuløs psoriasis

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. spesolimab
2. Forhandlingsnotat fra Amgros vedr. spesolimab
3. Ansøgers endelige ansøgning vedr. spesolimab

Reply to Draft Assessment Report – Spesolimab GPP flares

Boehringer Ingelheim response to DMC Draft Assessment Report for spesolimab for GPP flares

Boehringer Ingelheim would like to thank the Danish Medicines Council (DMC) for their draft assessment report. We acknowledge that there is uncertainty within the analysis of clinical efficacy, largely owing to the rarity of generalised pustular psoriasis (GPP) and the consequential challenges in running large, randomised trials; however, there are several issues with the current draft assessment report we would like to highlight.

Clinical efficacy of spesolimab versus placebo in Effisayil-1

Effisayil-1 showed a rapidly onsetting and sustained effect of spesolimab for the treatment of GPP flares.[1] The DMC argues that GPPGA pustulation subscore (the primary outcome of Effisayil-1) should not be used to judge the severity of GPP, based on a consensus statement from 2017; however, in the consensus statement, only "actual counting" of pustules is discouraged and the need for a novel tool to assess the severity of GPP is highlighted.[2] The GPPGA pustulation subscore does not rely on counting of pustules, rather it is based on clinician rating of the severity of pustulation, with a score of 0 indicating clear skin. Additionally, the leading author of the consensus statement has later argued that consistent implementation of the GPPGA score will improve the assessment and interpretation of the disease and was involved in the Effisayil-1 trial. The second author of the consensus statement referenced by the DMC played a major role in developing the GPPGA score.[3,4]

Nonetheless, we acknowledge that the GPPGA pustulation subscore alone does not give the full picture, when assessing the effects of treatments on GPP flares. The key secondary endpoint of Effisayil-1 was the proportion of patients achieving a GPPGA total score of 0 or 1 (indicating clear or almost clear skin). After one week significantly more patients receiving spesolimab than placebo achieved this (43% versus 11%, p-value = 0.02).[1] While some of this improvement might be driven by the clearance of pustules, numerically larger improvements were also seen on the erythema and scaling subscore for patients assigned to spesolimab; At day 8, 17.1% of patients treated with spesolimab versus 5.6% of patients treated with placebo had achieved a GPPGA erythema score of 0 or 1 and 17.1% of patients treated with spesolimab versus 11.1% of patients treated with placebo had achieved a GPPGA scaling subscore of 0 or 1 – these were exploratory outcomes in Effisayil-1 and were not included in the submission. Data on the individual subscores were not requested by the DMC doing clinical validation of the submission.

The DMC places large emphasis on GPPASI scores and claims that there were no differences between groups at day 8. We believe this relies on a misunderstanding. As shown in Table 2-5 in the Draft Assessment report there are clear differences between the groups in terms of the number of patients that achieve GPPASI50 (15%-point difference favouring spesolimab) and GPPASI75 (11%-point difference favouring spesolimab) as well as a much higher median change from baseline in GPPASI in the spesolimab group (-42.8 versus 1.02, estimate of difference = -16.88, p-value = 0.088).[5] In the submission only results after week 4 were included, and results at day 8 were not requested by the DMC. We acknowledge that the differences are not statistically significant, and thus should be interpreted with caution; however, Effisayil-1 was not powered to detect a difference for these outcomes, since the rarity of GPP poses significant challenges for patient accrual in randomised trials. All outcomes listed in the DMCs table 2-5 favour spesolimab and considering the highly statistically significant results seen on GPPGA pustulation subscore and GPPGA total score (for which the trial was powered), we do not agree with the DMCs conclusion that there is no difference between groups. While the differences are not statistically significant for some outcomes there is a clear trend favouring spesolimab and p-values above 0.05 should not be interpreted as proof there is no difference between groups.

Finally, the DMC has chosen to discard all results from Effisayil-1 collected after day 8, as patients in the placebo arm were allowed to crossover to spesolimab. This was done, as it was considered unethical to keep patients experiencing a GPP flare on placebo for an extended period. We acknowledge that this makes interpretation difficult, as there is no longer a control arm; however, we do not consider it appropriate to completely discard the results, as they show a sustained and increased

response to spesolimab as well as a rapidly onsetting effect in patients switching from placebo to spesolimab, like what was seen in the patients randomised to spesolimab.

Relative efficacy versus treatments used in Denmark

The DMC argues that the drugs currently used off-label for the treatment of GPP flares in Denmark are likely more effective than placebo; however, although an extensive systematic literature was conducted very little evidence on the benefits and harms for these drugs in GPP was identified. The identified studies were of low methodological quality, predominantly observational, and poorly reported. On the DMCs request we provided a narrative summary of the identified evidence for acitretin and infliximab, which, while made difficult by the issues described above, did not seem to indicate a faster onsetting effect of acitretin and infliximab than what was seen in the placebo arm in Effisayil-1.

We acknowledge that spesolimab must be compared to Danish clinical practice, however as none of the currently used treatments are approved for treatment of GPP and very little evidence or no evidence is available for these treatments, we do not consider it appropriate to expect valid comparisons of benefits and harms against these treatments. Additionally, we would like to point out that if results after day 8 from Effisayil are discarded as there is no control arm and all improvements seen past this point are considered due to the natural course of the disease, the same should be assumed for the treatment used in Danish clinical practice.

DMC changes to the health economic model

We acknowledge that using GPPGA pustulation subscore as a proxy for hospital discharge may not be entirely appropriate. Using GPPGA total score instead, as suggested by the DMC, would indeed have been preferable, but as explained during the validation of the submission, the timepoints at which GPPGA total score available from the trial did not allow for this. Based on conversations with Danish clinicians the results from Effisayil-1 clearly indicate that spesolimab will lead to shorter hospitalisations for patients hospitalised with acute GPP flares, thus the DMCs decision to completely remove efficacy from the model likely yields a very conservative estimate of the costs associated with a recommendation of spesolimab.

References

1. Bachelez H, Choon SE, Marrakchi S, et al. Trial of Spesolimab for Generalized Pustular Psoriasis. N Engl J Med 2021; 385(26): 2431-40.
2. Navarini AA, Burden AD, Capon F, et al. European consensus statement on phenotypes of pustular psoriasis. J Eur Acad Dermatol Venereol 2017; 31(11): 1792-9.
3. Burden AD, Choon SE, Gottlieb AB, Navarini AA, Warren RB. Clinical Disease Measures in Generalized Pustular Psoriasis. Am J Clin Dermatol 2022; 23(Suppl 1): 39-50.
4. Burden AD, Bachelez H, Choon SE, et al. Validation of the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) scale for assessing severity of GPP. AAD Annual Meeting; 2022; Boston; 2022.
5. Boehringer Ingelheim International GmbH. Clinical Study Report, Effisayil-1 [Data on file], 2021.

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

17.11.2023

DBS/BMC

Forhandlingsnotat

Dato for behandling i Medicinrådet	13.12.2023
Leverandør	Boehringer Ingelheim Danmark A/S
Lægemiddel	Spevigo (spesolimab)
Ansøgt indikation	Monoterapi ved exacerbation (flare) hos patienter med generaliseret pustuløs psoriasis (GPP)
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Spevigo (spesolimab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Spevigo	450 mg	2 stk.	126.195,00	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.

Lægemiddeludgifter

Den anbefalede dosis af Spevigo er 900 mg (2 hætteglas a 450 mg) som engangsbehandling, administreret som intravenøs infusion. Det betyder at en behandling koster [redacted] kroner.

Aftaleforhold

[redacted] Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Konkurrencesituationen

[redacted] Der er ikke andre lægemidler med indikation til behandling af GPP, hvorfor det ikke er aktuelt med en behandlingsvejledning.

AnaptysBio har imsidolimab på vej til samme indikation. [redacted]

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til vurdering
Sverige	Under vurdering	Link til vurdering
England	Under vurdering	Link til vurdering

Konklusion

[redacted]

Application for the assessment of spesolimab for treatment of flares in adult patients with generalised pustular psoriasis

Instructions for companies

This is the template for submission of evidence to the Danish Medicines Council (DMC) as part of the appraisal process for a new pharmaceutical or new indication for an existing pharmaceutical. The template is not exhaustive; companies must adhere to the current version of the guidelines alongside using this template when preparing their submission.

Appendices A-J, headings and subheadings are not to be removed. Additional subheadings can be added when appropriate. All sections in the template must be filled in. If a section or an appendix is not applicable, state "not applicable" and explain why. Examples of texts and tables are provided in the template. These can be edited or removed. The company can provide different table layouts to accommodate data, as long as the required information is provided.

The submission should be as brief and informative as possible. The main body of submission must not be longer than 100 pages, excluding the appendices. **Only material directly relevant for the application to the DMC should be included in the submission including appendices A-J. The application should not include information or descriptions about specific patients/medical history**. Submissions in Danish and English are accepted.

In addition to this template, the company must submit a health economic model in Excel, with full access to the programming code. All the information requested in this template and described in the guidelines must be presented in the application. The model can be accompanied by a technical document. The information in the technical document will, however, not be considered as part of the application. Hence, all relevant information for the application must also be described in the application (including appendices A-J) itself. This can be done by copying the relevant information from the technical document into the application, and by presenting it as described in this template and in the guidelines. Companies are encouraged to provide the European Public Assessment Report (EPAR) including the scientific discussion as an appendix to the submission (draft versions will be accepted).

When making an evidence submission, companies must ensure that all confidential information is highlighted in yellow and provide the expected date of publication. If confidential appendices are provided, these must be watermarked as "confidential". Later in the appraisal process the application material must be assembled in one version consisting of the application, the appendices and any following or requested analysis – send to the DMS in one blinded version and one highlighted version.

About macros in Excel - effective from 1 January 2023

Due to new IT security requirements at the Danish Medicines Council excel files in the applications contain macros, must be authorized and signed by the applicant before submission to the Danish Medicines Council. All code and macros in the submitted excel files must be original, meaning that the Danish Medicines Council will not accept excel files that have been modified by a third party. Furthermore all code and macros must be signed with a certificate from a trustworthy public certificate provider before submission.

Version 1.3

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table of contents

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Colour scheme for text highlighting	
Colour of highlighted text	Definition of highlighted text
	Confidential information
[other]	[definition of color-code]

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

1. Basic information

Contact information	
Name	**Jens Holt**
Title	National Market Access Manager
Phone number	+45 22 72 48 73
E-mail	jens.holt@boehringer-ingelheim.com
Name	**Susanne Clemen Capion**
Title	Medical & Patient Journey Manager
Phone number	+45 22 72 49 61
E-mail	susanne_clemen.capion@boehringer-ingelheim.com

Overview of the pharmaceutical	
Proprietary name	Spevigo®
Generic name	Spesolimab
Marketing authorization holder in Denmark	Boehringer Ingelheim Danmark A/S
ATC code	L04AC22
Pharmacotherapeutic group	Antineoplastic and immunomodulating agents, immunosuppressants, interleukin inhibitors
Active substance(s)	Spesolimab
Pharmaceutical form(s)	Solution for intravenous (IV) infusion
Mechanism of action	Spesolimab is a humanised antagonistic monoclonal immunoglobulin G1 (IgG1) antibody which blocks human IL-36 receptor (IL36R) signalling. The binding of spesolimab to IL36R prevents the subsequent activation of IL36R by cognate ligands (IL-36 α, β and γ) and downstream activation of pro-inflammatory pathways.
Dosage regimen	The recommended dose is a single dose of 900 mg (2 vials of 450 mg) administered as an intravenous infusion. If flare symptoms persist, an additional 900 mg dose may be administered 1 week after the initial dose

Overview of the pharmaceutical	
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Spesolimab is indicated for the treatment of flares in adult patients with generalised pustular psoriasis (GPP) as monotherapy.
Other approved therapeutic indications	No
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Spesolimab will be administered as monotherapy
Packaging – types, sizes/number of units, and concentrations	2 vials of 450 mg/7.5 mL each
Orphan drug designation	No

2. Abbreviations

Abbreviation term	Definition
ADA	Antidrug Antibody
AE	Adverse Event
AESI	Adverse Events of Special Interest
AIP	pharmacy purchase price
BAC	Best available care
BMI	Body Mass Index
CGI	Clinical Global Improvement
CHMP	Committee for Medicinal Products for Human Use
CUA	Cost-Utility Analysis
DKK	Danish kroner
DMC	Danish Medicines Council
DQLI	Dermatology Quality of Life Index
DRG	Diagnosis-related groups
DSA	Deterministic sensitivity analyses

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

EMA	European Medicines Agency
ES	Enrolled Set
FACIT	Functional Assessment of Chronic Illness Therapy
GPP	Generalised Pustular Psoriasis
GPPASI	A Psoriasis Area and Severity Index for Generalized Pustular Psoriasis
GPPGA	A Generalized Pustular Psoriasis Physician Global Assessment
HSUV	Health State Utility Value
ICU	Intensive Care Unit
IL-17	Interleukin-17
IL-23	Interleukin-23
IL-36	Interleukin-36
IV	Intravenous
JDA	Japanese Dermatological Association
LOCF	Last Observation Carried Forward
MoA	Method of Action
NAb	Neutralising Antibody
OWSA	One-way sensitivity analyses
PASI	Psoriasis Area and Severity Index
PGA	Physician Global Assessment
PPS	Per-Protocol Set
PSS	Psoriasis Symptom Scale
PT	Preferred Term
PV	Psoriasis vulgaris
QoL	Quality of life
RCTC	Rheumatology Common Toxicity Criteria
RS	Randomised Set
SAE	Serious Adverse Event

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

SAF	Safety Analysis Set
SC	Subcutaneous
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event
TNF-α	Tumor Necrosis Factor Alpha
TSAP	Trial Statistical Analysis Plan
VAS	Visual Analogue Scale

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

3. Tables and Figures

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

4. Summary

4.1 Indication

This submission is to support the use of spesolimab as first-line treatment flares in adult patients with generalized pustular psoriasis (GPP).

Generalised pustular psoriasis is a chronic, severe, and potentially life-threatening neutrophilic skin disease characterised by episodes of widespread eruption of sterile, macroscopically visible pustules that frequently occur with systemic inflammation (1-3). Generalised pustular psoriasis is a severe and rare subtype of psoriasis, and is clinically, genetically, and pathologically distinct from plaque psoriasis (2). Common extracutaneous symptoms of GPP flares include fever, general malaise with fatigue (1, 2, 4), polymyalgia, polyarthralgia, and arthritis (5).

The clinical course of generalised pustular psoriasis is heterogeneous and GPP can be considered as a relapsing disease with recurrent flares or a persistent disease with intermittent flares (2, 6). The severity and duration of flares varies between patients, and between individual flares in the same patient. However, flares can potentially progress to a life-threatening severity requiring hospitalisation and sometime intensive care unit (ICU) treatment. The best available estimates for mean duration of hospitalisation for patients hospitalised with GPP flares are approximately 10 days (7-9), and a French study found that 25% of hospitalised patients required ICU treatment for an average of 18 days, and 45% of intensive care unit (ICU) admissions required patient resuscitation (10).

Generalised pustular psoriasis is unpredictable and has a substantial negative impact on social relationships and mental health, with many patients diagnosed with depression and anxiety (11-13). In a study from 2021, patients with GPP had higher presenteeism (% impairment while working; 29 versus 13), and the percentage of daily life activities impaired (32 versus 17) than patients with plaque psoriasis (14). Similar findings were reported in a study by Sampogna et al. (13) The authors found a lower QoL in patients with pustular psoriasis than plaque psoriasis, using the SF-36 questionnaires. They additionally showed that QoL decreased with increasing severity of psoriasis ($p<0.01$) and that emotional problems such as shame, anger, worry, and difficulties in daily activities and social life were seen in patients with psoriasis, including those with pustular psoriasis. These problems also increased with increasing disease severity (15).

Estimates of incidence and prevalence vary between studies and between geographical regions (16). In Denmark, a registry study found a total of 645 GPP patients alive in Denmark on December 31st, 2018. Of these 358 were given a GPP diagnosis by a dermatologist (prevalence of 0.0061%) and 202 had been hospitalised due to GPP. The incidence in Denmark in 2018 was estimated as 0.22 per 100.000 person-years (9). Based on this and on interviews with Danish clinicians (17) the estimated number of patients eligible for spesolimab treatment per year is 10.

4.2 The pharmaceutical

Spesolimab is a first-in-class humanised monoclonal immunoglobulin (IgG) 1 antibody (mAb) against human interleukin-36 receptor (IL-36R). The antibody binds to human IL-36R and inhibits all three IL-36 ligands (IL-36 alpha, beta, and gamma). Blockade of the IL-36 pathway has a rapid biological effect, normalising cytokine signalling, immune cell activation and neutrophil recruitment, and inhibiting hyperkeratosis to restore epithelial barrier function in the skin. It is evident *in vitro* and *ex vivo* that binding of spesolimab to the IL-36 receptor modulates the activation of downstream effector, pro-inflammatory cytokines that are implicated in the pathogenesis of generalised pustular psoriasis, including tumour necrosis factor (TNF)-α, IL-17, IL-23 and IL-1β. The efficacy and safety of spesolimab in the treatment of GPP flares when compared to placebo was shown in the Effisayil-1 trial (18).

4.3 Comparators

Currently, there is no treatment guidelines for patients with GPP available from the Danish Medicines Council (DMC) or any other Danish treatment guideline, and all treatments are used off-label, with only very low-quality evidence (predominantly non-controlled retrospective studies and case reports) supporting their use. Based on a registry study (9) and interviews with Danish clinicians (17), the most commonly used treatments for GPP flares are retinoids (acitretin), cyclosporine and biological agents such as TNF-α inhibitors, IL-17 inhibitors, and IL-23 inhibitors (9, 17).

Based on the above acitretin, cyclosporine, infliximab, adalimumab, bimekizumab, and guselkumab were chosen as comparators for this submission, although these medicines are all used off-label and are not registered for use in GPP. Bimekizumab and guselkumab were chosen, as they are the IL-17 and IL-23 inhibitors listed highest in the DMCs treatment guideline for plaque psoriasis (19). Additionally, as no treatment guideline is available for GPP, no medicines are approved for GPP treatment outside Japan, Taiwan and Thailand, and as it was the comparator in the Effisayil-1 trial, placebo was also included as a comparator.

4.4 Efficacy and safety endpoints

The Effisayil-1 study is the only randomised controlled trial examining the efficacy and safety of spesolimab in patients with GPP flares. The primary endpoints in Effisayil-1 were a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 (indicating no visible pustules) at the end of week 1 and the key secondary endpoint was a GPPGA total score of 0 or 1 (indicating clear or almost clear skin) at week 1 (18).

At the end of week 1, 19 of the 35 patients (54.3%) assigned to the spesolimab group and 1 of the 18 (5.6%) assigned to the placebo group had a GPPGA pustulation subscore of 0 (no visible pustules), resulting in a clinically and statistically significant difference of 48.7 percentage points (95% CI: 21.5% to 67.2%; p = 0.0004) (18).

Similarly, at the end of week 1, 15 of the 35 patients (42.9%) assigned to the spesolimab group and 2 of the 18 (11.1%) assigned to the placebo group had a GPPGA total score of 0 or 1, resulting in a clinically and statistically significant difference of 31.7 percentage points (95% CI: 2.2% to 52.7%; p = 0.0118) (18).

In Effisayil-1, patients could qualify to receive an open-label treatment with spesolimab on Day 8 (if their GPPGA total score was ≥2 and their GPPGA pustulation subscore was ≥2 on Day 8). As this was the case for 15 out of 18 patients (83.3%) of patients assigned to placebo comparisons between spesolimab and placebo at timepoints after week 1 were challenging. However, the response seen in patients receiving spesolimab was maintained over time and patients assigned to placebo receiving open-label spesolimab showed responses very similar to those seen in patients assigned to spesolimab, indicating an effect of the open-label dose of spesolimab (20).

In Effisayil-1, spesolimab was generally well-tolerated with the proportions of patients with any adverse event (AE) or serious adverse event (SAE) being comparable between the spesolimab and the placebo groups. Among the System Organ Classes (SOC), the SOC infections and infestations were most frequently reported up to Week 1. The SOC infections and infestations were reported for a higher proportion of patients in the spesolimab group (17.1%) than for patients in the placebo group (5.6%). On the Preferred Term (PT) level, no clear pattern of infections was observed, and the AEs were mainly non-serious, non-severe, and not indicative of opportunistic infections.

As only very low-quality evidence is available for the currently used off label treatments an indirect treatment comparison was not possible.

4.5 Structure and results of the economic analysis

A simple cost analysis was developed in Microsoft Excel® to assess the cost of spesolimab versus best available care in patients experiencing an acute flare of GPP. This economic analysis is focussing on the acute phase of a GPP flare.

Consequently, a 12-week decision tree was deemed appropriate to represent the short-term nature and response/non-response nature of a single GPP flare. The health economic analysis is informed by data from the Effisayil-1 trial and other external sources following the DMC method (18, 21). Model outcomes includes costs of drug acquisition, administration, ressource use, AE management, patient time and transportation, and cost per patient. Deterministic sensitivity analysis (DSA) were used to investigate the uncertainty of the model parameters.

As per DMC guidance, the cost analysis takes a restricted societal perspective, using the best available clinical and economic evidence. Local Danish data inputs are used wherever available. The current model is based on results from the Effisayil-1 trial (18).

In the base case analysis, the cost of drug acquisition associated to spesolimab is higher versus best available care. Nevertheless, spesolimab is cost saving regarding the remaining cost parameters, such as administration, resource use, AE management, patient time, and transportation, when compared to the best available care. This can be explained by the fact that spesolimab is a single administration and has a rapid onset and therapeutic effect, leading to earlier patient discharge from the hospital compared to those treated with the best available care. The primary cost drivers are patient time and transportation expenses, in addition to drug acquisition costs. While the higher cost associated with spesolimab is primarily attributed to the cost of drug acquisition, the best available care arm's cost is due to the considerable expenses incurred in patient time and transportation. This reflects the expectation of Danish clinical experts that spesolimab treatment can result in a fifty percent reduction in hospitalisation time for patients experiencing a GPP flare. The base case resulted in an incremental cost per patient of 14,540 DKK.

Based on the projected uptake of spesolimab as a standard treatment for patients with a flare of GPP in case of a positive reimbursement recommendation, the annual budget impact in the first five years ranges from 1,185,610 DKK in year 1 to 5,928,050 DKK in year 5.

5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

5.1.1 Aetiology, pathophysiology and diagnosing of generalised pustular psoriasis

Generalised pustular psoriasis is a chronic, severe, and potentially life-threatening neutrophilic skin disease characterised by episodes of widespread eruption of sterile, macroscopically visible pustules that frequently occurs together with systemic inflammation (1, 2, 22).

Generalised pustular psoriasis is a predominantly monogenic disease and only a small number of single gene mutations have been identified in patients with generalised pustular psoriasis. In 2011, human genetic studies first established a strong and distinct link between mutations in the IL36RN gene (encoding interleukin (IL)-36 receptor antagonist (RA)) and the incidence of GPP (23, 24).

Subsequent research has identified further mutations in IL36RN and established IL-36RA and dysregulation of the IL-36 signalling pathway as the key component in the development of GPP (23, 25-28). Additional mutations outside of IL36RN have also been identified, including AP1S3 (encoding adaptor related protein complex 1 subunit sigma 3) and CARD14 (encoding caspase recruitment domain family member 14) (29-31). Alterations in AP1S3 result in upregulation of IL-1 activity and IL-36 expression, and lead to inhibition of keratinocyte autophagy (25, 32), which are likely to result in the pathology of GPP. AP1S3 alterations have additionally been reported in other pustular diseases, including palmoplantar pustulosis, Acrodermatitis continua of Hallopeau (ACH) and acute generalised exanthematous pustulosis (AGEP) (31). These genetic mutations specific to GPP suggest that GPP has a genetically different underlying cause from plaque psoriasis.

Additionally, GPP lesions have been shown to have higher levels of IL-1 and IL-36 and lower levels of IL-17A and interferon-γ than plaque psoriasis (30). In patients with GPP, neutrophils predominate in skin lesions(1, 2) and immunohistochemical analyses have revealed that the IL-36 expression is localized to keratinocytes that surround the neutrophilic pustules in GPP (30).

According to the European consensus statement on phenotypes of pustular psoriasis, GPP is diagnosed by the presence of primary, sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques) and can be further classified based on presence of systemic inflammation and presence of plaque psoriasis. Additionally, GPP can be classified as relapsing disease if the patients have experienced more than one episode or persistent if a flare has lasted longer than three months (2).

5.1.2 Clinical and humanistic burden of generalised pustular psoriasis

The clinical course of GPP is heterogenous; symptom severity may vary amongst patients and across flare episodes within the same patient and is very unpredictable (33). In most cases, a flare consists of the acute onset of a rapidly disseminating cutaneous eruption and an extensive skin rash covered with aseptic pustules, with or without systematic symptoms such as fever and general malaise with fatigue (1, 2, 4). Other extracutaneous manifestations such as polymyalgia and polyarthralgia are common, and arthritis may occur (5). The spectrum of severity of attacks ranges from the absence of any systemic symptoms to high fever, or even life-threatening complications requiring intensive care unit admission (34). Patients may experience a repeating pattern of flare and post-flare periods throughout their life, with the period between flares referred to as a quiescent phase (8). The pattern of recurring flares that spontaneously self-remit is a characteristic feature of GPP (5).

The frequency and pattern of flares in GPP patients is also highly variable. A retrospective study examined 86 GPP patients and found that 54% had predominantly relapsing disease, 14% had predominantly chronic persistent disease, and 8% had a combination of persistent and relapsing disease (6). A study of the French National Health Data System database showed that during a 3-7 year follow-up period, 452 out of 569 GPP patients (79.4%) had only one flare, 16.2% had two or three flares, and 4.4% had four or more flares (10). Other studies have shown similar results although there is some variability in the proportion of patients assumed to have more than one flare per year (7, 35).

Overall, these studies show that the nature of GPP is persistent or relapsing with patients experiencing multiple flares though their lifetime. While a genetic basis for generalised pustular psoriasis has been identified, disease flares can also be attributed to various precipitating factors, including infection, stress, medication withdrawal (e.g., corticosteroids), and pregnancy (7, 23, 34, 36, 37),

The visual appearance of GPP lesions is markedly different from that of plaque psoriasis lesions. Generalised pustular psoriasis lesions are characterised by sterile pustules and the lesions may merge forming so-called “lakes of pus” (1, 2), whereas plaque psoriasis lesions are generally red plaques covered with excess silvery scales, characterised by thickened stratum corneum, and have clear borders(38).

Skin symptoms commonly reported by patients living with GPP include pustules, pain, itching, scaling, redness, dryness, and burning(39). In addition to these, systemic symptoms such as fever, swelling, poor sleep, general malaise, joint pain, headache, and exhaustion are frequently reported (5-7, 40). While patients may be completely symptom free between flares, several studies have shown that more than 70% of GPP patients still have residual symptoms even after the treatment of flares(6, 35). Several co-morbidities, such as metabolic, hepatic, biliary, cardiac, respiratory, and neurological disorders have been linked to GPP further contributing to the clinical burden of the disease (5, 7).

Although the severity of GPP flares varies, they can potentially progress to a life-threatening severity requiring hospitalisation and sometime intensive care unit treatment. Studies have shown that GPP patients have more and longer hospital visits compared with the general population (41, 42). A study from 2014 found that the mean duration

of admission for patients with GPP was 10.3 days (range 3-44) (7). Similarly, a systematic review from 2020 found that included studies reported duration of hospitals ranging from 10 to 14 days (8). A Swedish study examining the length of in-patients stays for GPP patients in 2015 found slightly longer lengths of hospitalisation with a mean length of stay of 17.4 days (SD: 20.8) (43). An analysis of the French National Health Data System database also showed that 25% of hospitalised patients required intensive care unit treatment for an average of 18 days (10). Similarly, details of past flares were obtained from 53 GPP patients enrolled in the Effisayil-1 trial; 71% percent of the included patients had been hospitalised for 1-5 weeks for their most severe past flare, with 45% being hospitalised for 1-3 weeks and 26% being hospitalised for 3-5 weeks (33). For 57 patients hospitalised with GPP in Denmark between 2008 and 2018 the median duration of hospitalisation was 9 days (interquartile range (IQR): 6-15 days) (9). Danish clinical experts have stated that in Denmark moderate to severe flares usually lead to hospitalisations of 1-2 weeks, with patients requiring intensive care treatment being hospitalised for 2-3 weeks (17).

The total duration of GPP flares also varies significantly; for patients included in the Effisayil-1 study the duration of the most severe past flare was 1-<3 weeks for 26%, 3-<5 weeks for 32%, 5-12 weeks for 26%, and for 13% the most severe past flare lasted longer than 12 weeks. Similarly, for the most severe past flare the time to complete pustular clearance was 3-<9 weeks in 60% of patients, with 18% having a time to complete pustular clearance longer than 9 weeks (33).

Generalised pustular psoriasis has a substantial negative impact on social relationships and mental health and studies have shown that GPP patients are more likely to experience anxiety and depression than patients with PV or matched controls (11, 12, 15). There is limited evidence on the impact of GPP on quality of life (QoL), however a study from 2014 used the Dermatology Life Quality Index (DLQI) index to assess GPP patient's QoL. During a follow-up visit (i.e., non-flare period) the mean DLQI score reported by 102 patients was 12.4, with scores above 10 suggesting QoL impairment (7). For patients with GPP flares included in the Effisayil-1 study, the mean DLQI score at baseline was 19.5, indicating that GPP flares have a very large impact on patient's lives (44).

5.1.3 Epidemiology of generalised pustular psoriasis

Due to the rarity of the disease and the variability of diagnoses criteria, literature on the prevalence of generalised pustular psoriasis is sparse. Available studies note that the estimated prevalence of generalised pustular psoriasis in EU countries is in the range of 1.76 per 1,000,000 people in France to 460 per 1,000,000 people in Germany (45, 46).

A register study conducted in 2022 examined the incidence and prevalence of GPP in Denmark by linking data from the Civil Registration System, the Danish National Patient Registry, and the Danish Registry of Medicinal Products Statistics. The registry study found a total of 645 GPP patients alive in Denmark on December 31st, 2018. Of these 358 were given a GPP diagnosis by a dermatologist (prevalence of 0.0061%) and 202 had been hospitalised due to GPP. The incidence in Denmark in 2018 was estimated as 0.22 per 100.000 person-years (9). The incidence rates from 2014-2018 found in the registry study described above are provided in Table 1. No estimates for prevalence by year or incidence rates from 2019-2022 are available.

Table 1. Incidence of GPP in Denmark (2014-2018)

Year	2014	2015	2016	2017	2018
Incidence (per 100.000 patient years) in Denmark	0.18	0.14	0.15	0.14	0.22

A similar study, published in 2022, examined the prevalence and incidence of GPP by identifying cases in the Swedish National Patient Register. On 31 December 2015, the point prevalence was estimated at 9.1 per 100,000 and the incidence in 2015 was estimated at 0.82 per 100,000 (47). Applying these prevalence numbers to the Danish population

in 2022 would correspond to 510 GPP patients in Denmark which is slightly lower than what was found in the Danish study, although incidence estimates from Sweden are higher - these differences may be due to deviations in diagnostic criteria.

During market research, Boehringer Ingelheim has been in dialogue with Danish clinicians from Aarhus, Bispebjerg, Gentofte, and Roskilde hospitals. All clinicians report having seen two to four patients with acute GPP flares during the last couple of years, so the number of Danish patients for whom spesolimab would be indicated is likely very small.

As GPP is a very rare disease information on patient demographics and prognostic factors is very limited. While GPP can affect all age-groups, a study of 102 GPP patients in Malaysia found a mean age of onset of 40.9 years (range: 21-81 years) (7). The Danish registry study found that in 49 patients first diagnosed with GPP between 2014 and 2018 the mean age at diagnosis was 53.3 (9). In the study from Malaysia 66.6% of patients were female (7) - a finding reproduced in other studies (1, 11). Similar trends are seen in Denmark, where 32 out of 57 (56%) patients hospitalized with GPP between 2008 and 2018 were female (9).

As mentioned above, GPP is associated with various comorbidities. Out of 57 patients hospitalised with GPP in Denmark between 2008 and 2018, 12 (21%) had hypertension, five (9%) had dyslipidaemia, and seven (12%) had diabetes (9).

5.1.4 Patient population relevant for this application

Only patients with acute flares of GPP are relevant for this application; No published data on the number of flares in Danish patients are available, but the register study described above found that out of all people alive and resident in the Danish population on December 31st, 2018, 202 patients had been hospitalized due to GPP – 57 patients had their first-ever dermatology hospitalization for GPP between January 1st, 2008 and December 31st, 2017 (9).

While the variation in frequency of flares and the sparse data available makes estimation of the number of patients eligible for spesolimab treatment challenging, based on the numbers provided above and interviews with leading Danish physicians within the field of GPP (17), estimates of the number of patients in Denmark who are expected to use spesolimab in the coming years are provided in Table 2.

Table 2. Estimated number of patients eligible for treatment

Year	2023	2024	2025	2026	2027
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	10	10	10	10	10

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

There are currently no approved GPP-specific therapies in Europe (48), thus the relevant comparator in clinical trials of spesolimab is placebo. According to Danish dermatologists, acitretin, methotrexate and cyclosporine are the most widely used therapies to treat GPP in Denmark. Danish physicians also occasionally use biological medicines such as infliximab and adalimumab (17). However, no randomised evidence of the treatment effect of these pharmaceuticals is available for patients with GPP (48). A Danish registry study examined medication use in 57 patients with a first-ever dermatology hospitalisation due to GPP between January 2008 and December 2017, and found that six (11%) had received oral glucocorticoids within six months prior to hospitalisation, three (5%) had received acitretin, and less than three had received methotrexate, cyclosporine, adalimumab, certolizumab pegol, or ustekinumab. While in hospital nine patients (16%) received acitretin, four (7%) received methotrexate, and less than three received cyclosporine, etanercept or infliximab.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

No Danish or European treatment guidelines exist for the treatment of GPP flares. The United States National Psoriasis Foundation established guidelines for GPP in 2012 and updated these in 2020; for adults diagnosed with GPP first-line therapies include acitretin, cyclosporine, methotrexate, and infliximab. Second-line therapies include biological medicines such as adalimumab, etanercept and topicals (49).

5.2.2 Choice of comparator(s)

Based on the information above, information obtained through BI's market research and interviews with Danish clinicians (17) the comparators for spesolimab for the treatment of GPP flares are acitretin, cyclosporine, tumour necrosis factor (TNF)-α inhibitors (infliximab and adalimumab), IL-17 inhibitors (bimekizumab), and IL-23 inhibitors (guselkumab). Bimekizumab and guselkumab were chosen as comparators as they are the IL-17 and IL-23 inhibitors mentioned first in the DMC treatment guideline for moderate to severe plaque psoriasis (19). While no high-quality evidence for the effect of these treatments in patients with GPP flares exist, they are being used in Danish clinical practice and as such are the relevant comparators. Methotrexate is also used, albeit rarely; however, as this treatment was not mentioned by the clinicians interviewed it is not included as a comparator in this application.

No medicines for GPP flares have been evaluated by the Danish Medicines Council, thus placebo will also be included as a comparator.

5.2.3 Description of the comparator(s)

Details of included comparators are provided below.

Acitretin	
Generic name (ATC code)	Acitretin (D05BB02)
Mode of action	Acitretin is a retinoid and works by binding to specific retinoid receptors in epidermis. This reduces hyperproliferation and inflammation and normalises dyskeratosis.
Pharmaceutical form	Capsules for oral administration
Posology	
Method of administration	Capsules should be taken with a meal or a glass of milk
Dosing	In Denmark, acitretin is used as an off-label treatment for GPP flares, and thus no official information on dosing is available. Treatment with acitretin could be initiated at an initial dose of 25 mg/day; however, patients with severe generalised pustular psoriasis often require more aggressive treatment with higher initial doses of 50–75 mg/day) (50)
Should the pharmaceutical be administered with other medicines	If patients are unable to tolerate high doses of acitretin, combination therapy with other drugs can be considered
Treatment duration	In Denmark, acitretin is used as an off-label treatment for GPP flares, and thus no official information on treatment duration is available – for the purpose of this submission treatment is assumed to continue until remission of flare, although many patients may continue to take acitretin as maintenance treatment.
Necessary monitoring	Liver enzymes are monitored every second week for the first two months of treatment and subsequently every third month. Serum-cholesterol and -triglycerides are monitored at treatment start, after one month, and subsequently every third month. Adults in long-term treatment with acitretin should be monitored for ossification abnormities. Patients at high risk of cardiovascular disease should be monitored for increases in cardiovascular risk indicators (e.g., blood pressure).

Acitretin	
Need for diagnostics or other tests	Liver enzymes, serum-cholesterol, and – triglycerides should be measured at treatment initiation.
Packaging	Acitretin is available in packages of 50 capsules of either 10 or 25mg.

Source: (51)

Cyclosporine	
Generic name (ATC code)	Cyclosporine (L04AD01)
Mode of action	Cyclosporine is a calcineurin inhibitor, which works by inhibiting the signalling phosphatase calcineurin leading to immunosuppression.
Pharmaceutical form	Capsules for oral administration, as an oral solution, or as concentrate for infusion
Posology	
Method of administration	Cyclosporine can be administered as oral capsules, oral solution, or as intravenous infusions. The daily dosage of cyclosporine should be given over two doses given with a 12-hour interval.
Dosing	In Denmark, cyclosporine is used as an off-label treatment for GPP flares, and thus no official information on dosing is available. The initial oral dosage for treatment of plaque psoriasis is 2.5 mg/kg/day for four weeks; the dosage can be increased to maximum 5 mg/kg/day at 2-week intervals if clinical improvements are not achieved. Initial doses of 5 mg/kg/day can be used in patients where rapid improvements are necessary. For maintenance treatment the lowest effective tolerable dose should be identified for the individual patient.
Should the pharmaceutical be administered with other medicines	No
Treatment duration	In Denmark, cyclosporine is used as an off-label treatment for GPP flares, and thus no official information on treatment duration is available – for the purpose of this submission treatment is assumed to continue until remission of flare.
Necessary monitoring	Kidney and liver functioning should be closely monitored during cyclosporine treatment. Blood pressure must also be regularly monitored during treatment.
Need for diagnostics or other tests	Prior to treatment initiation a reliable estimate of kidney functioning must be established. Levels of bilirubin and other indicators of liver function should be measured prior to initiation of treatment.
Packaging	Cyclosporine is available in packages of 50 capsules of 25m, 50mg, or 100mg; as an oral solution (100mg/ml) in 50ml vials; and as a concentrate for solution (50mg/ml) in packages of 10 ampuls of 1 or 5 ml.

Source: (52)

Infliximab	
Generic name (ATC code)	Infliximab (L04AB02)

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Infliximab	
Mode of action	TNF-α inhibitor. Infliximab inhibits tumour necrosis factor alpha (TNF-α) activity by binding to transmembrane and soluble forms, as well as by preventing TNF-α from binding to its receptor.
Pharmaceutical form	Powder for concentrate for solution for infusion
Posology	
Method of administration	Infliximab should be administered intravenously over a 2-hour period. In carefully selected adult patients who have tolerated at least 3 initial 2-hour infusions of infliximab (induction phase) and are receiving maintenance therapy, consideration may be given to administering subsequent infusions over a period of not less than 1 hour.
Dosing	In Denmark, infliximab is used as an off-label treatment for GPP flares, so no official information on dosing is available. For chronic severe plaque psoriasis, the recommended dosage of infliximab in adult patients is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter.
Should the pharmaceutical be administered with other medicines	No
Treatment duration	In Denmark, infliximab is used as an off-label treatment for GPP flares, and thus no official information on treatment duration is available – for the purpose of this submission treatment is assumed to continue until remission of flare
Necessary monitoring	All patients administered infliximab are to be observed for at least 1-2 hours post-infusion for acute infusion-related reactions. Patients must be monitored closely for infections before, during, and after treatment with infliximab. If patients are re-treated after a prolonged period infliximab-free period, they must be closely monitored for signs and symptoms of delayed hypersensitivity. Patients with mild heart failure should be closely monitored, and infliximab must not be continued in patients who develop new or worsening symptoms of heart failure.
Need for diagnostics or other tests	Patients should be screened for active and latent tuberculosis and hepatitis B before initiation of treatment
Packaging	One vial of powder for concentrate (100mg)

Source: (53)

Adalimumab	
Generic name (ATC code)	Adalimumab (L04AB04)
Mode of action	TNF-α inhibitor. Adalimumab inhibits tumour necrosis factor alpha (TNF-α) activity by binding to transmembrane and soluble forms, as well as by preventing TNF-α from binding to its receptor
Pharmaceutical form	Solution for injection
Posology	
Method of administration	Adalimumab is administered subcutaneously. Treatment should be initiated and supervised by specialist physicians experienced in diagnosis and treatment of conditions for which adalimumab is indicated. After proper training in injection technique, patients may self-inject

Adalimumab	
	with adalimumab if their physician determines that it is appropriate and with medical follow-up as necessary.
Dosing	In Denmark, adalimumab is used as an off-label treatment for GPP flares, so no official information on dosing is available. For chronic severe plaque psoriasis, the recommended dosage of adalimumab in adult patients is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose
Should the pharmaceutical be administered with other medicines	No
Treatment duration	In Denmark, adalimumab is used as an off-label treatment for GPP flares, and thus no official information on treatment duration is available – for the purpose of this submission treatment is assumed to continue until remission of flare
Necessary monitoring	Patients treated with adalimumab should be monitored closely for infections, including tuberculosis, before, during and after treatment. Because the elimination of adalimumab may take up to four months, monitoring should be continued throughout this period. Carriers of HBV who require treatment with adalimumab should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Patients with cardiovascular disease treated with adalimumab should be closely monitored.
Need for diagnostics or other tests	Before initiation of therapy with adalimumab, all patients must be evaluated for both active and inactive ("latent") tuberculosis infection. Patients should be tested for HBV infection before initiating treatment with Adalimumab.
Packaging	Adalimumab is available as 20 or 40mg solution for injection in pre-filled syringes (two syringes per package) or as 40mg solution for injection in pre-filled pens (two pens per package).

Source: (54)

Bimekizumab	
Generic name (ATC code)	Bimekizumab (L04AC21)
Mode of action	IL-17 inhibitor. Bimekizumab binds with high affinity IL-17A, IL-17F and IL-17AF cytokines and blocks the biological activities of pro-inflammatory cytokines.
Pharmaceutical form	Solution for injection
Posology	
Method of administration	Bimekizumab is administered by subcutaneous injection. Suitable areas for injection include thigh, abdomen and upper arm. Injection sites should be rotated, and injections should not be given into psoriasis plaques or areas where the skin is tender, bruised, erythematous, or indurated. The pre-filled syringe or pre-filled pen must not be shaken. After proper training in subcutaneous injection technique, patients may self-inject bimekizumab with the pre-filled syringe or pre-filled pen if their physician determines that it is appropriate and with medical follow-up as necessary
Dosing	In Denmark, Bimekizumab is used as an off-label treatment for GPP flares, so no official information on dosing is available. For plaque psoriasis is 320 mg (given as 2 subcutaneous injections of 160 mg each) at week 0, 4, 8, 12, 16 and every 8 weeks thereafter.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Bimekizumab	
Should the pharmaceutical be administered with other medicines	No
Treatment duration	In Denmark, bimekizumab is used as an off-label treatment for GPP flares, and thus no official information on treatment duration is available – for the purpose of this submission treatment is assumed to continue until remission of flare
Necessary monitoring	Patients treated with bimekizumab should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a clinically important infection or is not responding to standard therapy, the patient should be monitored carefully and bimekizumab should not be administered until the infection resolves. Patients receiving bimekizumab should be monitored for signs and symptoms of active TB
Need for diagnostics or other tests	Prior to initiating treatment with bimekizumab, patients should be evaluated for TB infection
Packaging	Bimekizumab is available as 160 mg solution for injection in pre-filled syringe (two syringes per package)

Source: (55)

Guselkumab	
Generic name (ATC code)	Guselkumab (L04AC16)
Mode of action	IL-23 inhibitor. Guselkumab selectively binds with high affinity to the p19 subunit of human interleukin 23 (IL-23) cytokines without binding to IL12 and inhibits its interaction with the IL-23 receptor complex. By blocking IL-23 from binding to its receptor, guselkumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines
Pharmaceutical form	Solution for injection
Posology	
Method of administration	Subcutaneous use. If possible, areas of the skin that show psoriasis should be avoided as injection sites. After proper training in subcutaneous injection technique, patients may inject guselkumab if a physician determines that this is appropriate. However, the physician should ensure appropriate medical follow-up of patients
Dosing	In Denmark, guselkumab is used as an off-label treatment for GPP flares, so no official information on dosing is available. For plaque psoriasis the recommended dose is 100 mg by subcutaneous injection at weeks 0 and 4, followed by a maintenance dose every 8 weeks.
Should the pharmaceutical be administered with other medicines	No
Treatment duration	In Denmark, guselkumab is used as an off-label treatment for GPP flares, and thus no official information on treatment duration is available – for the purpose of this submission treatment is assumed to continue until remission of flare
Necessary monitoring	Patients treated with guselkumab should be instructed to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a clinically important or serious infection or is not responding to standard therapy, the patient

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Guselkumab	
	should be monitored closely, and treatment should be discontinued until the infection resolves. Patients receiving guselkumab should be monitored for signs and symptoms of active TB
Need for diagnostics or other tests	Prior to initiating treatment with guselkumab, patients should be evaluated for TB infection
Packaging	Guselkumab is available as 100 mg solution for injection in pre-filled syringe (two syringes per package)

Source: (56)

As described above all treatments currently used for the treatment of GPP flares in Danish clinical practice are used off-label. Randomised evidence of the safety and efficacy in patients experiencing GPP flares does not exist for any of the included comparators. A systematic literature review conducted in 2023 aimed to identify studies investigating the efficacy and safety of treatments for GPP potentially eligible for an ITC; the review considered RCTs, single arm trials, observational studies, and case series. The available evidence for each comparator is described below and summarised in Table 3.

5.2.3.1 Evidence for acitretin

To date, there is limited evidence that supports the use of acitretin in the treatment of GPP due to the rarity of the disease and the lack of controlled prospective studies. In the review described above a single RCT comparing acitretin and methotrexate (n = 40) (57) and a case series describing GPP patients treated with acitretin (n = 9) (58) were identified. While meta-analysis is not appropriate for the identified studies due to variations in study design, eligibility criteria and outcomes, using the GRADE approach to rate the quality of the available evidence leads to downgrading due to study limitations, indirectness, and a large potential for publication bias (59). This leads to an overall quality of evidence of very low meaning that the true effect is likely to be substantially different from the estimate of effect (60)

5.2.3.2 Evidence for cyclosporine

As with acitretin there is very limited evidence to support the use of cyclosporine in the treatment of GPP flares. In the systematic literature review described above, only a single arm trial (n = 9) was identified (61). As only one study was identified meta-analysis is not possible, but using the GRADE approach to rate the quality of the available evidence leads to downgrading due to study limitation, indirectness, and a large potential for publication bias, leading to an overall quality of evidence of very low (59).

5.2.3.3 Evidence for infliximab

For infliximab, three single-arm trials (N = 191 patients with pustular psoriasis) (62-64) , and five case series (65-69) were identified. As with the other comparators meta-analysis was not appropriate and the overall quality of evidence was graded as very low, due to downgrading for the same reasons as described above.

5.2.3.4 Evidence for adalimumab

For adalimumab, a single phase 3 single-arm trial (N = 10 patients) (70) was identified. As with the other comparators meta-analysis was not appropriate and the overall quality of evidence was graded as very low, due to downgrading for the same reasons as described above.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

5.2.3.5 Evidence for guselkumab

For guselkumab, two single-arm trials (N = 11 patients with GPP) (71) were identified, and thus the quality of evidence was graded as very low, for the same reasons as for the remaining comparators.

5.2.3.6 Evidence for bimekizumab

No studies examining bimekizumab as a treatment for GPP were identified in the SLR conducted to identify treatment studies of treatments for GPP flares potentially eligible for an ITC.

Table 3. Evidence quality for comparators

Comparator	Patients (N)	Randomised trials identified	Observational or single-arm studies identified	Case-series identified	Quality of evidence[1]
Acitretin	49	1	0	1	Very Low
Cyclosporine	109	0	4	6	Very Low
Infliximab	205	0	3	5	Very Low
Adalimumab	10	0	1	0	Very Low
Guselkumab	11	0	2	0	Very low
Bimekizumab	0	0	0	0	-

5.3 The intervention

Spesolimab is a first-in-class humanised IgG-1 mAb against human interleukin-36 receptor. The antibody binds to human IL-36R and inhibits all three IL-36 ligands (IL-36 alpha, beta and gamma). Blockade of the IL-36 pathway has a rapid biological effect, normalising cytokine signalling, immune cell activation and neutrophil recruitment, and inhibiting hyperkeratosis to restore epithelial barrier function in the skin. It is evident *in vitro* and *ex vivo* that binding of spesolimab to the IL-36 receptor modulates the activation of downstream effector, pro-inflammatory cytokines that are implicated in the pathogenesis of generalised pustular psoriasis, including TNF-α, IL-17, IL-23 and IL-1β.

Spesolimab is indicated for the treatment of flares in adult patients with GPP as monotherapy. The recommended dose is a single dose of 900 mg. Following dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, spesolimab is administered as a continuous intravenous infusion over 90 minutes. If flare symptoms persist an additional dose of 900mg may be administer one week after the initial dose (72). Concomitant use of other immunosuppressants and spesolimab is not recommended. At initiation of spesolimab treatment, other GPP treatments should be stopped and other treatments (e.g. with systemic immunosuppressants) should not be used concomitantly to treat the flare (72).

Before initiating treatment, patients should be evaluated for active or latent tuberculosis (TB) as spesolimab is contraindicated in patients with active TB. After treatment administration patients should be monitored for signs and symptoms of active TB (72).

During administration patients should be monitored for hypersensitivity and infusion-related reactions. After treatment physicians should be vigilant for symptoms of new-onset peripheral neuropathy (72).

All currently used treatments for patients with acute GPP flares are used off-label, thus spesolimab is the only available treatment with an indication for use in this population and should be used as the first line of treatment for eligible patients. Based on interviews with Danish clinical experts between 75% and 90% of patients with acute GPP flares are expected to be eligible for spesolimab treatment.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A systematic review was conducted with the following objectives:

- Identify suitable data sources for the indirect comparison of spesolimab versus off-label treatments currently used in GPP, and
- Assess any available data for its suitability for an ITC approach

The SLR was conducted in April 2023 and searches were performed via Ovid.com on:

- MEDLINE
- MEDLINE In-Process
- Embase

The search strategy was developed using population, intervention, comparator, outcomes, time, and study design (PICOT(S) criteria. The search was limited to the year 2000 based on the known literature, publication dates for comparable studies and approval dates for major competitors to spesolimab. In addition to the databases described above, grey literature searches were also performed (See Appendix A for details).

In the SLR a total of 81 studies were screened at full-text stage (most of these studies examined interventions not of interest for this submission), however none of the identified studies were considered feasible for inclusion in an indirect treatment comparison.

Details of the SLR methods, search strings and results are provided in Appendix A.

6.2 List of relevant studies

Table 4. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Trial of Spesolimab for Generalized Pustular Psoriasis, Bachelez, NEJM, 2021	**Effisayil™ 1:** Multi-center, double-blind, randomized, placebo-controlled, Phase II study to evaluate efficacy, safety and tolerability of a single intravenous dose	NCT03782792	**Start:** 20 February 2019 **End:** 05 Jan 2021	**Intervention:** Spesolimab **Comparator:** Placebo

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
	of BI 655130 in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity			
Safety, efficacy, and drug survival of the infliximab biosimilar CT-P13 in post-marketing surveillance of Japanese patients with psoriasis, Morita, J Dermatol, 2022	Safety, efficacy, and drug survival of the infliximab biosimilar CT-P13 in post-marketing surveillance of Japanese patients with psoriasis	Not registered	**Start:** July 2014 **End:** December 2019	**Single arm; intervention:** Infliximab
Efficacy and safety of dose escalation of infliximab therapy in Japanese patients with psoriasis: Results of the SPREAD study, Torii, J Dermatol, 2017	the Study on Psoriasis Treatment with Remicade Escalating Dosage	NCT01680159	**Start:** July 2012 **End:** March 2015	**Single arm, intervention:** Infliximab
Safety profiles and efficacy of infliximab therapy in Japanese patients with plaque psoriasis with or without psoriatic arthritis, pustular psoriasis or psoriatic erythroderma: Results from the prospective post-marketing surveillance, Torii, J Dermatol, 2016	Prospective post-marketing surveillance	Not registered	**Start:** 20 January 2010 **End:** 31 August 2010	**Single arm, intervention:** Infliximab
Comparative Study on the Clinical Efficacy and Safety of Acitretin and MTX in the Treatment of Pustular Psoriasis by TLR7/MyD88/CXCL16	Comparative Study on the Clinical Efficacy and Safety of Acitretin and MTX in the Treatment of Pustular Psoriasis	Not registered	Not reported	**Intervention:** Acitretin **Comparator:** Methotrexate

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Pathway, Lu, Appl Bionics Biomech, 2022	by TLR7/MyD88/CX CL16 Pathway			

For detailed information about included studies, refer to appendix B.

7. Efficacy and safety

7.1 Efficacy and safety of spesolimab compared to placebo for flares in adult patients with GPP

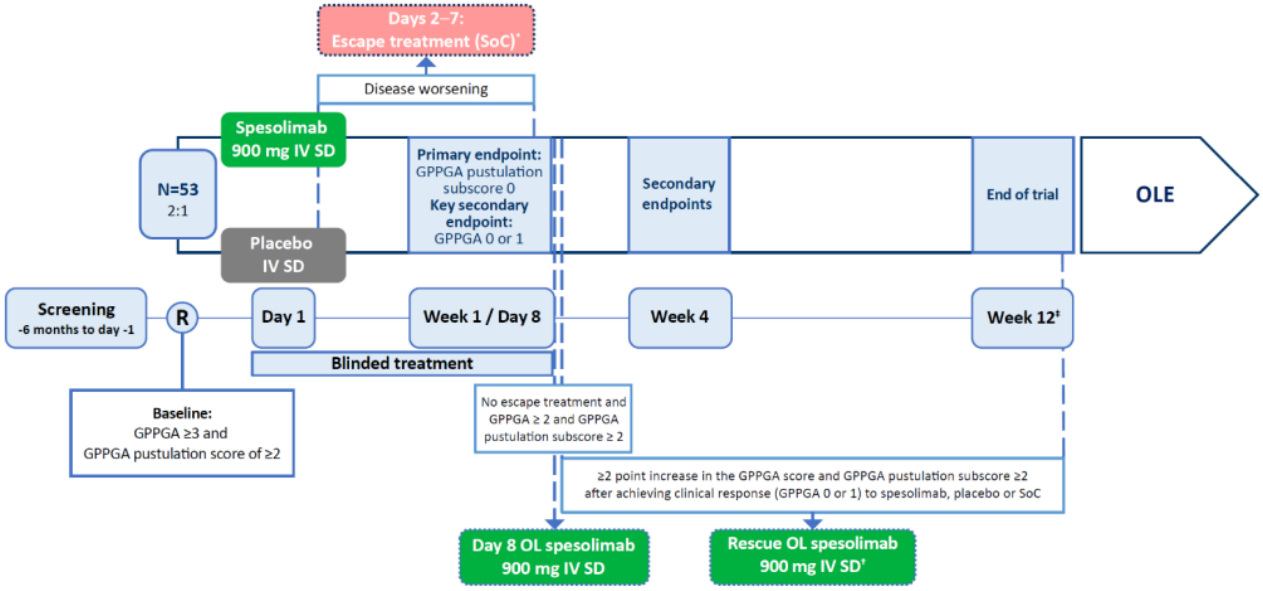
7.1.1 Relevant studies

The efficacy, tolerability, and safety of spesolimab was evaluated in patients with GPP presenting with an acute flare of moderate to severe intensity in the Effisayil-1 trial.

Effisayil-1 was a randomised, placebo-controlled, double-blind, parallel-group, single-dose trial with 2 treatment groups (spesolimab and placebo). Patients could qualify to receive an open-label treatment with spesolimab on Day 8 (if their Generalized Pustular Psoriasis Physician Global Assessment [GPPGA] total score was ≥2 and their GPPGA pustulation subscore was ≥2 on Day 8) and rescue treatment with spesolimab after Day 8 (if they had a ≥2-point increase in both the GPPGA total score and the GPPGA pustulation subscore after a previous clinical response to treatment [i.e. a GPPGA total score of 0 or 1]).

The study design of Effisayil-1 is summarised in Figure 1. The choice of comparator and the design of the study was discussed by the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) in the Public Assessment Report for spesolimab, and while the design with placebo control and option for rescue with spesolimab at week 1 makes interpretation of endpoints measured after week 1 challenging, the design of the study was considered adequate. The CHMP also noted that due to the heterogenous SoC in GPP and lack of adequate information about its effects, a comparative study vs. SoC would have been difficult to plan (73).

Figure 1. Study design for Effisayil™ 1



Abbreviations: IV, Intravenous; OL, Open Label; OLE, Open Label Extension; R, Randomisation; SD, Single Dose; SoC; Standard of Care

Study name	**Effisayil™ 1:** Multi-center, double-blind, randomized, placebo-controlled, Phase II study to evaluate efficacy, safety and tolerability of a single intravenous dose of BI 655130 in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity (**NCT03782792**)	
Study design	Randomised, placebo-controlled, double-blind, parallel-group, single-dose trial with 2 treatment groups (spesolimab and placebo).	
Sample size (n)	Randomised: 53	
Patient population(s)	Spesolimab (intervention)	Placebo (comparator)
	N=35	N=18
Intervention(s)	**Treatment regimen:** Spesolimab (BI 655130), solution for infusion 60 mg/mL ○ 900 mg, single dose ○ Intravenous infusion	
Comparator(s)	Matched intravenous placebo	
Follow-up period	All patients were followed for 12 weeks after the first dose of spesolimab. If patients entered the open-label extension study and received spesolimab as rescue medication between week 7 and week 12, the follow-up period was 6 weeks after this administration, i.e., up to 18 weeks	

	Patients that did not enter the open-label extension study the follow-up period was 16 weeks after the last spesolimab dose, i.e., up to 28 weeks
Key eligibility criteria[1]	**Inclusion:** • 18 to 75 years of age • History of GPP consistent with the diagnostic criteria of the European Rare and Severe Psoriasis Expert Network • GPP flare of moderate-to-severe intensity (defined as a GPPGA total score of ≥3, new or worsening pustules, a GPPGA pustulation subscore of ≥2, and ≥5% of body-surface area with erythema and the presence of pustules) **Exclusion:** • Plaque psoriasis without pustules or with pustules restricted to psoriatic plaques • Drug-triggered acute generalized exanthematous pustulosis • Immediate life-threatening flare of GPP warranting intensive care treatment • Current treatment with methotrexate, cyclosporine, retinoids, or other restricted medications (specified in Appendix B)
Primary endpoint(s)	• GPPGA pustulation subscore of 0 (no visible pustules) at the end of week 1
Secondary endpoint(s)[2]	• GPPGA total score of 0 or 1 (clear or almost clear skin) at the end of week 1 • 75% or greater decrease in the score on GPPASI (GPPASI 75) at the end of week 4 • Change from baseline in the assessment of pain on a visual analogue scale (pain VAS) at the end of week 4 • Change from baseline in the score on PSS at the end of week 4 • Change from baseline in the score on FACIT-Fatigue at the end of week 4 • GPPGA pustulation subscore of 0 (no visible pustules) at the end of week 4 • GPPGA total score of 0 or 1 (clear or almost clear skin) at the end of week 1 • Change from baseline in DLQI over time • Change in neutrophil count over time • Change in CRP over time
Baseline characteristics	Baseline characteristics are presented in detail in Appendix C
Predefined subgroups	Subgroup analyses are described in detail in Appendix B
Used in the health economic model?	Yes

[1]All inclusion and exclusion criteria are provided in Appendix B

[2]All secondary and explorative endpoints are provided in Appendix B

7.1.2 Efficacy and safety – Effisayil-1 (NCT03782792)

In Effisayil-1 all analyses were conducted on the randomised set (RS), unless otherwise specified. The RS consisted of all patients randomised and patients were analysed according to the assigned treatment, thus analyses using the RS followed the intention-to-treat principle.

Details of the operationalisation and validation of the GPPGA scale (which was used for the primary and key secondary endpoints in Effisayil-1), the GPPASI scale (which was used for secondary endpoints), and additional scales used are provided in Appendix D Overall the endpoints used in the Effisayil-1 trial were considered adequately supported and endorsed by the EMA CHMP (73).

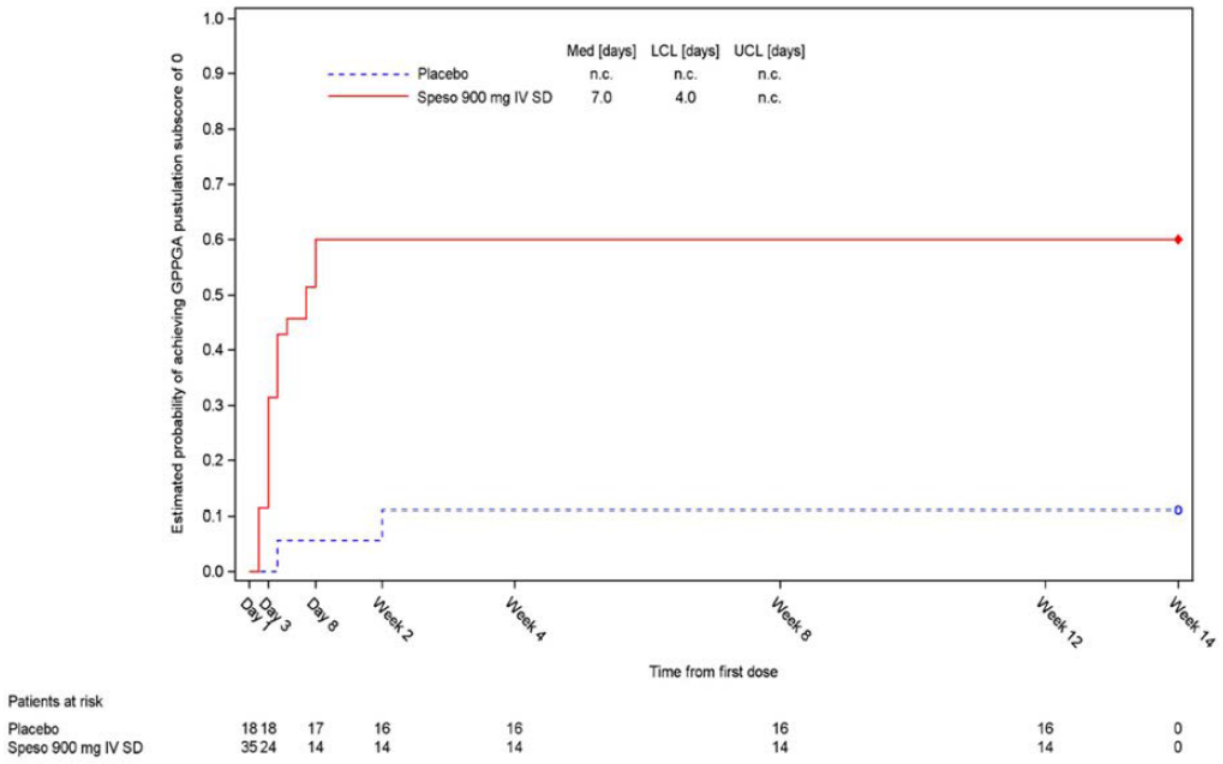
7.1.2.1 Proportion of patients with a GPPGA Pustulation subscore of 0 at week 1

The proportion of patients with a GPPGA pustulation subscore of 0 (indicating no visible pustules) after one week was the primary outcome in the Effisayil-1 trial. The primary analysis demonstrated the superiority of spesolimab compared to placebo (18).

At the end of week 1, 19 of the 35 patients (54.3%) assigned to the spesolimab group and 1 of the 18 (5.6%) assigned to the placebo group had a GPPGA pustulation subscore of 0 (no visible pustules), resulting in a clinically and statistically significant difference of 48.7 percentage points (95% CI: 21.5% to 67.2%; p = 0.0004) (18).

The time to first achievement of a GPPGA pustulation subscore of 0 (based on observed cases) is visualised in Figure 2.

Figure 2. Time to first achievement of GPPGA pustulation subscore of 0 – Randomised set (Observed cases)



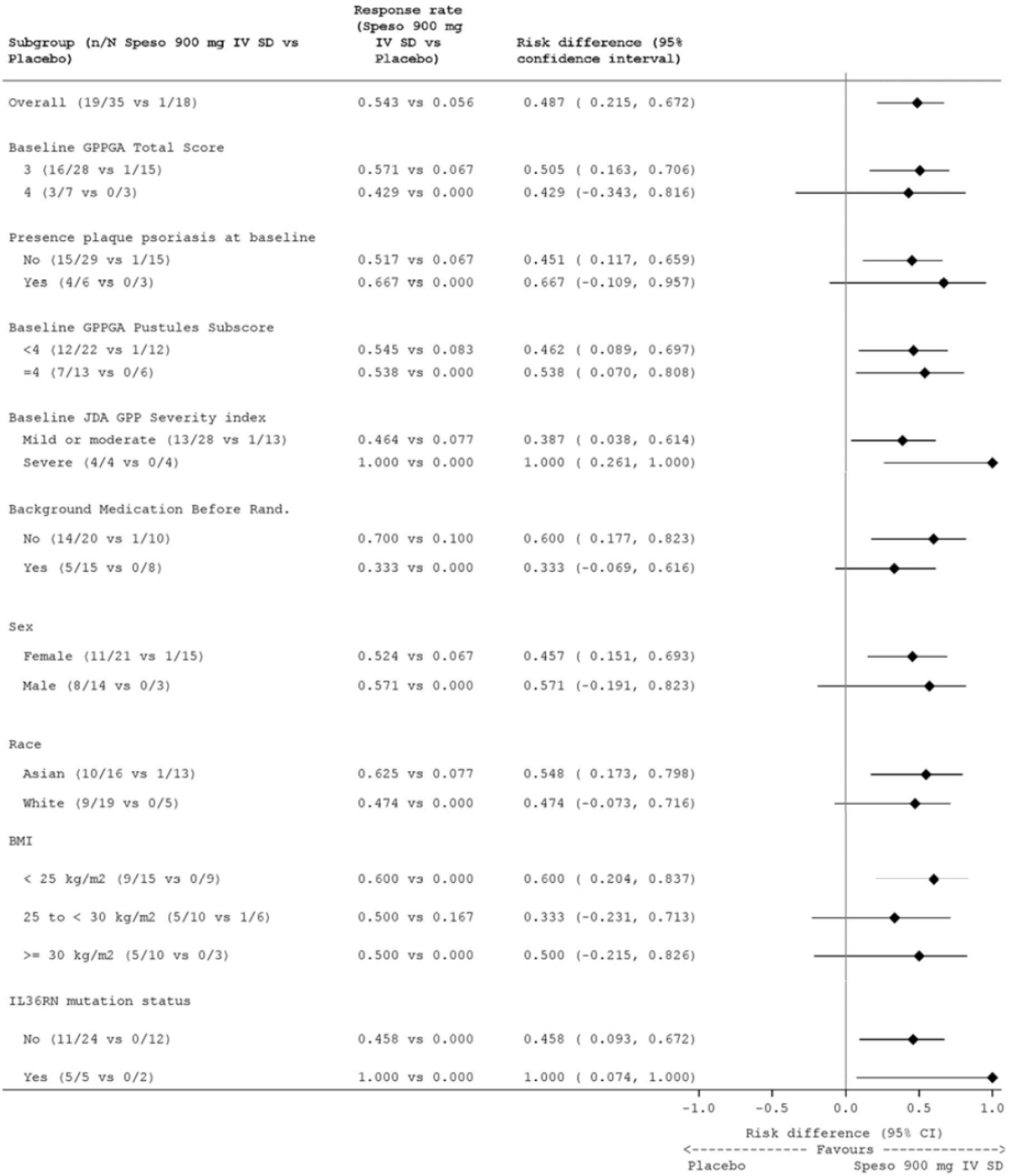
n.c. = not calculable; source: (74)

Separation between spesolimab and placebo was seen as early as day 2, demonstrating the rapid effect of spesolimab and the separation between arms was maintained throughout the trial period. For patients assigned to the spesolimab arm, the probability of response at day 2, 3 and 8 was 11.8%, 32.4% and 59.4% respectively. For patients assigned to the placebo arm no patients achieved response by day 2 or 3 and only one patient (5.9%) had achieved response by day 8.

Several sensitivity analyses were done to assess the handling of estimand and missing data by different estimand strategies and imputation methods. Logistic regression was used to analyse the impact of potential covariates. In all cases the results of the sensitivity analyses were consistent with the results of the primary analysis for the proportion of patients with a GPPGA pustulation subscore of 0 at Week 1 (74).

Additionally, the consistency of the treatment effect was investigated in predefined subgroups by sex, age, race, BMI category, GPPGA pustulation subscore at baseline, GPPGA total score at baseline, plaque psoriasis at baseline, background treatment prior to randomization, JDA GPP severity score at baseline, and mutation status in IL36RN. Overall, the results were consistent across the subgroups. The treatment effects estimates were generally comparable to the estimates of the primary analysis (Figure 3). Taking the small size of many of the subgroups into account, no evidence was found for a different effect of spesolimab compared to placebo on the treatment of GPP flares across all subgroups.

Figure 3. Subgroup analyses of the primary endpoint



Source: (74)

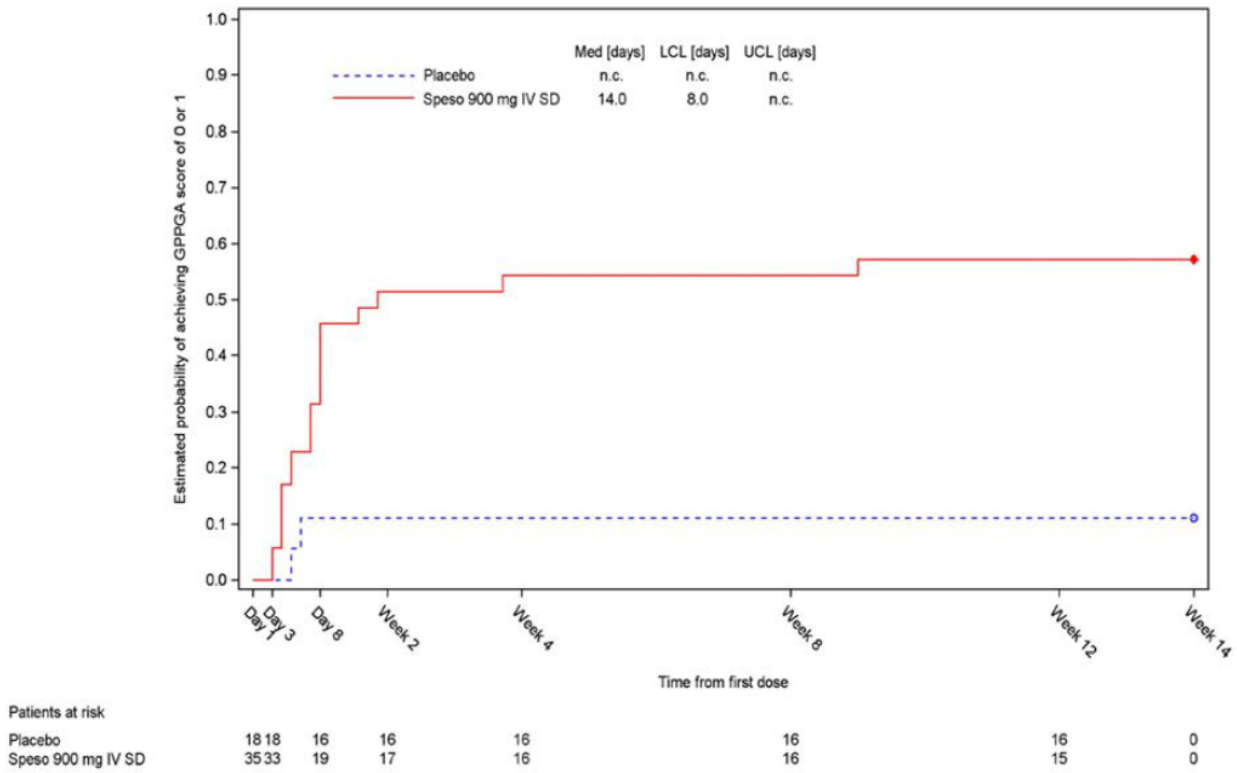
7.1.2.2 Proportion of patients with a GPPGA total score of 0 or 1 at Week 1

The proportion of patients with a GPPGA total score of 0 or 1 (indicating clear or almost clear skin) at the end of week 1 was the key secondary endpoint of Effisayil-1 (18).

At the end of week 1, 15 of the 35 patients (42.9%) assigned to the spesolimab group and 2 of the 18 (11.1%) assigned to the placebo group had a GPPGA total score of 0 or 1, resulting in a clinically and statistically significant difference of 31.7 percentage points (95% CI: 2.2% to 52.7%; p = 0.0118) (18).

The time to first achievement of a GPPGA total score of 0 or 1 is visualised in Figure 4.

Figure 4. Time to first achievement of GPPGA total score of 0 or 1 – Randomised set (observed cases)



As with the GPPGA pustulation subscore, separation between the curves is seen early on and is maintained throughout the study period.

Like for the primary endpoint, sensitivity and subgroup analyses were conducted to assess the robustness of findings. In all cases the results of the sensitivity analyses were consistent with the results of the primary analysis for the proportion of patients with a GPPGA total score of 0 or 1 at week 1 and no evidence was found for a different effect of spesolimab compared to placebo on the treatment of GPP flares across all subgroups (74).

7.1.2.3 Proportion of patients with a GPPASI 75 at week 4

The proportion of patients with a GPPASI 75 at week 4 was the first of four secondary outcomes that were planned to be included in a hierarchical testing strategy in Effisayil-1. However, as 16 out of 18 patients (88.9%) assigned to the placebo arm and 15 out of 35 patients (42.9%) assigned to the spesolimab arm received open-label spesolimab at day 8 or spesolimab as rescue treatment, a large proportion of patients in both arms were treated as non-responders at week 4, and the true efficacy outcomes for the randomised treatment at this time-point were never observed for the analysis (74).

When treating patients that received open label spesolimab as non-responders, a GPPASI 75 was achieved in 16 out of 35 patients (42.9%) in the spesolimab arm and in two out of 18 patients (11.1%) in the placebo arm. The difference between the two arms of 34.6% (95% CI: 5.8% to 55.4%) was clinically and statistically significant (p = 0.0081) (74). Of

the 15 patients assigned to placebo who received open-label spesolimab on day 8, 0 had achieved GPPASI 75 by day, but after receiving spesolimab on day 8, six (40.0%) achieved GPPASI 75 by week 4, indicating a similar response to spesolimab as was seen in the patients randomised to spesolimab on day 1 (74).

7.1.2.4 Change from baseline in Pain VAS score at week 4

As with the proportion of patients achieving a GPPASI 75 at week 4, the analysis of change from baseline in Pain VAS was complicated by the large proportion of patients in the placebo arm receiving open label spesolimab at day 8. When coding any values after use of escape medication, open-label spesolimab at day 8, or rescue medication with spesolimab as non-response in both treatment arms the median change from baseline in Pain VAS in the spesolimab arm was -22.45 (IQR: –70.41, non-response), while the median, and both the first and third quartile, in the placebo arm was non-response. Using the Wilcoxon rank test, and assigning the worst ranks to non-responders in both arms, the difference between arms was statistically significant with a p-value of 0.0118 (74)

7.1.2.5 Change from baseline in PSS score at week 4

Similarly, to the other secondary endpoints analysed at week 4, analysis and interpretation of changes from baseline in PSS score at week 4 were made difficult by the large number of patients in the placebo arm receiving open label spesolimab on day 8. When coding any values after use of escape medication, open label spesolimab at day 8, or rescue medication with spesolimab as non-response in both treatment arms the median change from baseline in Pain VAS in the spesolimab arm was -2.0 (IQR: -9.0, non-response), while the median, and both the first and third quartile, in the placebo arm was non-response. Using the Wilcoxon rank test, and assigning the worst ranks to non-responders in both arms, the difference between arms was statistically significant with a p-value of 0.0044 (74).

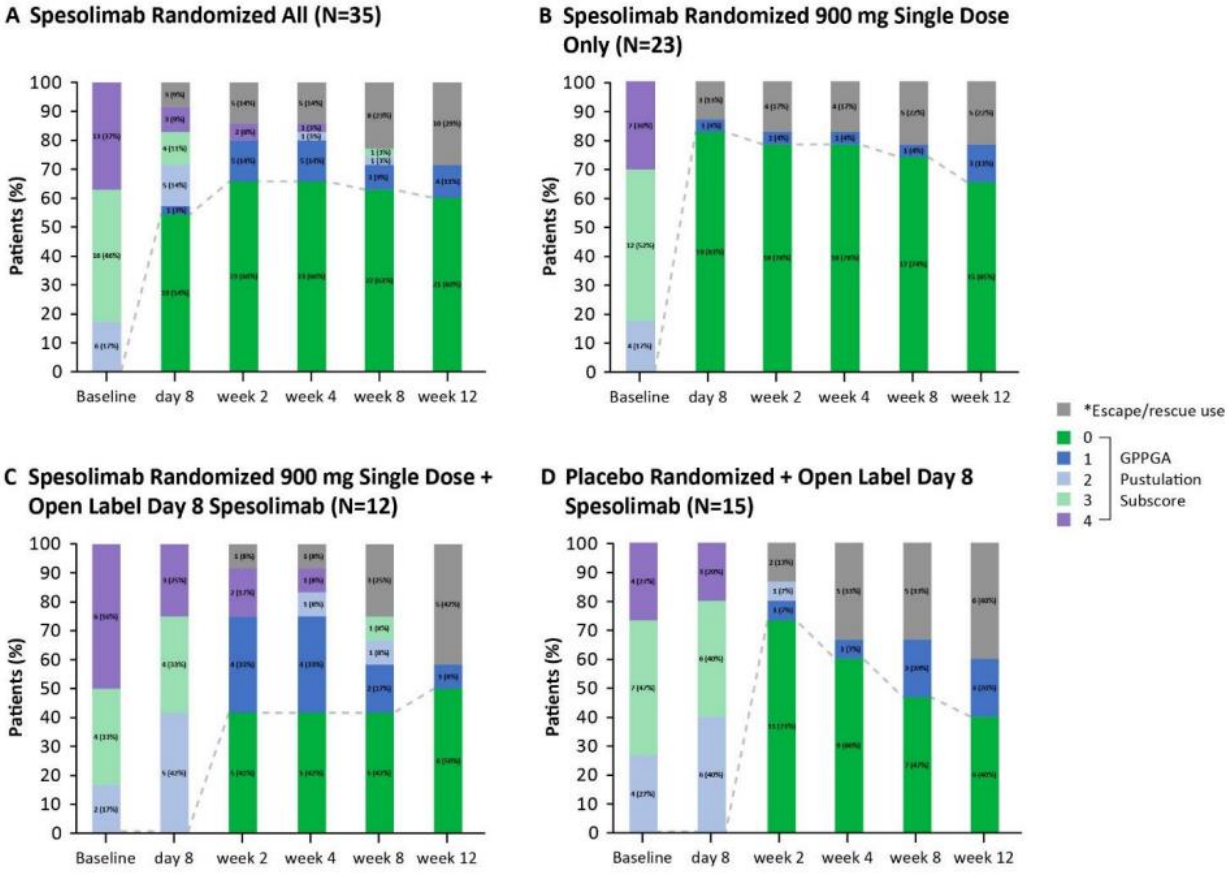
7.1.2.6 Change from baseline in FACIT-Fatigue score at week 4

The issues with analysing and interpreting data collected after a large proportion of patients received open label spesolimab described above, are also relevant for the change from baseline in FACIT-Fatigue score at week 4. When coding any values after use of escape medication, open label spesolimab at day 8, or rescue medication with spesolimab as non-response in both treatment arms the median change from baseline in Pain VAS in the spesolimab arm was 3.0 (IQR: non-response, 30.0), while the median, and both the first and third quartile, in the placebo arm was non-response. Using the Wilcoxon rank test,and assigning the worst ranks to non-responders in both arms, the difference between arms was statistically significant with a p-value of 0.0012 (74).

7.1.2.7 Proportion of patients with a Generalised Pustular Psoriasis Physician Global Assessment Pustulation subscore of 0 at week 4

The proportion of patients with a GPPGA pustulation subscore at week 4 was analysed as a secondary endpoint. Here, any values after receival of open label spesolimab at day 8 or rescue medication with spesolimab were coded as non-response. In the spesolimab group 18 patients (51.4%) had a GPPGA pustulation subscore of 0 (indicating no visible pustules) after the end of week 4, showing the sustained efficacy of spesolimab. In the placebo group two patients (11.1%) had a GPPGA pustulation subscore of 0, when coding patients who received open label spesolimab as non-responders. The difference between the two groups at week 4 was 40.3% (95% CI: 9.6% to 60.7%, p = 0.0033), showing the long-lasting efficacy of spesolimab compared to placebo (74). As with the other secondary outcomes, a large proportion of patients in the placebo received open label spesolimab on day 8 and were thus coded as non-responders. GPPGA pustulation subscore over time for all patients randomised to spesolimab is shown in Figure 5. As shown in Panel D, patients assigned to placebo that received open label spesolimab on day 8 showed a response very similar to that seen in patients assigned to spesolimab on day 1, indicating a response to open label spesolimab.

Figure 5. GPPGA Pustulation Subscore Over Time by Randomised Treatment at Day 1 and Open-Label Spesolimab Treatment at Day 8

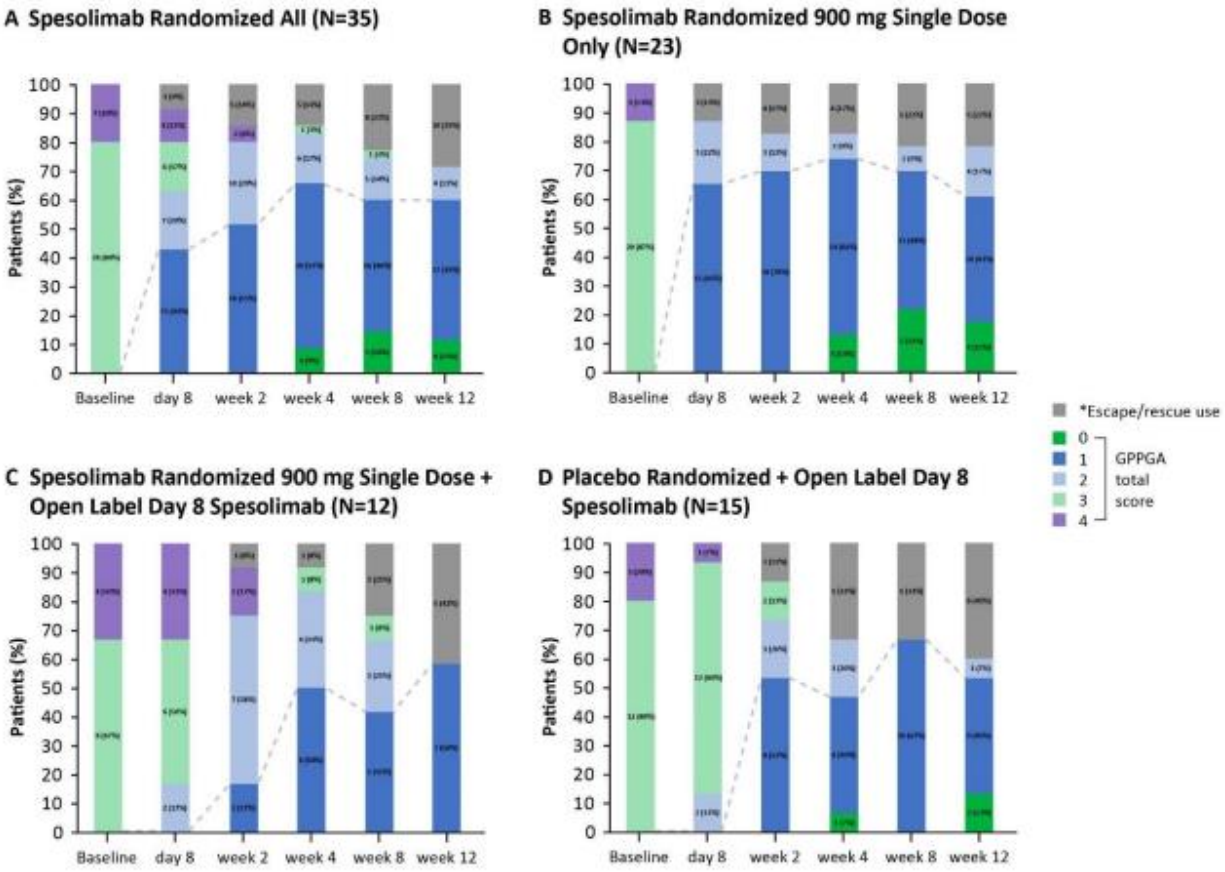


Source: (18)

7.1.2.8 Proportion of patients with a Generalised Pustular Psoriasis Physician Global Assessment total score of 0 or 1 at week 4

As with the proportion of patients who achieved a GPPGA pustulation subscore of 0 at week 4, the analysis of GPPGA total score at week 4 shows a sustained response to spesolimab treatment. Out of 35 patients assigned to the spesolimab arm, 17 (48.6%) achieved a GPPGA total score of 0 or 1 at week 4, versus only two patients (11.1%) assigned to placebo. The risk difference was 37.5% (95% CI 5.8% to 58.1%) with a p-value of 0.0056. However, it should be noted that in the analysis described above patients receiving open label spesolimab on day 8 were classified as non-responders. As shown in Panel D of Figure 6 patients assigned to placebo and receiving open label spesolimab at day 8 achieved a similar effect as was seen for patients randomised to spesolimab, indicating a response to open label spesolimab.

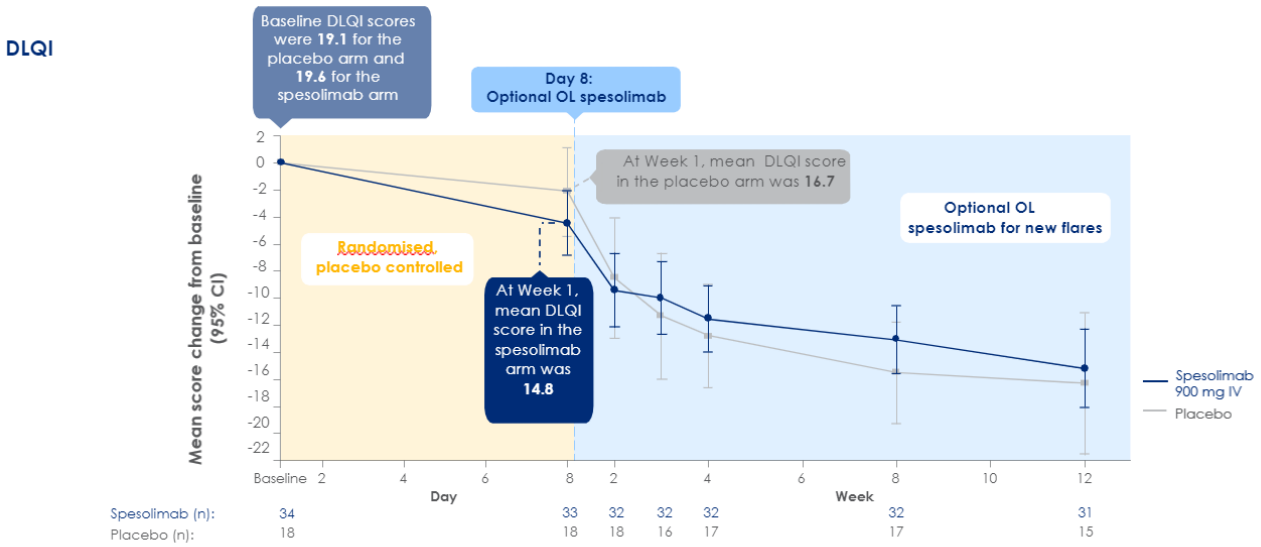
Figure 6. GPPGA Total Score Over Time by Randomised Treatment at Day 1 and Open-Label Spesolimab Treatment at Day 8



7.1.2.9 Change from baseline in Dermatology Life Quality Index score, by visit

As a large proportion of patients assigned to the placebo arm (83.3%) received open label spesolimab at day 8, analysis and interpretation of scores at visits after week 1 are challenging. Therefore, only results at week 1 are described in detail here. While Effisayil-1 was not powered to detect differences in DLQI, separation between arms was seen early on (Figure 7), and after week 1 the median change from baseline in the spesolimab arm was -2.5 (IQR: -8.0, 1.0) and -1.0 (IQR: -9.0, 3.0). Using the modified Hodges-Lehmann method the difference between the medians was estimated as -2.0 (95% CI: -7.0 to 3.0). As shown in Figure 7, the placebo curve begins to converge with the spesolimab curve after day 8, which is likely a consequence of the open label spesolimab administered on day 8 (20).

Figure 7. Mean DLQI score change from baseline – randomised set



Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index; IV, intravenous; OL, open-label; PRO, patient-reported outcome.

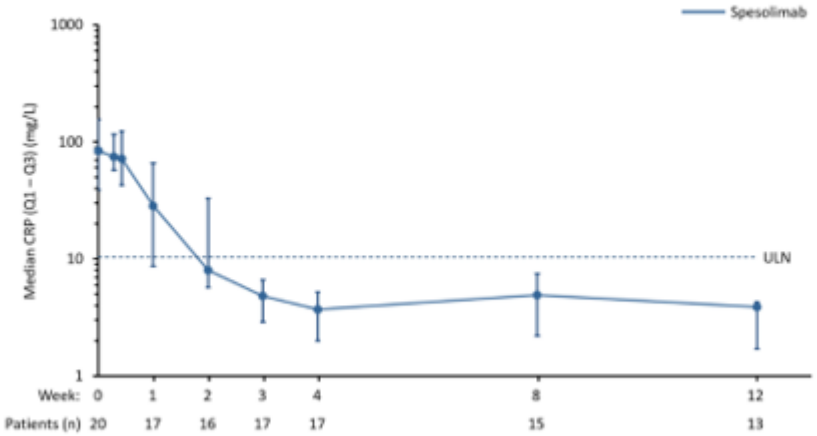
Source: (75)

7.1.2.10 CRP and neutrophil counts over time for patients treated with spesolimab

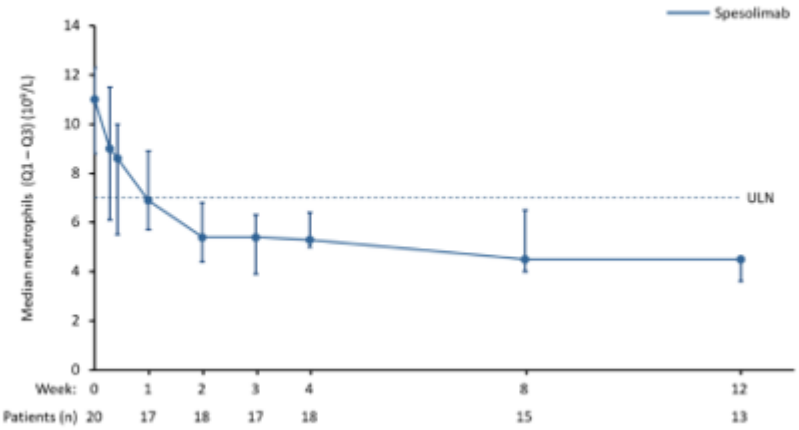
The effect of spesolimab on the systemic manifestations of the disease was assessed and showed significant decreases in CRP and neutrophils. After administration of up to two doses of spesolimab, the median CRP level normalised within 2 weeks and the median of absolute values in neutrophils normalised within 1 week for patients who had baseline values above the upper limit of normal (CRP: ULN=10 mg/L, neutrophils: ULN=7.23×109/L) (Figure 8). This effect was sustained through to Week 12.

Figure 8. CRP and absolute neutrophil count over time for patients treated with spesolimab

A. Q1, median, and Q3 of CRP over time for patients with baseline CRP > ULN (10 mg/L)



B. Q1, median, and Q3 of absolute values in neutrophils over time for patients with baseline neutrophils > ULN (7.23×109/L)



CRP, C-reactive protein; ULN, upper limit of normal. Source: (74)

7.1.2.11 Safety results from Effisayil-1

In Effisayil-1 all safety analyses were run on the SAF, which consisted of patients that were randomised and received at least one dose of their assigned intervention.

An overall summary of adverse events is provided in
Table 5. For the Week 1 period, the proportions of patients with any AE or SAE were comparable between the spesolimab and the placebo groups. The time-adjusted AE incidence rates were lower in the spesolimab treatment group at Week 12 (censored at use of any non-randomised spesolimab and up to the end of the residual effect period (REP)) for any spesolimab compared with both treatment groups at the end of Week 1 (Appendix E, Table 41).

Table 5. Summary of adverse events in Effisayil-1

	Up to Week 1 (double-blind period)	Up to Week 12 (patients initially randomised to spesolimab)[1]	Up to Week 12 (all patients treated with spesolimab, irrespective of randomisation)[2]

	Placebo		Spesolimab		Spesolimab		Post any spesolimab[2]	
	N (%)	Rate[3]	N (%)	Rate[3]	N (%)	Rate[3]	N (%)	Rate[3]
Number of patients	18 (100.0)		35 (100.0)		35 (100.0)		51 (100.0)	
Patients with any AE	12 (66.7)	6445.6	27 (77.1)	8650.7	29 (82.9)	2596.1	47 (92.2)	1874.1
Patients with severe AEs (RCTC grade 3 or 4)	2 (11.1)	640.8	6 (17.1)	1014.6	7 (20.0)	162.9	11 (21.6)	102.1
Patients with investigator-defined drug-related AEs	6 (33.3)	2306.8	12 (34.3)	2159.1	17 (48.6)	620.3	32 (62.7)	479.0
Patients with AEs leading to discontinuation of trial drug	0	0	0	0	0	0	0	0
Patients with SAEs	3 (16.7)	987.2	5 (14.3)	833.9	6 (17.1)	146.3	13 (25.5)	127.0

[1] Patients were censored if they received non-randomised spesolimab (i.e., open label spesolimab on Day 8 or spesolimab as rescue treatment later). For patients who did not receive non-randomised spesolimab, events are included until Day 113 (i.e., including a 16-week REP after double-blind treatment), EoS, or treatment in the extension trial, whichever was earlier.

[2] This includes patients who received at least 1 dose of spesolimab (i.e., double-blind, open label on Day 8, or as rescue treatment later). Events are included until 16 weeks after last spesolimab administration, EoS, or treatment in the extension trial, whichever was earlier.

[3] Incidence rate per 100 patient-years = 100 × number of patients with AE / total AE-specific time at risk [patient-years].

Source: (74)

Among the System Organ Classes (SOC), the SOC infections and infestations were most frequently reported up to Week 1. The SOC infections and infestations were reported for a higher proportion of patients in the spesolimab group (17.1%) than for patients in the placebo group (5.6%). On the Preferred Term (PT) level, no clear pattern of infections was observed, and the AEs were mainly non-serious, non-severe, and not indicative of opportunistic infections.

On the PT level, the proportions of patients were comparable between the spesolimab and the placebo groups up to Week 1. Within the spesolimab group, the proportions of patients with any of the most common AEs remained unchanged or slightly increased, whilst the time-adjusted incidence rates markedly decreased from Week 1 to Week 12 (for patients initially randomised to spesolimab and censored at use of any non-randomised spesolimab) (

Table 6).

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 6. AEs reported for more than 10% of patients in either treatment group on the PT level up to Week 1 or for more than 10% of patients in the spesolimab group up to the end of the REP – SAF

SOC/PT	Up to Week 1 (double-blind period)				Up to Week 12 (patients initially randomised to spesolimab)[1]		Up to Week 12 (all patients treated with spesolimab, irrespective of randomisation)[2]	
	Placebo		Spesolimab		Spesolimab		Post any spesolimab[2]	
	N (%)	Rate[3]	N (%)	Rate[3]	N (%)	Rate[3]	N (%)	Rate[3]
Number of patients	18 (100.0)		35 (100.0)		35 (100.0)		51 (100.0)	
Patients with any AE	12 (66.7)	6445.6	27 (77.1)	8650.7	29 (82.9)	2596.1	47 (92.2)	1874.1
Skin and subcutaneous tissue disorders	9 (50.0)	3612.4	18 (51.4)	3844.7	21 (60.0)	819.5	33 (64.7)	582.3
Pustular psoriasis	7 (38.9)	2719.9	13 (37.1)	2499.1	17 (48.6)	551.9	27 (52.9)	366.5
Nervous system disorders	3 (16.7)	961.2	4 (11.4)	655.2	5 (14.3)	114.8	7 (13.7)	60.5
Headache	1 (5.6)	299.4	3 (8.6)	478.5	4 (11.4)	87.4	5 (9.8)	41.8
Dizziness	2 (11.1)	619.1	0	0	0	0	0	0
General disorders and administration site conditions	5 (27.8)	1756.0	9 (25.7)	1543.3	9 (25.7)	224.8	13 (25.5)	127.5
Pyrexia	4 (22.2)	1404.8	2 (5.7)	313.5	2 (5.7)	40.7	5 (9.8)	41.3

[1] Patients were censored if they received non-randomised spesolimab (i.e., open label spesolimab on Day 8 or spesolimab as rescue treatment later). For patients who did not receive non-randomised spesolimab, events are included until Day 113 (i.e., including a 16-week REP after double-blind treatment), EoS, or treatment in the extension trial, whichever was earlier.

[2] This includes patients who received at least 1 dose of spesolimab (i.e., double-blind, open label on Day 8, or as rescue treatment later). Events are included until 16 weeks after last spesolimab administration, EoS, or treatment in the extension trial, whichever was earlier.

[3] Incidence rate per 100 patient-years = 100 × number of patients with AE / total AE-specific time at risk [patient-years]

Abbreviations: SOC, System Organ Classes; PT, preferred term. Source: (74)

The most frequently reported SAE with comparable frequencies in both treatment groups was pustular psoriasis. All SAEs are provided in appendix E, Table 42.

Overall, spesolimab showed an acceptable safety profile. The overall rates of AE were generally comparable between treatment groups at Week 1. Infections were reported with a higher rate in the spesolimab group compared with placebo, with no distinct pattern regarding pathogen or type of infection.

Within the spesolimab group, the proportions of patients with any of the most common AE remained unchanged or slightly increased, whilst the time-adjusted incidence rates markedly decreased from Week 1 to Week 12. Similarly, overall, AE frequencies and frequencies of the most common AE (up to Week 12) in the spesolimab group were comparable for patients after the first dose of spesolimab on Day 1 and following up to 3 doses of spesolimab in total (including open label on Day 8 and/or rescue spesolimab thereafter, with 12 patients receiving two total doses of spesolimab and two patients receiving 3 total doses of spesolimab). For two cases reported as drug reaction with eosinophilia and systemic symptoms DRESS, the rapid occurrence of symptoms after spesolimab administration in one case makes a causal relationship with spesolimab implausible, and in the other case, positive rechallenge with spiramycin suggests it as an alternative explanation (74).

7.1.2.12 Discussion of results of Effisayil-1

In summary, treatment with a single dose of 900 mg spesolimab led to rapid and sustained clinical improvement, as measured by various disease severity measures. For the patients who had persistent flare symptoms on day 8, the treatment with a second dose of spesolimab on day 8 also led to clinical improvement. The overall treatment effect of up to two doses of spesolimab was sustained over time and correlated with improvement in patient reported outcomes

(PROs) and quality-of-life measures. Improvement in systemic markers support that the effect of spesolimab addresses both skin and systemic components of the disease (74).

Effisayil-1 also provided evidence on the natural course of generalised pustular psoriasis flare in the placebo arm. With currently available treatment options, the mean duration of generalised pustular psoriasis flares usually ranges from one week up to three months (33). The time to pustular clearance, when treated, can take more than five weeks or longer depending on the severity of flares (33). As shown in Effisayil-1 the time to pustular clearance is much shorter in a large proportion of patients treated with spesolimab.

While length of hospitalisation was not studied in Effisayil-1, based on interviews with Danish clinicians, patients with a GPPGA total score of 0 or 1 would be ready for discharge from hospital, indicating that spesolimab treatment can substantially decrease the length of hospitalisations for patients with GPP flares (17). Additionally, clinicians interviewed underlined the value of the rapid effect of spesolimab treatment and noted that this is essential for patients with GPP flares.

Overall, spesolimab showed an acceptable safety profile. The overall rates of AE were generally comparable between treatment groups at Week 1. Infections were reported with a higher rate in the spesolimab group compared with placebo, with no distinct pattern regarding pathogen or type of infection. Within the spesolimab group, the proportions of patients with any of the most common AE remained unchanged or slightly increased, whilst the time-adjusted incidence rates markedly decreased from Week 1 to Week 12.

The safety data from Effisayil-1 was presented to Danish clinicians; generally, the safety profile was considered acceptable and it was noted that since spesolimab is targeting the underlying cause of GPP it should be used before other biologics (17).

7.1.3 Comparative analyses of efficacy and safety

As only one randomised trial examining the efficacy and safety of spesolimab for the treatment of GPP flares was identified no comparative analyses of efficacy and safety were done. Additionally, as only one randomised trial was identified for any of the included comparators, and this trial did not have a common comparator with Effisayil-1 and it was not possible to determine whether treatment setting and baseline characteristics matched between the trials, it was not possible to conduct an indirect treatment comparison.

While it is possible that the treatments currently used off-label for patients with GPP flares are more effective than placebo, the very low quality of evidence for the efficacy and safety of all the treatments also makes a narrative comparison challenging. Generally, while current treatments may have some effect in treating GPP flares, several studies have highlighted the unmet need for fast-acting and effective treatments, with the immediate treatment goals being to improve skin symptoms and reduce the burden of systemic manifestations (48, 76).

As no studies eligible for an ITC were identified the results of identified studies of relevant comparators are described narratively below:

7.1.3.1 Infliximab

Three single arm studies were identified for infliximab. None of the studies examined the use of infliximab for GPP flares specifically, rather patients were included if they had a diagnosis of pustular psoriasis and required treatment, indicating that the patients in these trials had less severe disease than in Effisayil-1(62-64). None of the studies assessed any of the primary or secondary outcomes included in the Effisayil-1 trial; however, the versions of the Physician Global Assessment (PGA) score not specific to GPP was assessed in one trial, and the Psoriasis Area Severity Index (PASI) not specific to GPP were assessed in all the trials. The results are described below, however as the trials are uncontrolled these naïve comparisons should be interpreted with caution:

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Physician Global Assessment (PGA):

One study included 20 patients with pustular psoriasis and assessed the proportion of patients who achieved a Physician Global Assessment (PGA) score of 0 or 1 (clear or almost clear skin, not specific for pustular psoriasis). After six weeks no patients had achieved a PGA score of 0 and 5 patients (25%) had achieved a PGA score of 1(62).

In Effisayil-1 15 out of 35 patients (42.9%) randomised to spesolimab achieved a GPPGA total score of 0 or 1 after 1 week, further increasing to 17 patients (48.6%) by week four when categorising patients receiving open-label spesolimab on day 8, indicating a larger and faster onsetting effect of spesolimab (18).

Physician Area Severity Index (PASI)

In the study with 20 pustular psoriasis patients, zero patients had achieved PASI75 after 6 weeks. After 14 weeks 16 out of 20 patients (80%) had achieved PASI75 (62).

In another study, out of 7 patients with pustular psoriasis zero had achieved PASI75 after 4 weeks, increasing to 2 (out of 6, 33.3%) after 8 weeks and plateauing at 50% (3 patients) after 12 weeks (NCT01680159)

In the final study, PASI75 was assessed in 164 patients with pustular psoriasis, however the assessment was done after 6 months making comparisons with the Effisayil-1 study difficult. The PASI75 rates are not reported for pustular psoriasis but the rate of PASI75 in 764 with various types of psoriasis was 60.1% and the authors noted that the results were similar across psoriasis types (64).

In Effisayil-1 when treating patients that received open label spesolimab as non-responders, a GPPASI 75 was achieved in 16 out of 35 patients (42.9%) in the spesolimab arm after 4 weeks, again indicating a stronger and faster onsetting response (18).

DLQI

While DLQI was measured in all of the three studies described above, data for GPP patients alone is not presented in any of the publications and thus a narrative summary of the results is not possible.

Safety

In one single-arm trial of infliximab 6 out of 7 patients with GPP (86%) experienced an adverse event and one patient (14%) experienced an adverse event. Five of the 7 patients (14%) with GPP experienced infections after infliximab treatment; however, none of these were classified as serious infections (63).

Another study, including 20 patients with GPP, found much lower rates of adverse events, with five patients (25%) experiencing an adverse event and one patient (5%) experiencing a serious adverse event (62).

Finally in a study of 764 patients with various types of psoriasis, including 164 patients with GPP, 172 patients (22.51%) experienced an adverse drug reaction and 53 (6.94%) experienced a serious drug reaction. Thirty-nine patients (5.1%) had infections after infliximab treatment and 19 (2.49%) of these were classified as being serious (64).

Considering the more severe disease experienced by patients in Effisayil-1 and the differing methods between the studies, the comparative safety of infliximab and spesolimab is difficult to assess, however spesolimab was generally well tolerated in the Effisayil-1 trial with similar rates for spesolimab and placebo within the first week of treatment (where the randomisation was intact) and few serious adverse events overall (18). Additionally, spesolimab has been examined in a total of 1.059 patients across various indications (e.g., GPP, palmoplantar pustulosis, and colitis ulcerosis) and has shown an acceptable safety profile (77).

7.1.3.2 Acitretin

One randomised trial comparing acitretin (n = 30) and methotrexate (n = 14) in GPP was identified – however, the included patients were not required to be experiencing an active flare making comparisons to spesolimab difficult (57).

GPPASI75

The proportion of patients achieving a GPPASI75 was an outcome of the trial, however in the trial publication by Lu et al. approximately 40% of patients are presented as having GPPASI75 at baseline. Since GPPASI75 is usually defined as a 75% improvement in GPPASI relative to the baseline this indicates either an error or that a different definition of GPPASI75 was used. Numbers are not reported in the publication, but visual inspection of the provided figures indicate approximately a 5% increase in the proportion of patients with GPPASI75 over 12 weeks of treatment (57).

In Effisayil-1 when treating patients that received open label spesolimab as non-responders, a GPPASI 75 was achieved in 16 out of 35 patients (42.9%) in the spesolimab arm after 4 weeks, indicating a stronger and faster onsetting response (18); however, due to the uncertainties about the results reported by Lu et al. it is unclear whether this comparison is meaningful.

DLQI

DLQI was also assessed in the trial, however numbers are not reported and the low quality of the available figure makes interpretation difficult – additionally, mean baseline DLQI was much lower in the trial reported by Lu et al (approximately 8 based on visual inspection of graph) than in Effisayil-1 (19.6 for the spesolimab arm) (18, 57). Based on visual inspection of the graph patients receiving acitretin experienced a decrease in mean DLQI of approximately 1-2 points after 8 weeks of treatment (57).

In Effisayil-1 the patients assigned to spesolimab experienced approximately 8 points improvement in DLQI by week 2, indicating a much larger and faster effect of spesolimab, although the large differences in baseline DLQI makes interpretation difficult.

Safety

In the trial reported by Lu et al., the proportion of patients experiencing adverse events were 8.1%, 10.3%, and 14.7% in the low-dose, medium-dose, and high-dose group respectively. No information on serious adverse events or the type of events is reported (57).

These rates are lower than what was reported in Effisayil-1; however, differences in baseline characteristics (e.g., disease severity) and study design make comparisons between the two studies difficult.

7.1.3.3 Length of hospitalisation

The best available estimate of the median duration of hospitalisation in Denmark for patients treated with currently available treatments is 9 days (interquartile range (IQR): 6-15 days) (9), and Danish clinicians have estimated that patients with severe GPP flares will generally be hospitalised for 2-3 weeks. Since patients with a GPPGA total score of 0 or 1 will generally be ready for discharge and that 42.9% of patients treated with spesolimab in Effisayil-1 achieved this, it is likely that spesolimab will substantially decrease the length of hospitalisation for patients with GPP flares. This is supported by statements from interviewed clinicians, who estimated that treatment with spesolimab would half the length of hospitalisation compared to the treatments currently used (17).

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

8. Health economic analysis

Spesolimab is indicated for the treatment of acute flares in adult patients with GPP. Given the brief and critical nature of acute GPP flares, the economic analysis focuses on this period. In this context, a cost-utility analysis (CUA) is deemed unsuitable as it fails to capture the primary characteristics of the disease during this short-term episode. The use of QALYs to assess morbidity in acute conditions is problematic due to both measurement and evaluation issues, as identified by Bala et al. in 2000 (78). Measurement issues relate to the difficulty in eliciting accurate utility values that are valid and reliable. Part of this problem stems from the requirement for patients to trade-off quantity and quality of life when they know the impact of the acute condition on their quality of life is temporary. Evaluation issues relate to the challenge of using elicited health utility values to make optimal healthcare decisions (78, 79).

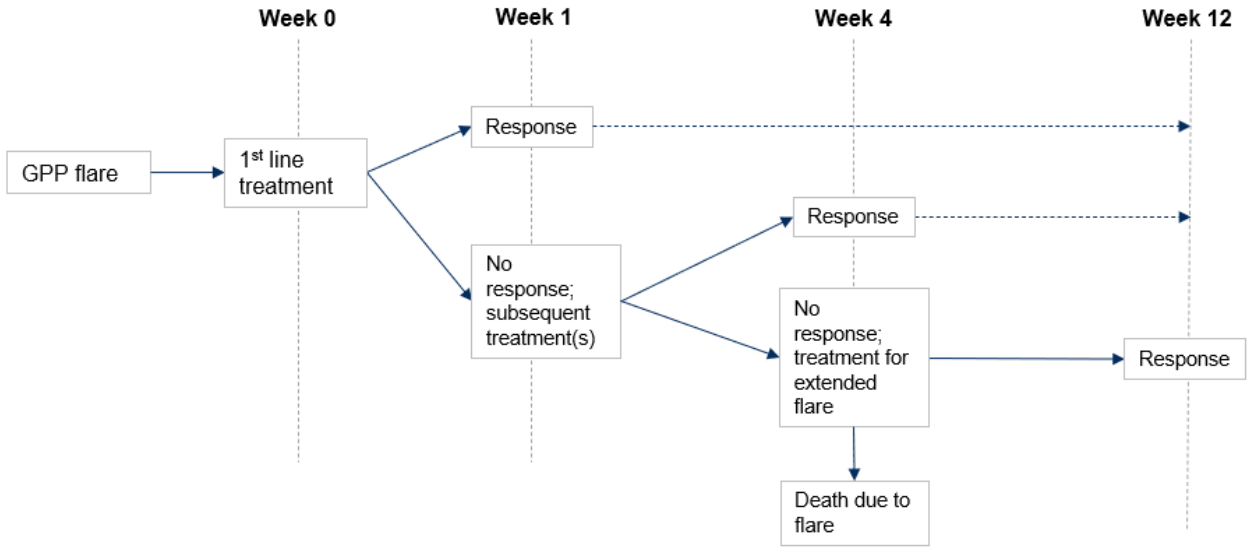
These problems, highlighted by Bala et al., support that a CUA is inappropriate as it fails to capture the impact of acute flares, which are the primary driver of the disease. The patient's quality of life decreases for a short period during an acute flare and then recovers. The frequency of flare recurrences varies among patients, with some patients experiencing no flares for several years while others experience them more frequently. Assessing GPP from a lifetime perspective poses an additional challenge due to the uncertainty surrounding the number of flares that may occur during the patient's life and the impact of GPP flares over a lifetime, given the brief nature of a flare. Consequently, utility values are unsuitable for capturing the full impact of acute GPP flares to implement in a CUA with a lifetime horizon. Furthermore, as discussed in section 5, GPP is a severe, chronic, rare skin disease that can be life-threatening, characterised by episodes of a widespread eruption of sterile, macroscopically visible pustules that frequently occur alongside systemic inflammation. Section 6.2.1 of the DMC method guideline recognises that a CUA may present difficulties in certain circumstances, such as with drugs used to treat rare diseases(21). In such cases, a CUA can result in a fragile foundation for decision-making, as it may fail to adequately reflect the actual impact of treatment on the disease of interest. Accordingly, the DMC method guideline allows for deviation from the use of CUA in such cases. Consequently, a simple costing analysis is performed to reflect the cost of an acute GPP flare.

8.1 Model

8.1.1 Model structure

The analysis uses a 12-week decision tree to perform a cost analysis to determine the costs of the intervention spesolimab compared to the best available care for patients experiencing a flare of GPP, see Figure 9. This economic analysis is focussing on the acute phase of a GPP flare. Consequently, a decision tree was deemed appropriate with its model structure to simply represent the short-term nature and response/non-response nature of a single GPP flare. The decision tree nodes capture a binary outcome of response or non-response to treatment for the GPP flare. This reflects the nature of treatment since patients are treated until a satisfactory response is shown and their flare is considered resolved (17).

Figure 9. Decision tree for the acute flare of GPP.



Abbreviations: GGP, Generalised Pustular Psoriasis

The decision tree allows the assessment of responses to a sequence of treatments for both moderate and severe GPP flare at 1, 4 and 12 weeks. Response was measured daily for the first week and weekly in the three subsequent weeks in the Effisayil-1 trial (see section 8.2). These data are populated in the model for the intervention and comparator arm. For Week 12, 100% of patients are assumed to respond since this is the expected maximum duration of a flare in clinical practice. Costs as drug acquisition, administration, resource use, adverse event, along with patient time and transportation costs are applied in line with the DMC method guideline (21).

Upon entry to the decision tree, patients receive their first line treatment and are daily assessed for response in the first week. In this first week of the model, patients can incur the above-mentioned costs. Patients who respond to first line treatment are assumed to remain responders for the remainder of the decision tree and no additional costs will incur as maintenance treatment is assumed equal in both treatment arms.

Patients who do not respond to first line treatment receive subsequent treatment(s) for their flare. In weeks 2–4, patients can incur costs of treatment, administration, resource use, management of adverse events together with patient time and transportation costs. The response is evaluated weekly and like responders in the first week, patients responding are assumed to remain responders for the remainder of the decision tree.

Patients who have not responded by week 4 are considered to have an 'extended flare'. This time point was discussed with clinicians who considered that '*four weeks from the time a patient arrives in an acute care setting can be deemed as a reasonable threshold to define when a person with GPP can be considered to have an "extended flare"'.* This is expected to comprise a small number of patients who represent those with the most difficult-to-treat GPP flare. At the point of extended flare, a probability of death due to the flare is applied. Death due to a GPP flare was discussed with clinical experts, who advised that patients with GPP very rarely die due to a GPP flare at onset; this usually occurs only after an extended period.

8.1.2 Time horizon

The DMC method guideline states that the selected time horizon should be long enough to reflect all important differences in costs and efficacy between the technologies being compared (21).

The time horizon of 12 weeks was selected to capture the majority of costs and consequences associated with a GPP flare. GPP flares are typically resolved within 2–3 weeks, though some flares may last for up to 3 months (80). In a study of 102 people with adult-onset GPP in Malaysia, the mean flare duration was estimated to be 16 days, up to a maximum of 60 days (7). Additionally, in a survey of 29 clinicians carried out in the US, most clinicians reported the average length of a flare to be less than 4 weeks (N = 17, 59%), and a further 12 clinicians estimated the average length of flare to be between 1–3 months (41%). As such, 12 weeks is expected to be sufficient to model the GPP flare and, furthermore, this matches the duration of Effisayil-1, the key source of data for this GPP flare analysis (18).

8.1.3 Perspective

The perspective of the economic model is a restricted Danish societal perspective, which includes costs related to drug acquisition, drug administration, resource use, AE management, patient time, and transportation. Indirect costs are not included in line with the DMC's guidelines (21).

8.1.4 Discounting, and Half-cycle correction

Discounting

The method guidelines from the DMC refers to the Danish Ministry of Finance guidelines with an annual discounting rate for future costs of 3.5% for model years >1 to ≤35 and 2.5% for model year 35 to 70 (21, 81). The health economic model time horizon is 12 weeks days and consequently, discounting will not affect the results as the first year is not discounted. Therefore, no discount rates are applied to the model.

Half-cycle correction

No half cycle correction (HCC) was applied in the model. This was omitted due to the short time horizon of 12 weeks reflecting the maximum duration of a flare in line with the follow-up in the Effisayil-1 trial (18).

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

Table 7 below presents the key parameters used in the health economic model and how these have been obtained.

Table 7. Input data used in the model

Clinical efficacy outcome	Used in the model (value)				How is the input value obtained/estimated
	Spesolimab		Best available care		
	Moderate flare	Severe flare	Moderate flare	Severe flare	
Response = GPPGA pustulation subscore of 0 or 1					Source(82)*
Probability of responding on day 2	50% (11/22)	15.4% (2/13)	0% (0/12)	0% (0/6)	GPPGA pustulation subscore of 0 or 1 at day 2, Effisayil-1, by treatment arm (spesolimab or placebo) and by severity (GPPGA pustulation subscore < or = 4)
Probability of responding on day 3 among the non-responders of day 2	36% (15-11)/ (22-11) = 4/11	18% (4-2)/ (13-2) =2/11	8% (1/12)	0% (0/6)	Nominator = GPPGA pustulation subscore of 0 or 1 at Day 3, Effisayil-1, by treatment arm (spesolimab or placebo) and by severity (GPPGA pustulation subscore < or = 4) among those who did not meet 0 on day 2. Denominator = patients who are still at risk to reach 0 or 1, corresponding with the non-responders of day 2
Probability of responding on day 4 among the non-responders of day 3	0%	6.7% 0.6/ (13-4) =0.6/9	1.8% 0.2/ (11-0) =0.2/11	3.3% 0.2/ (6-0) =0.2/6	Assumed a linear response between day 3 and day 8: To estimate the number of responders the difference is taken from day 8 minus the responders at day 3 based on Effisayil-1, by treatment arm (spesolimab or placebo) and by severity (GPPGA pustulation subscore < or = 4) For moderate flare of spesolimab this was 0 (no new responders at day 8 compared with day 8), for severe flare this was 3 (=7-4), for the BAC moderate this was 0 and for BAC severe this was 1 (=1-0). Then, an equal number of responders is assumed over the 5 days, which corresponds with 0, 0.6, 0 and respectively 0.2 responders per day. To estimate the number of patients at risk (denominator), the non-responders from the previous period are taken each time.
Probability of responding on day 5 among the non-responders of day 4	0%	7.1% 0.6/ (9-0.6) =0.6/8.4	1.9% 0.2/ (11-0.2) =0.2/10.8	3.4% 0.2/ (6-0.2) =0.2/5.8	
Probability of responding on day 6 among the non-responders of day 5	0%	7.7% 0.6/ (8.4-0.6 =0.6/7.8	1.9% 0.2/ (10.8-0.2) =0.2/10.6	3.6% 0.2/ (5.8-0.2) =0.2/5.6	
Probability of responding on day 7 among the non-responders of day 6	0%	8.3% 0.6/ (7.8-0.6) =0.6/7.2	1.9% 0.2/ (10.6-0.2) =0.2/10.4	3.7% 0.2/ (5.6-0.2) =0.2/5.4	

Probability of responding on day 8 among the non-responders of day 7	0%	9.1% 0.6/ (7.2-0.6) =0.8/6.6	2.0% 0.2/ (10.4-0.2) =0.2/10.2	3.8% 0.2/ (5.4-0.2) =0.2/5.2	GPPGA pustulation subscore of zero at Day 8, Effisayil-1, by treatment arm spesolimab or placebo, and by severity (GPPGA pustulation subscore < or = 4)
Probability of responding by week 2 among the non-responders of week 1	62% =8/13	62% =8/13	0%	0%	*Pooled (by severity) analysis* Nominator = GPPGA pustulation subscore of 0 or 1 at week 2, Effisayil-1, by treatment arm (spesolimab or placebo) but not by severity, among those who did not meet 0 or 1 by week 1. Denominator = patients who are still at risk to reach 0 or 1, corresponding with the non-responders by week 1
Probability of responding by week 3 among the non-responders of week 2	0%	0%	0%	0%	*Pooled (by severity) analysis* Nominator = GPPGA pustulation subscore of 0 or 1 at week 3, Effisayil-1, by treatment arm (spesolimab or placebo), among those who did not meet 0 or 1 by week 2. Denominator = patients who are still at risk to reach 0 or 1, corresponding with the non-responders by week 2
Probability of responding by week 4 among the non-responders of week 3	0%	0%	0%	0%	*Pooled (by severity) analysis* Nominator = GPPGA pustulation subscore of 0 or 1 at week 4, Effisayil-1, by treatment arm (spesolimab or placebo), among those who did not meet 0 or 1 by week 3. Denominator = patients who are still at risk to reach 0 or 1, corresponding with the non-responders by week 3

Adverse events		**Source (44)**
Adverse events	See section 8.2.2.5	
Cost and resource use		**Source (83, 84)**
Drug costs	See section 8.5.1	Medicinpriser.dk (83)
Drug administration costs	See section 8.5.2	Interaktivdrg.dk (84)
Resource use and costs	See section 8.5.3	Interaktivdrg.dk (84)
Adverse events	See section 8.2.2.5	Interaktivdrg.dk (84)

Abbreviations: GPPGA, Generalized Pustular Psoriasis Physician Global Assessment.

*Based on additional subgroup (GPPGA pustulation subscore < or = 4 at baseline) analysis

The health economic model allows the user to explore the impact of partial response. The applied definition of response is based on complete response (GPPGA Pustulation subscore of 0) or the combination of full and partial response (GPPGA Pustulation subscore of 0 or 1). The partial response models the fact that a proportion of patients, although they have not experienced a complete response yet, have experienced some response to treatment. The partial response assumption is applied in the base case (see Table 7), and a scenario using the complete response is included in the deterministic sensitivity analysis to explore the impact of partial + full response vs full response.

Probabilities associated with response to treatment for an acute flare at Day 2 – 8 and week 2-4 are included, with the probability of response at Week 12 set to 100%. The probability applied in the model of responding to treatment for a GPP flare is presented in Table 7 by intervention/comparator and by flare severity (as defined in the model by GPPGA pustulation subscore at baseline).

In the model, the user can select which type of response and accompanying data should be used. The response data are obtained from Effisayil-1 using data for spesolimab from the spesolimab trial arm and data for best available care from the placebo trial arm. Data are presented separately for patients with a 'moderate' and 'severe' GPP flare, defined using the GPPGA pustulation subscore of 4 ('severe') or less than 3 ('moderate'). Response is defined as pustulation subscore of 0 or 1. The data is presented daily for the first week, and weekly for week 2-4. In the model it assumed that if a patient responds, the responds is kept.

Response data at week 2,3,4 are populated using pooled data (combining data from patients with a severe and a moderate flare per treatment arm) from Effisayil-1 for non-responders at Week 1 subsequently responding at Week 2, 3 and 4. Pooled data were used because all patients in Effisayil-1 who did not respond at Week 1 either received open-label spesolimab or escape treatment. For the best available care arm, no additional response after Week 1 was observed.

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

The patient population of interest in Danish clinical practice is adult patients with:

- A moderate acute flare of GPP is characterised as patients who exhibit a GPPGA pustulation subscore of 3 or less at the onset of the GPP flare (64% patients within Effisayil-1) (82)
- A severe acute flare of GPP is characterised as patients who exhibit a GPPGA pustulation subscore of equal to 4 at the onset of the GPP flare (36% patients within Effisayil-1) (82)

Table 8 presents a summary of the patient population expected in Danish clinical practice, as per the trial data and the cost model. The health economic model includes data that is derived from the primary documentation and population characteristics of patients who underwent an acute moderate or severe flare of GPP as evidenced in the Effisayil-1 trial (82).

The baseline characteristics from the Effisayil-1 trial are consistent with the patient characteristics seen in Denmark for patients with GPP. According to an incidence and prevalence study conducted by Bispebjerg Hospital in Denmark, the mean age at the time of diagnosis for the studied GPP population was reported to be between 49 and 64 years (9). The mean age of patients included in the Effisayil-1 trial was reported to be 43 years. Nevertheless, the average age of patients incorporated in the model does not have any significant impact on the outcomes due to the short 12-week time horizon of the analysis. Consequently, the mean age was set to 57 years to reflect the data observed in the Danish clinical practice (9).

Table 8. Patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc. (including source)	Used in the model (number/value including source)	Danish clinical practice (including source)
Age (mean)	43 years (82)	57 years (9)	49-64 years (9)
Gender (% female)	68 % (82)	68 % (82)	More prevalent in women (9, 85)
Weight (kg)	72 kg (82)	72 kg (82)	NA
Patient population	Adult patients with an acute flare of GPP, with a severity level of "moderate" and "severe" (82)*	Adult patients with an acute flare of GPP, with a severity level of "moderate" and "severe" (82)*	Adult patients with an acute flare of GPP, with a severity level of "moderate" and "severe"

Abbreviations: kg, Kilograms

* Moderate severity is defined as people with a GPPGA pustulation subscore of less than 4 at the start of their GPP flare and severe is defined as people with a GPPGA pustulation subscore of equal to 4 at the start of their GPP flare

8.2.2.2 Intervention

The intervention of interest is the humanised IgG Ab against human IL-36R, spesolimab. Spesolimab is approved by the EMA for the following therapeutic indication: "*Spevigo is indicated for the treatment of flares in adult patients with GPP as monotherapy".*

The administration of spesolimab in the Effisayil-1 trial adhered to the label instructions and the recommended dosage regimen, which involves a single intravenous infusion of 900 mg (equivalent to 2 vials of 450 mg) (44, 86).

Consequently, it is assumed that spesolimab is administrated as a one-off dose of 900 mg (monotherapy) IV during an acute flare in the model.

Table 9. Intervention

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	Spesolimab: Single dose of 900 mg (2 vials of 450 mg), IV (86)	Spesolimab: Single dose of 900 mg (2 vials of 450 mg), IV (86)	Spesolimab: Single dose of 900 mg (2 vials of 450 mg), IV (86)
Length of treatment (time on treatment) (mean/median)	One-off treatment when patients experiencing an acute flare of GPP	One-off treatment when patients experiencing an acute flare of GPP	One-off treatment when patients experiencing an acute flare of GPP
Criteria for discontinuation	If a patient develops signs of anaphylaxis or other serious hypersensitivity (86)	If a patient develops signs of anaphylaxis or other serious hypersensitivity (86)	If a patient develops signs of anaphylaxis or other serious hypersensitivity (86)

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
The pharmaceutical's position in Danish clinical practice	N/A	1L	1L

Abbreviations: 1L, First-line; IV, Intravenous; mg, milligrams

8.2.2.3 Comparators

Currently, no approved therapies specific to GPP are available in Europe (48). Therefore, placebo was used as the appropriate comparator in clinical trial assessing the efficacy of spesolimab.

According to Danish clinicians, patients with moderate GPP flares will receive off-label treatment with acitretin, while patients with severe flares will be treated off-label with infliximab (17).

Hence, for first line treatment, acitretin was utilized as the comparator for patients with moderate GPP flares, and infliximab was used as the comparator for patients with severe GPP flares, see Table 10.

Table 10. Comparator

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Acitretin		**1L treatment for a moderate GPP flare**	
Posology	Acitretin: Could be initiated at an initial dose of 25 mg/day, oral; however, patients with severe generalised pustular psoriasis often require more aggressive treatment with higher initial doses of 50–75 mg/day, oral) (50)	Acitretin: 50 mg/day, oral	In Denmark, acitretin is used as an off-label treatment for GPP flares, and thus no official information on dosing is available. Treatment with acitretin could be initiated at an initial dose of 25 mg/day, oral; however, patients with severe generalised pustular psoriasis often require more aggressive treatment with higher initial doses of 50–75 mg/day, oral) (17, 50)
Length of treatment	In Denmark, acitretin is used as an off-label treatment for GPP flares, and thus no official information on treatment duration is available – for the purpose of this submission treatment is assumed to continue until remission of flare, although many patients may continue to take acitretin as maintenance treatment.	Every day until response assessment in the model for 1L in week 1 and subsequent treatment week 2-4 (3 weeks).	In Denmark, acitretin is used as an off-label treatment for GPP flares, and thus no official information on treatment duration is available – for the purpose of this submission treatment is assumed to continue until remission of flare, although many patients may continue to take acitretin as maintenance treatment.
The comparator's position in the	Acitretin is used as an off-label treatment for GPP flares in Denmark, and thus no official	1L for patients with moderate GPP flares	Acitretin is used as an off-label treatment for GPP flares in Denmark, and thus no official guidelines.

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Danish clinical practice	guidelines on position in Danish clinical practice.		However, Danish experts stated that it is used as 1L treatment for patients with a moderate flare of GPP (17)
Infliximab		**1L treatment for a severe GPP flare**	
Posology	In Denmark, infliximab is used as an off-label treatment for GPP flares, so no official information on dosing is available. For chronic severe plaque psoriasis the recommended dosage of infliximab in adult patients is 5 mg/kg given as an IV induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter (87).	Infliximab: Induction dose 5 mg/kg, IV, at week 0, 2 and 6 Maintenance: 5 mg/kg every 8 weeks	In Denmark, infliximab is used as an off-label treatment for GPP flares, so no official information on dosing is available. For chronic severe plaque psoriasis the recommended dosage of infliximab in adult patients is 5 mg/kg given as an IV induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter (87).
Length of treatment	In Denmark, infliximab is used as an off-label treatment for GPP flares, and thus no official information on treatment duration is available – for the purpose of this submission treatment is assumed to continue until remission of flare	Every day until response assessment in the model for 1L in week 1 and subsequent treatment week 2-4 (3 weeks).	In Denmark, infliximab is used as an off-label treatment for GPP flares, and thus no official information on treatment duration is available – for the purpose of this submission treatment is assumed to continue until remission of flare
The comparator's position in the Danish clinical practice	Infliximab is used as an off-label treatment for GPP flares in Denmark, and thus no official guidelines on position in Danish clinical practice.	1L for patients with severe GPP flares	Infliximab is used as an off-label treatment for GPP flares in Denmark, and thus no official guidelines on position in Danish clinical practice.

Abbreviations: 1L, First-line; IV, Intravenous; mg, milligrams

8.2.2.4 Relative efficacy outcomes

Section 7 provides a summary of the relative efficacy outcomes. The clinical trial, Effisayil-1, which was a multi-centre, double-blind, randomised, placebo-controlled, Phase II study, evaluated the efficacy, safety, and tolerability of a single IV dose of spesolimab administered to patients with GPP who presented with an acute flare of moderate to severe intensity. The relative efficacy outcomes for GPPGA and safety were estimated directly from the trial Effisayil-1 (44).

In very rare cases, a GPP flare can result in death due to systemic complications (8). To capture this rare but important event, mortality associated with an acute flare is captured when patients are considered to have an extended flare, at 4 weeks from the onset of their GPP flare. Death due to a GPP flare was discussed with clinical experts, who advised that patients with GPP very rarely die due to a GPP flare at onset; this usually occurs only after an extended period (17).

In the health economic model, a probability of death due to a GPP flare is used. The probability of death was estimated using data from Augey et al.(88) and Kromer et al.(89):

- For the study of Augey et al. from 2006 carried out in France, there were 2 deaths recorded out of 99 patients with acute GPP
- In the study of Kromer from 2021, 2 deaths were reported among 66 patients with acute GPP treated in Germany

This resulted in a probability of 2.5% of death. This estimate of mortality is applied to patients who experience a flare of 4 weeks or longer, i.e. the more serious flares. The estimated mortality is assumed to reflect the mortality for patients with GPP in Denmark; this assumption is necessary due to the lack of equivalent data for the Danish population.

Table 11. Summary of text regarding *value*

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score and pustulation subscore	Effisayil-1 trial (44)	See Table 7

Abbreviations: GPPGA, Generalized Pustular Psoriasis Physician Global Assessment

Table 12. Summary of text regarding *relevance*

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score and pustulation subscore	See section 7, Effisayil-1 trial	GPPGA is a clinical assessment of overall GPP severity that scores pustules, erythema and scaling of all psoriatic lesions. It is a modified PGA, which has been adapted for the evaluation of patients with GPP (replacement of the induration component with pustulation).	GPPGA is a clinical assessment of overall GPP severity that scores pustules, erythema and scaling of all psoriatic lesions. It is a modified PGA, which has been adapted for the evaluation of patients with GPP (replacement of the induration component with pustulation).

Abbreviations: GPP, Generalized Pustular Psoriasis; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

8.2.2.5 Adverse reaction outcomes

In the base case, two adverse events are included: serious infection and tuberculosis reactivation. These adverse events were identified as important via a Cochrane review of biological side effects and via review of related NICE technology appraisals for psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis and Crohn's disease (TA134(90), TA442(91), TA350(92), TA537(93), TA375(94), TA383(95), TA329(96), TA187(97)). The Cochrane review presented evidence showing that people receiving biological therapies were more likely to experience serious infections or tuberculosis than people receiving placebo treatment(98). In addition, adverse events of treatment were only considered in TA375 (serious infection) and TA383 (serious infection and tuberculosis reactivation) (94, 95). Incidence data identified in these two technology appraisals alongside data for spesolimab from Effisayil-1 is used to populate the base case analysis. Data used in the analysis are presented in Table 13.

Table 13. Adverse events

Treatment	Incidence of serious infection	Source (94)	Incidence of tuberculosis reactivation	Source(95)
Spesolimab IV	2.9%	Week one probability of serious infection from Effisayil-1	0.2%	Assumed equivalent to other biologicals
Abatacept IV	3.5%	TA375: incidence of serious infection modelled by the technology assessment group	0.2%	TA383: incidence of tuberculosis reaction for intervention
Abatacept SC	3.5%	TA375: incidence of serious infection modelled by the technology assessment group	0.2%	TA383: incidence of tuberculosis reaction for intervention
Acitretin	2.6%	Assumed equivalent to cDMARDs	0.0%	TA383: incidence of tuberculosis reaction for comparator
Adalimumab	3.5%	TA375: incidence of serious infection modelled by the technology assessment group	0.2%	TA383: incidence of tuberculosis reaction for intervention
Apremilast	2.6%	Assumed equivalent to cDMARDs	0.0%	TA383: incidence of tuberculosis reaction for comparator
Brodalumab	3.5%	Assumed equivalent to bDMARDs	0.2%	TA383: incidence of tuberculosis reaction for intervention
Certolizumab	3.5%	TA375: incidence of serious infection modelled by the technology assessment group	0.2%	TA383: incidence of tuberculosis reaction for intervention
Ciclosporin	2.6%	Assumed equivalent to cDMARDs	0.0%	TA383: incidence of tuberculosis reaction for comparator
Etanercept	3.5%	TA375: incidence of serious infection modelled by the technology assessment group	0.2%	TA383: incidence of tuberculosis reaction for intervention
Guselkumab	3.5%	Assumed equivalent to bDMARDs	0.2%	TA383: incidence of tuberculosis reaction for intervention
Infliximab	3.5%	TA375: incidence of serious infection modelled by the technology assessment group	0.2%	TA383: incidence of tuberculosis reaction for intervention

Ixekizumab	3.5%	Assumed equivalent to bDMARDs	0.2%	TA383: incidence of tuberculosis reaction for intervention
Methotrexate (capsule)	2.6%	Assumed equivalent to cDMARDs	0.0%	TA383: incidence of tuberculosis reaction for comparator
Methotrexate (SC)	2.6%	TA375: incidence of serious infection modelled by the technology assessment group for cDMARDs	0.0%	TA383: incidence of tuberculosis reaction for comparator
Risankizumab	3.5%	Assumed equivalent to bDMARDs	0.2%	TA383: incidence of tuberculosis reaction for intervention
Secukinumab	3.5%	Assumed equivalent to bDMARDs	0.2%	TA383: incidence of tuberculosis reaction for intervention
Tildrakizumab	3.5%	Assumed equivalent to bDMARDs	0.2%	TA383: incidence of tuberculosis reaction for intervention
Tofacitinib	2.6%	Assumed equivalent to cDMARDs	0.0%	TA383: incidence of tuberculosis reaction for comparator
Ustekinumab	3.5%	Assumed equivalent to bDMARDs	0.2%	TA383: incidence of tuberculosis reaction for intervention
Bimekizumab	3.5%	Assumed equivalent to bDMARDs	0.2%	TA383: incidence of tuberculosis reaction for intervention

Abbreviations: bDMARDs, biologic disease-modifying anti-rheumatic drugs; cDMARDs, conventional disease-modifying anti-rheumatic drugs; IV, intravenous; SC, subcutaneous.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

8.3 Extrapolation of relative efficacy

The health economic analysis is based on data from the Effisayil-1 trial focusing on the acute stage of a GPP flare (18). Due to the focus on the acute phase of a GPP flare, the short follow-up of 12 weeks in the trial, and the 12 weeks model time horizon, no extrapolation was needed for this health economic analysis.

8.3.1 Time to event data – summarized:

No extrapolation is performed as described in section 8.3.

8.4 Documentation of health-related quality of life (HRQoL)

Considering the focus on an acute flare of GPP where rapid treatment of the acute phase is paramount, a CUA is deemed unsuitable to reflect this critical period and capture the primary characteristics of this condition. As described in section 8, using QALYs to value morbidity for acute diseases or conditions has both measurement and evaluation problems, since the impact on quality of life is temporary due to the acute condition (40). Consequently, no HSUVs are included in this health economic analysis.

8.4.1 Overview of health state utility values (HSUV)

No HSUVs are included in this health economic analysis as described in section 8.4.

8.4.2 Health state utility values used in the health economic model

No HSUVs are included in this health economic analysis as described in section 8.4.

8.5 Resource use and costs

In order to gain insight into the patient pathway and resource utilization related to the relevant patient population in Denmark, two clinical experts who is specialised in the treatment of patients with GPP in Denmark were consulted(17).

All costs reported are in Danish kroner (DKK) and are based on diagnosis-related groups (DRG) tariffs 2023, official unit cost catalogues, and medicinpriser.dk (83, 84, 99). All drug costs were reported as pharmacy purchase prices (PPP), where the lowest cost alternative was used in the health economic assessment.

8.5.1 Drug acquisition cost

The model uses the PPP for all pharmaceuticals utilized in the analysis. The drug acquisition costs are applied to patients in first-line treatment, patients who are not responding in week 2 (subsequent treatment), and non-responders >4 who experience an extended flare. The model includes more treatment options than those used in the model. This is to enhance the flexibility of the model to select among treatment options. All estimated drug costs are presented in Table 14. The model selects the cheapest per milligram package available.

At the onset of a moderate flare (64% of patients in the model), patients will receive either spesolimab or acitretin, while at the onset of a severe flare (36% of patients in the model), patients will receive either spesolimab or infliximab based on historical data from Effisayil-1 (44). No guidelines are available for the treatment of GPP flares. According to the Danish clinical experts inputs, the majority of patients with moderate GPP flares would receive acitretin, with a minority receiving other treatments due to potential contraindications (17). The assumption regarding first-line treatment was made to provide a conservative choice in the model.

Table 14. Drug acquisition cost

Drug		Mode of administration	Capsules/vials per pack	Vial (mg)	Vial (cost)	Source (83)
Spesolimab		IV	2	450	126,195 DKK	Boehringer Ingelheim
Abatacept	Orencia	IV	1	250	2,256 DKK	Medicinpriser.dk (2023)
	Orencia	SC	4	125	6,857 DKK	Medicinpriser.dk (2023)
Acitretin	Neotigason	Oral	50	10	127 DKK	Medicinpriser.dk (2023)
	Neotigason	Oral	50	25	321 DKK	Medicinpriser.dk (2023)
	Acitretin	Oral	50	10	127 DKK	Medicinpriser.dk (2023)
	Acitretin	Oral	50	25	320 DKK	Medicinpriser.dk (2023)
Adalimumab	Amgevita	SC	1	20	1,232 DKK	Medicinpriser.dk (2023)
	Amgevita	SC	2	40	4,535 DKK	Medicinpriser.dk (2023)
	Humira	SC	2	40	6,863 DKK	Medicinpriser.dk (2023)
	Humira	SC	2	20	3,500 DKK	Medicinpriser.dk (2023)
	Hyrimoz	SC	2	40	4,651 DKK	Medicinpriser.dk (2023)
	Imraldi	SC	2	40	4,480 DKK	Medicinpriser.dk (2023)
Apremilast	Otezla	Oral	56	30	4,939 DKK	Medicinpriser.dk (2023)
Brodalumab	Kyntheum	SC	2	210	8,077 DKK	Medicinpriser.dk (2023)
Certolizumab	Cimzia	SC	2	200	7,114 DKK	Medicinpriser.dk (2023)

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Ciclosporin	Ciqorin	Oral	50	25	391 DKK	Medicinpriser.dk (2023)
	Ciqorin	Oral	50	50	748 DKK	Medicinpriser.dk (2023)
	Ciqorin	Oral	50	100	1,405 DKK	Medicinpriser.dk (2023)
Etanercept	Benepali	SC	4	25	3,012 DKK	Medicinpriser.dk (2023)
	Benepali	SC	4	50	6,023 DKK	Medicinpriser.dk (2023)
	Enbrel	SC	4	10	1,400 DKK	Medicinpriser.dk (2023)
	Enbrel	SC	4	25	3,499 DKK	Medicinpriser.dk (2023)
	Enbrel	SC	4	50	6,593 DKK	Medicinpriser.dk (2023)
	Erelzi	SC	4	25	3,168 DKK	Medicinpriser.dk (2023)
	Erelzi	SC	4	50	6,336 DKK	Medicinpriser.dk (2023)
Guselkumab	Tremfya	SC	1	100	15,198 DKK	Medicinpriser.dk (2023)
Infliximab	Flixabi	IV	1	100	2,320 DKK	Medicinpriser.dk (2023)
	Remicade	IV	1	100	3,421 DKK	Medicinpriser.dk (2023)
	Remsima	IV	1	100	2,441 DKK	Medicinpriser.dk (2023)
	Zessly	IV	1	100	3,683 DKK	Medicinpriser.dk (2023)
Ixekizumab	Taltz	SC	1	80	7,192 DKK	Medicinpriser.dk (2023)
Methotrexate	Methotrexat "Paranova"	Oral	100	3	22 DKK	Medicinpriser.dk (2023)

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

	Metex	SC	1	8	148 DKK	Medicinpriser.dk (2023)
	Metex	SC	1	10	160 DKK	Medicinpriser.dk (2023)
	Metex	SC	1	13	166 DKK	Medicinpriser.dk (2023)
	Metex	SC	1	15	172 DKK	Medicinpriser.dk (2023)
	Metex	SC	1	18	175 DKK	Medicinpriser.dk (2023)
	Metex	SC	1	20	171 DKK	Medicinpriser.dk (2023)
	Metex	SC	1	23	196 DKK	Medicinpriser.dk (2023)
	Metex	SC	1	25	198 DKK	Medicinpriser.dk (2023)
	Metex	SC	1	30	203 DKK	Medicinpriser.dk (2023)
Risankizumab	Skyrizi	SC	1	150	24,666 DKK	Medicinpriser.dk (2023)
Secukinumab	Cosentyx	SC	2	150	7,908 DKK	Medicinpriser.dk (2023)
Tildrakizumab	Ilumetri	SC	1	100	22,365 DKK	Medicinpriser.dk (2023)
Tofacitinib	Xeljanz	Oral	56	5	5,249 DKK	Medicinpriser.dk (2023)
	Xeljanz	Oral	56	10	10,497 DKK	Medicinpriser.dk (2023)
Ustekinumab	Stelara	SC	1	90	21,019 DKK	Medicinpriser.dk (2023)
	Stelara	SC	1	90	21,019 DKK	Medicinpriser.dk (2023)
Bimekizumab	Bimzelx	SC	2	160	16,703.31 DKK	Medicinpriser.dk (2023)

Abbreviations: IV, intravenous injection; SC, Subcutaneous injections

Subsequent treatment

The subsequent treatment options depend on the first-line treatment, and the consensus among Danish experts was to use another retinoid, biological medicine, IL-17 or -23 inhibitor. For the model base case, the following subsequent treatments were included: acitretin, cyclosporin, infliximab, adalimumab, guselkumab, and bimekizumab. The selection of the aforementioned medicines and the proportion of patients treated with different treatment regimes in the model were based on the recommendations and statements of clinical experts in Denmark, as well as the drug recommendation and treatment guideline from the DMC for moderate to severe plaque psoriasis, version 1.3 (87), see Table 15.

Table 15. Subsequent treatments

First-line treatment	Spesolimab	% patients	Weeks of treatment	Best available care	% patients	Weeks of treatment
Moderate flare						
Subsequent treatment	**Acitretin**	75.00%	3	**Acitretin**	0.00%	-
	Ciclosporin	6.25%	3	**Ciclosporin**	25.00%	3
	Bimekizumab	6.25%	3	**Bimekizumab**	25.00%	3
	Infliximab	6.25%	3	**Infliximab**	25.00%	3
	Guselkumab	6.25%	3	**Guselkumab**	25.00%	3
Severe flare						
Subsequent treatment	**Adalimumab**	-	-	**Adalimumab**	10.00%	3
	Infliximab	75.00%	3	**Infliximab**	-	-
	Bimekizumab	8.33%	3	**Bimekizumab**	50.00%	3
	Guselkumab	8.33%	3	**Guselkumab**	30.00%	3
	Ciclosporin	8.33%	3	**Ciclosporin**	10.00%	3

Abbreviations: N/A

Extended flares

Following input from clinical experts, it was postulated that patients who remain unresponsive to treatments would be administered biological medicines. To account for the distinct modes of action of these medications, a treatment approach was devised that entails the utilization of a TNF-α inhibitor (infliximab), an IL-17 inhibitor (bimekizumab), and an IL-23 inhibitor (guselkumab) in the event of an extended flare. It is assumed that 33.33% of patients will receive either infliximab, bimekizumab, or guselkumab, as outlined in Table 16.

Table 16. Extended flare treatments

	Treatment	% patients	Weeks of treatment
Extended flares	**Infliximab**	33.33%	3
	Bimekizumab	33.33%	3
	Guselkumab	33.33%	3

Abbreviations: N/A

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

8.5.2 Administration costs

The preceding section, specifically section 8.5.1, Table 14, contains information regarding the costs of drugs and the mode of administration for each treatment regimen. Notably, the cost associated with the intravenous administration of spesolimab and infliximab is 1,634 DKK, while the subcutaneous administration of guselkumab, bimekizumab, and adalimumab incurs the same cost per administration. In contrast, the oral administration of acitretin and cyclosporine does not involve any cost, see Table 17. To calculate the administration cost, the proportion of patients receiving each treatment regimen is multiplied by the corresponding price and the frequency of treatment administration within the weeks of treatment, as specified in the model based on the drug recommendation and treatment guideline from the DMC for moderate to severe plaque psoriasis, version 1.3 (92).

Table 17. Administration costs

Administration form	Unit cost	Source (84)
Oral	0 DKK	Assumption: No costs associated with oral administration
IV	1,634 DKK	Interaktiv DRG 2023, 09MA98: DL409 DL401 Psoriasis pustulosa generalisata, BWAA6 Medicingivning intravenøst
SC	1,634 DKK	Interaktiv DRG 2023, 09MA98: DL401 Psoriasis pustulosa generalisata, BWAAA31 Medicingivning ved subkutan injektion

Abbreviations: IV, intravenous injection; SC, Subcutaneous injections

8.5.3 Resource use and costs

In order to estimate the resource consumption in connection with an acute flare of GPP, Danish clinical experts were consulted (17). The following resource use is captured in the model for a GPP flare:

- Patients presenting to an emergency room for their flare
- Patients monitored in hospital as outpatients during a flare
- Patients monitored in hospital as inpatients during their flare
- Inpatients requiring critical care

The costs related to monitoring during a GPP flare are presented in Table 18, including the unit costs associated with each service estimated on www.interaktivdrg.dk. The estimated cost for patients treated in the emergency rooms or outpatient appointments was estimated using a tariff of 1,634 DKK (DRG code 09MA98). The cost of inpatient care on a dermatology ward or ICU department was estimated by using the DRG code 09MA03, which includes a long-term tariff as patients are admitted for more than 12 hours. The daily cost associated with this DRG code is estimated to be 50.474 DKK. Patients hospitalised in a dermatology ward incurs the cost of 2,240 DKK per day reflecting the long-term tariff of the DRG code. No DRG tariff was available for the daily cost of patients admitted to the ICU department. Therefore, the ICU costs were estimated using the visual DRG approach. This involved dividing the 50,474 DKK tariff, which was obtained using the DRG code 09MA03, by the trim-point of 15 resulting in a cost of 3,365 DKK per day at the ICU department, see Table 18.

Table 18. Resource costs

Administration form	Unit cost	Source (84)
Outpatient appointment	1,634 DKK	Interaktiv DRG 2023, 09MA98: DL401 Psoriasis pustulosa generalisata, BVAA91 Samtale med speciallæge
Daily cost of inpatient care	2,240 DKK	Interaktiv DRG 2023, 09MA03: DL401 Psoriasis pustulosa generalisata, NABE Intensiv observation, 50.474 DKK, langliggertakst 2.240 DKK
Daily cost of ICU care	3,365 DKK	Interaktiv DRG 2023, 09MA03: DL401 Psoriasis pustulosa generalisata, NABE Intensiv observation, 50.474 DKK, trimpunkt 15, 50.474/15=3.364,93 DKK

Abbreviation: N/A

Based on the inputs provided by Danish clinical experts, Table 19 presents the estimated resource utilization for patients experiencing a moderate, severe, and extended flare of GPP. It is estimated that 60% of patients experiencing a moderate GPP flare will be treated in an outpatient setting, with an average of two outpatient appointments during the first week of the flare and an additional two appointments in the subsequent week. The remaining 40% of patients with a moderate GPP flare will be hospitalised in a dermatology ward for an average of 10 days, as per the recommendations of Danish experts (17).

The Danish clinical experts estimated that all patients experiencing a severe flare would be admitted to the hospital, and 5% of these patients would be treated in the ICU department. Patients admitted to the dermatology ward, or the ICU are assumed to stay in the hospital for 7 days during the first week. According to Danish experts, patients who initially have been admitted to the ICU department will be transferred to the dermatology ward after the first week of hospitalisation. Therefore, it is assumed that all patients experiencing a severe flare after the first week of onset will be hospitalised for an additional 14 days in a dermatology ward, as presented in Table 19 (17).

The model accounts for the management of patients experiencing an extended flare of GPP. It is estimated that 64% of patients experiencing an extended flare are hospitalised, whereas the remaining 36% receive outpatient care based on historical data from Effisayil-1. Patients treated as outpatients are assumed to have four appointments during the extended flare. While patients admitted to the hospital for an extended flare are assumed to stay for an additional seven days in a dermatology ward.

Following hospitalisation, patients will receive several follow-up sessions from clinicians. Based on inputs from Danish clinical experts, it is assumed that patients who have experienced a moderate, severe, or extended flare will have three, five, or seven outpatient appointments, respectively, after hospital discharge (17). The costs are applied as a one-time cost occurring on day 1, week 2, and week 5, which considers the proportion of patients experiencing GPP flares of various severity and the duration of their flare. These assumptions are presented in Table 20.

Table 19. Resource use during a flare

	During Week 1 of the flare		After Week 1		Extended flare
	Moderate flare	Severe flare	Moderate flare	Severe flare	Extended flare
% patients treated as outpatients	60%	0%	60%	0%	36%

Average number of outpatient appointments	2	0	2	0	4
% of patients treated as inpatients	40%	100%	40%	100%	64%
Average number of days length of stay on non-ICU	7	7	3	14	7
% of patients treated in ICU	0%	5%	0%	0%	0%
Average number of days length of stay ICU	0	7	0	0	0

Abbreviations: ICU, Intensive care unit

Table 20. Number of outpatient appointments after hospital discharge and costs

Severity of flare	Number of outpatient appointment after discharge	Unit cost per outpatient appointment	Total cost
Moderate flares	3	1,634 DKK	4,902 DKK
Severe flares	5		8,170 DKK
Extended flares	7		11,438 DKK

Abbreviations: N/A

8.5.4 Adverse event costs

The model incorporates the costs related to the management of treatment-related AEs as outlined in Table 13, section 8.2.2.5. Specifically, two AEs, namely serious infections and tuberculosis reactivation, are included in the analysis. The cost of a serious infection was estimated to be 46,987 DKK using DRG code 18MA01, while the cost of tuberculosis reactivation was estimated at 6,442 DKK. It is assumed that these associated costs will be incurred once for each patient whenever a treatment is selected, irrespective of the duration of the treatment, which will be at Day 1, Week 2, and Week 5.

Table 21. Adverse event costs

AEs	Grade	Unit cost	Source (84)
Serious infection	>3	46,987 DKK	Interaktiv DRG 2023, DA419: Sepsis UNS. 18MA01 - Sepsis, Varighed >=12 timer (lang): Liggedag 1
Tuberculosis reactivation	>3	6,442 DKK	Interaktiv DRG 2023, DZ227: Latent tuberkulose, 23MA05 - Anden kontaktårsag til sundhedsvæsenet, Varighed >= 12 timer (lang): Liggedag 1

Abbreviations: N/A

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

8.5.5 Patient time and transportation costs

Patient and transportation costs are included in the model in line with the DMC method guidelines (21). The unit cost per patient hour was estimated to be 181 DKK and the transportation cost was estimated to be 3.51 DKK per km with the assumption of an average distance to the hospital of 40 km (roundtrip) in line with the DMC guidelines, see Table 22 (21, 100). It is further assumed that patients would spend 60 minutes on transportation per visit (roundtrip).

Table 22. Patient and transportation cost per unit

	Costs	Source
Patient cost per hour	181 DKK	DMC method guidelines (21, 100)
Transport cost per kilometer	3.51 KK	DMC method guidelines (21, 100)
Transport cost per visit	140 DKK	DMC method guidelines (21, 100)

Abbreviations: N/A

Patient time and transportation costs are distributed based on the severity of the GPP flare. The preceding section, specifically section 8.5.3, provides information on the resource use associated with each severity level of the GPP flare. Hence, the patient time and transportation costs incurred by a patient with GPP flare of severity follow the same pattern of incurrence.

As described in section 8.5.3 above, patients experiencing a moderate flare will be treated in an outpatient setting in 60% of cases. It is assumed that these patients will require an average of two outpatient appointments lasting 20 minutes each during the first week of the flare, and an additional two appointments during the subsequent week. This will result in a time cost of 434 DKK, including transportation time for the two appointments. Furthermore, based on the inputs provided by clinical experts in Denmark in section 8.5.3, patients who experience moderate flares and require hospitalisation will incur a patient time cost of 8,181 DKK and 3,620 DKK during the first week of the flare and the subsequent weeks of the flare, respectively. These costs are based on an assumption that the patient time per day of hospitalisation is 16 hours, which reflects the average number of daily hours when the patient is awake. Following hospitalisation, patients will require to attend follow-up visits (section 8.5.3), which will result in a time cost of 261 DKK. Transportation costs during the first and subsequent period will amount to 225 DKK, and an additional 421 DKK will be incurred after discharge from the hospital, see Table 23.

Table 23. Patient time and transportation costs - Moderate flare

Moderate flare		
	During week 1 of the flare	**During week 2-4 of the flare**
Patient time costs (calculated)		
Patient time cost, Outpatients	434 DKK	434 DKK
Patient time cost, Inpatient (Non-ICU)	8,181 DKK	3,620 DKK
Patient time cost, Inpatient (ICU)	- DKK	- DKK
Patient time cost, Outpatients after discharging from hospital	261 DKK	261 DKK
Transportation costs (calculated)		
Transportation costs (All)	225 DKK	225 DKK
Transportation cost after discharging		421 DKK

Abbreviations: ICU, Intensive care unit

In accordance with the inputs provided in section 8.5.3 and following the same pattern as for patients experiencing moderate flares, those with severe flares requiring hospitalization will incur a patient time cost of 19,430 DKK when admitted to a dermatology ward, and 1,023 DKK for those requiring hospitalisation to the ICU during the first week of the flare. In the weeks following the first week of hospitalisation, patients experiencing a severe flare will incur a patient time cost of 40,725 DKK due to their continued hospitalisation in a dermatology ward, as described in section 8.5.3.

Following hospitalisation, patients will also be required to attend follow-up visits, which will result in a patient time cost of 1,086 DKK. Transportation costs during both the initial and subsequent periods will amount to 140 DKK, as all patients will be hospitalised. An additional transportation cost of 702 DKK will also be incurred after discharge from the hospital, see Table 24.

Table 24. Patient time and transportation costs - Severe flare

Severe flare		
	During week 1 of the flare	**During week 2-4 of the flare**
Patient time costs (calculated)		
Patient time cost, Outpatients	- DKK	- DKK
Patient time cost, Inpatient (Non-ICU)	19,430 DKK	40,725 DKK
Patient time cost, Inpatient (ICU)	1,014 DKK	- DKK
Patient time cost, Outpatients after discharging from hospital	1,086 DKK	1,086 DKK
Transportation costs (calculated)		
Transportation costs (All)	140 DKK	140 DKK
Transportation cost after discharging		702 DKK

Abbreviations: ICU, Intensive care unit

Patients undergoing treatment for an extended flare of GPP on an outpatient setting will incur a patient time cost of 517 DKK, based on the resource use estimated in section 8.5.3, the assumed duration of an outpatient appointment, and the time required for a roundtrip to the hospital. For patients who require additional hospitalisation, the time cost will be 5,999 DKK. After hospitalisation, patients will primarily attend follow-up visits, resulting in a patient time cost of 977 DKK, based on the proportion of patients remaining admitted to the hospital in the model.

During the extended period, transportation costs will amount to 291 DKK, and an additional cost of 983 DKK will be incurred after the patient is discharged from the hospital, based on the estimates of visits provided in section 8.5.3 (see Table 25).

Table 25. Patient time and transportation costs - Extended flare

Extended flare	
	During an extended flare (8 weeks)
Patient time cost (calculated)	
Patient time cost, Outpatients	517 DKK
Patient time cost, Inpatient (Non-ICU)	5,999 DKK
Patient time cost, Inpatient (ICU)	- DKK
Patient time cost, Outpatients after discharging from hospital	977 DKK
Transportation costs (calculated)	
Transportation costs (All)	291 DKK
Transportation cost after discharging	983 DKK

Abbreviations: ICU, Intensive care unit

8.6 Results

8.6.1 Base case overview

Table 26 Base case overview

Parameter	Value
General model parameters	
Type of model	Decision Tree
Time horizon	12 weeks
Data source	Effisayil-1
Intervention	Spesolimab
Comparator	Best available care *Moderate flare:* Acitretin *Severe flare:* Infliximab
Population parameters	
Age	57
Weight	72 kg
% of females	68%
Efficacy	
Response = GPPGA pustulation subscore of 0 or 1	Effisayil-1, Table 7
Costs	
Included costs	Drug acquisition costs, Table 14 Administration costs, Table 17 Resource use and costs, Table 18 Adverse events costs, Table 21 Patient time and transportation costs, Table 22

Abbreviations: GPPGA, Generalized Pustular Psoriasis Physician Global Assessment

8.6.2 Base case results

The results of the base case analysis for patients experiencing an acute flare of GPP are presented in Table 27. Spesolimab was found to be less expensive in all cost parameters, except for drug cost. The analysis estimated a mean incremental cost per patient for spesolimab compared to the best available care of 14,540 DKK per acute flare of GPP.

Table 27. Base case results

	Spesolimab	Best available care	Difference
Drug costs	130,086 DKK	23,566 DKK	106,520 DKK
Administrative costs	2,171 DKK	3,056 DKK	-886 DKK
Resource use and costs	23,705 DKK	46,213 DKK	-22,508 DKK
Adverse events costs	2,120 DKK	4,038 DKK	-1,919 DKK
Patient time and transport costs	34,106 DKK	100,773 DKK	-66,667 DKK
Total cost	**192,188 DKK**	**177,647 DKK**	
Incremental results			**14,540 DKK**

8.7 Sensitivity analyses

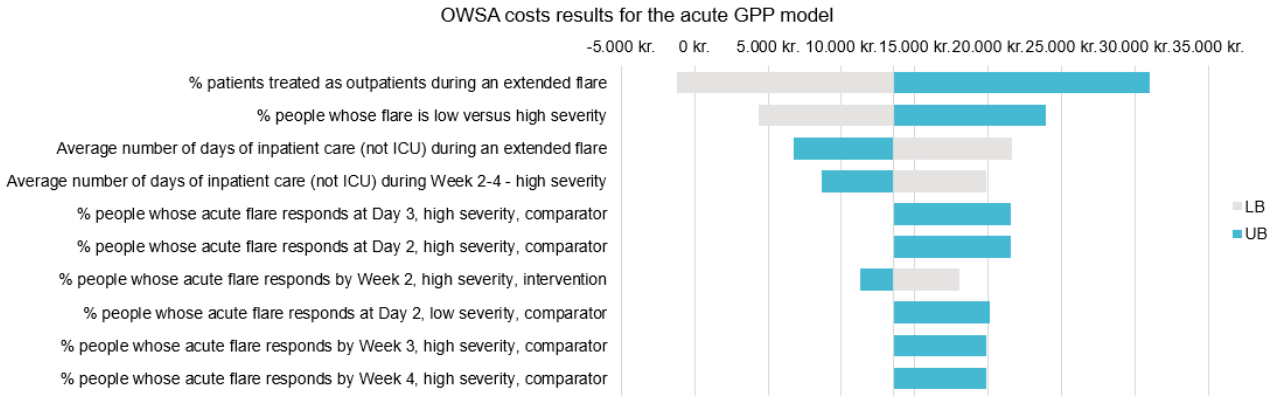
In order to identify the key drivers of the model and assess the influence of parameter uncertainty, one-way deterministic sensitivity analyses (DSA) were performed using alternative values for the model parameters.

To assess the impact of applying different assumptions, scenario analyses were conducted for the key model parameters.

8.7.1 Deterministic sensitivity analyses

Impact on the incremental cost of the range of key parameters is illustrated in Figure 10 and Table 28 below. The tornado diagram displays the proportionate influence of model parameters on the incremental cost based on list-price (14,540 DKK per patient).

Figure 10. Deterministic sensitivity analyses



Abbreviations: GPP, Generalised pustular psoriasis; ICU, Intensive care unit; OWSA, One-way sensitivity analyses; LB, Lower bound; UB, Upper bound

Table 28. One-way sensitivity analysis

Parameter name	Rank costs	Lower Bound	Upper Bound	Incremental cost
% patients treated as outpatients during an extended flare	1	-1,198 DKK	30.975 DKK	32,173 DKK
% people whose flare is low versus high severity	2	4,3646 DKK	23.953 DKK	19.589 DKK
Average number of days of inpatient care (not ICU) during an extended flare	3	21,624 DKK	6,738 DKK	14,886 DKK
Average number of days of inpatient care (not ICU) during Week 2-4 - high severity	4	19,879 DKK	8,659 DKK	11,220 DKK
% people whose acute flare responds at Day 3, high severity, comparator	5	14,540 DKK	21,527 DKK	6,986 DKK
% people whose acute flare responds at Day 2, high severity, comparator	6	14,540 DKK	21,527 DKK	6,986 DKK
% people whose acute flare responds by Week 2, high severity, intervention	7	18,029 DKK	11,253 DKK	6,776 DKK
% people whose acute flare responds at Day 2, low severity, comparator	8	14,540 DKK	20,121 DKK.	5,581 DKK
% people whose acute flare responds by Week 3, high severity, comparator	9	14,540 DKK	19,900 DKK	5,360 DKK
% people whose acute flare responds by Week 4, high severity, comparator	10	14,540 DKK	19,890 DKK	5,349 DKK

Abbreviations: GPP, Generalised pustular psoriasis; ICU, Intensive care unit; OWSA, One-way sensitivity analyses; LB, Lower bound; UB, Upper bound

8.7.2 Scenario analyses

Scenario analyses were conducted to investigate how changes in key model parameters would affect the model results. Table 29 below provides a summary of the main scenario results. Based on the various parameter settings explored in the scenario analyses, the incremental costs associated with spesolimab compared to the best available care ranged from 50.200 DKK to 66,667 DKK per patient. The highest incremental cost per patient was observed when patient time and transportation costs were excluded from the analysis. This scenario was examined as patient time and transportation costs were identified as the main cost drivers, along with drug cost, in the base case. Conversely, the lowest incremental cost per patient was observed when assuming that all patients in the model experienced a severe flare of GPP.

Table 29. Scenario analyses exploring changes to key parameters

Parameter	Inc. cost per patient spesolimab vs. best available care	DKK Δ cost vs base case
Base case	**14,540 DKK**	
Assumptions		
100% low severity flares	42,593 DKK	28,053 DKK
100% high severity flares	-35,659 DKK	-50.200 DKK
Full response definition for efficacy data	20,354 DKK	5,814 DKK
Excluding patient time and transportation costs	81,208 DKK	66,667 DKK
Zero drug and admin cost during Week 1 for BAC	19,559 DKK	5,018 DKK

Abbreviations: BAC, best available care

8.7.3 Probabilistic sensitivity analyses

No probabilistic sensitivity analysis is performed for the simple cost analysis.

9. Budget impact analysis

The budget impact model is developed to estimate the expected budget impact of recommending spesolimab as a treatment option in Denmark. The budget impact analysis has been embedded within the health economic model and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the populations in the health economic model.

The analysis is developed by comparing the costs for the Danish regions per year over five years in the scenario where spesolimab is recommended as a standard treatment and the scenario where spesolimab is not recommended as a standard treatment. The total budget impact per year is the difference between the two scenarios.

9.1 Market shares and number of patients

As explained in section **5.1.3**, it is estimated that there will be around 20 patients experiencing a flare of GPP. Based on the incidence and prevalence study conducted in Denmark and the inputs from the Danish clinical experts, it is expected that 10 patients will be eligible for treatment with spesolimab in the first year(9, 17). For the budget impact analysis, 10 new patients are assumed in every year for five years, see Table 30.

The future market share of spesolimab is influenced by various factors, such as changes in the treatment landscape and availability of economic and physical resources. However, these estimates are subject to uncertainty. Table 30 reports the potential market share of spesolimab, with or without a recommendation. Based on interviews with Danish clinicians it is expected that 75% of patients requiring treatment for an acute GPP flare will receive spesolimab if a recommendation is given (17).

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 30. Number of patients expected to be treated over the next five-year period

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of new eligible patients	10	10	10	10	10
Scenario where spesolimab is not recommended					
Spesolimab	0%	0%	0%	0%	0%
Best available care	100%	100%	100%	100%	100%
Scenario where spesolimab is recommended					
Spesolimab	75%	75%	75%	75%	75%
Best available care	25%	25%	25%	25%	25%

Abbreviations: N/A

9.2 Budget impact results

Based on the assumptions made in the base case analysis, the budget impact of recommending spesolimab as a potential standard treatment for patients experiencing acute GPP flares in Denmark is estimated to be 1,185,610 DKK in the first year and 5,928,050 DKK in the fifth year, reported in Table 31.

Table 31. Expected budget impact of recommending spesolimab as standard of care

	Year 1	Year 2	Year 3	Year 4	Year 5
Without recommendation	768,735 DKK	1,537,470 DKK	2,306.205 DKK	3,074,940 DKK	3,843,675 DKK
With recommendation	1,954,345 DKK	3,908,690 DKK	5,863,036 DKK	7,817,381 DKK	9,771,726 DKK
Budget impact of recommendation	1,185,610 DKK	2,371,220 DKK	3,556,830 DKK	4,742,440 DKK	5,928,050 DKK

Abbreviations: N/A

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

10. Discussion on the submitted documentation

Effisayil-1 is the first randomised trial examining the efficacy and safety of a GPP-specific therapy for the treatment of GPP flares. The trial was double-blinded and lives up to common methodological requirements – e.g., using the Cochrane risk of bias tool as recommended in the Cochrane Handbook would lead to a low risk of bias for all domains, and thus a low risk of bias overall (101). The primary and key secondary endpoints were based on the GPPGA scale, which has been validated, and has shown excellent inter- and intrarater variability (102). The remaining outcome measures used are not yet validated in GPP, but have been validated in other types of psoriasis, and are commonly used and well understood (103). Overall the endpoints used in the Effisayil-1 trial were considered adequately supported and endorsed by the EMA CHMP (73).

While Effisayil-1 was a methodologically sound trial, the rarity of GPP and the lack of established, evidence-based standard of care led to some challenges in designing the trial. Because of the rarity of GPP, and the fact that flares are unpredictable, the trial was not powered to detect differences in PROs at week 1. Additionally, as it was considered unethical to withhold effective treatment from patients assigned to placebo for an extended period and as no evidence-based standard of care exists, patients assigned to placebo were allowed to cross over to spesolimab treatment on day 8, making interpretation of outcomes measured after this point in time challenging. This was commented on by the EMA CHMP; however, it was acknowledged that this was an acceptable approach given the difficult circumstances and overall design of the study was considered adequate. The CHMP also noted that due to the heterogenous standard of care in GPP and lack of adequate information about its effects, a comparative study vs. standard of care would have been difficult to plan (73).

The limitations described above notwithstanding, Effisayil-1 showed robust and clinically and statistically significant effects of spesolimab compared to placebo for GPPGA pustulation subscore and GPPGA total score after one week (18). The response to spesolimab was rapid, and while the design of the trial makes comparisons between placebo and spesolimab after week 1 challenging, the response was maintained over time and patients assigned to placebo crossing over to spesolimab achieved responses very similar to those observed in patients assigned to spesolimab at day 1 (18). While Effisayil-1 was not powered to show a difference between spesolimab and placebo for PROs after week 1, separation between the treatment arms was shown for outcome measures (74).

As only very low quality evidence is available for off-label treatments for GPP flares currently used in Denmark an indirect treatment comparison was not possible, and while it is likely that current treatments are more effective than placebo, it is difficult to quantify the difference between spesolimab and the current standard of care; however, based on interviews with Danish clinicians the responses seen in patients treated with spesolimab are larger than what would be expected with the current standard of care. The interviewed clinicians stated that based on the results of Effisayil-1 spesolimab would be an important and valuable treatment option and that patients hospitalised with GPP flares would likely be discharged sooner when treated with spesolimab (17). This is supported by the fact that patients with a GPPGA total score of 0 or 1, which was achieved for more than 40% of patients treated with spesolimab(18), would likely be ready for discharge from hospital (17).

A simple cost analysis was performed as a CUA was deemed unsuitable as it would fail to capture the primary characteristics of the disease during this short-term episode (78). This simple cost analysis assesses the clinical efficacy and safety with direct evidence from one pivotal Phase II study, Effisayil-1 (18). Currently, no approved therapies specific to GPP are available in Europe (46), hence no treatment guidelines are available in Denmark. Therefore, results are compared to the current best available care in Denmark, aligned with Danish clinical experts statements.

This simple cost analysis resulted in a base case incremental cost per patient of 14,540 DKK. For the intervention spesolimab, higher drug acquisition costs are observed compared to best available care. Nevertheless, spesolimab is cost saving regarding the remaining cost parameters, such as administration, resource use, AE management, patient

time, and transportation, when compared to the best available care. This can be explained by the fact that spesolimab entails a single administration and has a rapid onset and therapeutic effect, leading to earlier patient discharge from the hospital compared to those treated with the best available care. The primary cost drivers are patient time and transportation expenses, in addition to drug acquisition costs. While the higher cost associated with spesolimab is primarily attributed to the cost of drug acquisition, the best available care arm's cost is due to the considerable expenses incurred in patient time and transportation. This reflects the expectation of Danish clinical experts that spesolimab treatment can result in a fifty percent reduction in hospitalisation time for patients experiencing a GPP flare.

The main uncertainty in this simple cost analysis is that the comparator arm is informed by the Effisayil-1 trial placebo arm and consequently potentially underestimates the efficacy of response for the best available care. This uncertainty cannot be mitigated. However, the uncertainty in the structural and parametric assumptions was carried out to demonstrate the overall uncertainty. Finally, these predicted results are considered plausible considering the significant benefit of spesolimab versus best available care on patients with an acute flare of GPP.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

11. List of experts

Lars Iversen, MD, DMSc, Professor, Former chief physician of the Department of Dermatology, Aarhus University Hospital, Denmark

Alexander Egeberg, MD, PhD, DMSc, Professor, Department of Dermatology, Bispebjerg Hospital, Denmark

12. References

1. Fujita H, Terui T, Hayama K, Akiyama M, Ikeda S, Mabuchi T, et al. Japanese guidelines for the management and treatment of generalized pustular psoriasis: The new pathogenesis and treatment of GPP. J Dermatol. 2018;45(11):1235-70.
2. Navarini AA, Burden AD, Capon F, Mrowietz U, Puig L, Koks S, et al. European consensus statement on phenotypes of pustular psoriasis. J Eur Acad Dermatol Venereol. 2017;31(11):1792-9.
3. Takeichi T, Akiyama M. Generalized Pustular Psoriasis: Clinical Management and Update on Autoinflammatory Aspects. American Journal of Clinical Dermatology. 2020;21(2):227-36.
4. Bachelez H, Barker J, Burden D, Krueger J, Navarini AA. Evidence and expert opinion supporting generalized pustular psoriasis as a distinct disease from psoriasis vulgaris. 2021.
5. Bachelez H. Pustular Psoriasis: The Dawn of a New Era. Acta Derm Venereol. 2020;100(3):adv00034.
6. Kromer C, Loewe E, Schaarschmidt ML, Pinter A, Gerdes S, Herr R, et al. Drug survival in the treatment of generalized pustular psoriasis: A retrospective multicenter study. Dermatologic Therapy. 2021.
7. Choon SE, Lai NM, Mohammad NA, Nanu NM, Tey KE, Chew SF. Clinical profile, morbidity, and outcome of adult-onset generalized pustular psoriasis: analysis of 102 cases seen in a tertiary hospital in Johor, Malaysia. Int J Dermatol. 2014;53(6):676-84.
8. Kharawala S, Golembesky AK, Bohn RL, Esser D. The clinical, humanistic, and economic burden of generalized pustular psoriasis: a structured review. Expert Rev Clin Immunol. 2020;16(3):239-52.
9. Egeberg A. Prevalence, incidence and characteristics of patients with generalized pustular psoriasis [Data on file]. 2022.
10. Bachelez H MJ, Pouvourville G, Gloede T, Medina P, Esser D, Bentayeb M, Lay K, Thoma C, Viguier M, editor Characterization of flares in patients with generalized pustular psoriasis – a population-based study from the French National Health Data System database (SNDS). AAD; 2021; Virtual.
11. Kotowsky N ea, editor Characteristics of patients with generalized pustular psoriasis compared with those with psoriasis vulgaris: A claims database study. Annual Maui Dermatology Meeting; 2020; Hawaii, US.
12. Pfohler C, Muller CS, Vogt T. Psoriasis vulgaris and psoriasis pustulosa - epidemiology, quality of life, comorbidities and treatment. Curr Rheumatol Rev. 2013;9(1):2-7.
13. Sampogna F, Tabolli S, Soderfeldt B, Axtelius B, Aparo U, Abeni D, et al. Measuring quality of life of patients with different clinical types of psoriasis using the SF-36. Br J Dermatol. 2006;154(5):844-9.
14. Boehringer Ingelheim. Patient Experience Dossier for Generalized Pustular Psoriasis. 2021.
15. Sampogna F, Tabolli S, Söderfeldt B, Axtelius B, Aparo U, Abeni D. Measuring quality of life of patients with different clinical types of psoriasis using the SF-36. Br J Dermatol. 2006;154(5):844-9.
16. Prinz JC, Choon SE, Griffiths CEM, Merola JF, Morita A, Ashcroft DM, et al. Prevalence, comorbidities and mortality of generalized pustular psoriasis: a literature review. J Eur Acad Dermatol Venereol. 2022.
17. Boehringer Ingelheim. Danish Clinical Expert Statements. In: Boehringer Ingelheim, editor. 2023.
18. Bachelez H, Choon SE, Marrakchi S, Burden AD, Tsai TF, Morita A, et al. Trial of Spesolimab for Generalized Pustular Psoriasis. N Engl J Med. 2021;385(26):2431-40.
19. Danish Medicines Council. Medicinrådets lægemiddelrekommandation og behandlingsvejledning vedrørende lægemidler til moderat til svær plaque psoriasis. 2022.
20. Elewski B, Lebwohl MG, Anadkat MJ, Barker J, Ghoreschi K, Imafuku S, et al. Rapid and sustained improvements in GPPGA scores with spesolimab for treatment of generalized pustular psoriasis flares in the randomized, placebo-controlled Effisayil 1 study. J Am Acad Dermatol. 2023.
21. Medicinrådet. Medicinrådets metodevejledning for vurdering af nye lægemidler. 2021.

22. Takeichi T, Akiyama M. Generalized Pustular Psoriasis: Clinical Management and Update on Autoinflammatory Aspects. Am J Clin Dermatol. 2020;21(2):227-36.
23. Marrakchi S, Guigue P, Renshaw BR, Puel A, Pei XY, Fraitag S, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. N Engl J Med. 2011;365(7):620-8.
24. Onoufriadis A, Simpson MA, Pink AE, Di Meglio P, Smith CH, Pullabhatla V, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. Am J Hum Genet. 2011;89(3):432-7.
25. Setta-Kaffetzi N, Simpson MA, Navarini AA, Patel VM, Lu HC, Allen MH, et al. AP1S3 mutations are associated with pustular psoriasis and impaired Toll-like receptor 3 trafficking. Am J Hum Genet. 2014;94(5):790-7.
26. Farooq M, Nakai H, Fujimoto A, Fujikawa H, Matsuyama A, Kariya N, et al. Mutation analysis of the IL36RN gene in 14 Japanese patients with generalized pustular psoriasis. Hum Mutat. 2013;34(1):176-83.
27. Liu ZJ, Tian YT, Shi BY, Zhou Y, Jia XS. Association between mutation of interleukin 36 receptor antagonist and generalized pustular psoriasis: A PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore). 2020;99(45):e23068.
28. Sugiura K, Takemoto A, Yamaguchi M, Takahashi H, Shoda Y, Mitsuma T, et al. The majority of generalized pustular psoriasis without psoriasis vulgaris is caused by deficiency of interleukin-36 receptor antagonist. J Invest Dermatol. 2013;133(11):2514-21.
29. Berki DM, Liu L, Choon SE, David Burden A, Griffiths CEM, Navarini AA, et al. Activating CARD14 Mutations Are Associated with Generalized Pustular Psoriasis but Rarely Account for Familial Recurrence in Psoriasis Vulgaris. J Invest Dermatol. 2015;135(12):2964-70.
30. Johnston A, Xing X, Wolterink L, Barnes DH, Yin Z, Reingold L, et al. IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. J Allergy Clin Immunol. 2017;140(1):109-20.
31. Mossner R, Wilsmann-Theis D, Oji V, Gkogkolou P, Lohr S, Schulz P, et al. The genetic basis for most patients with pustular skin disease remains elusive. Br J Dermatol. 2018;178(3):740-8.
32. Mahil SK, Twelves S, Farkas K, Setta-Kaffetzi N, Burden AD, Gach JE, et al. AP1S3 Mutations Cause Skin Autoinflammation by Disrupting Keratinocyte Autophagy and Up-Regulating IL-36 Production. Journal of Investigative Dermatology. 2016;136(11):2251-9.
33. Choon S-E, Turki H, Seminario-Vidal L, Zheng M, Burden AD, Hua H, et al. Clinical characterisation of GPP flares: Historical data of patients enrolled in the Effisayil-1 trial. EADV2021.
34. Zelickson BD, Muller SA. Generalized pustular psoriasis. A review of 63 cases. Arch Dermatol. 1991;127(9):1339-45.
35. Strober B, Kotowsky N, Medeiros R, Mackey RH, Harrold LR, Valdecantos WC, et al. Unmet Medical Needs in the Treatment and Management of Generalized Pustular Psoriasis Flares: Evidence from a Survey of Corrona Registry Dermatologists. Dermatol Ther (Heidelb). 2021;11(2):529-41.
36. Baker H, Ryan TJ. Generalized pustular psoriasis. A clinical and epidemiological study of 104 cases. Br J Dermatol. 1968;80(12):771-93.
37. Bachelez H. Pustular psoriasis and related pustular skin diseases. Br J Dermatol. 2018;178(3):614-8.
38. Oji V, Luger T. The skin in psoriasis: assessment and challenges. Clin Exp Rheumatol. 2015;33:14-9.
39. Skalicky A. Symptom experience of patients with generalized pustular psoriasis. Value Health. 2020;23:S345.
40. Viguier M, Allez M, Zagdanski A-M, Bertheau P, de Kerviler E, Rybojad M, et al. High frequency of cholestasis in generalized pustular psoriasis: Evidence for neutrophilic involvement of the biliary tract. Hepatology. 2004;40(2):452-8.
41. Golembesky AK, Kotowsky N, Gao R, Yamazaki H. PRO16 Healthcare Resource Utilization (HCRU) in Patients with Generalized Pustular Psoriasis (GPP) in JAPAN: A Claims Database Study. Value in Health Regional Issues. 2020;22:S98.
42. Kotowsky N ea, editor Healthcare resource utilization (HCRU) in patients with generalized pustular psoriasis (GPP): A claims database study. ISPOR US Annual Meeting; 2020; Orlando, USA.
43. Lofvendahl S, Norlin JM, Schmitt-Egenolf M. Economic Burden of Generalized Pustular Psoriasis in Sweden: A Population-Based Register Study. Psoriasis (Auckl). 2022;12:89-98.
44. Bachelez H, Choon SE, Marrakchi S, Burden AD, Tsai T-F, Morita A, et al., editors. Effisayil™ 1: A multicentre, randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of

spesolimab in patients with a generalized pustular psoriasis flare. The 6th World Psoriasis and Psoriatic Arthritis Conference; 2021.
45. Augey FR, P. Nicolas, J. F. Generalized pustular psoriasis (Zumbusch): A French epidemiological survey. European Journal of Dermatology. 2006;16(6):669-73.
46. Schäfer I, Rustenbach SJ, Radtke M, Augustin J, Glaeske G, Augustin M. [Epidemiology of psoriasis in Germany--analysis of secondary health insurance data]. Gesundheitswesen. 2011;73(5):308-13.
47. Lofvendahl S, Norlin JM, Schmitt-Egenolf M. Prevalence and incidence of generalized pustular psoriasis in Sweden: a population-based register study. Br J Dermatol. 2022;186(6):970-6.
48. Krueger J, Puig L, Thaci D. Treatment Options and Goals for Patients with Generalized Pustular Psoriasis. Am J Clin Dermatol. 2022;23(Suppl 1):51-64.
49. Menter A, Strober BE, Kaplan DH, Kivelevitch D, Prater EF, Stoff B, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. J Am Acad Dermatol. 2019;80(4):1029-72.
50. Smith CH. Use of hydroxyurea in psoriasis. Clin Exp Dermatol. 1999;24(1):2-6.
51. Lægemiddelstyrelsen. Produktresume for Neotigason, hårde kapsler. 2021.
52. Lægemiddelstyrelsen. Produktresume for Sandimmun Neoral, bløde kapsler. 2022.
53. European Medicines Agency. Remicade - EPAR - Product Information [Summary of Product Characteristics]. 2009.
54. European Medicines Agency. Hyrimoz - EPAR - Product Information [Summary of Product Characteristics]. 2018.
55. European Medicines Agency. Bimzelx - EPAR - Product Information [Summary of Product Characteristics]. 2021.
56. European Medicines Agency. Tremfya - EPAR - Product Information [Summary of Product Characteristics]. 2017.
57. Lu J, Wang Y, Li Y, Gong Y, Ding Y, Shi Y. Comparative Study on the Clinical Efficacy and Safety of Acitretin and MTX in the Treatment of Pustular Psoriasis by TLR7/MyD88/CXCL16 Pathway. Appl Bionics Biomech. 2022;2022:9640326.
58. Yu N, Li Y, Ding Y, Shi Y. Combination therapy with acitretin and glycyrrhizin in generalized pustular psoriasis with liver test abnormalities: A case series. Dermatol Ther. 2020;33(3):e13318.
59. Schünemann H BJ, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations2013.
60. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.
61. El-Reshaid K, Shaima A. Long-term maintenance therapy with Cyclosporine A in adults with generalized pustular psoriasis. Journal of Drug Delivery and Therapeutics. 2019.
62. Morita A, Nishikawa K, Yamada F, Yamanaka K, Nakajima H, Ohtsuki M. Safety, efficacy, and drug survival of the infliximab biosimilar CT-P13 in post-marketing surveillance of Japanese patients with psoriasis. J Dermatol. 2022;49(10):957-69.
63. Torii H, Nakano M, Yano T, Kondo K, Nakagawa H, Group TSS. Efficacy and safety of dose escalation of infliximab therapy in Japanese patients with psoriasis: Results of the SPREAD study. The Journal of Dermatology. 2017;44(5):552-9.
64. Torii H, Terui T, Matsukawa M, Takesaki K, Ohtsuki M, Nakagawa H, et al. Safety profiles and efficacy of infliximab therapy in Japanese patients with plaque psoriasis with or without psoriatic arthritis, pustular psoriasis or psoriatic erythroderma: Results from the prospective post-marketing surveillance. J Dermatol. 2016;43(7):767-78.
65. Kolt-Kaminska M, Zychowska M, Reich A. Infliximab in Combination with Low-Dose Acitretin in Generalized Pustular Psoriasis: A Report of Two Cases and Review of the Literature. Biologics. 2021;15:317-27.
66. Kim HS, You HS, Cho HH, Kim WJ, Mun JH, Song M, et al. Two cases of generalized pustular psoriasis: successful treatment with infliximab. Ann Dermatol. 2014;26(6):787-8.
67. Routhouska SB, Sheth PB, Korman NJ. Long-term management of generalized pustular psoriasis with infliximab: case series. J Cutan Med Surg. 2008;12(4):184-8.
68. Poulalhon N, Begon E, Lebbe C, Liote F, Lahfa M, Bengoufa D, et al. A follow-up study in 28 patients treated with infliximab for severe recalcitrant psoriasis: evidence for efficacy and high incidence of biological autoimmunity. Br J Dermatol. 2007;156(2):329-36.

69. Trent JT, Kerdel FA. Successful treatment of Von Zumbusch pustular psoriasis with infliximab. J Cutan Med Surg. 2004;8(4):224-8.
70. Morita AY, F. Matsuyama, T. Takahashi, K. Arai, S. Asahina, A. Imafuku, S. Nakagawa, H. Hasegawa, Y. Williams, D. Matsuda, N. Kitamura, S. Adalimumab treatment in Japanese patients with generalized pustular psoriasis: Results of an open-label phase 3 study. Journal of Dermatology. 2018;45(12):1371-80.
71. Sano S, Kubo H, Morishima H, Goto R, Zheng R, Nakagawa H. Guselkumab, a human interleukin-23 monoclonal antibody in Japanese patients with generalized pustular psoriasis and erythrodermic psoriasis: Efficacy and safety analyses of a 52-week, phase 3, multicenter, open-label study. J Dermatol. 2018;45(5):529-39.
72. European Medicines Agency. Spevigo - EPAR - Product Information [Summary of Product Characteristics]. 2023.
73. European Medicines Agency. Spevigo: EPAR - Public Assessment Report. 2022.
74. Boehringer Ingelheim International GmbH. Clinical Study Report, Effisayil-1 [Data on file]. 2021.
75. Navarini AA, Viguier M, Tsai T-F, Morita A, Reich K, Hu N, et al. Spesolimab treatment improves pain, symptoms of psoriasis, fatigue and quality of life inpatients with generalized pustular psoriasis: Patient-reported outcomes from the Effisayil™ 1 study. EADV2021.
76. Puig L, Choon SE, Gottlieb AB, Marrakchi S, Prinz JC, Romiti R, et al., editors. Global consensus on the clinical course, treatment and management of generalized pustular psoriasis (GPP). EADV; 2022.
77. Boehringer Ingelheim International GmbH. Periodic Benefit-Risk Evaluation Report [Data on file]. 2023.
78. Bala MV, Zarkin GA. Are QALYs an appropriate measure for valuing morbidity in acute diseases? Health Econ. 2000;9(2):177-80.
79. Postma MJ, Noone D, Rozenbaum MH, Carter JA, Botteman MF, Fenwick E, et al. Assessing the value of orphan drugs using conventional cost-effectiveness analysis: Is it fit for purpose? Orphanet J Rare Dis. 2022;17(1):157.
80. Corrona L. Corrona Report: Generalized Pustular Psoriasis (GPP) Clinician Survey. Data on file.; 2019.
81. Finansministeriet. Dokumentationsnotat – den samfundsøkonomiske diskonteringsrente. 2021.
82. Boehringer Ingelheim. Effisayil™ 1: Multi-center, double-blind, randomized, placebocontrolled,Phase II study to evaluate efficacy, safety and tolerability of a single intravenous dose of BI 655130 in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity. 2019.
83. Danish Medicines Agency. Medicinpriser.dk 2023 [Available from: https://medicinpriser.dk/.
84. Sundhedsdatastyrelsen. Interaktiv DRG. 2023.
85. Sundhed.dk. Psoriasis, forskellige typer 2020 [Available from: https://www.sundhed.dk/borger/patienthaandbogen/hud/sygdomme/psoriasis/psoriasis-forskellige-typer/.
86. European Medicines Agency. CHMP summary of positive opinion for Spevigo. 2022.
87. Medicinrådet. Medicinrådets lægemiddelrekommandation og behandlingsvejledning vedrørende lægemidler til moderat til svær plaque psoriasis 2022 [1.3:[Available from: https://medicinraadet.dk/media/ksinknvs/medicinr%C3%A5dets-l%C3%A6gemiddelrek-og-behandlingsvejl-vedr-moderat-til-sv%C3%A6r-plaque-psoriasis-vers-1-3.pdf.
88. Augey F, Renaudier P, Nicolas JF. Generalized pustular psoriasis (Zumbusch): a French epidemiological survey. Eur J Dermatol. 2006;16(6):669-73.
89. Kromer C, Loewe E, Schaarschmidt ML, Pinter A, Gerdes S, Herr R, et al. Drug survival in the treatment of generalized pustular psoriasis: A retrospective multicenter study. Dermatol Ther. 2021;34(2):e14814.
90. National Institute for Health and Care Excellence (NICE). TA134: Infliximab for the treatment of adults with psoriasis 2008 [Available from: https://www.nice.org.uk/guidance/ta134.
91. (NICE) NIfHaCE. Ixekizumab for treating moderate to severe plaque psoriasis: Technology appraisal guidance [TA442] 2017 [Available from: https://www.nice.org.uk/guidance/ta442.
92. (NICE) NIfHaCE. TA350: Secukinumab for treating moderate to severe plaque psoriasis secukinumab 2015 [Available from: https://www.nice.org.uk/guidance/ta350.
93. National Institute for Health and Care Excellence (NICE). Ixekizumab for treating active psoriatic arthritis after inadequate response to DMARDs: Technology appraisal guidance [TA537] 2018 [Available from: https://www.nice.org.uk/guidance/ta537.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

94. (NICE) NIfHaCE. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed: Technology appraisal guidance [TA375] 2016 [Available from: https://www.nice.org.uk/guidance/ta375.
95. National Institute for Health and Care Excellence (NICE). TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis: Technology appraisal guidance [TA383] 2016 [Available from: https://www.nice.org.uk/guidance/ta383.
96. (NICE) NIfHaCE. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy: Technology appraisal guidance [TA329] 2015 [Available from: https://www.nice.org.uk/guidance/ta329.
97. National Institute for Health and Care Excellence (NICE). Infliximab and adalimumab for the treatment of Crohn's disease: Technology appraisal guidance [TA187] 2010 [Available from: https://www.nice.org.uk/guidance/ta187.
98. Singh J. Adverse effects of biologics: a network meta-analysis and Cochrane overview. The Cochrane Li-brary. 2012.
99. Medicinrådet. Værdisætning af enhedsomkostninger 2022 [1.6:[Available from: https://medicinraadet.dk/media/aunbprvq/v%C3%A6rdis%C3%A6tning-af-enhedsomkostninger-vers-1-6_adlegacy.pdf.
100. Medicinrådet. Værdisætning af enhedsomkostninger. 2022.
101. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane; 2022.
102. Burden AD, Bachelez H, Choon SE, Marrakchi S, Tsai TF, Morita A, et al., editors. Validation of the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) scale for assessing severity of GPP. AAD Annual Meeting; 2022; Boston.
103. Burden AD, Choon SE, Gottlieb AB, Navarini AA, Warren RB. Clinical Disease Measures in Generalized Pustular Psoriasis. Am J Clin Dermatol. 2022;23(Suppl 1):39-50.
104. Choon SE, Lebwohl MG, Marrakchi S, Burden AD, Tsai TF, Morita A, et al. Study protocol of the global Effisayil™ 1 Phase II, multicentre, randomised, double-blind, placebo-controlled trial of spesolimab in patients with generalized pustular psoriasis presenting with an acute flare BMJ Open. 2021;In Press.
105. Ashcroft DM, Wan Po AL, Williams HC, Griffiths CE. Clinical measures of disease severity and outcome in psoriasis: a critical appraisal of their quality. Br J Dermatol. 1999;141(2):185-91.
106. Carlin CS, Feldman SR, Krueger JG, Menter A, Krueger GG. A 50% reduction in the Psoriasis Area and Severity Index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. J Am Acad Dermatol. 2004;50(6):859-66.
107. Feldman SR, Menter A, Koo JY. Improved health-related quality of life following a randomized controlled trial of alefacept treatment in patients with chronic plaque psoriasis. Br J Dermatol. 2004;150(2):317-26.
108. Gourraud PA, Le Gall C, Puzenat E, Aubin F, Ortonne JP, Paul CF. Why statistics matter: limited inter-rater agreement prevents using the psoriasis area and severity index as a unique determinant of therapeutic decision in psoriasis. J Invest Dermatol. 2012;132(9):2171-5.
109. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol. 2005;32(5):811-9.
110. Thong ISK, Jensen MP, Miro J, Tan G. The validity of pain intensity measures: what do the NRS, VAS, VRS, and FPS-R measure? Scand J Pain. 2018;18(1):99-107.
111. Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. Acad Emerg Med. 2001;8(12):1153-7.
112. Boonstra AM, Schiphorst Preuper HR, Reneman MF, Posthumus JB, Stewart RE. Reliability and validity of the visual analogue scale for disability in patients with chronic musculoskeletal pain. Int J Rehabil Res. 2008;31(2):165-9.
113. Rentz AM, Skalicky AM, Burslem K, Becker K, Kaschinski D, Esser D, et al. The content validity of the PSS in patients with plaque psoriasis. J Patient Rep Outcomes. 2017;1(1):4.
114. Bushnell DM, Martin ML, McCarrier K, Gordon K, Chiou CF, Huang X, et al. Validation of the Psoriasis Symptom Inventory (PSI), a patient-reported outcome measure to assess psoriasis symptom severity. J Dermatolog Treat. 2013;24(5):356-60.

115. Strober BE, Nyirady J, Mallya UG, Guettner A, Papavassilis C, Gottlieb AB, et al. Item-level psychometric properties for a new patient-reported psoriasis symptom diary. Value Health. 2013;16(6):1014-22.
116. Mazzotti E, Barbaranelli C, Picardi A, Abeni D, Pasquini P. Psychometric properties of the Dermatology Life Quality Index (DLQI) in 900 Italian patients with psoriasis. Acta Derm Venereol. 2005;85(5):409-13.
117. Lewis V, Finlay AY. 10 years experience of the Dermatology Life Quality Index (DLQI). J Investig Dermatol Symp Proc. 2004;9(2):169-80.
118. Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. Br J Dermatol. 2008;159(5):997-1035.
119. Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. Dermatology. 2015;230(1):27-33.
120. Olivier J, May WL. Weighted confidence interval construction for binomial parameters. Stat Methods Med Res. 2006;15(1):37-46.
121. Chan IS, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics. 1999;55(4):1202-9.
122. ClinicalTrials.gov. (NCT03782792). Effisayil™ 1:Multi-center, Double-blind, Randomised, Placebo-controlled, Phase II Study to Evaluate Efficacy, Safety and Tolerability of a Single Intravenous Dose of BI 655130 in Patients With Generalized Pustular Psoriasis (GPP) Presenting With an Acute Flare of Moderate to Severe Intensity 2021 [Available from: https://clinicaltrials.gov/ct2/show/NCT03782792.
123. ClinicalTrials.gov. (NCT03886246). An Open-label, Long Term Extension Study to Assess the Safety and Efficacy of BI 655130 Treatment in Patients With Generalized Pustular Psoriasis (GPP) 2021 [Available from: https://www.clinicaltrials.gov/ct2/show/NCT03886246.

Version log

Version	Date	Change
1.0	27 November 2020	Application form for assessment made available on the website of the Danish Medicines Council.
1.1	9 February 2022	Appendix K and onwards have been deleted (company specific appendices) Color scheme for text highlighting table added after table of contents Section 6: Specified requirements for literature search Section 7: Stated it explicitly that statistical methods used need to be described Section 8.3.1: Listed the standard parametric models Section 8.4.1: Added the need for description of quality of life mapping Appendix A: Specified that the literature search needs to be specific for the Danish context and the application Appendices B and D: Stated it explicitly that statistical methods need to be described in the tables in the appendices
1.2	20 June 2022	Clarification of the introduction, including instructions on how to complete the form.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Version log		
1.3	6 December 2022	Clarification regarding new IT security requirements concerning macros in excel files has been added, see page 1.

Appendix A Literature search for efficacy and safety of intervention and comparator(s)

A systematic review was conducted to identify studies potentially eligible for an indirect treatment comparison of efficacy and safety of interventions for the treatment of GPP flares.

The databases searched and the dates of the search are presented in Table 32 and clinical trial registries searched are presented in Table 33.

Table 32. Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid	January 2000 – 12 April 2023	12.04.2023
Medline	Ovid	January 2000 – 12 April 2023	12.04.2023
Medline In-Process	Ovid	January 2000 – 12 April 2023	12.04.2023

Table 33. Registers included in the search

Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov	*"generalized pustular psoriasis"*	12.04.2023
EU Clinical Trials Register	EU Clinical Trials Register	*"generalized pustular psoriasis" OR ""generalised pustular psoriasis"*	12.04.2023

Additionally, the following grey literature databases were searched:

- opengrey.eu
- greylit.org
- the OAIster database (https://oaister.on.worldcat.org/discovery)
- the New York Academy of Medicine (https://www.nyam.org/library/collections-and-resources/grey-literature-report/)

In each case, the primary search terms used were: "generalized pustular psoriasis" and "pustular psoriasis". Filters for study type were not used as part of the grey literature search, to maintain broad criteria and maximize potential article capture. A supplemental online Google search was also conducted to identify any studies not

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

captured by the systematic search. For this search, search terms specific to the GPP-specific outcomes used in the Effisayil™ 1 trial, i.e., “GPPASI” and “GPPGA” were used.

Regarding HTA bodies, the search was focused on the following bodies for materials related to drug approvals for GPP:

- the Canadian Agency for Drugs and Technologies in Health (CADTH)
- the National Institute for Health and Care Excellence (NICE; United Kingdom)
- the Scottish Medicines Consortium (SMC)
- the Pharmaceutical Benefits Advisory Committee (PBAC; Australia)
- the Institute for Clinical and Economic Review (ICER; USA)

For each HTA body, the area of interest was defined by searching the terms “Generalized Pustular Psoriasis” and “von Zumbusch”. The number of total records returned and number of records specific to GPP were collected. In cases where the first search term yielded zero records, we then searched for “Pustular Psoriasis”. For the NICE search, we filtered by “Technology Appraisal Guidance”. For the ICER website, “Generalized Pustular Psoriasis”, “Pustular Psoriasis” and “von Zumbusch” terms were filtered by the disease condition “Psoriasis”. We also conducted a search by leaving the search field blank while filtering on disease condition “Psoriasis”, to maximize relevant records.

12.1 Search strategy

The systematic search included peer-reviewed, published articles published from the year 2000 to 12 April 2023. The search was limited to the year 2000 based on the known literature, publication dates for comparable studies and approval dates for major competitors to spesolimab. Table 34 summarizes the search strategy and search terms utilized for the search including number of hits per string.

Table 34. Search strategy for Embase and MEDLINE searched trough Ovid (12 April 2023)

No.	Query	Results
#1	generalized pustular psoriasis.mp.	1,982
#2	pustular psoriasis.mp.	5,447
#3	1 or 2	5,447
#4	(random* controlled trial or controlled clinical trial).pt.	681,476
#5	("real world" or "electronic medical record*" or "electronic health record" or EHR or EMR).ti,ab.	340,225
#6	(register* or registry or prospective* or survey or (cohort adj (study or studies)) or Cohort analy$ or (observational adj (study or studies)) or longitudinal or retrospective*).ti,ab.	7,698,968
#7	(Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.	80,194
#8	(phase 1 or phase 2 or phase 3 or phase 4).ti,ab.	177,312
#9	("cohort studies" or "case-control studies" or "comparative study").pt. or "cohort".tw. or "compared".tw. or "groups".tw. or "case control".pt. or "multivariate".tw.	16,940,598
#10	case series.ti,ab. or case series.pt.	248,099
#11	4 or 5 or 6 or 7 or 8 or 9 or 10	21,141,540

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

No.	Query	Results
#12	3 and 11	1,220
#13	limit 12 to english language	1,167
#14	limit 13 to human	1,068
#15	limit 14 to yr="2000 -Current"	983
#16	remove duplicates from 15	736

The inclusion criteria and exclusion criteria used to select studies for inclusion are presented in Table 35. The global SLR aimed to identify all treatments for GPP as seen in the inclusion/exclusion criteria, but for this submission only studies examining relevant comparators are considered relevant.

Table 35. Inclusion and Exclusion Criteria for SLR (PICOT(S))

	Inclusion	Exclusion
Population	Male/female, 18-75 years of age Diagnosed with generalized pustular psoriasis (documented history of GPP per ERASPEN criteria, GPPGA score 0 to 1 at screening)	Outside age requirements Other forms of psoriasis (plaque, vulgaris, etc.)
Intervention	Any or none	n/a
Comparator	Any or none	n/a
Outcome(s)	GPPASI (Δ baseline) GPPASI 100 GPPASI 90 GPPASI 75 GPPASI 50 GPPGA PSS VAS FACIT-fatigue DLQI	Studies reporting outcomes other than those of interest
Time	2000+	Pre-2000
Study design	RCT Observational study (including registry studies) Case series	Case reports Laboratory studies

ITC: indirect treatment comparison, GPP: generalized pustular psoriasis, GPPASI: GPP Area and Severity Index, GPPGA: GPP Physician's Global Assessment, PSS: Psoriasis Severity Score, VAS: visual analogue scale, FACIT: Functional Assessment of Chronic Illness Therapy, DLQI: Dermatology Life Quality Index, RCT: randomized controlled trial

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

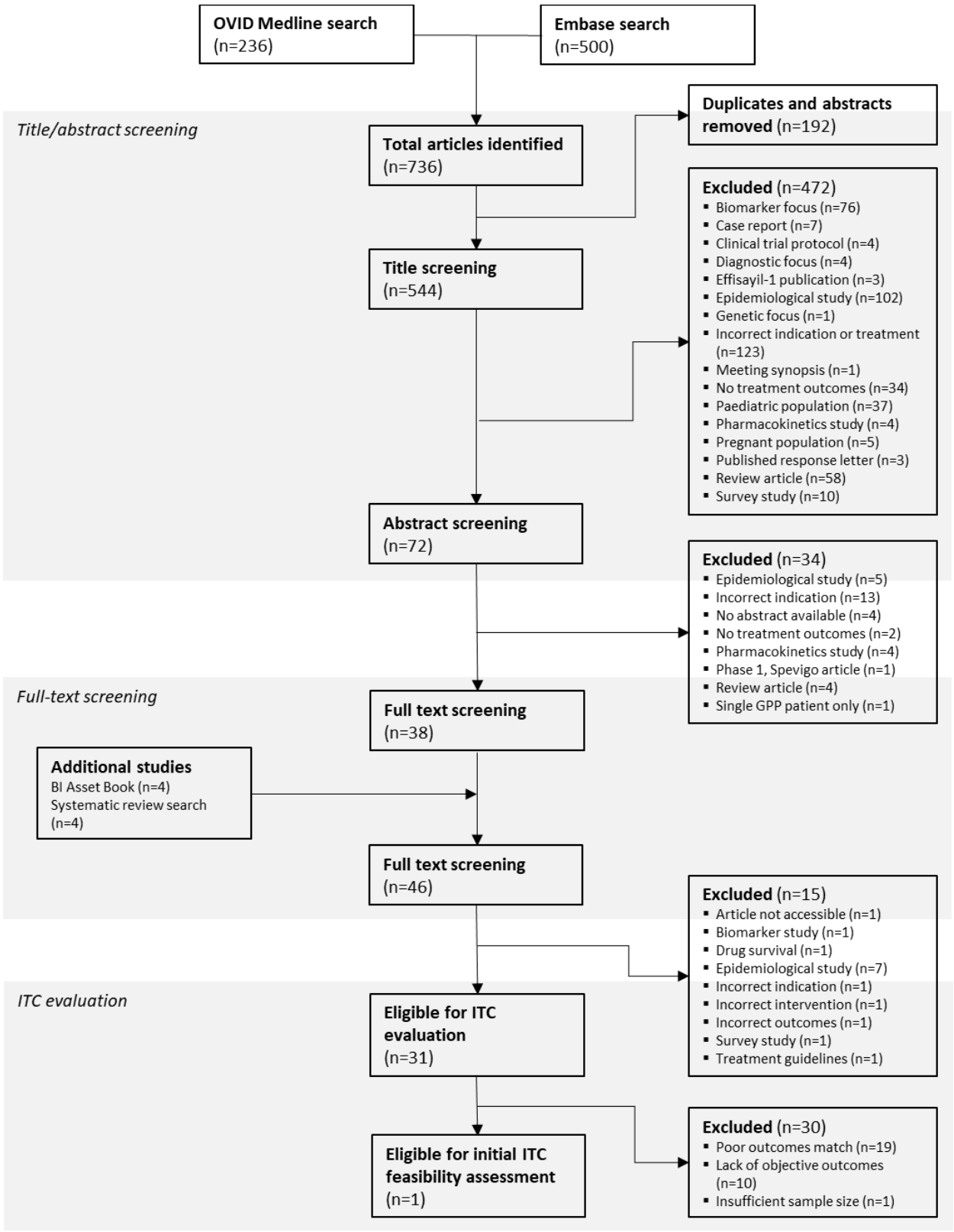
12.2 Systematic selection of studies

Eligibility screening was completed in three stages: title screening, abstract screening and full-text screening, with each article screened by a single reviewer based on the PICOT(S) criteria established *a priori* (Table 35). As a quality assurance measure, a second reviewer independently screened a random selection of 15% of the articles identified in our search. Any discrepancies or queries were discussed with the team to reach a consensus, with a third reviewer available to resolve any remaining disagreements. The following information was collected from each article: author list, title, citation, institution(s) if listed, abstract, publication type and publication year. From each study, the following data elements were extracted: population (age, sex), sample size, intervention, comparator (if any), study outcomes, publication date and study design. Eligible articles were limited to those involving human subjects and published in English. No limits were placed on geographic setting.

The PRISMA flow-chart for the Embase and MEDLINE searches is shown in Figure 11 and the PRISMA flow-chart for grey literature searches are shown in Figure 12.

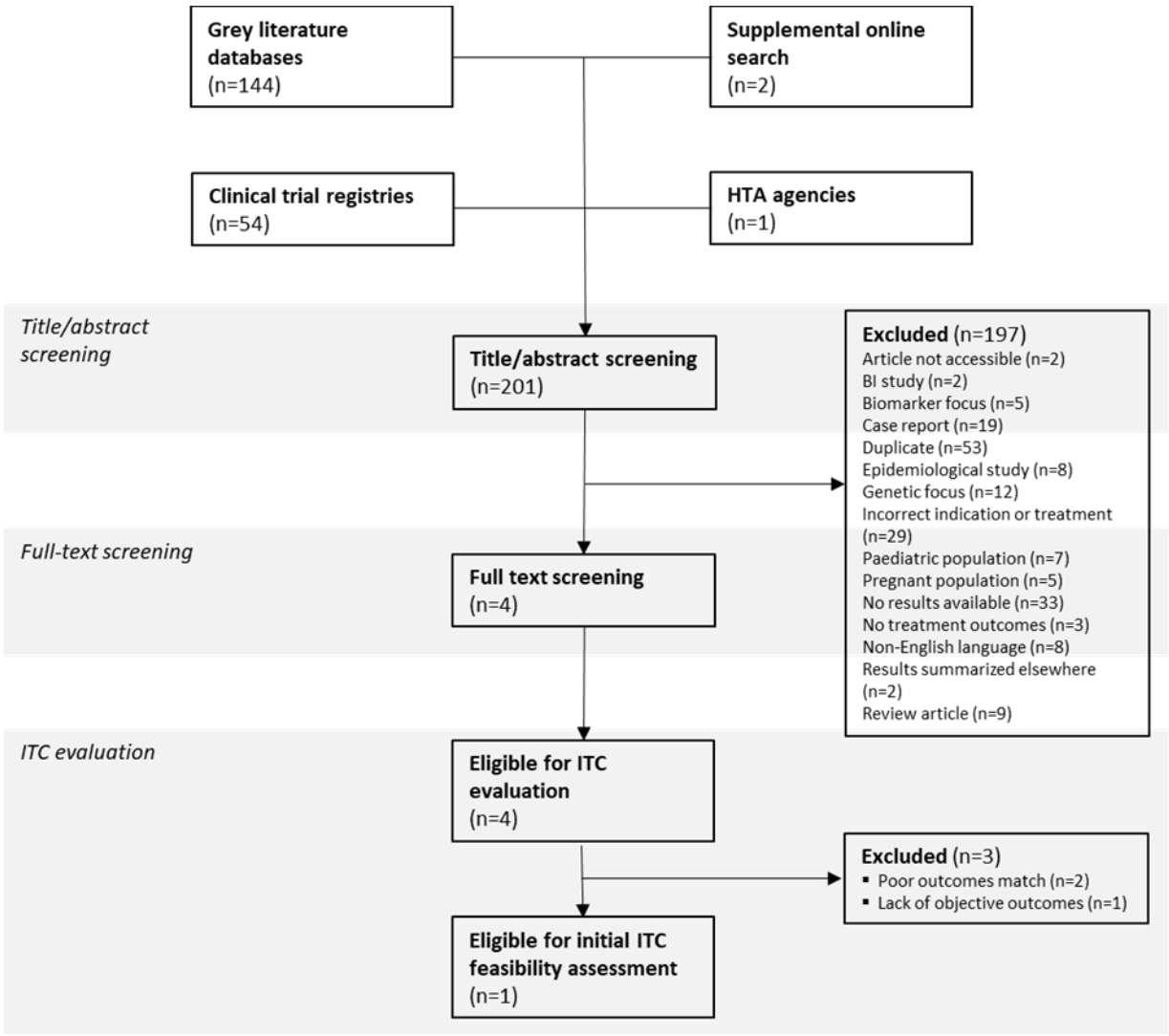
Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 11. PRISMA flowchart for Embase and MEDLINE searches



Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 12. PRISMA flowchart for grey literature search



No studies besides Effisayil-1 eligible for an indirect treatment comparison were identified for the comparators included in this application. The studies identified as potentially relevant but excluded for the relevant comparators are provided in Table 36.

Table 36. Studies identified examining relevant comparators

Study/ID	Study design	Intervention and comparator (sample size (n))	Reason for ineligibility for ITC
Morita 2022b	Single arm trial	Infliximab (n = 20)	Poor matching of outcomes and follow-up period

Study/ID	Study design	Intervention and comparator (sample size (n))	Reason for ineligibility for ITC
Kolt-Kaminska 2021	Case series	Infliximab + acitretin (n = 2)	Lack of objective outcomes
Torii 2017	Single arm trial	Infliximab (n = 7)	Poor matching of outcomes and follow-up period
Torii 2016	Single arm trial	Infliximab (n = 164)	Poor matching of outcomes and follow-up period
Kim 2014	Case series	Infliximab (n = 2)	Lack of objective outcomes
Routhouska 2008	Case series	Infliximab (n = 3)	Lack of objective outcomes
Poulalhon 2006	Case series	Infliximab (n = 3)	Lack of objective outcomes
Trent 2004	Case series	Infliximab (n = 4)	Lack of objective outcomes
Lu 2022	RCT	Acitretin (n = 40) Methotrexate (n = 14)	Lack of information on baseline characteristics and study objectives
Yu 2020	Case series	Acictretin and glycyrrhizin (n = 9)	Lack of objective outcomes
El-Reshaid 2019	Single arm trial	Cyclosporine A (n = 9)	Poor matching of outcomes
Morita 2018	Single arm trial	Adalimumab (n = 10)	Poor matching of outcomes
Ruiz-Villaverde 2021	Single arm trial	Guselkumab (n = 1)	Poor matching of outcomes and sample size limitations
Sano 2018	Single arm trial	Guselkumab (n = 10)	Poor matching of outcomes and follow-up period

12.3 Quality Assessment

As no other studies than Effisayil-1 were included, no quality assessment was performed.

12.4 Strengths and limitations of the systematic literature review

The SLR employed a comprehensive search strategy in several databases (MEDLINE and Embase) which was supplemented by grey literature searches and searches of clinical trial registries. Inclusion and exclusion criteria were specified a priori.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Screening on title, abstract and full-text level were done by a single reviewer, which could be considered a limitation; however, a second reviewer independently screened a random selection of 15% of the articles identified in our search to verify the validity of the process.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix B Main characteristics of included studies

Trial name: Effisayil 1		NCT number: NCT03782792
Objective	To evaluate the efficacy, safety, and tolerability of spesolimab (BI 655130) compared to placebo in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity.	
Publications – title, author, journal, year	Trial of Spesolimab for Generalized Pustular Psoriasis. Bachelez H, et al. New England Journal of Medicine, 2021, 385:2431-2440	
Study type and design	Double-blinded randomised placebo-controlled phase 2 study in patients with GPP presenting with acute flare of moderate to severe intensity. Participants were randomised to spesolimab or placebo in a 2:1 ratio. Patients and investigators were unaware of whether spesolimab or placebo on day 1 throughout the trial. If participants showed persistent symptoms by day 8 they were eligible for an open-label dose of spesolimab, meaning that some patients crossed over from the placebo group to the spesolimab group	
Sample size (n)	Spesolimab (intervention)	Placebo (comparator)
	n = 35	n = 18

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Main inclusion and exclusion criteria

Inclusion criteria:

- a. Patients with GPPGA score of 0 or 1 and a known and documented history of GPP (per ERASPEN criteria) regardless of IL-36RN mutation status, and in addition with previous evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leukocytosis with peripheral blood neutrophilia (above ULN) OR
    - b. Patients with an acute flare of moderate to severe intensity meeting the ERASPEN criteria of GPP with a known and documented history of GPP (per ERASPEN criteria)regardless of IL-36RN mutation status, and in addition with previous evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leukocytosis with peripheral blood neutrophilia (above ULN). OR
    - c. Patients with first episode of an acute GPP flare of moderate to severe intensity with evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leukocytosis with peripheral blood neutrophilia (above ULN). For these patients the diagnosis was to be confirmed retrospectively by a central external expert/committee.
- Patients may or may not have been receiving background treatment with retinoids and/or methotrexate and/or cyclosporine. Patients had to discontinue retinoids/methotrexate/cyclosporine prior to receiving the first dose of BI 655130 or placebo.
- Male or female patients, aged 18 to 75 years at screening.
- Signed and dated written informed consent prior to admission to the study in accordance with ICH-GCP and local legislation prior to start of any screening procedures.
- Women of childbearing potential must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. Note: A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is not a method of permanent sterilization. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause

Exclusion criteria:

- Patients with SAPHO (Synovitis-acne-pustulosis-hyperostosis-osteitis) syndrome.
- Patients with primary erythrodermic psoriasis vulgaris.
- Patients with primary plaque psoriasis vulgaris without presence of pustules or with pustules that were restricted to psoriatic plaques.
- Drug-triggered Acute Generalized Exanthematous Pustulosis (AGEP).
- Immediate life-threatening flare of GPP or requiring intensive care treatment, according to the investigator's judgement. Life-threatening complications mainly included, but were not limited to, cardiovascular/cytokine driven shock, pulmonary distress syndrome, or renal failure.
- Severe, progressive, or uncontrolled hepatic disease, defined as >3-fold Upper Limit of Normal (ULN) elevation in AST or ALT or alkaline phosphatase, or >2-fold ULN elevation in total bilirubin.
- Treatment with:

  - Any restricted medication, or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator.
  - Any prior exposure to BI 655130 or another IL-36R inhibitor

- Patients with dose escalation of their maintenance therapy with cyclosporine and/or methotrexate and/or retinoids within the 2 weeks prior to receiving the first dose of BI 655130/placebo.
- The initiation of systemic agents such as cyclosporine and/or retinoids and/or methotrexate 2 weeks prior to receiving the first dose of BI 655130/placebo.
- Patients with congestive heart disease, as assessed by the investigator.
- Active systemic infections (Fungal and bacterial disease) during the last 2 weeks prior to receiving first drug administration, as assessed by the investigator.
- Increased risk of infectious complications (e.g. recent pyogenic infection, any congenital or acquired immunodeficiency [e.g. HIV], past organ or stem cell transplantation), as assessed by the investigator.
- Relevant chronic or acute infections including HIV or viral hepatitis. For patients screened while having a flare (inclusion criteria 1b or 1c), if Visit 1 HIV or viral hepatitis results were not available in time for randomization, these patients may have received randomised treatment as long as the investigator had ruled out active disease based on available documented history (i.e. negative HIV and viral hepatitis test results) within 3 months prior to Visit 2. A patient could be re-screened if the patient had been treated and was cured from acute infection.
- Active or Latent TB: QuantiFERON® (or if applicable, T-Spot®, introduced with global CTP amendment 1) TB test was to be performed at screening. If the result was positive, the patient may have participated in the study if further work up (according to local practice/guidelines) established conclusively that the patient had no evidence of active tuberculosis. Active TB patients had to be excluded. If presence of latent tuberculosis was established, then treatment should have been initiated and maintained according to local country guidelines. For patients screened while having a flare (inclusion criteria 1b or 1c), if the TB test results were not available in time for randomization, these patients may have received randomised treatment (provided they met all other inclusion/exclusion criteria) as long as the investigator had ruled out active disease based on available documented history (i.e. negative for active TB) within 3 months prior to Visit 2.
- History of allergy/hypersensitivity to a systemically administered trial medication agent or its excipients.
- Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal or squamous cell carcinoma of the skin or in-situ carcinoma of uterine cervix.
- Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational treatment(s).
- Women who were pregnant, nursing, or who planned to become pregnant while in the trial. Women who stopped nursing before the study drug administration did not need to be excluded from participating; they should have refrained from breastfeeding up to 16 weeks after the study drug administration.
- Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to receiving first dose of study drug or planned during the study, e.g. hip replacement, aneurysm removal, stomach ligation), as assessed by the investigator.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Trial name: Effisayil 1	NCT number: NCT03782792
	• Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse or any condition) other than GPP, surgical procedure, psychiatric or social problems, medical examination finding (including vital signs and electrocardiogram [ECG]), or laboratory value at the screening outside the reference range that in the opinion of the investigator was clinically significant and would have made the study participant unreliable to adhere to the protocol, comply with all study visits/procedures or to complete the trial, compromise the safety of the patient or compromise the quality of the data.
Intervention	One-time intravenous infusion of 900mg spesolimab, with the possibility of an additional open-label dose of spesolimab if persistent symptoms are present by day 8. Thirty-five patients were randomised to spesolimab.
Comparator(s)	One-time intravenous infusion of matching placebo, with the possibility of an additional open-label dose of spesolimab if persistent symptoms are present by day 8. Eighteen patients were randomised to spesolimab
Follow-up time	All patients were followed for 12 weeks after the first dose of spesolimab. If patients entered the open-label extension study and received spesolimab as rescue medication between week 7 and week 12, the follow-up period was 6 weeks after this administration, i.e., up to 18 weeks Patients that did not enter the open-label extension study the follow-up period was 16 weeks after the last spesolimab dose, i.e., up to 28 weeks
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints

Primary endpoint:

- A Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0, indicating no visible pustules, at Week 1

Key secondary endpoint:

- A GPPGA total score of 0 or 1 at Week 1

Secondary endpoints included in the hierachial testing strategy:

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

Other secondary efficacy endpoints:

- A GPPGA pustulation subscore of 0 at Week 4
- A GPPGA total score of 0 or 1 at Week 4
- Percent change from baseline in GPPASI total score at Week 1
- Percent change from baseline in GPPASI total score at Week 4
- A GPPASI 50 at Week 1
- A GPPASI 50 at Week 4

Further efficacy endpoints for comparison of the effects of single randomised doses of spesolimab with placebo administered on day 1:

- Time to first achievement of a GPPGA pustulation subscore of 0, indicating no visible Pustules
- A GPPGA pustulation subscore of 0, by visit
- Time to first achievement of a GPPGA total score of 0 or 1
- A GPPGA total score of 0 or 1, by visit
- Change from baseline in GPPGA pustulation subscore, by visit
- Change from baseline in GPPGA total score, by visit
- Percent change from baseline in GPPASI total score, by visit
- A GPPASI 50, by visit
- A GPPASI 75, by visit
- Treatment success measured by improvement of Clinical Global Improvement (CGI) as per the Japanese Dermatological Association (JDA) severity index guidelines at Week 1, Week 2, and Week 4
- Change from baseline in Pain Visual Analog Scale (VAS) score, by visit
- Change from baseline in PSS score, by visit
- Change from baseline in FACIT-Fatigue score, by visit
- Change from baseline in Dermatology Quality of Life Index (DLQI) score, by visit
- A DLQI score of 0 or 1, by visit
- Change from baseline in EQ-5D-5L VAS score, by visit

Further efficacy endpoints introduced via the trial statistical analysis plan (TSAP):

- A reduction from baseline in the GPPGA pustulation subscore by ≥2, by visit
- A GPPGA total score of 0 or 1 (modified, i.e. with all subscores <3), by visit
- A GPPGA erythema subscore of 0 or 1, by visit
- A GPPGA scaling subscore of 0 or 1, by visit
- Percent change from baseline in each of GPPASI pustulation, erythema, and scaling severities
- Change from baseline in JDA GPP severity index, by visit
- A reduction from baseline in the Pain VAS score by ≥30, by visit

Trial name: Effisayil 1	NCT number: NCT03782792

- A PSS score of 0, by visit
- An increase from baseline in the FACIT-Fatigue score by ≥4, by visit
- Change from baseline in EQ-5D-5L health index, by visit

Further efficacy endpoints for exploration of the effect of open-label spesolimab administered on day 8 after randomised treatment on day 1:

- A GPPGA pustulation subscore of 0, by visit
- A GPPGA total score of 0 or 1, by visit
- Percent change from baseline in GPPASI total score, by visit
- A GPPASI 50, by visit
- A GPPASI 75, by visit
- Change in Pain VAS score, by visit
- Change in PSS score, by visit
- Change in FACIT-Fatigue score, by visit

Further efficacy endpoints for exploration of the effect of open-label spesolimab administered on day 8 after randomised treatment on day 1 introduced via the TSAP:

- A GPPGA total score of 0 or 1 (modified, i.e. with all subscores <3), by visit
- A GPPGA erythema subscore of 0 or 1, by visit
- A GPPGA scaling subscore of 0 or 1, by visit

Secondary safety endpoints:

- The occurrence of treatment-emergent adverse events (TEAEs)

Additionally, safety was assessed descriptively based on adverse events (including drug-related AEs), adverse events of special interest (AESI), serious adverse events (SAEs), intensity of adverse events as assessed by the Rheumatology Common Toxicity Criteria (RCTC) version 2.0, safety laboratory tests, physical examination, vital signs (blood pressure, pulse rate, body temperature), relevant findings in 12-lead Electrocardiogram (ECG) documented as AE, infusion site reactions, and immunogenicity (Anti-drug antibodies (ADA), Neutralising antibodies (Nab))

Trial name: Effisayil 1	NCT number: NCT03782792

Method of analysis

Four patient analysis sets were defined: the enrolled set (ES), the randomised set (RS), the safety analysis set (SAF), and the per-protocol set (PPS). The ES included all patients who signed informed consent and was used for analyses of patient disposition. The RS included all randomised patients with treatment assignment as randomised; this set was used for the analyses of efficacy endpoints, as well as for analyses of demographics, baseline characteristics, concomitant medications, and DNA sequencing results. The SAF included all randomised patients who received at least one dose of study drug on day 1 with patients analysed according to the actual treatment received; this set was used for analyses of safety. The PPS included all patients in the RS that adhered to the clinical trial protocol without any important protocol deviations; this set was used for sensitivity analyses on the primary and key secondary endpoints.

Given the small sample size of the trial, an exact statistical test, the Suissa-Shuster Z-pooled test, was used for the primary and key secondary endpoint. Any use of rescue-medication was considered a non-response. Formal statistical hypothesis testing was performed at an overall 1-sided alpha level of 0.025.

As the null-hypotheses of no statistically significant difference between spesolimab and placebo for the primary and key secondary outcomes were rejected, the following secondary outcomes were tested in a hierarchical manner:

- The proportion of patients achieving a GPPASI 75 at week 4
- Change from baseline in pain VAS score at Week 4
- Change from baseline in PSS score at Week 4
- Change from baseline in total FACIT-Fatigue score at Week 4

The proportion of patients achieving a GPPASI 75 at week 4 was analysed using the same approach as the primary and key secondary endpoints. Continuous secondary endpoints were analyses using a Wilcoxon rank test using the RS. Any assessments after death, the use of escape medication, OL spesolimab on Day 8, or rescue medication with spesolimab were assigned worst ranks for the testing. Missing data at Week 4 were imputed and handled via assessment of ranks. All other secondary endpoints were analysed using the methods described above.

All safety analyses were conducted on the SAF. In general, safety analyses were descriptive in nature and were based on Boehringer Ingelheim standards. No hypothesis testing was planned. Statistical analysis and reporting of AEs focused on treatment-emergent AEs (TEAEs), which were all AEs occurring between start of treatment and end of the residual effect period (REP). The REP was defined as 16 weeks after the last dose of trial medication.

Subgroup analyses

The following subgroup analyses were specified in the protocol:

Subgroup	Categories	Endpoints		
		Primary, key secondary	**Secondary** (included in hierachial testing)	Safety
Sex	Female vs. male	Yes	No	Yes
Age	<65 years vs. ≥65 years	Yes	No	Yes
Race	Asian vs. White vs. Other	Yes	No	Yes

Trial name: Effisayil 1					NCT number: NCT03782792
	BMI	<25 kg/m2 vs. 25 to <30 kg/m2 vs. ≥30 kg/m2	Yes	No	Yes
	GPPGA pustulation subscore at baseline	<4 vs. 4	Yes	Yes	Yes
	GPPGA total score at baseline	3 vs. 4	Yes	Yes	Yes
	JDA GPP Severity Score at baseline	Severe vs. moderate vs. mild	Yes	Yes	No
	Pain VAS score at baseline	≤40 vs. >40	Yes	No	No
	Plaque psoriasis at baseline	Yes vs. no	Yes	Yes	No
	Mutation status in IL-36RN	Yes vs. no	Yes	Yes	Yes
	Renal impairment[1]	Normal vs. mild vs. moderate vs. severe	No	No	Yes
	Hepatic impairment[2]	Yes vs. no	No	No	Yes
	Background treatment prior to randomisation	Yes vs. no	Yes	Yes	No
Other relevant information	Not applicable				

[1]Classification of renal function based on estimated CLCR calculated according to the Cockcroft-Gault formula, with the following CLCR categories: normal (≥90 mL/min), mild decrease in GFR (60-89 mL/min), moderate decrease in GFR (30-59 mL/min), and severe decrease in GFR (15-29 mL/min) [R10-2511]

[2]Defined as International Normalized Ratio ≥2.2 and total serum bilirubin >51.3 µmol/L; see TSAP (Appendix 16.1.9, Table 7.8.7: 1)

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 37. Baseline demographic data from Effisayil-1

		ECOG-1912 (NCT02048813)		
Characteristic		**Spesolimab (N = 35)**	**Placebo (N = 18)**	**Total (N = 53)**
Sex (n, %)	Male	14 (40.0%)	3 (16.7)	17 (32.1)
	Female	21 (60.0%)	15 (83.3)	36 (67.9)
Race	Asian	16 (45.7)	13 (72.2)	29 (54.7)
	White	19 (54.3)	5 (27.8)	24 (45.3)
Age (years)	Mean (SD)	43.2 (12.1)	42.6 (8.4)	43.0 (10.9)
	Median (range)	41.0 (21-69)	41.5 (30-57)	41.0 (21-69)
Age (categories)	<50 years	24 (68.6)	14 (77.8)	38 (71.7)
	50 to <65 years	9 (25.7)	4 (22.2)	13 (24.5)
	≥65 years	2 (5.7)	0	2 (3.8)
Weight (kg)	Mean (SD)	73.71 (23.95)	68.75 (26.55)	72.03 (24.72)
	Median (range)	69.30 (47.1, 163.8)	62.90 (36.2, 152.5)	67.00 (36.2, 163.8)
BMI (kg/m^2)	Mean (SD)	27.36 (7.64)	26.29 (9.62)	26.99 (8.29)
	Median (range)	26.17 (17.4, 54.7)	24.87 (15.7, 53.4)	25.34 (15.7, 54.7)
BMI categories	< 25 kg/m^2	15 (42.9)	9 (50.0)	24 (45.3)
	25 to <30 kg/m^2	10 (28.6)	6 (33.3)	16 (30.2)
	≥30 kg/m2	10 (28.6)	3 (16.7)	13 (24.5)
Smoking status (n, %)	Never	24 (68.6)	14 (77.8)	38 (71.7)
	Former	2 (5.7)	2 (11.1)	4 (7.5)
	Current	9 (25.7)	2 (11.1)	11 (20.8)
Renal function based on eGFR/CLCR[1] (n, %)	Normal	26 (74.3)	16 (88.9)	42 (79.2)
	Mild	6 (17.1)	1 (5.6)	7 (13.2)
	Moderate	1 (2.9)	0	1 (1.9)
	Severe	0	0	0
	Missing	2 (5.7)	1 (5.6)	3 (5.7)
Hepatic impairment[2] (N, %)	No	32 (91.4)	18 (100.0)	50 (94.3)
	Yes	0	0	0
	Missing	3 (8.6)	0	3 (5.7)

[1]Classification of renal function based on estimated CLCR calculated according to the Cockcroft-Gault formula, with the following CLCR categories: normal (≥90 mL/min), mild decrease in GFR (60-89 mL/min), moderate decrease in GFR (30-59 mL/min), and severe decrease in GFR (15-29 mL/min) [R10-2511]

[2]Defined as International Normalized Ratio ≥2.2 and total serum bilirubin >51.3 µmol/L

Source: Effisayil-1 Clinical Trial Report [Data on file]

Table 38. Baseline data for GPPGA, GPPASI, and JDA GPP severity index from Effisayil-1

		ECOG-1912 (NCT02048813)		
Characteristic		**Spesolimab (N = 35)**	**Placebo (N = 18)**	**Total (N = 53)**
GPPGA total score (n, %)	3	28 (80.0)	15 (83.3)	43 (81.1)
	4	7 (20.0)	3 (16.7)	10 (18.9)
GPPGA pustulation subscore (n, %)	2	6 (17.1)	5 (27.8)	11 (20.8)
	3	16 (45.7)	7 (38.9)	23 (43.4)
	4	13 (37.1)	6 (33.3)	19 (35.8)
GPPASI total score	Mean (SD)	27.789 (13.436)	24.056 (15.209)	26.521 (14.030)
	Median (range)	27.40 (7.5-54.2)	20.90 (5.2-68.8)	27.20 (5.2-68.8)
GPPASI pustules severity	Mean (SD)	2.350 (0.841)	1.972 (0.826)	2.222 (0.847)
	Median (range)	2.250 (1.00-4.00)	2.125 (0.75-3.75)	2.250 (0.75-4.00)
Pain VAS score	Mean (SD)	76.4 (16.8)	64.6 (27.6)	72.4 (21.6)
	Median (range)	79.8 (20-100)	70.0 (0-100)	77.9 (0-100)
PSS total score	Mean (SD)	10.4 (3.6)	10.3 (3.1)	10.4 (3.4)
	Median (range)	11.0 (3-16)	10.5 (2-16)	11.0 (2-16)
FACIT-fatigue score	Mean (SD)	18.1 (14.2)	19.0 (14.9)	18.4 (14.3)
	Median (range)	14.0 (1-49)	18.0 (0-49)	15.0 (0-49)
DLQI score	Mean (SD)	19.6 (7.1)	19.1 (7.1)	19.4 (7.0)
	Median (range)	19.5 (2-30)	19.5 (5-30)	19.5 (2-30)
JDA GPP severity index	Mean (SD)	7.9 (3.0)	8.4 (2.8)	8.0 (2.9)
	Median (range)	8.0 (2-14)	8.0 (4-14)	8.0 (2-14)
JDA GPP severity index – categories (n, %)	Mild	9 (25.7)	5 (27.8)	14 (26.4)
	Moderate	19 (54.3)	8 (44.4)	27 (50.9)
	Severe	4 (11.4)	4 (22.2)	8 (15.1)
	Missing	3 (8.6)	1 (5.6)	4 (7.5)

Source: Effisayil-1 Clinical Trial Report [Data on file]

12.5 Comparability of the study populations with Danish patients eligible for treatment

The mean age of patients included in Effisayil-1 was 43.2 (SD: 12.1), while the mean age of 57 patients hospitalised in Denmark between 1 Jan 2008 and 31 Dec 2017 was 56.2 (SD: 18.1) (9). Thus, patients in Denmark seem to be older than those included in Effisayil-1. In Effisayil-1 approximately half of the included patients were categorised as Asian (54.7%), while 54 out of 57 patients hospitalised in Denmark were of Danish ethnicity (9).

We do not believe that there are other significant differences between patients included in Effisayil-1 and Danish patients eligible for treatment.

As results of subgroup analyses of age and ethnicity were comparable with the results of the primary analysis, we believe the results of transferable to Danish clinical practice.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix D Efficacy and safety results per study

12.6 Definition, validity and clinical relevance of included outcome measures

Table 39. Efficacy and safety outcome measures for Effisayil-1 (NCT03782792)

Outcome measure	Definition	Validity	Clinical relevance
GPPGA	GPPGA relies on clinical assessment of the GPP patient's skin presentation. It is a modified PGA, a physician's assessment of psoriatic lesions, which has been adapted to the evaluation of GPP patients. The investigator (or qualified site personnel) scores the erythema, pustules, and scaling of all GPP lesions from 0 to 4. Each component is graded separately, the average is calculated, and the final GPPGA is determined from this composite score. A lower score indicates a lesser severity, with 0 being clear and 1 being almost clear (18).	The GPPGA was validated in a study by Burden et al. (102) A panel of GPP clinical experts selected 16 images representing all GPP severities. Twenty-six dermatologists with experience in treating GPP and three additional "expert raters" scored GPPGA components during two separate online sessions. Intrarater reliability was excellent for both experts and dermatologists with a intraclass correlation coefficient above 0.75 for all components. Interrater variability was excellent for all components for dermatologists, and for experts for all domains but pustules (ICC = 0.69). The results of the inter- and intrarater assessments demonstrated a high level of reliability for scoring of GPPGA by physicians globally; dermatologists were consistent over time with individual assessments of disease severity (102).	The GPP-specific clinical efficacy endpoints (GPPGA, GPPASI) were created with minimal modification of the PGA and PASI (replacement of the induration component with pustulation), which are widely used and understood clinical instruments by dermatologists and were created with the help of leading global experts in GPP and psoriasis vulgaris. The proposed primary endpoint of a GPPGA pustulation subscore of 0 (clear) at Week 1 and the key secondary endpoint of a GPPGA score of 0 or 1 at Week 1 are clinically meaningful as pustules are the primary lesion of the disease and reflect the desired rapid pustule clearance and overall improvement in GPP skin symptoms (104).
GPPASI	The GPPASI is an adaptation for GPP patients of the PASI, an established measure of severity and area of psoriatic lesions in patients with psoriasis. Similar adaptions have been used for palmar-plantar pustulosis. In the GPPASI, the induration component has been substituted	The GPPASI has not yet been clinically validated in patients with GPP, however it was created with minimal modification to the PASI score, which is widely used and has been validated in patients with other forms of psoriasis (105-108).	The GPP-specific clinical efficacy endpoints (GPPGA, GPPASI) were created with minimal modification of the PGA and PASI (replacement of the induration component with pustulation), which are widely used and understood clinical instruments by dermatologists and were created with the help of leading global experts in GPP and psoriasis vulgaris. The proposed primary endpoint of a GPPGA pustulation subscore of 0 (clear)

Outcome measure	Definition	Validity	Clinical relevance
	with the pustules component. It is a tool that provides a numeric scoring for a patient's overall GPP disease state, ranging from 0 to 72. It is a linear combination of percent of surface area of skin that is affected by erythema, pustules and scaling and the severity of erythema, pustules, and scaling (desquamation) over 4 body regions (18).		at Week 1 and the key secondary endpoint of a GPPGA score of 0 or 1 at Week 1 are clinically meaningful as pustules are the primary lesion of the disease and reflect the desired rapid pustule clearance and overall improvement in GPP skin symptoms (104).
FACIT-Fatigue	The FACIT-Fatigue is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function. Answers are based on a 5-point Likert scale. Responses of "not at all," "a little," "somewhat", "quite a bit," and "very much" are available for each question, and correspond to scores of 0, 1, 2, 3, and 4, respectively (total score range: 0-52). The recall period for items is 7 days (18).	While the FACIT-Fatigue has not yet been validated in patients with GPP, it has been validated in patients with psoriatic arthritis, where it showed good internal consistency and test-retest reliability (109)	FACIT-Fatigue has been shown to be strongly associated with SF-36 Vitality and is able to differentiate patients with rheumatoid arthritis according to clinical change using the American College of Rheumatology (ACR) response criteria (109). In a study of patients with psoriatic arthritis, most considered the FACIT-Fatigue items relevant to their disease experience, and understood item content and response options as intended (109). A minimal clinically important difference (MCID) of 3-4 points in change score has been reported (109).
Pain VAS	The Pain VAS is a psychometric scale commonly used in the clinical research to study the pain intensity reported by patients. Pain VAS is scored on a 0 mm to 100 mm horizontal line on which 0 represents "no pain" and the 100 mm mark represents "pain as severe as can be imagined"	While the pain VAS has not been validated in patients with GPP, it is a widely used and well understood tool to assess the severity of pain, and has been validated across a variety of indications (110-112).	No MCID is available for the pain VAS, however it is a widely used and recognised tool for measuring pain severity.
PSS	The PSS is a 4-item patient-reported outcome (PRO) instrument that was developed to assess the severity of psoriasis symptoms in patients	While the validity of the PSS has not been clinically validated in GPP, it has been validated in plaque psoriasis, with patients providing positive feedback	No MCID is available for the PSS.

Outcome measure	Definition	Validity	Clinical relevance
	with moderate to severe psoriasis. The symptoms included are: pain, redness, itching, and burning. Current symptom severity is assessed using a 5-point scale ranging from 0 (none) to 4 (very severe). The symptom scores are added to an unweighted total score (range: 0 to 16) (18).	on the PSS and feeling that it was comprehensive and relevant to their experience with psoriasis. The item meaning and response options were well-understood for the majority of the items (113). The PSS is based on the Psoriasis Symptoms Inventory and the Psoriasis Symptom Diary, which both have evidence of validity (114, 115).	Patients with plaque psoriasis administered the PSS provided positive feedback on the PSS and felt that it was comprehensive and relevant to their experience with psoriasis (113).
DLQI	The DLQI is a patient-administered, ten-question, quality of life questionnaire that covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. The DLQI has a one-week recall period. Response categories include "not relevant" (score of 0), "not at all" (score of 0), "a little" (score of 1), "a lot" (score of 2) and "very much" (score of 3). Question 7 is a "yes"/ "no" question where "yes" is scored as 3. DLQI total score is calculated by summing the scores of each question resulting in a range of 0 to 30 where 0-1 = no effect on patient's life, 2-5 = small effect, 6-10 = moderate effect, 11-20 = very large effect, and 21-30 = extremely large effect on patient's life. The higher the score, the more the quality of life is impaired (18).	While the validity of the DLQI has not been clinically validated in GPP (103), it is a widely used instrument that has been validated in various dermatological disorders, including psoriasis (116-118)	The DLQI measures QoL in patients with dermatological disorders, that seeks to measure the impact of these disorders on different aspects of a patients QoL over the last week (119). A study examining the MCID of DLQI found that a change of 3.3 points on the DLQI scale corresponded to a "small change" in QoL as measured by the Global Rating of Change Questionnaire, suggesting that the MCID of DLQI is 3.3 (119).

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

12.7 Results per study

Table 40. Results of Effisayil-1 (NCT03782792)

				Estimated absolute difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**		
GPPGA pustulation subscore of 0 at 1 week	Spesolimab	35	n = 19, 54.3% (38.2% - 69.5%)	48.7%	21.5% - 67.2%	0.0004	Confidence intervals around the proportion of patients achieving the outcome were calculated using the method of Wilson (120). Confidence intervals around the risk difference were calculated using the method of Chan and Zhang (121).	(35)
	Placebo	18	n = 1, 5.6% (1.0% - 25.8)				The P value was calculated using the Suissa-Shuster Z-pooled test	(35)
GPPGA total score of 0 or 1 at 1 week	Spesolimab	35	n = 15, 42.9% (28.0% - 59.1%)	31.7%	2.2% - 52.7%	0.0118	Confidence intervals around the proportion of patients achieving the outcome were calculated using the method of Wilson (120). Confidence intervals around the risk difference were calculated using the method of Chan and Zhang (121).	(35)
	Placebo	18	n = 2, 11.1% (3.1% - 32.8%)				The P value was calculated using the Suissa-Shuster Z-pooled test	(35)

				Estimated absolute difference in effect			Description of methods used for estimation	References
Proportion of patients with a GPPASI 75 at week 4	Spesolimab	35	n = 16, 45.7% (30.5% - 61.8%)	34.6%	5.8% - 55.4%	0.0081	Confidence intervals around the proportion of patients achieving the outcome were calculated using the method of Wilson (120). Confidence intervals around the risk difference were calculated using the method of Chan and Zhang (121). The P value was calculated using the Suissa-Shuster Z-pooled test	(35)
	Placebo	18	n = 2, 11.1% (3.1% - 32.8%)				Any values after use of escape medication, open-label spesolimab at day 8, or rescue medication with spesolimab was coded as non-response	(35)
Change from baseline in Pain VAS score at week 4	Spesolimab	35	Number of failures: 15 (42.9%) Median (IQR): -22.45 (70.41 – Non-response)	Not calculable	Not calculable	0.0118	Any values after use of escape medication, open-label spesolimab at day 8, or rescue medication with spesolimab was coded as non-response As almost all patients receiving placebo were classified as non-responders, a treatment difference to placebo was not calculable. The P value was calculated using the Wilcoxon rank test, where the worst ranks were assigned to the non-responders in both treatment arms	(35)
	Placebo	18	Number of failures: 16 (88.9%) Median: Non-response)					(35)

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

				Estimated absolute difference in effect			Description of methods used for estimation	References
Change from baseline in PSS score at Week 4	Spesolimab	35	Number of failures: 15 (42.9%) Median (IQR): -2.0 (9.0 – Non-response)	Not calculable	Not calculable	0.0044	Any values after use of escape medication, open-label spesolimab at day 8, or rescue medication with spesolimab was coded as non-response As almost all patients receiving placebo were classified as non-responders, a treatment difference to placebo was not calculable. The P value was calculated using the Wilcoxon rank test, where the worst ranks were assigned to the non-responders in both treatment arms	(35)
	Placebo	18	Number of failures: 16 (88.9%) Median: Non-response)					
Change from baseline in FACIT-Fatigue score at Week 4	Spesolimab	35	Number of failures: 15 (42.9%) Median (IQR): 3.0 (Non-response – 30.0)	Not calculable	Not calculable	0.0012	Any values after use of escape medication, open-label spesolimab at day 8, or rescue medication with spesolimab was coded as non-response As almost all patients receiving placebo were classified as non-responders, a treatment difference to placebo was not calculable. The P value was calculated using the Wilcoxon rank test, where the worst ranks were assigned to the non-responders in both treatment arms	(35)
	Placebo	18	Number of failures: 16 (88.9%) Median: Non-response					

				Estimated absolute difference in effect			Description of methods used for estimation	References
GPPGA pustulation subscore of 0 at Week 4	Spesolimab	35	n = 18, 51.4% (35.6% - 67.0%)	40.3%	9.6% - 60.7%	0.0033	Any values after use of escape medication, open-label spesolimab at day 8, or rescue medication with spesolimab was coded as non-response Confidence intervals around the proportion of patients achieving the outcome were calculated using the method of Wilson (120). Confidence intervals around the risk difference were calculated using the method of Chan and Zhang (121). The P value was calculated using the Suissa-Shuster Z-pooled test	(35)
	Placebo	18	n = 2, 11.1% (3.1% - 32.8%)					(35)
GPPGA total score of 0 or 1 at Week 4	Spesolimab	35	n = 17, 48.6% (33.0% - 64.4%)	37.5%	5.8% - 58.1%	0.0056	Any values after use of escape medication, open-label spesolimab at day 8, or rescue medication with spesolimab was coded as non-response Confidence intervals around the proportion of patients achieving the outcome were calculated using the method of Wilson (120).	(35)

				Estimated absolute difference in effect			Description of methods used for estimation	References
							Confidence intervals around the risk difference were calculated using the method of Chan and Zhang (121). The P value was calculated using the Suissa-Shuster Z-pooled test	(35)
Change from baseline in DLQI score by week 1	Spesolimab	34	Median = -2.5 (IQR: -8.0, 1.0)	−2.00	(−7.00 to 3.00)	Not calculated	Any values after use of escape medication was coded as non-response Median difference and 95% CIs were calculated using the modified Hodges-Lehmann method	(74)
	Placebo	18	Median = -1.0 (IQR: -8.0, 3.0)					

Appendix E Safety data for intervention and placebo

Safety analyses were performed on the SAF, which included all randomised patients who received at least 1 dose of study medication. A summary of adverse events between the start of treatment and the end of the residual effect period (defined as 16 weeks after the last dose of medication) is presented in Table 41. The number of patients experiencing adverse events reported for more than 10% of patients in either treatment group between the start of treatment and the end of the residual effect period are presented in Table 41. Patients who received open-label spesolimab on day 8 were censored for the week 12 analyses. As 83.3% patients in the placebo group received open-label spesolimab on day 8, the number and proportion of patients with AEs in the week 12 and week 1 analyses are nearly identical. In the spesolimab group only 34.3% of patients received open-label spesolimab on day 8, and thus for this group the number and proportion of patients with AEs are higher in the week 12 analysis than in the week 1 analysis.

Table 41. Summary of adverse events in Effisayil-1 (NCT03782792) – Start of treatment to end of residual effect period)

	Spesolimab		Placebo	
	N (%)	Rate / 100 Patient-years	N (%)	Rate / 100 Patient-years
Number of patients	35 (100%)		18 (100%)	
Time at risk (patient-years)	5.6		0.9	
Patients with any AE **Time at risk (patient years)**	29 (82.9) 1.2	2391	13 (72.2%) 0.4	3083
Patients with severe AEs (RCTC grade 3 or 4) **Time at risk (patient years)**	7 (20.0%) 4.9	143	2 (11.1%) 0.8	257
Patients with investigator defined drug-related AEs **Time at risk (patient years)**	17 (48.6%) 3.0	571	6 (33.3%) 0.5	1211
Patients with AEs leading to discontinuation of trial drug **Time at risk (patient years)**	0 5.6	0	0 0.9	0
Patients with investigator defined AESIs **Time at risk (patient years)**	1 (2.9%) 2.9	19	0 0.9	0

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Patients with other significant AEs (according to project def.) **Time at risk (patient years)**	0 5.6	0	0 0.9	0
Patients with SAEs **Time at risk (patient years)**	6 (17.1%) 4.6	130	3 (16.7%) 0.8	390
Resulted in death **Time at risk (patient years)**	0 5.6	0	0 0.9	0
Was life-threatening **Time at risk (patient years)**	1 (2.9%) 5.6	19	0 0.9	0
Required or prolonged hospitalization **Time at risk (patient years)**	6 (17.1) 4.6	130	3 (16.7%) 0.8	390

Table 42. SAEs – safety analysis set

SOC/PT	Up to Week 1 (double-blind period)				Up to Week 12 (patients initially randomised to spesolimab)[1]		Up to Week 12 (all patients treated with spesolimab, irrespective of randomisation)[2]	
	Placebo		Spesolimab		Spesolimab		Post any spesolimab[2]	
	N (%)	Rate[3]	N (%)	Rate[3]	N (%)	Rate[3]	N (%)	Rate[3]
Number of patients	18 (100.0)		35 (100.0)		35 (100.0)		51 (100.0)	
Patients with any SAE	3 (16.7)	987.2	5 (14.3)	833.9	6 (17.1)	146.3	13 (25.5)	127.0
Skin and subcutaneous tissue disorders	3 (16.7)	987.2	5 (14.3)	833.9	6 (17.1)	146.3	11 (21.6)	106.0
Pustular psoriasis	3 (16.7)	987.2	4 (11.4)	655.2	4 (11.4)	92.5	9 (17.6)	83.0

DRESS[4]	0	0	1 (2.9)	154.1	2 (5.7)	41.8	2 (3.9)	15.9
Psoriasis	0	0	0	0	0	0	1 (2.0)	7.8
Infections and infestations	0	0	1 (2.9)	154.1	1 (2.9)	20.9	2 (3.9)	15.8
Urinary tract infection	0	0	1 (2.9)	154.1	1 (2.9)	20.9	1 (2.0)	7.8
Influenza	0	0	0	0	0	0	1 (2.0)	7.7
Hepatobiliary disorders	0	0	1 (2.9)	154.1	1 (2.9)	20.9	1 (2.0)	7.8
Drug-induced liver injury	0	0	1 (2.9)	154.1	1 (2.9)	20.9	1 (2.0)	7.8
Musculoskeletal and connective tissue disorders	0	0	1 (2.9)	152.2	1 (2.9)	20.8	1 (2.0)	7.8
Arthritis	0	0	1 (2.9)	152.2	1 (2.9)	20.8	1 (2.0)	7.8
Neoplasms benign, malignant, and unspecified	0	0	0	0	0	0	1 (2.0)	7.7
Squamous cell carcinoma of the skin	0	0	0	0	0	0	1 (2.0)	7.7

1 Patients were censored if they received non-randomised spesolimab (i.e. open-label spesolimab on Day 8 or spesolimab as rescue treatment later). For patients who did not receive non-randomised spesolimab, events are included until Day 113 (i.e. including a 16-week REP after double-blind treatment), EoS, or treatment in the extension trial, whichever was earlier.

2 This includes patients who received at least 1 dose of spesolimab (i.e. double-blind, open-label on Day 8, or as rescue treatment later). Events are included until 16 weeks after last spesolimab administration, EoS, or treatment in the extension trial, whichever was earlier.

3 Incidence rate per 100 patient-years = 100 × number of patients with AE / total AE-specific time at risk [patient-years]

Table 43. User-defined adverse event categories – safety analysis set

UDAEC/PT	Up to Week 1 (double-blind period)				Up to Week 12 (patients initially randomised to spesolimab)[1]		Up to Week 12 (all patients treated with spesolimab, irrespective of randomisation)[2]	
	Placebo		Spesolimab		Spesolimab		Post any spesolimab[2]	
	N (%)	Rate[3]	N (%)	Rate[3]	N (%)	Rate[3]	N (%)	Rate[3]
Number of patients	18 (100.0)		35 (100.0)		35 (100.0)		51 (100.0)	
Patients with any UDAEC[4]	1 (5.6)	289.9	3 (8.6)	478.5	4 (11.4)	87.9	8 (15.7)	68.9
Hypersensitivity "all"[4]	1 (5.6)	289.9	3 (8.6)	478.5	4 (11.4)	87.9	5 (9.8)	42.3
DRESS[5]	0	0	1 (2.9)	154.1	2 (5.7)	41.8	2 (3.9)	15.9
Urticaria	0	0	1 (2.9)	154.1	1 (2.9)	20.0	2 (3.9)	15.9
Eye oedema	0	0	1 (2.9)	154.1	1 (2.9)	20.9	1 (2.0)	7.8
Dermatitis	0	0	0	0	1 (2.9)	20.8	1 (2.0)	7.8
Dermatitis allergic	1 (5.6)	289.9	0	0	0	0	0	0
Infections "all"[4]	0	0	1 (2.9)	154.1	1 (2.9)	20.9	3 (5.9)	23.8
Urinary tract infection[5]	0	0	1 (2.9)	154.1	1 (2.9)	20.9	1 (2.0)	7.8

Influenza[5]	0	0	0	0	0	0	1 (2.0)	7.7
Latent tuberculosis[6]	0	0	0	0	0	0	1 (2.0)	7.7
Malignant tumours[4]	0	0	0	0	0	0	1 (2.0)	7.7
Squamous cell carcinoma of the skin[5, 7]	0	0	0	0	0	0	1 (2.0)	7.7
Torsades de pointes[4]	0	0	0	0	0	0	1 (2.0)	7.8
Syncope[8]	0	0	0	0	0	0	1 (2.0)	7.8
3-point MACE[4]	0	0	0	0	0	0	0	0

[1] Patients were censored if they received non-randomised spesolimab (i.e. open-label spesolimab on Day 8 or spesolimab as rescue treatment later). For patients who did not receive non-randomised spesolimab, events are included until Day 113 (i.e. including a 16-week REP after double-blind treatment), EoS, or treatment in the extension trial, whichever was earlier.

[2] This includes patients who received at least 1 dose of spesolimab (i.e. double-blind, open-label on Day 8, or as rescue treatment later). Events are included until 16 weeks after last spesolimab administration, EoS, or treatment in the extension trial, whichever was earlier.

[3] Incidence rate per 100 patient-years = 100 × number of patients with AE / total AE-specific time at risk [patient-years]

[4] For the definition of UDAECs, see trial 1368-0013.(122) Infections "all" refer to serious and/ or severe and/or opportunistic infections.

[5] Serious AE

[6] Diagnosis based on regular Quantiferon testing according to the clinical trial protocol. The patient had no respiratory symptoms or abnormalities on pulmonary function tests; chest X-ray was normal; active tuberculosis was excluded; treatment with isoniazid and roll-over into the open-label extension trial 1368-0025.(123)

[7] Squamous cell carcinoma of the skin in a patient with longstanding lesion of Acrodermatitis continua of Hallopeau (ACH); diagnosed approximately 2.5 months after start of IMP.

[8] Occurred during infusion of open-label rescue treatment (2nd dose of spesolimab) and was accompanied by hypotension, nausea, vomiting, and cyanosis. Blood pressure normalised after 10 minutes of infusion interruption.

Source: (35)

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix F Comparative analysis of efficacy and safety

No comparative analyses of efficacy and safety were conducted, due to the very low quality of evidence for all included comparators and differences in study design, diagnostic criteria, and definitions of endpoints.

Appendix G Extrapolation

N/A

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix H – Literature search for HRQoL data

N/A

12.7.1 Search strategy

N/A

12.7.2 Quality assessment and generalizability of estimates

N/A

12.7.3 Unpublished data

N/A

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix I Mapping of HRQoL data

N/A

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix J Probabilistic sensitivity analyses

N/A

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk