Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende guselkumab til behandling af psoriasisartrit

Vers. 1.0

Bilagsoversigt

1. Høringssvar fra ansøger
2. Medicinrådets vurdering vedr. guselkumab til behandling af psoriasisartrit, version 1.0
3. Ansøgers endelige ansøgning
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Consultative response to the Medicines Council evaluation of Tremfya® for treatment of psoriatic arthritis

Upon the receipt of the Tremfya® (guselkumab) assessment report, Janssen does not agree with the scientific committee´s conclusion, that guselkumab is less effective in preventing chronic injuries in the joints as well as controlling patients' disease activity compared to ixekizumab.

More specifically, Janssen believes that the scientific committee´s conclusion is unsubstantiated and that the reasons provided for concluding guselkumab as being less effective than ixekizumab are unvalid i.e. extrapolation of comparative data for guselkumab vs. adalimumab in a bio-naïve population to reflect efficacy in a bio-experienced population for guselkumab vs. ixekizumab, that the ACR-50 absolute difference points in a negative direction, Guselkumab having same mode of action as Stelara and uncertainty associated with the assessment due to differences in the underlying studies.

Consequently, Janssen suggests that the clincal categorization for clinical question 2 and 4 should remain “cannot be categorized”. However, the conclusion should be changed to state that the evidence shows that there is no significant differences in efficacy between guselkumab and ixekizumab for the treatment of bio-experienced patients. Furthermore, we believe that guselkumab should be positioned in line with ixekizumab in the RADS´s clinical guidelines. This change should be done based on this consultative response with main arguments summarized in bullets.

- The Scientific Committee states, on page 45 of the evaluation, that “*no data are available on sub-endpoint mTSS but in treatment-naïve patients (clinical question 1), there were significantly more patients who had radiological progression after 24 weeks of treatment with guselkumab compared to adalimumab. The Scientific Committee estimates that the evidence can reasonably be extrapolated to the treatment-experienced patients.”* Janssen does not agree that it is reasonable to extrapolate the evidence to treatment-experienced patients when guselkumab is compared to a different comparator (Ixekizumab) in the treatment- experienced population.

- It is, on page 45 of the evaluation, stated that the Scientific Committee in the overall assessment emphasizes that the absolute efficacy difference on the sub-endpoint ACR50 points in a negative direction compared with ixekizumab. Janssen does not agree that this data should be emphasized and that it should substaintiate guselkumab being inferior to ixekizumab, as the point estimate for the absolute difference as stated in the evaluation “does not exceed the minimal clinically relevant difference and thus does not reflect a clinically relevant efficacy difference.

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Extrapolation of treatment-naïve data to the bio-experienced population

The Scientific Committee states, on page 45 of the evaluation, that "*no data are available on sub-endpoint mTSS but in treatment-naïve patients (clinical question 1), there were significantly more patients who had radiological progression after 24 weeks of treatment with guselkumab compared to adalimumab. The Scientific Committee estimates that the evidence can reasonably be extrapolated to the treatment-experienced patients.*"

First of all Janssen would like to emphazise that we encourage the evaluation be made on the data that is actually available (e.g. all the other endpoints for which there is data), as has been the standard methodology used in previous the Medicines Council previous evaluations ixekizumab for PsA. More specifically, in the evaluation of ixekizumab mTSS results were not available in the SPIRIT-2 study which investigated ixekizumab for treatment-experienced PsA patients and therefore a comparative analysis against secukinumab could not be done. In contrary to the extrapolation conducted in this assessment of guselkumab, the scientitic committee did not extrapolate evidence from the treatment-naïve population comparison of ixekizumab against adalimumab but solely concluded that ixekizumab has "no documented added value" against secukinumab.(1)

Consequently, the methodology used is inconsistent between the evaluation of treatments for psoriatic arthritis, which we believe is very problematic and should not occur.

Furthermore, Janssen does not agree that it is reasonable to extrapolate the evidence from a comparison of guselkumab vs. adalimumab in a treatment-naïve population to treatment-experienced patients, when guselkumab is compared to a different comparator (Ixekizumab) in the treatment-experienced population.

Instead Janssen believes that if such extrapolation should be done, it should at the very least be done based on the evidence from a comparison of guselkumab vs. ixekizumab in a treatment-naïve population. Consequently, we have made this comparison which underlines that the guselkumab has comparable efficacy to ixekuzmab in preventing chronic injuries in the joints as well as controlling patients' disease activity in both treatment-naïve and treatment-experienced patients.
Detailed comparison substantiating this claim is available in the following section:

Proportion of patients without progression cf. mTSS

Gusekumab has not been directly compared to ixekizumab for the treatment of PsA in any published randomized trials. Consequently, an indirect comparison between guselkumab and ixekizumab for treatment-naïve patients has been performed utilizing Bucher's methodology with the results available in table 2. Absolute difference in effect were calculated using the estimated risk ratio and the formula provided in the Handbook of the Medicines Council's process and methodologies.

As guselkumab efficacy results on mTSS for treatment naive patients with PsA without moderate to severe plaque PsO are already available in the clinical evaluation, we only present the ixekizumab efficacy results on mTSS from SPIRIT-P1 for treatment naive patients with PsA without moderate to severe plaque PsO in this consultative response.(2) These results for ixekizumab are used in the indirect comparison and are available in table 1.

Table 1 Results of study SPIRIT-P1 treatment naive

Trial name:	SPIRIT-P1
NCT nr.	NCT01695239

				Estimated relative difference in effect				Description of methods used for estimation	References
Outcome	**Study arm**	**n/N**	**Result (CI)**	**Measurement**	**Difference**	**95% CI**	***P* value**		
Pt. without progression, cf. mTSS	IXE Q4W	89/107	83.2%	Relative	1.16	1.00-1.34	n/a	*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(2)
	PBO	76/106	72%						

The relative difference in RR between guselkumab Q8W and ixekizumab Q4W in the proportion of patients without progression at week 24 is 0.85 (0.69-1.03), based on the guselkumab efficacy results on mTSS that are available in the clinical evaluation and the ixekizumab efficacy results presented in table 1. As the confidence interval of the relative difference does not correspond to any of the specified confidence limits as per the Handbook of the Medicines Council´s process and methodologies for new pharmaceuticals and indication expansions, the preliminary clinically added value cannot be categorized, see table 3.

In addition, the absolute difference in effect is -12.8% (-25.4% to 2.6%) Thus, the preliminary added value cannot be categorized. This is evident when the confidence interval around the absolute effect difference is compared with the least clinically relevant difference of 10%-point and the criteria for the different preliminary categorizations. More specifically the upper bound of 2.6% is not equal to; upper limit (UL) < -10%-point and the lower limit (LL) of -25.4% is not equal to; LL > -10%-point nor equal to; LL ≥ 10%-point.

Conclusively, based on the Scientific committee´s own methodology, this comparative evidence of guselkumab vs. ixekizumab in treatment-naïve patients can reasonably be extrapolated to the treatment-experienced patients. Based on this the same the conclusion, as for all other endpoints, can be drawn, namely that there is no significant differences in efficacy between guselkumab and ixekizumab for the treatment of bio-experienced patients.

Table 2: Clinically added value of guselkumab compared to ixekizumab in regard to treatment-naïve patients without progression, cf. mTSS at week 24.

Clinically added value – patients without progression, cf. mTSS		
Absolute difference – mTSS	**Least clinically relevant difference – 10%**	**Estimated absolute difference (CI)**
Merværdi af ukendt størrelse	LL ≥ MKRF	
Ingen dokumenteret merværdi	LL > -MKRF	
Negativ merværdi	UL < -MKRF	
Kan ikke kategoriseres		-12.8% (-25.4% to 2.6%)
Relative difference - mTSS	**Specified confidence limit - mTSS**	**RR (CI)**
Stor merværdi	LL>1.33	
Moderat merværdi	1.33 ≥ LL > 1.11	
Lille merværdi	1.11 ≥ LL > 1.00 og UL ≤ 1.33	
Merværdi af ukendt størrelse	1.11 ≥ LL > 1.00 og UL > 1.33	
Ingen dokumenteret merværdi	0.90<LL=<1.00 og UL>=1.00	
Negativ merværdi	UL<1.00	
Kan ikke kategoriseres		0.85 (0.69-1.03)

KEY: CI = confidence interval; Upper limit = UL; LL= lower limit; MKRF = Mindste klinisk relevante forskel

Inconsistency

Besides the inconsistency observed between the evaluation of treatments for psoriatic arthritis, Janssen believes that the evaluation conducted by the Scientific Committee in some instances is inconsistent throughout the evaluation and not in line with the Medicines Council´s methodology.

This problem appears for the interpretation and weight applied to the result on ACR50 for bio-experienced patients and statement regarding ixekizumabs effect in SF-36 bodily pain and physical functioning subdomains. Furthermore, in consistency of the evaluation method used for guselkumab versus previous Medicines Council evaluation are observed.

Inconsistency in the evaluation of ACR50

The evaluation by the scientific committee, on page 39 of the evaluation, regarding the proportion of treatment-experienced patients achieving ACR50 at week 24, states following:

- In the proctocol, the scientific committee has defined MKRF as 15%-pionts. The point estimate for the absolute difference in efficacy of -8.6%-points, thus **does not** reflect a clinically relevant difference in efficacy.

- The confidence interval is very broad, which means that it holds the possibility that guselkumab has a positive, no or negative value.
- Guselkumab has a preliminary value that cannot be categorized for the proportion of patients who achieve ACR50 response, as the confidence interval includes 1. (i.e. no statistical significant difference).

When comparing the Scientific Committee´s conclusion for clinical question 2 with the remarks stated above it is evident that the evaluation is inconsistent. More specifically it is, on page 45 of the evaluation, stated that the Scientific Committee in the overall assessment emphasizes that the absolute efficacy difference on the sub-endpoint ACR50 points in a negative direction compared with ixekizumab. However, as outlined in the bullets above the scientific committe have previously in the evaluation themselves concluded that this absolute difference **does not** reflect a clinically relevant difference in efficacy and in fact also state that guselkumab possibly could a positive efficacy compared to ixekizumab.

Consequently, Janssen does not agree that ACR50 should be emphasized in the conclusion and that it should substaintiate guselkumab being inferior to ixekizumab. Instead we believe the conclusion should be changed to state that the evidence shows that there is no significant differences in efficacy between guselkumab and ixekizumab for the treatment of bio-experienced patients.

The claim is further supported by when conducting a comparison of guselkumab vs. ixekizumab on ACR50 in a treatment-naïve population. Detailed comparison substantiating this claim is available in the following section.

Proportion of patients experiencing ACR50 response

Gusekumab has not been directly compared to ixekizumab for the treatment of PsA in any published randomized trials. Consequently, an indirect comparison between guselkumab and ixekizumab for treatment-naïve patients has been performed utilizing Bucher's methodology with the results available in table 4. Furthermore, meta-analysis was used to combine the results of the DISCOVER-1 and DISCOVER-2 studies for guselkumab on ACR50, and these results are available at page 54 of the evaluation. Absolute difference in effect were calculated using the estimated risk ratio and the formula provided in the Handbook of the Medicines Council's process and methodologies.

As guselkumab efficacy results on ACR50 for <u>treatment naive</u> patients with PsA <u>without</u> moderate to severe plaque PsO is already available in the clinical evaluation, we only present the ixekizumab efficacy results on ACR50 from SPIRIT-P1 for <u>treatment naive</u> patients with PsA <u>without</u> moderate to severe plaque PsO in this consultative response.(2) These results for ixekizumab are used in the indirect comparison and are available in table 3.

Table 3 Results of study SPIRIT-P1 treatment naive									
Trial name:	SPIRIT-P1								
NCT number:	NCT01695239								
					Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**n/N**	**Result (CI)**	**Measurement**	**Difference**	**95% CI**	***P* value**		
ACR50 at week 24	IXE Q4W	43/107	40.2%	Relative	2.66	1.60-4.42	n/a	*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(2)
	PBO	16/106	15.1%						

The relative difference in RR between guselkumab Q8W and ixekizumab Q4W in the proportion of patients achieving ACR50 response at week 24 is 0.89 (0.49-1.61), based on the guselkumab meta-analysis results on ACR50 that are available in the clinical evaluation and the ixekizumab efficacy results presented in table 3. As the confidence interval of the relative difference does not correspond to any of the specified confidence limits as per the Handbook of the Medicines Council´s process and methodologies for new pharmaceuticals and indication expansions, the preliminary clinically added value cannot be categorized, see table 4.

In addition, the absolute difference in effect is -4.5% (-20.6%-24.7%) Thus, the preliminary added value cannot be categorized. This is evident when the confidence interval around the absolute effect difference is compared with the least clinically relevant difference of 15%-point and the criteria for the different preliminary categorize. More specifically the upper bound of 24.7% is neither equal to; upper limit (UL) < -15%-point and the lower limit (LL) of -20.6 is not equal to; LL > -15%-point nor equal to; LL ≥ 15%-point.

Table 4: Clinically added value of guselkumab compared to ixekizumab in regards to ACR50 response at week 24.

Clinically added value – ACR50		
Absolute difference – ACR50	**Least clinically relevant difference – 15%**	**Estimated absolute difference (CI)**
Merværdi af ukendt størrelse	LL ≥ MKRF	
Ingen dokumenteret merværdi	LL > -MKRF	
Negativ merværdi	UL < -MKRF	
Kan ikke kategoriseres		-4.5% (-20.6%-24.7%)
Relative difference - ACR50	**Specified confidence limit - ACR50**	**RR (CI)**
Stor merværdi	LL>1.33	
Moderat merværdi	1.33 ≥ LL > 1.11	
Lille merværdi	1.11 ≥ LL > 1.00 og UL ≤ 1.33	
Merværdi af ukendt størrelse	1.11 ≥ LL > 1.00 og UL > 1.33	
Ingen dokumenteret merværdi	0.90<LL=<1.00 og UL>=1.00	
Negativ merværdi	UL<1.00	
Kan ikke kategoriseres		0.89 (0.49-1.61)

KEY: ACR=American College of Rheumatology; CI = confidence interval; Upper limit = UL; LL= lower limit; MKRF = Mindste klinisk relevante forskel

Conclusively, these results show that the efficacy of guselkumab vs. ixekizumab is comparable on ACR50 across treatment-naïve and treatment-experienced population, as there are no statistically significant in efficacy and the point estimate of -4.5% **does not** reflect a clinically relevant difference in efficacy as the scientific committee has defined MKRF as 15%-points. Thus, no evidence support guselkumab being inferior to ixekizumab on ACR50.

Inconsistency in the evaluation on SF-36 bodily pain and physical functioning subdomais

The Scientific Committee states, on page 43 and 44 of the evaluation, that *"data indicates that ixekizumab gives patients a better functional level and data indicates that ixekizumab is better at treating patients´ pain compared to guselkumab, respectively."*
We object this conclusion as there is missing data for the PBO arm in the SPIRIT-2 study and therefore the it is not possible to even state whether ixekizumab has an increased effect against PBO or whether the efficacy is comparable to PBO as has been the conclusion for ixekizumab on the endpoints SF-36 PCS and SF-36 MCS.

Inconsistency versus previous evaluations

In addition to the statement regarding mTSS data from the treatment-naïve population comparison of ixekizumab against adalimumab not being extrapolated in the Medicnes

Council´s evaluation of ixekizumab, Janssen want to highlight that the same procedure was done in the Medicines Council´s evaluation of tofacitinib.(3)
More specifically, the Scientitic Committee did not extrapolate evidence from the treatment-naïve population comparison of tofacitinib against adalimumab but solely concluded that ixekizumab has "no documented added value" against secukinumab as data was not availbale.(3)

Consequently, Janssen finds the methodology of extrapolating the evidence from a comparison of guselkumab vs. adalimumab in a treatment-naïve population to treatment-experienced patients as a highly irregular approach and inconsistent with previous evaluations which constitutes a foundational discriminating evaluation issue.

Furthermore, Janssen finds that the scientific committee is inconsistent regarding the assigned importance to ACR50 in different evaluations of treatments for PsA. This is evident as the scientific committee, even though a negative categorization for the criitical outcome ACR50 was present, stated that the overall category remained "no clinical added value" for tofacitinib. In addition the scientific commmittee assessed that tofacitinib could be equated with the existing first-line treatments.(3)

Janssen therefore finds it unjustified and unsubstiated that the scientific committee without a negative categorization or other evidence of a inferior efficacy of guselkumab vs. ixekizumab on any endpoint (incl. ACR50) can conclude that guselkumab is inferior to ixekizumab.
Likewise, Janssen finds the positioning after ixekizumab in the RADS´guidelines ~~for~~ unjustified as this conclusion should not be drawn without any evidence of guselkumab having a statistical significant inferior efficacy compared to ixekizumab.

Adverse events – long term data

The Scientific Committee states, on page 43 of the evaluation, that *"due to the short follow-up of the guselkumab studies and the lack of clinical experience with guselkumab, there is no knowledge of the potential long-term side effects, as there is for ixekizumab."* It is true that long-term data exceeding one year is not available for the PsA population. However to commodate the request of long-term safety data, data from the VOYAGE-1 and VOYAGE-2 studies evaluating 3 and 4 year safety data of guselkumab for the treatment of moderate to severe psoriasis will be provided in the following section.(4, 5)

3-years safety data

Reich and colleagues report the combined 3-year results from the VOYAGE-1 and VOYAGE-2 phase III trials, evaluating the safety and efficacy of guselkumab in patients with moderate to severe psoriasis.(5) The safety profile of guselkumab through up to 3 years of treatment is consistent with previous findings across the VOYAGE-1 and VOYAGE-2 studies up to week 100. Also, the safety data were generally similar for the guselkumab group (including week 16 placebo crossover individuals) at week 156 compared with week 100 (Table 5).(5)

Table 5: Incidence of adverse events per 100 patients-years (CI) of follow-up integrated across VOYAGE-1 and VOYAGE-2 trough week 100 and week 156, for patients treated with guselkumab.(5)

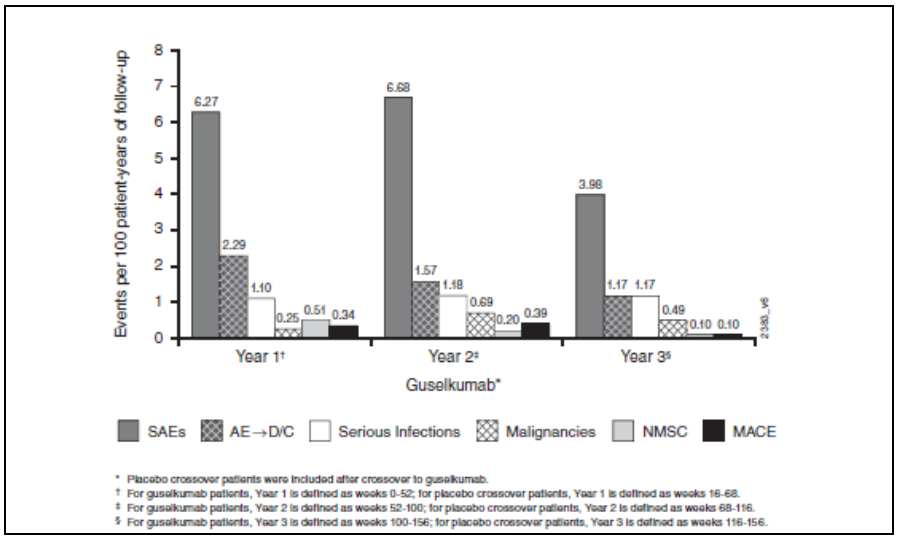
	Weeks 100		Weeks 156	
	Guselkumab*	Combined guselkumab**	Guselkumab*	Combined guselkumab**
Patients treated with guselkumab, n	1221	1721	1221	1721
Total patient-years follow-up	2084	2579	3222	4224
Adverse events	210.41 (204.23-216.73)	200.75 (195.32-206.29)	185.66 (180.98-190.42)	178.17 (174.16-182.24)
Discontinuation due to adverse event	1.83 (1.30-2.51)	1.79 (1.31-2.39)	1.71 (1.29-2.22)	1.61 (1.25-2.04)
Infections	81.74 (77.90-85.71)	79.71 (76.30-83.23)	74.03 (71.09-77.06)	72.49 (69.94-75.10)
Infections requiering treatment	23.76 (21.71-25.95)	22.87 (21.07-24.80)	21.98 (20.39-23.66)	21.59 (20.21-23.04)
Serious adverse events	6.29 (5.26-7.46)	5.93 (5.03-695)	5.68 (4.89-6.57)	5.40 (4.72-6.15)
Serious infections	1.06 (0.66-1.60)	0.85 (0.53-1.29)	1.15 (0.81-1.58)	0.97 (0.70-1.32)
Malignancies				
Non-melanoma skin cancer	0.39 (0.17-0.76)	0.47 (0.24-0.82)	0.28 (0.13-0.53)	0.33 (0.18-0.56)
Other than non-melanoma skin cancer	0.38 (0.17-0.76)	0.39 (0.19-0.71)	0.47 (0.26-0.77)	0.45 (0.27-0.70)
Major adverse cardiovascular events	0.38 (0.17-0.76)	0.35 (0.16-0.66)	0.28 (0.13-0.53)	0.28 (0.15-0.50)

*Includes patients randomly assigned to recieve placebo at baseline who crossed over to guselkumab at week 16

** Includes guselkumab group and patients randomly assigned to adalimumab at baseline who crossed over to recive guselkumab at or after week 52 in VOYAGE-1 and at or after week 28 in VOYAGE-2

When evaluated by year across studies, rates of AEs, serious AEs, serious infections, malignancies, and major adverse cardiovascular events were either stable or decreased over time (Figure 1).(5)

Figure 1: Adverse events by year across VOYAGE-1 and VOYAGE-2.(5)



AE: adverse event; D/C: discontinuation; MACE: major adverse cardiovascular events; NMCS:non-melanoma skin cancer; SAE: Serious adverse events

4-years safety data

Griffiths and colleagues report 4-year results from the VOYAGE-1 phase III trial, which evaluates the safety and efficacy of guselkumab in patients with moderate to severe psoriasis.(4) Safety was assessed in 774 patients receiving at least one dose of guselkumab for a mean duration of 166.95 weeks. Rates of adverse events through week 204 were reported for a guselkumab group (including placebo crossovers at week 16) and an adalimumab→guselkumab group (including patients randomized to adalimumab who crossed over to receive guselkumab starting at week 52), and a combined guselkumab group (Table 6).(4)

Table 6: Proportion of guselkumab-treated patients reporting safety events through week 204.(4)

	Guselkumab*	Adalimumab → guselkumab**	Combined guselkumab ***
Patients treated with guselkumab, n	494	280	774
Average duration of follow-up, weeks	179.03	145.64	166.95
At least one adverse event	437 (88.5)	223 (79.6)	660 (85.3)
Adverse event -> discontinuation	29 (5.9)	9 (3.2)	38 (4.9)
Infections	347 (70.2)	173 (61.8)	520 (67.2)
Infections requiering treatment	169 (34.2)	85 (30.4)	254 (32.8)
At least one serious adverse events	82 (16.6)	27 (9.6)	109 (14.1)
Serious infections	15 (3.0)	4 (1.4)	19 (2.5)
Malignancies			
Non-melanoma skin cancer	8 (1.6)	3 (1.1)	11 (1.4)
Other than non-melanoma skin cancer	13 (2.6)	2 (0.7)	15 (1.9) §
Major adverse cardiovascular events	3 (0.6)	3 (1.1)	6 (0.8) ¥

Data are presented as number of patients (%), unless otherwise indicated.
* Includes patients randomized to guselkumab and those randomized to placebo who crossed over to receive guselkumab starting at week 16.
**Includes patients randomized to adalimumab who crossed over to receive guselkumab starting at week 52.
*** Includes the guselkumab and adalimumab -> guselkumab groups, as defined above.
§Includes three breast cancers; two each colorectal cancer, head and neck cancer, melanoma, and prostate cancer; and one each bladder
cancer, brain cancer, lymphoma, and sarcoma.
¥Includes four myocardial infarctions and two cerebrovascular accidents, one of which led to death.

The safety profile of guselkumab remained favorable, with no new signals of concern revealed with longer treatment through four years. While cumulative rates of adverse events increased with time as expected, rates of serious adverse events and targeted adverse events (including serious infections, malignancies, and major adverse cardiovascular events) remained low at week 204. Cumulative rates of adverse events, discontinuations due to adverse events, and serious adverse events were generally comparable between the guselkumab and the combined guselkumab groups. Through week 204, five deaths were reported in patients receiving guselkumab (i.e., completed suicide, epiglottic cancer, liver failure, and astrocytoma in the guselkumab group and stroke in the adalimumab→guselkumab group). No systemic

hypersensitivity reactions, including anaphylactic reactions or serum sickness-like reactions, occurred in any guselkumab-treated patient through week 204.(4)

5-years safety data for guselkumab based on the VOYAGE-1 and VOYAGE-2 trials has recently been published.(6) Of the 1721 patients treated with guselkumab, 78.4% (1349/1721) completed treatment with study drug through week 252 (7166 PY of follow-up). The proportion of patients discontinuing due to adverse events was low (6.0% [104/1721]). Through Week 264 of guselkumab exposure, SIRs (95% CI) for malignancies (other than NMSC and cervical cancer in situ) in all 3 groups were generally consistent with rates observed in the general US population: guselkumab group: 1.03 (0.67, 1.50); adalimumab→guselkumab Group: 0.67 (0.24, 1.45) and combined guselkumab group: 0.93 (0.64, 1.31). The long-term extensions of pivotal studies of GUS in patients with moderate to severe psoriasis identified no new safety concerns. The adverse event rates were low and generally remained stable over time with continuous guselkumab exposure through 5 years.(6)

Conclusively, the safety data presented for moderate to severe psoriasis, shows that guselkumab has highly favorable safety profile that can reasonably be extrapolated to reflect the safety profile in PsA.

GRAPPA treatment guidelines

The development and updating of treatment recommendations for optimal treatment approaches for patients with psoriatic arthritis (PsA) has been an important mission of the Group for Research and Assessment of Psoriasis and PsA (GRAPPA) since its establishment. The 2021 GRAPPA treatment recommendation submitted as abstract at EULAR 2021, the recommendation is strong for IL23, and is in the same line as anti-TNF and IL-17 for all indications but axial diseases, see table 7.(7)

Table 7: Updated 2021 evidence-based treatment recommendations from GRAPPA.(7)

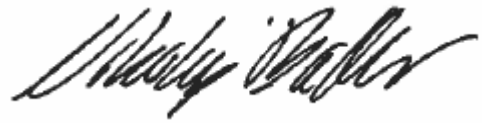
Indication	Strong For	Conditional For	Conditional Against	Strong Against	Insufficient evidence
Peripheral Arthritis DMARD Naïve	csDMARDs, TNFi, PDE4i, IL-12/23i, IL-17i, IL-23i, JAKi	NSAIDs, oral CS, IA CS,	IL-6i,		
Peripheral Arthritis DMARD IR	TNFi, IL-12/23i, IL-17i, IL-23i, JAKi	PDE4i, other csDMARD, NSAIDs, oral CS, IA CS,	IL-6i,		
Peripheral Arthritis bDMARD IR	TNFi, IL-17i, IL-23i, JAKi,	NSAIDs, oral CS, IA CS, IL-12/23i, PDE4i, CTLA-4-Ig	IL-6i,		
Axial arthritis, Biologic Naïve	NSAIDs, Physiotherapy, simple	CS SIJ injections, bisphosphonates		cs DMARDs, IL-6i,	IL-12/23i, IL-23i

	analgesia, TNFi, IL-17i, JAKi				
Axial PsA, Biologic IR	NSAIDs, Physiotherapy, simple analgesia, TNFi, IL-17i, JAKi			csDMARDs, IL-6i,	IL-12/23i, IL-23i
Enthesitis	TNFi, IL-12/23i, IL-17i, PDE4i, IL-23i, JAKi	NSAIDs, physiotherapy, CS injections, MTX		IL-6i,	Other cs DMARDs
Dactylitis	TNFi IL-12/23i, IL-17i, IL-23i, JAKi, PDE4i	NSAIDs, CS injections, MTX	csDMARDs		
Psoriasis	Topicals, phototherapy, csDMARDs, TNFi, IL-12/23i, IL-17i, IL-23i, PDE4i, JAKi	Acitretin			
Nail psoriasis	TNFi, IL12/23i, IL17i, IL23i, PDE4i	Topical CS, tacrolimus and calcipotriol combination or individual therapies, Pulsed dye laser, csDMARDs, acitretin, JAKi			Topical Cyclosporine / Tazarotene, Fumarate, Fumaric Acid Esters, UVA and UVB Phototherapy
IBD	TNFi (not ETN), IL-12/23i, JAKi			IL-17i	
Uveitis	TNFi (not ETN				

These GRAPPA treatment recommendations provide up to date, evidence-based guidance to providers who manage and treat adult patients with PsA and Janssen finds it discouraging that the evaluation in Denmark differs so substantially from the European guidelines based on GRADE methodology. Furthermore, NICE has recommended guselkumab, alone or with methotrexate, as an option for treating active psoriatic arthritis in adults whose disease has not responded well enough to disease-modifying antirheumatic drugs (DMARDs) or who cannot tolerate them, only if they have (8):

- peripheral arthritis with 3 or more tender joints and 3 or more swollen joints
- moderate to severe psoriasis (a body surface area of at least 3% affected by plaque psoriasis and a Psoriasis Area and Severity Index [PASI] score greater than 10)
- had 2 conventional DMARDs and at least 1 biological DMARD

Best regards,
Janssen-Cilag A/S



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Medicinrådet

Medicinrådets vurdering vedrørende guselkumab til behandling af psoriasisartrit

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Dokumentoplysninger	
Godkendelsesdato	23. juni 2021
Dokumentnummer	113799
Versionsnummer	1.0

Indholdsfortegnelse

1. Medicinrådets konklusion

Guselkumab er blevet vurderet til fire patientpopulationer med psoriasisartrit. Medicinrådet vurderer:

- At til patienter med psoriasisartrit *uden* moderat til svær plaque psoriasis:
  - har guselkumab en negativ værdi til behandlingsnaive patienter sammenlignet med nuværende standardbehandling.
  - kan guselkumabs værdi til behandlingserfarne patienter ikke kategoriseres efter Medicinrådets metoder pga. brede konfidensintervaller.
- At til patienter med psoriasisartrit *og* moderat til svær plaque psoriasis:
  - kan guselkumabs værdi til hverken behandlingsnaive eller behandlingserfarne patienter ikke kategoriseres, fordi der ikke foreligger evidens på patientpopulationerne.

Vurderingen gælder for patienter uden og med samtidig moderat til svær plaque psoriasis, som har haft et utilstrækkeligt respons på, eller som har været intolerante over for, en forudgående behandling med et sygdomsmodificerende antireumatisk lægemiddel (DMARD).

Forebyggelse af kroniske ledskader og kontrol af patienternes sygdomsaktivitet er de primære mål med behandlingen. På baggrund af fagudvalgets vurdering og klinisk erfaring, finder Medicinrådet det sandsynligt, at guselkumab er en mindre effektiv behandling til at forebygge kroniske skader i leddene, sammenlignet med nuværende standardbehandling, som er enten adalimumab eller ixekizumab. Derudover er guselkumab sandsynligvis også mindre effektivt til at kontrollere patienternes sygdomsaktivitet, sammenlignet med nuværende standardbehandling.

Medicinrådet fremhæver, at nye studier med direkte sammenligninger af guselkumab med nuværende standardbehandling muligvis kan ændre konklusionen.

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 23. juni 2021

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

- **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.
- **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.
- **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.
- **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (fx på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

MEDICINRÅDET VURDERER KVALITETEN AF DE DATA, DER LIGGER TIL GRUND FOR VURDERINGEN AF LÆGEMIDLET (EVIDENSENS KVALITET) I EN AF FØLGENDE GRADE-KATEGORIER:

- **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.
- **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.
- **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.
- **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2. Begreber og forkortelser

ACR50: *American College of Rheumatology 50 % response*

bDMARD: Biologisk *Disease Modifying Anti-Rheumatic Drug*

CRP: C-Reaktivt Protein

csDMARD: Konventionel *Disease Modifying Anti-Rheumatic Drug*

DANBIO Dansk Reumatologisk Database

DMARD: Sygdomsmodificerende antireumatisk lægemiddel (*Disease Modifying Anti-Rheumatic Drug)*

EMA: Det Europæiske Lægemiddelagentur (*European Medicines Agency*)

EPAR: *European Public Assessment Report*

EUnetHTA: *European Network for Health Technology Assessment*

FDA: *The Food and Drug Administration*

FINOSE: Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger

GRADE: System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)

HTA: Medicinsk teknologivurdering (*Health Technology Assessment)*

IL-17: Interleukin 17

IL-23: Interleukin 23

IQWIG: *The Institute for Quality and Efficiency in Healthcare*

ITT: *Intention-to-treat*

MKRF: Mindste klinisk relevante forskel

mTSS: *Modified Total Sharp Score*

MTX: Methotrexat

NICE: *The National Institute for Health and Care Excellence*

NSAID Non-steroide antiinflammatoriske lægemidler

PASI: *Psoriasis Area Severity Index*

PICO: Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*

PsA: Psoriasisartrit

SF-36: Short Form 36

SMD: *Standardized Mean Difference*

tsDMARD: Targeteret syntetisk *Disease Modifying Anti-Rheumatic Drug*

VAS: *Visual Assessment/Analouge Scale*

3. Introduktion

Formålet med Medicinrådets vurdering af guselkumab til psoriasisartrit er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Janssen-Cilag A/S. Medicinrådet modtog ansøgningen den 7. maj 2021.

De kliniske spørgsmål er:

1. *Hvilken værdi har guselkumab sammenlignet med adalimumab for behandlingsnaive patienter med PsA uden moderat til svær plaque psoriasis?*
2. *Hvilken værdi har guselkumab sammenlignet med ixekizumab for behandlingserfarne patienter med PsA uden moderat til svær plaque psoriasis?*
3. *Hvilken værdi har guselkumab sammenlignet med adalimumab for behandlingsnaive patienter med PsA og moderat til svær plaque psoriasis?*
4. *Hvilken værdi har guselkumab sammenlignet med ixekizumab for behandlingserfarne patienter med PsA og moderat til svær plaque psoriasis?*

3.1 Psoriasisartrit

Psoriasisartrit (PsA) er en kronisk inflammatorisk ledsygdom, der ofte (men ikke nødvendigvis) optræder sammen med den kroniske hudsygdom psoriasis [1,2]. Patogenesen er en T-celle-medieret inflammation og involverer en kompleks række interaktioner mellem immunceller og proinflammatoriske cytokiner, hvor T-celler og makrofager rekrutteres til led- og hudvæv [3]. Disse immunceller fremmer derefter inflammatoriske processer involveret i sygdommen, hvoraf inflammation medieret af det ekstracellulære interleukin 17 og 23 (IL-17 og IL-23) ser ud til at spille en nøglerolle [3–6]. Sygdommen er multifaktoriel og betinget af både genetiske og miljømæssige faktorer [7].

PsA kan både manifestere sig ved inflammation i perifere led og i rygsøjlen, og der kan desuden optræde ekstraartikulære symptomer som inflammation i senetilhæftninger (entesit), hævede fingre eller tæer (daktylit) og negledystrofi [8]. Patienterne kan også have betændelse i øjets regnbue- og årehinde (uveitis) eller have kronisk inflammatorisk tarmsygdom. Det kan være vanskeligt at skelne diagnostisk mellem PsA med aksial involvering og rygsøjlegigt (spondylartrit) af anden art. De kliniske manifestationer varierer betydeligt mellem patienter [9–11] og har stor betydning for patienternes liv. PsA-patienter rapporterer ofte om smerter, nedsat fysisk funktion, træthed og vanskeligheder med daglige aktiviteter [12,13].

I den nationale behandlingsvejledning for PsA fra Dansk Reumatologisk Selskab fremgår det, at der mangler validerede kliniske diagnosekriterier for PsA, men at der er udviklet klassifikationskriterier, som kan benyttes som støtte. Diagnosen stilles på baggrund af en objektiv undersøgelse af bevægeapparat og hud sammen med serologi og biokemi [8].

Prævalensen er svær at estimere grundet manglen på klare diagnostiske kriterier. Baseret på estimater fra et studie fra 2008 og beregninger fra Gigtforeningen finder Medicinrådet, at prævalensen formentlig er mellem 6.000 og 25.000 personer [14,15]. Det skønnes desuden, at op til ca. 15 % af patienter med psoriasis udvikler PsA [8]. Sygdommen debuterer oftest i alderen 40-50 år, og prævalensen er ens for mænd og kvinder.

3.2 Guselkumab

Guselkumab (Tremfya) er en systemisk biologisk antistofbehandling, der virker ved, at det aktive stof binder sig til IL-23. Herved bliver IL-23 forhindret i at bidrage til immunaktivering, og den inflammatoriske reaktion, der spiller en central rolle i udviklingen af PsA, begrænses.

Guselkumab har fået følgende indikation til PsA hos Det Europæiske Lægemiddelagentur (European Medicines Agency (EMA)):

Tremfya® alene eller i kombination med methotrexat (MTX) er indiceret til behandling af aktiv psoriasisartrit hos voksne patienter, som har haft et utilstrækkeligt respons på, eller som har været intolerante over for, en forudgående behandling med et sygdomsmodificerende antireumatisk lægemiddel (DMARD).

Guselkumab gives som subkutan injektion à 100 mg i uge 0 og 4 samt herefter hver 8. uge. For patienter med høj risiko for ledskade, i henhold til klinisk vurdering, kan der overvejes en dosis på 100 mg hver 4. uge.

Guselkumab er desuden indiceret til behandling af moderat til svær plaque psoriasis [16]. Guselkumab blev i 2018 anbefalet som mulig standardbehandling til behandling af moderat til svær plaque psoriasis hos voksne, som er kandidater til 2. generations immunmodulerende behandling.

3.3 Nuværende behandling

Der findes ingen behandling, som kan kurere PsA. Den nuværende behandling er i stedet målrettet patienternes smerter og symptomer, som beskrevet i afsnit 2.1.

Behandlingsmålet er, at patienterne opnår så lav sygdomsaktivitet som muligt og helst remission, så symptomer og inflammation er kontrollerede. Dette er blandt andet for at optimere patientens livskvalitet og sociale liv, forhindre progredierende strukturelle ledskader og bevare funktionsevne.

Sygdomsmodificerende behandling (disease modifying antirheumatic drugs (DMARDs)) gives ved betydelig affektion af led. Til patienter med lav sygdomsaktivitet og lav risiko for progressiv ledsygdom (ledaffektion i mindre end fem led) anvendes monoterapi med lægemidler af typen konventionelle DMARDs (csDMARDs), hvor MTX sædvanligvis er førstevalg i dansk klinisk praksis [8].

Hos patienter med betydelig ledaffektion (mere end fire led) eller ved utilstrækkelig effekt af csDMARDs, eventuelt i kombination med lokale steroidinjektioner [17], kan biologisk behandling med antistoffer (bDMARDs) eller targeteret syntetisk behandling med små molekyler (tsDMARDs) indledes. Kriterierne for at indlede b/tsDMARD-behandling omfatter sygdomsaktivitet, fravær af kontraindikationer, og at beslutningen træffes på konference med speciallæger i reumatologi [8]. Af b/tsDMARDs-behandling benyttes på nuværende tidspunkt forskellige TNF-alfa-hæmmere, monoklonale antistoffer rettet mod IL-12, - 17 og -23 samt en Janus kinase-hæmmer.

Den nuværende lægemiddelrekommandation for biologisk behandling af PsA [18] er delt op i behandling til flere forskellige patientgrupper, afhængigt af om patienten har samtidig moderat til svær psoriasis, uveitis eller inflammatorisk tarmsygdom. Flere af lægemidlerne er godkendt til både PsA og en eller flere af de nævnte indikationer, hvilket har betydning for, hvilke lægemidler der anvendes til de relevante patientgrupper.

TNF-hæmmeren adalimumab er p.t. førstevalg for behandling af alle patientpopulationerne i Medicinrådets lægemiddelrekommandation [18]. Jf. RADS' baggrundsnotat for biologiske og syntetiske targeterede lægemidler til behandling af PsA udelukker behandlingssvigt ved anvendelse af en TNF-hæmmer ikke muligheden for effekt af en ny TNF-hæmmer eller lægemidler med anden virkningsprofil. Efter svigt af to effektfulde TNF-hæmmere (sekundært svigt) eller ved manglende respons fra start (primært svigt) kan lægemiddel med anden virkningsprofil overvejes [19]. Ixekizumab er p.t. andet valg efter forudgående behandling med TNF-hæmmer [18].

I DANBIO (Dansk Reumatologisk Database) var der ved udgangen af 2019 registreret ca. 2560 patienter i biologisk behandling for PsA, hvoraf ca. 330 patienter startede på biologisk behandling (behandlingsnaive), og ca. 860 patienter skiftede behandling (behandlingserfarne). Tallene dækker over alle PsA-patienter, inklusive dem der har følgesygdommene uveitis, Crohns sygdom og colitis ulcerosa.

4. Metode

Medicinrådets protokol for vurdering vedrørende guselkumab beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

De kliniske spørgsmål afspejler populationerne i lægemiddelrekommandationen. Da guselkumab imidlertid ikke er godkendt til behandling af uveitis, Crohns sygdom og colitis ulcerosa, vil Medicinrådets vurdering af guselkumab ikke omhandle patienter med PsA, der har en af disse sygdomme, men alene tage stilling til patienter med og uden samtidig moderat til svær plaque psoriasis. Derudover afspejler de kliniske spørgsmål, at der i dansk klinisk praksis skelnes mellem behandlingsnaive patienter (der ikke tidligere har været behandlet med b/tsDMARDs og skal begynde behandling med en af disse) og behandlingserfarne patienter (der tidligere har været behandlet med b/tsDMARDs og skal skifte til en anden behandling).

5.1 Klinisk spørgsmål 1

Det kliniske spørgsmål er:

Hvilken værdi har guselkumab sammenlignet med adalimumab for behandlingsnaive patienter med PsA uden moderat til svær plaque psoriasis?

5.1.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt syv fuldtekstartikler fra fire kliniske studier, der stemmer overens med in- og eksklusionskriterierne fra Medicinrådets protokol. Artiklerne omhandler to kliniske studier for guselkumab (DISCOVER 1 og DISCOVER 2) [19–21] og to kliniske studier for adalimumab (ADEPT og SPIRIT-P1) [22–25] (se tabel 1). Derudover har ansøger tilføjet én publikation fra DISCOVER 1-studiet, som ikke blev identificeret i litteratursøgningen men blev vurderet af ansøger som værende relevant for det kliniske spørgsmål [26]. Desuden indgår EMAs EPAR og produktresuméerne for guselkumab [16,27] og adalimumab [28].

Tabel 1. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Population	Intervention vs. komparator
Deodhar et al. 2020 [19] Ritchlin et al. 2021 [26]	DISCOVER 1	NCT03162796	Behandlingsnaive og behandlingserfarne patienter med aktiv psoriasisartrit	Guselkumab vs. placebo

Publikationer	Klinisk forsøg	NCT-nummer	Population	Intervention vs. komparator
Mease et al. 2020 [20] McInnes et al. 2020 [21]	DISCOVER 2	NCT03158285	Behandlingsnaive patienter med aktiv psoriasisartrit	Guselkumab vs. placebo
Mease et al. 2005 [22] Mease et al. 2009 [23]	ADEPT	NCT00195689	Behandlingsnaive patienter med aktiv psoriasisartrit	Adalimumab vs. placebo
Mease et al. 2017 [24] Gottlieb et al. 2018 [25]	SPIRIT-P1	NCT01695239	Behandlingsnaive patienter med aktiv psoriasisartrit	Ixekizumab vs. adalimumab eller placebo

DISCOVER 1

Dette er et randomiseret, dobbeltblindet fase III-studie, der undersøgte effekten og sikkerheden af guselkumab sammenlignet med placebo hos behandlingsnaive og behandlingserfarne patienter med aktiv PsA. Omkring 70 % af patienterne var behandlingsnaive og skulle tidligere have haft et utilstrækkeligt respons eller være intolerante overfor csDMARDs og/eller non-steroide antiinflammatoriske lægemidler (NSAIDs). De øvrige ca. 30 % af patienterne var behandlingserfarne med fortsat sygdomsaktivitet trods behandling med ≤ 2 TNF-hæmmere. Patienterne skulle opfylde CASPAR-kriterierne (*Classification criteria for Psoriatic Arthritis*) og have aktiv sygdom defineret som ≥ 3 hævede led, ≥ 3 ømme led og C-reaktiv-protein (CRP)-niveau ≥ 0,3 mg/dL. Derudover skulle patienterne have ≥ 1 PsA subtype og nuværende plaque psoriasis i hud (minimum 1 psoriasis plaque ≥ 2 cm i diameter) eller negle eller tidligere dokumenteret plaque psoriasis.

Patienterne blev randomiseret 1:1:1 til guselkumab 100 mg hver 4. uge (Q4W, n = 128), guselkumab 100 mg ved uge 0, 4 og derefter hver 8. uge (Q8W, n = 127) eller placebo (n = 126). Patienter kunne fortsætter deres behandling med NSAIDs (godkendte standard doser), orale kortikosteroider (tilsvarende ≤ 10 mg prednisolon /dag) og/eller csDMARDs (MTX ≤ 25 mg/uge, sulfasalazin ≤ 3 g dagligt, hydroxychloroquin ≤ 400 mg dagligt, eller leflunomid ≤ 20 mg dagligt). Hvis patienterne ikke modtog disse behandlinger ved baseline, skulle de være stoppet ≥ 4 uger (csDMARDs) eller ≥ 2 uger (NSAIDs og orale kortikosteroider) før første administration med studiemedicin. Randomiseringen var stratificeret efter csDMARDs ved baseline (ja eller nej) og tidligere behandling med TNF-hæmmere (ja eller nej). Efter 24-ugers dobbeltblindet periode krydsede patienter i placeboarmen over til guselkumab Q4W.

Effektanalyser blev udført efter opfølgningstid på 52 uger, mens sikkerhed havde en opfølgningstid på 60 uger.

Effektanalyser op til uge 24 blev foretaget på data fra alle randomiserede patienter (*intention-to-treat* (ITT)-population) og sikkerhedsanalyser på alle patienter, der modtog minimum én studiedosis. Studiets primære effektmål var andel patienter, der opnåede *American College of Rheumatology* 20 % response (ACR20) ved uge 24. Sekundære effektmål af relevans er andel patienter, der opnåede ACR50 ved uge 24, gennemsnitlig ændring fra baseline i livskvalitet målt ved *short form 36* (SF-36) ved uge 24, andel patienter, der opnåede 90 % reduktion i *Psoriasis Area Severity Index (PASI)*-score og sikkerhed.

DISCOVER 2

DISCOVER 2-studiet er sammenligneligt med DISCOVER 1-studiet. Det er et randomiseret, dobbeltblindet fase III-studie, der undersøgte effekten og sikkerheden af guselkumab sammenlignet med placebo hos behandlingsnaive patienter med PsA (havde utilstrækkeligt respons eller var intolerante overfor csDMARDs (≥ 3 måneder), NSAIDs (≥ 4 uger) eller apremilast (≥ 4 måneder)). Patienterne skulle opfylde CASPAR-kriterierne og have aktiv sygdom defineret som ≥ 5 hævede led, ≥ 5 ømme led og CRP-niveau ≥ 0,6 mg/dL. Derudover skulle patienterne opfylde samme kriterier som ved DISCOVER 1, hvad angår PsA subtype og plaque psoriasis.

Patienterne blev randomiseret 1:1:1 til guselkumab 100 mg hver 4. uge (Q4W, n = 245), guselkumab 100 mg ved uge 0, 4 og derefter hver 8. uge (Q8W, n = 248) eller placebo (n = 246). Randomiseringen var stratificeret efter csDMARDs ved baseline (ja eller nej) og seneste måling af høj-sensitivitet CRP før randomisering (< 2,0 mg/dL vs. ≥ 2,0 mg/dL). Studiet indeholdt en placebo-kontrolleret periode fra uge 0-24, en aktiv blindet behandlingsperiode fra uge 24-100 efterfulgt af 12 ugers sikkerheds opfølgningstid efter administration af sidste studiemedicin. Efter 24-ugers dobbeltblindet periode krydsede patienter i placebo- armen over til guselkumab Q4W.

DISCOVER 2 ligner DISCOVER 1 i øvrige parametre (se ovenfor). I studiet blev det radiografiske effektmål *van der Heijde-Sharp* (vdHS)-score undersøgt fremfor *modified Total Sharp Score* (mTSS).

ADEPT

Dette er et randomiseret, dobbeltblindet fase III-studie, der undersøgte effekten og sikkerheden af adalimumab sammenlignet med placebo hos behandlingsnaive patienter med moderat til svær aktiv PsA (havde utilstrækkeligt respons eller var intolerante overfor behandling med NSAIDs for PsA). Patienterne skulle have aktiv sygdom defineret som ≥ 3 hævede led, ≥ 3 ømme led og nuværende eller tidligere plaque psoriasis i hud.

Patienterne blev randomiseret 1:1 til adalimumab 40 mg hver 2. uge (Q2W, n = 151), eller placebo Q2W (n = 162). Randomiseringen var stratificeret efter MTX-behandling ved baseline (ja eller nej) og deres grad af psoriasis involvering (≥ 3 % eller < 3 % af kroppen ved baseline). Patienter kunne fortsætter deres MTX-behandling under studiet, hvis patienterne havde modtaget MTX i over 3 måneder og i en stabil dosis 4 uger før

studiestart. Studiet havde en 24-ugers dobbeltblindet periode, hvorefter patienter fra begge arme kunne fortsætte i et ublindet ekstensionstudie.

Effektanalyser op til uge 24 blev foretaget på data fra alle randomiserede patienter (ITT-population) og sikkerhedsanalyser på alle patienter, der modtog minimum én studiedosis. Studiets primære effektmål var andel patienter, der opnåede ACR20 ved uge 12 samt ændring i mTSS ved uge 24. Sekundære effektmål af relevans er andel patienter, der opnåede ACR50 ved uge 24, gennemsnitlig ændring fra baseline i livskvalitet målt ved SF-36 ved uge 24, andel patienter, der opnåede 90 % reduktion i PASI-score (kun hos patienter, hvor ≥ 3 % af kroppen er ramt af psoriasis) og sikkerhed.

SPIRIT-P1

Dette er et randomiseret, dobbeltblindet fase III-studie, der undersøgte effekten og sikkerheden af ixekizumab sammenlignet med adalimumab og placebo hos behandlingsnaive patienter med PsA (har ikke tidligere været behandlet med b/tsDMARDs). Patienterne skulle opfylde CASPAR-kriterierne og have aktiv sygdom defineret som ≥ 3 hævede led, ≥ 3 ømme led og ≥ 1 PsA-relateret hånd/fod-erosion på røntgen eller CRP-niveau ≥ 0,6 mg/dL. Derudover skulle patienterne have nuværende eller tidligere plaque psoriasis.

Patienterne blev randomiseret 1:1:1:1 til ixekizumab 80 mg hver 2. uge (IXEQ2W, n = 103), ixekizumab 80 mg hver 4. uge (IXEQ4W, n = 107), adalimumab 40 mg hver 2. uge (Q2W, n = 101) eller placebo (n = 106). Randomiseringen var stratificeret efter region og tidligere/nuværende/ingen behandling med csDMARDs. Patienter kunne fortsætte deres stabile behandling med tilladte csDMARDs, orale kortikosteroider, opiater og/eller NSAIDs/cyclo-oxygenase-2-hæmmere under studiet. Studiet havde en 24-ugers dobbeltblindet periode, hvorefter patienter fra adalimumab- og placeboarmene blev re-randomiseret til enten IXEQ2W eller IXEQ4W i et ublindet ekstensionsstudie op til uge 52.

Effektanalyser op til uge 24 blev foretaget på data fra alle randomiserede patienter (ITT-population) og sikkerhedsanalyser på alle patienter, der modtog minimum én studiedosis. Studiets primære effektmål var andel patienter, der opnåede ACR20 ved uge 24. Sekundære effektmål af relevans er andel patienter, der opnåede ACR50, gennemsnitlig ændring fra baseline i livskvalitet målt ved SF-36, andel patienter, der opnåede 90 % reduktion i PASI-score, ændring fra baseline i mTSS og sikkerhed.

Tabel 2. Baselinekarakteristika fra DISCOVER 1 og -2, ADEPT og SPIRIT-P1-studierne*

	DISCOVER 1	DISCOVER 2	ADEPT	SPIRIT-P1
	Guselkumab Q8W (n = 126)	Guselkumab Q8W (n = 248)	Adalimumab (n = 151)	Adalimumab (n = 101)
Alder, år	48,9 (11,5)	44,9 (11,9)	48,6 (12,5)	48,6 (12,4)
Mænd, antal (%)	68 (54 %)	129 (52 %)	85 (56,3 %)	51 (50,5)

	DISCOVER 1	DISCOVER 2	ADEPT	SPIRIT-P1
	Guselkumab Q8W (n = 126)	Guselkumab Q8W (n = 248)	Adalimumab (n = 151)	Adalimumab (n = 101)
Etnicitet, antal (%)				
Kaukasisk	116 (91 %)	240 (97 %)	147 (97,4 %)	95 (94,1 %)
Asiatisk	NA	8 (3 %)	NA	3 (3,0 %)
Andet	11 (9 %)		4 (2,6 %)	3 (3,0 %)
PsA sygdomsvarighed, år	6,4 (5,9)	5,1 (5,5)	9,8 (8,3)	6,9 (7,5)
Antal hævede led, 0-66	10,9 (9,3)	11,7 (6,8)	14,3 (12,2)	9,9 (6,5)
Antal ømme led, 0-68	20,2 (14,5)	19,8 (11,9)	23,9 (17,3)	19,3 (13,0)
Baseline CRP, mg/dL	0,7 (0,4–1,9)	1,3 (0,7–2,5)	1,4 (2,1)	1,3 (1,9)
Kropsoverflade berørt af psoriasis (BSA), gennemsnit	13,1 % (18,0)	17,0 % (21,0)	NA	14,8 % (19,2)
Psoriasis BSA ≥ 3 %, antal (%)	82 (65 %)	176 (71 %)	70 (46,4 %)	68 (72,3 %)
PASI-score, 0-72	8,4 (9,8)	9,7 (11,7)	7,4 (6,0)	5,5 (6,5)
IGA score ≥ 2 (dvs. mild til svær psoriasis), (%)	78,7 %	NA	NA	NA
IGA score 4 (dvs. svær psoriasis) (%)	NA	9,3 %	NA	NA
Patientens vurdering af smerte, 0-10 cm VAS	6,0 (2,1)	6,3 (2,0)	5,1 (2,1)	5,9 (2,0)
Patientens globale vurdering-gigt, 0-10 cm VAS	6,5 (2,0)	6,5 (1,9)	4,7 (2,3)**	5,9 (1,9)**
Lægens globale vurdering, 0-10 cm VAS	6,2 (1,7)	6,6 (1,6)	5,4 (1,6)**	5,5 (1,9)**
Baseline HAQ DI (fra 0-3)	1,2 (0,6)	1,3 (0,6)	1,0 (0,6)	1,1 (0,6)

	DISCOVER 1	DISCOVER 2	ADEPT	SPIRIT-P1
	Guselkumab Q8W (n = 126)	Guselkumab Q8W (n = 248)	Adalimumab (n = 151)	Adalimumab (n = 101)
Baseline SF-36				
PCS	34,1 (7,6)	32,6 (7,9)	NA	33,9 (8,8)
MCS	47,0 (11,1)	47,4 (10,8)	NA	NA
Tidligere behandling, antal (%)				
TNF-hæmmer	39 (31 %)	0	0	0
csDMARDs	115 (91,3 %)	221 (89,1 %)	NA	20 (19,8 %)
MTX	101 (80,3 %)	199 (80,2 %)	NA	NA
Behandling ved baseline, antal (%)				
csDMARD	83 (65 %)	170 (69 %)	NA	68 (63,6 %)
MTX	68 (54 %)	141 (57 %)	77 (51 %)	57 (56,4 %)
Orale kortikosteroider mod PsA	18 (14 %)	50 (20 %)	NA	NA
NSAIDs mod PsA	69 (54 %)	165 (67 %)	NA	NA

*Alle værdier er opgjort som gennemsnit (SD), medmindre andet er specificeret.
** *Patient's/Physician's global assessment of disease activity (0–10 cm VAS).*
PsA = psoriasisartrit, CRP = C-reaktiv protein, BSA = *Body Surface Area*, PASI = *Psoriasis Area Severity Index*, VAS = *Visual Analouge Scale*, SF-36 = *Short Form 36*, PCS = *Physical Component Score*, MCS = *Mental Component Score*, csDMARD = Konventionelt syntetisk *Disease Modifiying Anti-Rheumatic Drug*, MTX = methotrexat, NSAID = Non-steroide antiinflammatoriske lægemidler, NA = *Not Available*.

Fagudvalget bemærker, at der er visse forskelle i studiernes inklusionskriterier (f.eks. antal hævede og ømme led), men at der ikke er forskel i patienternes baselinekarakteristika ift. sygdomsbyrde, og at studiernes patientpopulationer på den baggrund er sammenlignelige. Overordnet set har patienterne ikke moderat til svær psoriasis, da deres PASI-score er under 10, hvilket svarer til den efterspurgte patientpopulation i det kliniske spørgsmål. Patientpopulation er dog heterogen, hvor nogle patienter vil kunne klassificeres som havende moderat til svær psoriasis, og der foreligger ikke data på subpopulationsniveau, hvad angår sværhedsgraden af psoriasis. Dertil er alle patienterne behandlingsnaive, bortset fra ca. 30 % i DISCOVER 1-studiet. Der findes ikke en opgørelse af baselinekarakteristika på den behandlingsnaive subpopulation fra DISCOVER 1, og derfor fremgår karakteristika for den samlede ITT-population i tabellen. I de komparative analyser indgår imidlertid kun data for den behandlingsnaive subpopulation.

Der er andre mindre forskelle mellem studierne, f.eks. hvad angår baseline CRP, PASI-score og tidligere behandling med csDMARDs, men størrelsesorden af disse er små, således at det ikke forventes at påvirke effektestimaterne eller vurderingen. Fagudvalget bemærker desuden, at man i dansk klinisk praksis ikke behandler PsA-patienter med orale kortikosteroider, hvilket er tilfældet for hhv. 20 og 14 % af patienterne i DISCOVER 1 og 2. Dette har dog ikke stor betydning for effektestimaterne, da det gælder for begge studiearme i de to studier.

Fagudvalget påpeger, at patienter med PsA generelt er en heterogen patientpopulation med forskelle i sygdomsaktivitet, hvilket medfører usikkerhed i sammenligninger på tværs af studier. Baseret på studiepopulationernes baselinekarakteristika kan fagudvalget ikke påpege forskelle, der er af væsentlig betydning i sammenligningen af studierne. Dertil afviger patientkarakteristika i studierne ikke væsentligt fra den danske patientpopulation og patientpopulationen defineret i det kliniske spørgsmål, hvilket særligt skyldes deres manglende eller utilstrækkelige effekt af/intolerance over for csDMARDs.

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål ved klinisk spørgsmål 1 beskrevet.

Da der ikke findes en direkte sammenligning af guselkumab og adalimumab til behandlingsnaive patienter med PsA, har ansøger lavet en indirekte komparativ analyse på baggrund af DISCOVER 1 og 2, ADEPT og SPIRIT-P1-studierne. Da der foreligger to studier på guselkumab og to på adalimumab, har ansøger udført en metaanalyse (se bilag 1) på baggrund af hhv. DISCOVER 1 (den behandlingsnaive subpopulation) og DISCOVER 2-studierne samt ADEPT og SPIRIT-P1-studierne ved de effektmål, hvor det har været muligt. Resultaterne fra metaanalysen indgår i den indirekte sammenligning, hvor de relative og absolutte forskelle er estimeret ved brug af Buchers metode. Dette begrundes i sammenligneligheden af studierne – både hvad angår studiepopulationerne og studiedesign. Se yderligere i nedenstående tabel.

Tabel 3. Oversigt over data, der indgår i den indirekte sammenligning *

Effektmål	Datagrundlag	Forklaring
ACR50	Metaanalyser for både guselkumab (på baggrund af DISCOVER 1 og 2) og adalimumab (på baggrund af ADEPT og SPIRIT-P1)	
mTSS	Guselkumab fra DISCOVER 2 og adalimumab fra SPRIT-P1	Effektmålet indgik ikke i DISCOVER 1, og i ADEPT foreligger der ikke data på andel patienter uden progression jf. mTSS.

Effektmål	Datagrundlag	Forklaring
Alvorlige bivirkninger	**Metaanalyser for både guselkumab (på baggrund af DISCOVER 1 og 2) og adalimumab (på baggrund af ADEPT og SPIRIT-P1)**	
SF-36, det fysiske funktion-subdomæne	Kvalitativ sammenligning. Guselkumab fra DISCOVER 2 og adalimumab fra SPIRIT-P1	Der foreligger ikke data på behandlingsnaive patienter i DISCOVER 1, og der foreligger ikke data på subdomænet i ADEPT. På grund af forskelle i dataopgørelse mellem studierne, kan data ikke indgå i en formel indirekte sammenligning.
SF-36, det fysiske smerte-subdomæne	Kvalitativ sammenligning. Guselkumab fra DISCOVER 2 og adalimumab fra SPIRIT-P1	Der foreligger ikke data kun på behandlingsnaive patienter fra DISCOVER 1, og der foreligger ikke data på subdomænet fra ADEPT. På grund af forskelle i dataopgørelse mellem studierne, kan data ikke indgå i en formel indirekte sammenligning.
SF-36, den fysiske komponent summary	Kvalitativ sammenligning Guselkumab fra DISCOVER 2 og adalimumab fra en metaanalyse fra ADEPT og SPIRIT-P1	Der foreligger ikke data kun på behandlingsnaive patienter fra DISCOVER 1. På grund af forskelle i dataopgørelse mellem studierne, kan data ikke indgå i en formel indirekte sammenligning.
SF-36, den mentale komponent summary	Kvalitativ sammenligning Guselkumab fra DISCOVER 2 og adalimumab fra en metaanalyse fra ADEPT og SPIRIT-P1	Der foreligger ikke data kun på behandlingsnaive patienter fra DISCOVER 1. På grund af forskelle i dataopgørelse mellem studierne, kan data ikke indgå i en formel indirekte sammenligning.

*Opfølgningstid på 24 uger

Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

Fagudvalget fremhæver følgende vedr. den indirekte sammenligning:

- Pga. sygdommens heterogenicitet er enhver sammenligning på tværs af studier forbundet med usikkerhed.
- For mange af effektmålene indgår der data i metaanalysen, hvor konfidensintervallet fra de to studier kun overlapper delvist, hvilket giver et bredt konfidensinterval i

metaanalysen (se bilag 1). Dette betyder, at der er væsentlig usikkerhed forbundet med resultaterne fra den indirekte sammenligning, i de tilfælde hvor metaanalysen ligger til grund, fordi der er stor spredning i konfidensintervallet fra metaanalysen.

- Ansøger har indsendt data på alvorlige uønskede hændelser (*serious adverse events* (SAE)) fremfor alvorlige bivirkninger (*serious adverse reactions* (SAR)) som specificeret i protokollen, da der ikke foreligger data på SAR fra DISCOVER 1 og 2. Fagudvalget tager højde for afvigelsen i vurderingen af evidensens kvalitet.
- Da data på livskvalitet ikke kan indgå i en formel statistisk sammenligning, vil fagudvalget kvalitativt gennemgå de data, der foreligger fra studierne. Fagudvalget fremhæver, at sammenligningen er forbundet med usikkerhed pga. forskelle i opgørelsen af data mellem studierne.
- Følgende data fra DISCOVER 1 og 2 er data-on-file og stammer fra studiets fortrolige *clinical study report (CSR)*:
    - Data på *andel patienter, der oplever alvorlige bivirkninger* for behandlingsnaive og -erfarne patienter fra DISCOVER 1.
    - Den absolutte effektforskel for *SF-36, det fysiske funktion-subdomæne* og *SF-36, det fysiske smerte-subdomæne* fra DISCOVER 2.

5.1.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Vurdering af risikoen for bias ved Cochrane risk of bias tool 2.0 ved de enkelte studier fremgår af bilag 2. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 3).

Indledningsvis blev lægemidlernes direkte sammenligninger med placebo vurderet.

- Overordnet var DISCOVER 1 og 2-studierne af guselkumab sammenlignet med placebo af lav kvalitet. Der foreligger en metaanalyse fra de to studier for ACR50 og SAE. Her er evidensen nedgraderet for indirekthed (data opgjort som alvorlige uønskede hændelser (SAE) fremfor alvorlige bivirkninger (SAR)) samt unøjagtighed (konfidensintervallet for SAE indeholder en beslutningsgrænse). For de øvrige effektmål indgår der data fra DISCOVER 2-studiet. Her er evidensen nedgraderet på baggrund af inkonsistens (kun ét studie) og unøjagtighed (konfidensintervallet for mTSS indeholder en beslutningsgrænse).
- Overordnet var ADEPT og SPIRIT-P1-studierne af adalimumab sammenlignet med placebo af lav kvalitet. Der foreligger en metaanalyse fra de to studier for ACR50, SAE og SF-36-den fysiske og mentale komponent summary. Her er evidensen nedgraderet for indirekthed (data opgjort som alvorlige uønskede hændelser (SAE) fremfor alvorlige bivirkninger (SAR)) samt unøjagtighed (konfidensintervallet for SAE indeholder en beslutningsgrænse). For de øvrige effektmål indgår der data fra SPIRIT-P1-studiet. Her er evidensen nedgraderet på baggrund af inkonsistens (kun ét studie).

Da den kliniske værdi af guselkumab sammenlignet med adalimumab er vurderet via indirekte sammenligninger, er der for alle effektmål yderligere nedjusteret for indirekte evidens. Den samlede evidenskvalitet for klinisk spørgsmål 1 er vurderet ud fra det lavest vurderede kritiske effektmål (alvorlige uønskede hændelser ved både DISCOVER 1 og 2-studierne og ADEPT og SPIRIT-P1-studierne samt mTSS ved DISCOVER 2-studiet).

Evidensens kvalitet er meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Tabel 4. Resultater for klinisk spørgsmål 1 - guselkumab sammenlignet med adalimumab til behandlingsnaive patienter med PsA uden moderat til svær psoriasis

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Sygdomsaktivitet - ledaffektion	Andel patienter, der oplever respons på ACR50 (MKRF: 15 %-point)	Kritisk	-15,6 %-point [-29,8; 20,9]	Kan ikke kategoriseres	RR: 0,6 [0,23-1,54]	Kan ikke kategoriseres	Negativ værdi
	Andel patienter uden progression, jf. mTSS (MKRF: 10 %-point)		-20,9 %-point [-33; -6,3]	Negativ værdi	RR: 0,77 [0,64-0,93]	Negativ værdi	
Bivirkninger	Andel patienter, der oplever alvorlige bivirkninger (MKRF: 5 %-point)	Kritisk	-2,5 %-point [-3,7; 3,5]	Kan ikke kategoriseres	RR: 0,36 [0,07-1,89]	Kan ikke kategoriseres	Kan ikke kategoriseres
	Gennemgang af bivirkningsprofil		Se nedenfor				
Livskvalitet	Gennemsnitlig ændring fra baseline på SF-36, det fysiske funktion-subdomæne (MKRF: 7,1 point)*	Kritisk	[redacted] ADA vs. PBO: 8,8 point [3,6; 14,0]	Kan ikke kategoriseres§	NA	Kan ikke kategoriseres§	Kan ikke kategoriseres§

Gennemsnitlig ændring fra baseline på SF-36, det fysiske smerte-subdomæne (MKRF: 4,9 point)*	[redacted] ADA vs. PBO: 8,5 point [2,9; 14,1]	Kan ikke kategoriseres§	NA	Kan ikke kategoriseres§
Gennemsnitlig ændring fra baseline på SF-36, den fysiske komponent summary (MKRF: 7,2 point)**	GUS vs. PBO: 4,0 point [2,8; 5,2] ADA vs. PBO: 5,7 point [1,5; 10,0]	Kan ikke kategoriseres§	NA	Kan ikke kategoriseres§
Gennemsnitlig ændring fra baseline på SF-36, den mentale komponent summary (MKRF: 3,1 point)**	GUS vs. PBO: 2,0 point [0,6; 3,5] ADA vs. PBO: 1,9 point (0,2; 3,6]	Kan ikke kategoriseres§	NA	Kan ikke kategoriseres§

Konklusion	
Samlet kategori for lægemidlets værdi	Negativ værdi
Kvalitet af den samlede evidens	Meget lav

CI = konfidensinterval, RR = relativ risiko, ACR50 = *American College of Rheumatology 50 % response*, mTSS = *modified Total Sharp Score*, SF-36 = *Short form*-36, GUS = guselkumab, ADA = adalimumab, PBO = placebo.
***** Data for absolut effekforskel mellem guselkumab eller adalimumab og placebo. Data for guselkumab stammer fra DISCOVER 2 og for adalimumab fra SPIRIT-P1.
** Data for absolut effekforskel mellem guselkumab eller adalimumab og placebo. Data for guselkumab stammer fra DISCOVER 2 og for adalimumab fra en metaanalyse fra ADEPT og SPIRIT-P1.
§ Kategorisering ikke mulig pga. manglende komparative analyser.

Sygdomsaktivitet - ledaffektion

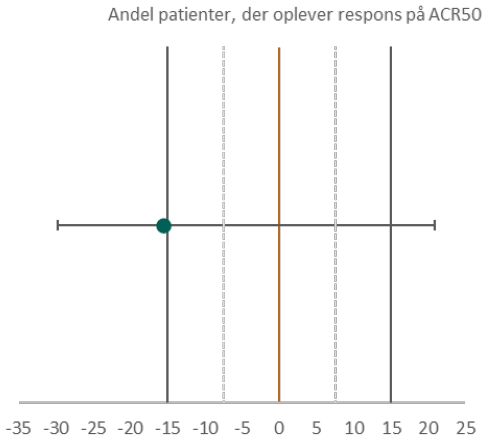
Som beskrevet i protokollen er effektmålet *Sygdomsaktivitet – ledaffektion* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi patienter, der oplever nedsat sygdomsaktivitet, opnår forbedret funktionsniveau, livskvalitet og tilknytning til arbejdsmarkedet [29,30]. Fagudvalget ønsker effektmålet belyst ved data på andel patienter, der oplever respons på ACR50 og andel patienter uden progression, jf. mTSS.

ACR50

Det primære mål for effekt på sygdomsaktivitet er ACR50. Dette er defineret som en 50 %'s forbedring i både ømme og hævede led samt 50 %'s forbedring inden for mindst tre ud af følgende fem domæner: patientens overordnede vurdering af, hvor meget gigten som helhed påvirker hverdagen (Visual Assessment Scale (VAS) global), patientens vurdering af smerte, lægens overordnede vurdering af patientens samlede sygdomsaktivitet (VAS doctor), HAQ-DI score, som måler patientens funktionsniveau, og C-Reaktivt Protein (CRP). Medicinrådet vurderer, at en 50 %'s forbedring er et patientrelevant effektmål og betragtes her som tilstrækkeligt for at definere respons.

Der foreligger data fra metaanalyser for både guselkumab (DISCOVER 1 og 2) og adalimumab (ADEPT og SPIRIT-P1), som indgår i en indirekte sammenligning.

Efter 24 ugers opfølgning havde 105 ud af 334 patienter (31,4 %) opnået ACR50 i guselkumab-armene i DISCOVER 1 og -2, hvilket var tilfældet for 98 ud af 252 patienter (38,9 %) i adalimumab-armene i ADEPT og SPIRIT-P1. For placeboarmene var andelen 13,2 % og 9,7 % i hhv. DISCOVER 1 og -2 samt ADEPT og SPIRIT P1 (se bilag 1). Den absolutte forskel er vist i figur 1 nedenfor.



Figur 1. Punktestimat og 95 % konfidensinterval for den absolutte forskel for *Andel patienter, der oplever respons på ACR50.* De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget har i protokollen defineret MKRF til 15 %-point. Punktestimatet for den absolutte effektforskel på -15,6 %-point afspejler dermed en negativ klinisk relevant effektforskel. Konfidensintervallet er bredt, hvilket betyder, at det rummer muligheden for, at guselkumab har en positiv, ingen og negativ værdi. Derfor kan den foreløbige værdi af guselkumab vedr. delmålet *Andel patienter, der oplever respons på ACR50,* ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, opgjort som en relativ risiko på 0,6 [0,23-1,54] (fremgår af tabel 4), har guselkumab foreløbigt en værdi, som ikke kan kategoriseres vedr. delmålet *Andel patienter, der oplever respons på ACR50*, fordi konfidensintervallet inkluderer 1.

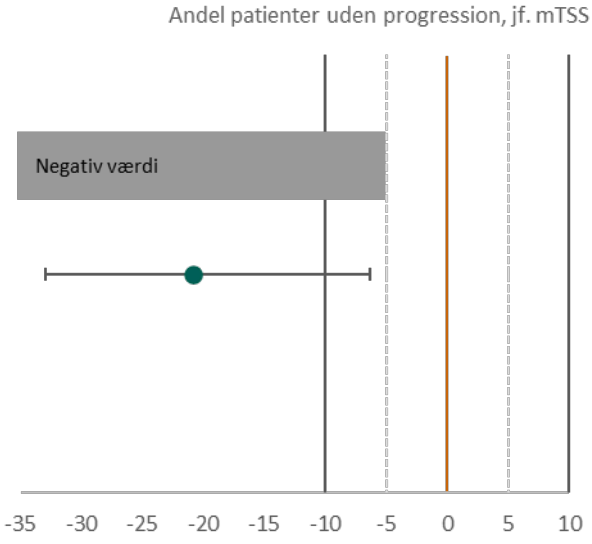
Fagudvalget fremhæver, at konfidensintervallet for både den absolutte og relative effektforskel er bredt og rummer muligheden for, at guselkumab har en positiv, ingen eller negativ værdi sammenlignet med adalimumab.

mTSS

Medicinrådet ønsker at benytte et radiografisk effektmål, der kan tolkes som udtryk for leddestruktion og dermed sygdomsprogression. Medicinrådet ønsker at benytte en modificeret udgave af Total Sharp Score (mTSS), som er udviklet til scoring af patienter med PsA [31].

Der indgår data på guselkumab fra DISCOVER 2 og på adalimumab fra SPIRIT-P1 i en indirekte sammenligning.

Efter 24 ugers opfølgning havde 157 ud af 248 patienter (63,5 %) opnået en ændring ≤ 0 i *modified van der Heijde–Sharp* score i guselkumab-armen (Q8W) i DISCOVER 2-studiet [32], hvilket var tilfældet for 93 ud af 101 patienter (91,6 %) i adalimumab-armen i SPIRIT-P1-studiet [24]. For placeboarmene var andelen 64,7 % og 72 % i hhv. DISCOVER 2- og SPIRIT P1-studiet. Den absolutte forskel er vist i figur 2 nedenfor.



Figur 2. Punktestimat og 95 % konfidensinterval for den absolutte forskel for *Andel patienter uden progression, jf. mTSS*. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget har i protokollen defineret MKRF til 10 %-point. Punktestimatet for den absolutte effektforskel på -20,9 %-point afspejler dermed en negativ klinisk relevant effektforskel. Den øvre grænse for konfidensintervallet er tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Derfor har guselkumab foreløbigt en negativ værdi vedr. delmålet *Andel patienter uden progression, jf. mTSS*.

Baseret på den relative effektforskel, opgjort som en relativ risiko på 0,77 [0,64-0,93] (fremgår af tabel 4), har guselkumab foreløbigt en negativ værdi vedr. delmålet *Andel patienter uden progression, jf. mTSS*, fordi den øvre grænse af konfidensintervallet er under 1.

Samlet for effektmålet *Sygdomsaktivitet - ledaffektion*

Baseret på ovenstående gennemgang af effektmålets to delmål vurderer fagudvalget, at guselkumab aggregeret har **negativ værdi** vedr. effektmålet *Sygdomsaktivitet - ledaffektion*.

For delmålet ACR50 kan hverken den absolutte eller relative effektforskel kategoriseres efter Medicinrådets metoder pga. af de brede konfidensintervaller som følge af den indirekte sammenligning. For delmålet mTSS har guselkumab negativ værdi for både den absolutte og relative effektforskel. I den samlede konklusion lægger fagudvalget vægt på den negative værdi ved mTSS, og at det for ACR50 ligeledes tyder på en negativ værdi, om end det ikke kan kategoriseres grundet brede konfidensintervaller i analysen. Fagudvalget finder det bekymrende, at signifikant flere patienter i guselkumab behandling havde radiologisk progression efter 24 uger sammenlignet med patienter behandlet med adalimumab, hvilket tyder på et markant ringere behandlingsrespons, særligt set i lyset af at den radiologiske progression er målbar med en kort behandlingstid på 24 uger.

Bivirkninger

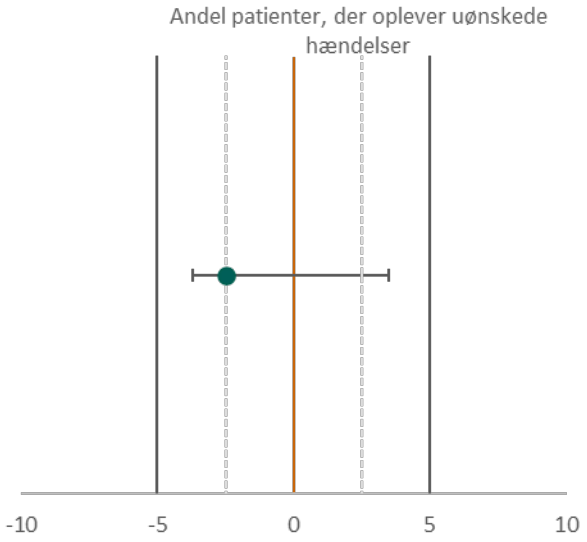
Som beskrevet i protokollen er effektmålet *Bivirkninger* kritisk for vurderingen af lægemidlets værdi for patienterne. Effektmålet er delt op på to delmål: alvorlige bivirkninger og en kvalitativ gennemgang af de to lægemidlers bivirkningsprofiler.

Andel patienter, der oplever alvorlige bivirkninger

Medicinrådet ønsker data på alvorlige bivirkninger (SAR), da disse særligt frygtes af patienter og klinikere, siden de kan forårsage pauser i behandlingen med risiko for forværring af symptomer og sygdomsprogression.

Der foreligger data fra metaanalyser for både guselkumab (DISCOVER 1 og 2) og adalimumab (ADEPT og SPIRIT-P1), som indgår i en indirekte sammenligning. Ansøger har indsendt data på andel patienter, der oplever alvorlige uønskede hændelser (SAE), da der ikke foreligger data på SAR fra DISCOVER 1 og 2.

Efter 24 ugers opfølgning havde [redacted] oplevet alvorlige uønskede hændelser i guselkumab-armene i DISCOVER 1 og -2, hvilket var tilfældet for 10 ud af 252 patienter (4,0 %) i adalimumab-armene i ADEPT og SPIRIT-P1. For placeboarmene var andelen [redacted] og 3,4 % i hhv. DISCOVER 1 og 2 samt ADEPT og SPIRIT P1 (se bilag 1). Den absolutte forskel er vist i figur 3 nedenfor.



Figur 3. Punktestimat og 95 % konfidensinterval for den absolutte forskel for *Andel patienter, der oplever uønskede hændelser*. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget har i protokollen defineret MKRF til 5 %-point. Punktestimatet for den absolutte effektforskel på -2,5 %-point afspejler dermed ikke en klinisk relevant effektforskel. Konfidensintervallet er bredt, hvilket betyder, at det rummer muligheden for, at guselkumab har en positiv, ingen og negativ værdi. Derfor kan den foreløbige værdi af guselkumab vedr. delmålet *Andel patienter, der oplever alvorlige uønskede hændelser,* ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, opgjort som en relativ risiko på 0,36 [0,07-1,89] (fremgår af tabel 4), har guselkumab foreløbigt en værdi, som ikke kan kategoriseres vedr. delmålet *Andel patienter, der oplever alvorlige uønskede hændelser*, fordi konfidensintervallet inkluderer 1.

Gennemgang af bivirkningsprofil

Gennemgangen af bivirkningsprofilerne for guselkumab og adalimumab tager udgangspunkt i lægemidlernes produktresuméer [16,28], hvor bivirkningsprofilerne er sammenlagt fra de underliggende kliniske studier. Derudover sammenligner fagudvalget udvalgte bivirkninger mellem de to lægemidler fra de underliggende studier.

Guselkumab
Den hyppigst rapporterede bivirkning er øvre luftvejsinfektioner. Behandling med guselkumab kan øge risikoen for infektioner og forhøjede levertal. Ved brug af guselkumab er der rapporteret alvorlige overfølsomhedsreaktioner, herunder anafylaksi [16].

Adalimumab
De hyppigst rapporterede bivirkninger er øvre luftvejsinfektioner, reaktioner på injektionsstedet (udslæt (erytem), kløe, blødning, smerter eller hævelse), hovedpine og muskuloskeletal smerte. Ved brug af adalimumab er der rapporteret om dødelige og livstruende infektioner (inkl. blodforgiftning, opportunistiske infektioner og tuberkulose), hepatitis B-reaktivering og leverenzymforhøjelse. Dertil kan en øget risiko for malignt melanom og non-melanom hudkræft ikke udelukkes. Der er også rapporteret om alvorlige hæmatologiske (blodmangel, leukopeni og pancytopeni), neurologiske (Guillain-Barrés syndrom) og autoimmune reaktioner. Sjældne bivirkninger er bl.a. tarmperforation, lungefibrose, Stevens-Johnson syndrom og dissemineret sklerose [28].

Nedenstående tabel giver et overblik over de rapporterede uønskede hændelser i de underliggende studier.

Tabel 5. Oversigt over uønskede hændelser ved 24 uger fra DISCOVER 1 og 2, ADEPT og SPIRIT-P1

	DISCOVER 1		DISCOVER 2		ADEPT		SPIRIT-P1	
	Placebo (n = 126)	Guselkumab Q8W (n = 127)	Placebo (n = 246)	Guselkumab Q8W (n = 248)	Placebo (n = 162)	Adalimumab (n = 151)	Placebo (n = 106)	Adalimumab (n = 101)
Uønskede hændelser (AE)	59,5 %	53,5 %	40,7 %	46 %	80,2 %	80,8 %	47,2 %	64,4 %
Alvorlige uønskede hændelser (SAE)	4,0 %	3,1 %	2,8 %	1,2 %	4,3 %	3,3 %	1,9 %	5,0 %
Infektioner	25,4 %	26,0 %	18,3 %	16,1 %	39,5 %	45 %	25,5 %	25,7 %
Alvorlige infektioner	1,6 %	0 %	0,4 %	0,4 %	0,6 %	0,7 %	0 %	2,0 %
Behandlingsophør	9,5 %	3,1 %	2,4 %	3,2 %	8,0 %	7,3 %	14,2 %	4,0 %
Grundet AE	1,6 %	2,4 %	1,6 %	0,8 %	0,6 %	2,0 %	1,9 %	2,0 %
Forhøjet alanin aminotransferase	2 %	6 %	4 %	6 %	NA	NA	0 %	3 %
Forhøjet aspartat aminotransferase	2 %	7 %	2 %	6 %	NA	NA	0 %	2 %
Nasopharyngitis	6 %	13 %	4 %	4 %	9,3 %	9,9 %	4,7 %	6,9 %
Øvre luftvejsinfektion	6 %	6 %	3 %	2 %	14,8 %	12,6 %	6,6 %	5,0 %

Sammenligning af opgørelser over uønskede hændelser i forskellige studier skal tages med forbehold, da der kan være forskel på, hvordan uønskede hændelser bliver opgjort i forskellige studier. Overordnet kan fagudvalget ikke konkludere, at der er forskel i bivirkninger mellem guselkumab og adalimumab til patienter med PsA på baggrund af ovenstående data.

Samlet vurdering af bivirkningsprofiler
Fagudvalget bemærker, at på baggrund af guselkumabs og adalimumabs produktresuméer ser behandling med guselkumab ud til at være forbundet med færre bivirkninger. I den forbindelse understreger fagudvalget, at den klinisk erfaring med adalimumab er langt mere omfattende end med guselkumab, hvilket kan være med til at forklare denne forskel. Overordnet finder fagudvalget, at guselkumabs og adalimumabs bivirkningsprofiler er forskellige, hvor begge lægemidler kan medføre en række uønskede hændelser. Fagudvalget finder dog, at lægemidlerne er sammenlignelige, hvad angår bivirkningernes sværhedsgrad, og at potentielle risikofyldte bivirkninger bliver fremhævet i lægemidlernes produktresuméer.

Samlet for effektmålet *Bivirkninger*
Baseret på ovenstående gennemgang af effektmålets to delmål vurderer fagudvalget, at guselkumab aggregeret har en værdi, som **ikke kan kategoriseres** vedr. effektmålet *Bivirkninger*.

Hverken den absolutte og relative effektforskel for delmålet *Andel patienter, der oplever uønskede hændelser,* kan kategoriseres efter Medicinrådets metoder pga. brede konfidensintervaller. Fagudvalget understreger, at den absolutte effektforskel ikke er af klinisk betydning, da den ligger under den mindste klinisk relevante forskel.

Guselkumabs og adalimumabs bivirkningsprofiler er forskellige, men lægemidlerne er sammenlignelige, hvad angår bivirkningernes sværhedsgrad. Fagudvalget understreger, at der, grundet den korte opfølgningstid i guselkumab-studierne og den manglende klinisk erfaring med guselkumab, ikke er kendskab til potentielle langtidsbivirkninger, som der er ved adalimumab.

Livskvalitet
Som beskrevet i protokollen er effektmålet ***Livskvalitet*** kritisk for vurderingen af lægemidlets værdi for patienterne, fordi det giver et indblik i sygdomsbyrden og kan indikere, om bivirkningerne ved lægemidlet påvirker patienternes livskvalitet. Patienter med PsA er ofte mærket af deres sygdom både fysisk og mentalt, og det er derfor af stor betydning, om et nyt lægemiddel kan afhjælpe dette. Effektmålet ønskes opgjort med det generiske instrument SF-36 som gennemsnitlig ændring fra baseline i følgende domæner: det fysiske funktion-subdomæne, det fysiske smerte-subdomæne, den fysiske komponent summary og den mentale komponent summary.

På grund af forskelle i dataopgørelse mellem studierne kan data ikke indgå i en formel indirekte sammenligning. Den foreløbige værdi af guselkumab vedr. delmålet kan dermed ikke kategoriseres. Fagudvalget vil kvalitativt gennemgå det data, der foreligger,

fra de to studier. Fagudvalget fremhæver, at forskellen i opgørelsen af data mellem studierne medfører, at sammenligningen er forbundet med usikkerhed.

Det fysiske funktion-subdomæne

Der foreligger data for guselkumab fra DISCOVER 2 og for adalimumab fra SPIRIT-P1.

Den gennemsnitlige forbedring i det fysiske funktion-subdomæne var 6,7 point i guselkumab-armen (Q8W) i DISCOVER 2-studiet [32] sammenlignet med 14,4 point i adalimumab-armen i SPIRIT-P1-studiet [24]. I placeboarmene var den gennemsnitlige forbedring på 3,3 og 5,6 point i hhv. DISCOVER 2- og SPIRIT-P1-studierne. Den absolutte effektforskel mellem guselkumab og placebo var således [redacted] point, mens det for adalimumab og placebo var 8,8 [3,6-14,0] point.

Fagudvalget bemærker, at data indikerer, at guselkumabs effekt på patienternes funktionsniveau er lavere end for adalimumab. På baggrund af datagrundlaget er det dog ikke muligt at konkludere, om der er en klinisk relevant forskel mellem de to lægemidler, hvad angår delmålet.

Det fysiske smerte-subdomæne

Der foreligger data for guselkumab fra DISCOVER 2 og for adalimumab fra SPIRIT-P1.

Den gennemsnitlige forbedring i det fysiske smerte-subdomæne var 7,8 point i guselkumab-armen (Q8W) i DISCOVER 2-studiet [32] sammenlignet med 16,8 point i adalimumab-armen i SPIRIT-P1-studiet [24]. I placeboarmene var den gennemsnitlige forbedring på 3,5 og 8,3 point i hhv. DISCOVER 2- og SPIRIT-P1-studierne. Den absolutte effektforskel mellem guselkumab og placebo var således [redacted] point, mens det for adalimumab og placebo var 8,5 [2,9-14,1] point.

Fagudvalget bemærker, at data indikerer, at guselkumabs effekt på patienternes smerteniveau er lavere end for adalimumab. På baggrund af datagrundlaget er det dog ikke muligt at konkludere, om der er en klinisk relevant forskel mellem de to lægemidler, hvad angår delmålet.

Den fysiske komponent summary

Der foreligger data for guselkumab fra DISCOVER 2 og for adalimumab fra en metaanalyse fra ADEPT og SPIRIT-P1.

Efter 24-ugers opfølgning var den gennemsnitlige forbedring i den fysiske komponent summary 7,4 point i guselkumab-armen (Q8W) i DISCOVER 2-studiet [20] sammenlignet med 9,3 og 6,3 point i adalimumab-armen i hhv. ADEPT og SPIRIT-P1-studierne [22,24]. I placeboarmene var den gennemsnitlige forbedring på 3,4, 1,4 og 2,7 point i hhv. DISCOVER 2-, ADEPT- og SPIRIT-P1-studierne. Den absolutte effektforskel mellem guselkumab og placebo var således 4,0 [2,8-5,2] point, mens det for adalimumab (på baggrund af metaanalysen) og placebo var 5,7 [1,5-10,0] point.

Baseret på ovenstående gennemgang samt klinisk erfaring vurderer fagudvalget, at det er sandsynligt, at der ikke er betydende forskel mellem guselkumab og adalimumab, hvad angår delmålet *Den fysiske komponent summary*.

Den mentale komponent summary

Der foreligger data for guselkumab fra DISCOVER 2 og for adalimumab fra en metaanalyse fra ADEPT og SPIRIT-P1.

Efter 24-ugers opfølgning var den gennemsnitlige forbedring i den mentale komponent summary 4,2 point i guselkumab-armen (Q8W) i DISCOVER 2-studiet [20] sammenlignet med 1,8 og 4,6 point i adalimumab-armen i hhv. ADEPT og SPIRIT-P1-studierne [22,24]. I placeboarmene var den gennemsnitlige forbedring på 2,1, 0,6 og 1,8 point i hhv. DISCOVER 2-, ADEPT- og SPIRIT-P1-studierne. Den absolutte effektforskel mellem guselkumab og placebo var således 2,0 [0,6-3,5] point, mens det for adalimumab (på baggrund af metaanalysen) og placebo var 1,9 [0,2-3,6] point.

Baseret på ovenstående gennemgang samt klinisk erfaring vurderer fagudvalget, at det er sandsynligt, at der ikke er betydende forskel mellem guselkumab og adalimumab, hvad angår delmålet *Den mentale komponent summary*.

Samlet for effektmålet *Livskvalitet*

Baseret på ovenstående gennemgang af effektmålets fire delmål vurderer fagudvalget, at guselkumab aggregeret har en værdi, som **ikke kan kategoriseres** vedr. effektmålet *Livskvalitet*.

Det skyldes, at der ikke foreligger komparative analyser for nogen af de fire deleffektmål. Fagudvalget bemærker, at data indikerer, at guselkumabs effekt på patienternes funktions- og smerteniveau er lavere end adalimumabs. Hvad angår den fysiske og mentale komponent summary, er guselkumabs og adalimumabs effekt sammenlignet med placebo sammenlignelig.

Overordnet vurderer fagudvalget, at det på baggrund af det sparsomme datagrundlag ikke er muligt at konkludere, om der er en klinisk relevant forskel mellem de to lægemidler, hvad angår effektmålet *Livskvalitet*.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at guselkumab til behandlingsnaive patienter med PsA uden moderat til svær plaque psoriasis har en **negativ værdi** sammenlignet med adalimumab.

Fagudvalget lægger i sin konklusion særligt vægt på, at guselkumab ved det kritiske effektmål *Sygdomsaktivitet – ledaffektion*, har negativ værdi sammenlignet med adalimumab. Effektmålet blev belyst ved data på andel patienter, der oplever respons på ACR50 og andel patienter uden progression, jf. mTSS. Data på mTSS viser, at guselkumab er mindre effektivt til at forebygge kroniske skader i leddene end nuværende standardbehandling med adalimumab. Der var signifikant flere patienter, der havde radiologisk progression efter 24 ugers behandling med guselkumab sammenlignet med adalimumab, hvilket ifølge fagudvalget er bekymrende efter så kort opfølgningstid. Derudover ser guselkumab til at være mindre effektivt end nuværende standardbehandling til at kontrollere patienternes sygdomsaktivitet, målt ved det kompositte værktøj ACR50.

Fagudvalget fremhæver, at der er usikkerhed forbundet med vurderingen pga. forskelle i de underliggende studier, hvilket betyder, at nye studier med en direkte sammenligning af guselkumab og adalimumab med høj sandsynlighed kan ændre konklusionen.

5.2 Klinisk spørgsmål 2

5.2.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning. Det kliniske spørgsmål er:

Hvilken værdi har guselkumab sammenlignet med ixekizumab for behandlingserfarne patienter med PsA uden moderat til svær plaque psoriasis?

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt fem fuldtekstartikler fra to kliniske studier, der stemmer overens med in- og eksklusionskriterierne fra Medicinrådets protokol. Artiklerne omhandler ét klinisk studie for guselkumab (DISCOVER 1) [19] og ét klinisk studie for ixekizumab (SPIRIT-P2) [33–35] (se tabel 8). Derudover har ansøger tilføjet én publikation fra DISCOVER 1-studiet, som ikke blev identificeret i litteratursøgningen men blev vurderet af ansøger som værende relevant for det kliniske spørgsmål [26]. Desuden indgår EMAs EPAR og produktresuméerne for guselkumab [16,27] og ixekizumab [36,37].

Tabel 6. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Population	Intervention vs. komparator
Deodhar et al. 2020 [19] Ritchlin et al. 2021 [26]	DISCOVER 1	NCT03162796	Behandlingsnaive og -erfarne patienter med aktiv psoriasisartrit	Guselkumab vs. placebo
Nash et al. 2017 [33] Orbai et al. 2021 [34] Kavanaugh et al. 2019 [35]	SPIRIT-P2	NCT02349295	Behandlingserfarne patienter med aktiv psoriasisartrit	Ixekizumab vs. placebo

DISCOVER 1

Se studiebeskrivelse i afsnit 5.1.1. Ca. 30 % af ITT-populationen havde tidligere modtaget TNF-hæmmere og var dermed behandlingserfarne.

SPIRIT-P2

Dette er et randomiseret, dobbeltblindet fase III-studie, der undersøgte effekten og sikkerheden af ixekizumab sammenlignet med placebo hos behandlingserfarne (fortsat sygdomsaktivitet trods behandling med TNF-hæmmere) med aktiv PsA. Patienterne skulle opfylde CASPAR-kriterierne og have aktiv sygdom defineret som ≥ 3 hævede led og ≥ 3 ømme led trods tidligere behandling (1-2 præparater) eller intolerance overfor TNF-hæmmere. Derudover skulle patienterne have nuværende eller tidligere plaque psoriasis.

Patienterne blev randomiseret 1:1:1 til ixekizumab 80 mg hver 2. uge (IXEQ2W, n = 123), ixekizumab 80 mg hver 4. uge (IXEQ4W, n = 122) eller placebo (n = 118). Randomiseringen var stratificeret efter region og tidligere behandling med TNF-hæmmere (utilstrækkelig respons efter behandling med én TNF-hæmmer, to TNF-hæmmere eller intolerance overfor TNF-hæmmere). Patienterne skulle tidligere have været behandlet med ≥ 1 csDMARDs. Under studiets dobbeltblindede 24-ugers periode (eller op til uge 16 hos patienter, der ikke responderede på behandlingen) kunne patienter fortsætte deres stabile behandling, dog uden justering, med csDMARDs, topikale kortikosteroider (*WHO group 1 classification*), orale kortikosteroider, opiater, NSAIDs og cyclo-oxygenase-2-hæmmere. Studiet havde en 24-ugers dobbeltblindet periode, hvorefter patienter fra placeboarmene blev re-randomiseret 1:1 til enten IXEQ2W eller IXEQ4W i et ublindet ekstensionsstudie op til uge 156.

Effektanalyser op til uge 24 blev foretaget på data fra alle randomiserede patienter (*intention-to-treat* (ITT)-population) og sikkerhedsanalyser på alle patienter, der modtog minimum én studiedosis. Studiets primære effektmål var andel patienter, der opnåede ACR20 ved uge 24. Sekundære effektmål af relevans er andel patienter, der opnåede ACR50, gennemsnitlig ændring fra baseline i livskvalitet målt ved *short form 36* (SF-36), andel patienter, der opnåede 90 % reduktion i *PASI*-score og sikkerhed.

Tabel 7. Baselinekarakteristika fra DISCOVER 1 og SPIRIT-P2-studierne*

	DISCOVER 1	SPIRIT-P2
	Guselkumab Q8W (n = 126)	Ixekizumab Q4W (n = 122)
Alder, år	48,9 (11,5)	52,6 (13,6)
Mænd, antal (%)	68 (54 %)	63 (52 %)
Etnicitet, antal (%)		
Kaukasisk	116 (91 %)	111 (91 %)
Asiatisk	NA	7 (6 %)
Andet	11 (9 %)	4 (3,0 %)
PsA sygdomsvarighed, år	6,4 (5,9)	11,0 (9,6)

	DISCOVER 1	SPIRIT-P2
	Guselkumab Q8W (n = 126)	Ixekizumab Q4W (n = 122)
Antal hævede led, 0-66	10,9 (9,3)	13,1 (11,2)
Antal ømme led, 0-68	20,2 (14,5)	22,0 (14,1)
Baseline CRP, mg/dL	0,7 (0,4–1,9)	1,7 (2,8)
Kropsoverflade berørt af psoriasis (BSA), gennemsnit	13,1 % (18,0)	12,5 % (17,0)
Psoriasis BSA ≥ 3 %, antal (%)	NA	68 (56 %)
PASI-score, 0-72	8,4 (9,8)	6,4 (7,9)
IGA-score ≥ 2 (dvs. mild til svær psoriasis), (%)	78,7 %	NA
IGA-score 4 (dvs. svær psoriasis) (%)	NA	NA
Patientens vurdering af smerte, 0-10 cm VAS	6,0 (2,1)	6,4 (2,1)
Patientens globale vurdering-gigt, 0-10 cm VAS	6,5 (2,0)	6,6 (2,1)
Lægens globale vurdering, 0-10 cm VAS	6,2 (1,7)	6,0 (2,1)
Baseline HAQ DI (fra 0-3)	1,2 (0,6)	1,2 (0,6)
Baseline SF-36		
PCS	34,1 (7,6)	34,8 (8,8)
MCS	47,0 (11,1)	49,6 (11,3)
Tidligere behandling med TNF-hæmmer, antal (%)	41 (32 %)	122 (100 %)
Én TNF-hæmmer	34 (27 %)	71 (58 %)
To TNF-hæmmere	7 (6 %)	41 (34 %)
Ingen respons ved tidligere behandling med TNF-hæmmer	15 (12 %)	10 (8 %)

	DISCOVER 1	SPIRIT-P2
	Guselkumab Q8W (n = 126)	Ixekizumab Q4W (n = 122)
Behandling ved baseline, antal (%)		
csDMARDs	83 (65 %)	60 (49 %)
MTX	68 (54 %)	48 (39 %)
Orale kortikosteroider mod PsA	18 (14 %)	NA
NSAIDs mod PsA	69 (54 %)	NA

*Alle værdier er opgjort som gennemsnit (SD), medmindre andet er specificeret.
PsA = psoriasisartrit, CRP = C-reaktiv protein, BSA = *Body Surface Area*, PASI = *Psoriasis Area Severity Index*, SF-36 = *Short Form 36*, PCS = *Physical Component Score*, MCS = *Mental Component Score*, csDMARD = Konventionelt syntetisk *Disease Modifiying Anti-Rheumatic Drug*, MTX = methotrexat, NSAID = Non-steroide antiinflammatoriske lægemidler , NA = *Not Available*.

Fagudvalget bemærker, at der ikke er betydende forskel i patienternes baselinekarakteristika ift. sygdomsbyrde, og at studiernes patientpopulationer på den baggrund er sammenlignelige. Overordnet set har patienterne ikke moderat til svær psoriasis, da deres PASI-score er under 10, hvilket svarer til den efterspurgte patientpopulation i det kliniske spørgsmål. Patientpopulation er dog heterogen, hvor nogle patienter vil kunne klassificeres som havende moderat til svær psoriasis, og der foreligger ikke data på subpopulationsniveau, hvad angår sværhedsgraden af psoriasis. Dertil er kun ca. 30 % af patienterne i DISCOVER 1 behandlingserfarne. Der findes ikke en opgørelse af baselinekarakteristika på den behandlingserfarne subpopulation fra DISCOVER 1, og derfor fremgår karakteristika for den samlede ITT-population i tabellen. I de komparative analyser indgår imidlertid kun data for den behandlingserfarne subpopulation.

Der er andre mindre forskelle mellem studierne, f.eks. hvad angår baseline PsA, sygdomsvarighed, CRP- og PASI-score, men størrelsesorden af disse er små, således at det ikke forventes at påvirke effektestimaterne eller vurderingen. Fagudvalget bemærker desuden, at man i dansk klinisk praksis ikke behandler PsA-patienter med orale kortikosteroider, hvilket er tilfældet for 20 % af patienterne i DISCOVER 1. Dette har dog ikke stor betydning for effektestimaterne, da det gælder for begge studiearme.

Fagudvalget påpeger, at patienter med PsA generelt er en heterogen patientpopulation med forskelle i sygdomsaktivitet, hvilket medfører usikkerhed i sammenligninger på tværs af studier. Baseret på studiepopulationernes baselinekarakteristika kan fagudvalget ikke påpege forskelle, der er af væsentlig betydning i sammenligningen af studierne. Dertil afviger patientkarakteristika i studierne ikke væsentligt fra den danske patientpopulation og patientpopulationen defineret i det kliniske spørgsmål, hvilket særligt skyldes deres manglende eller utilstrækkelige effekt af/intolerance over for TNF-alfa hæmmere.

5.2.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål ved klinisk spørgsmål 2 beskrevet.

Da der ikke findes en direkte sammenligning af guselkumab og ixekizumab til behandlingserfarne patienter med PsA, har ansøger lavet en indirekte komparativ analyse på baggrund af DISCOVER 1 (den behandlingserfarne subpopulation) og SPIRIT-P2-studierne, hvor den relative og absolutte forskel er estimeret ved brug af Buchers metode. Dette begrundes i sammenligneligheden af studierne – både hvad angår studiepopulationerne og studiedesign.

Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

Fagudvalget fremhæver følgende vedr. den indirekte sammenligning:

- Fagudvalget vurderer, at den indirekte sammenligning er forbundet med stor usikkerhed, pga. sygdommens heterogenicitet, hvilket medfører usikkerhed ved sammenligning af data på tværs af studier. Derudover baserer den indirekte sammenligning sig på en relativ lille subpopulation fra DISCOVER 1-studiet (n = 41 i guselkumab-armen) sammenlignet med Q4W i ixekizumab-armen (n = 122) fra SPIRIT-P2, hvilket ligeledes medfører en vis usikkerhed til resultaterne.
- Der foreligger kun data på ACR50 og alvorlige bivirkninger fra den indirekte sammenligning.
- Der foreligger ikke data på mTSS, da effektmålet ikke indgik i de to studier.
- Ansøger har indsendt data på alvorlige uønskede hændelser (*serious adverse events* (SAE)) fremfor alvorlige bivirkninger (*serious adverse reactions* (SAR)), som specificeret i protokollen, da der ikke foreligger data på SAR fra DISCOVER 1. Fagudvalget tager højde for afvigelsen i vurderingen af evidensens kvalitet.
- For begge studier foreligger der data på de 4 livskvalitetsdelmål, men på grund af forskelle i dataopgørelsen mellem studierne kan data ikke indgå i en formel statistisk sammenligning. Fagudvalget vil kvalitativt gennemgå de data, der foreligger, fra de to studier.
- Livskvalitetsdata fra DISCOVER 1 er ikke opgjort på subpopulationsniveau. Data på ITT ligger dermed til grund for vurderingen. Da kun 30 % af patienterne var behandlingserfarne, afviger studiepopulationen fra patientpopulationen i det kliniske spørgsmål. Fagudvalget kan ikke udelukke, at denne afvigelse har betydning for effektestimaterne, og tager derfor resultaterne med forbehold. Dertil tager fagudvalget højde for afvigelsen i vurderingen af evidensens kvalitet.
- Fra SPIRIT-P2 foreligger der kun data fra ixekizumab-armen for livskvalitetsdelmålene *SF-36, det fysiske funktion-subdomæne* og *SF-36, det fysiske smerte-subdomæne*. Dermed kan den absolutte effektforskel mod placebo ikke beregnes.
- Følgende data fra DISCOVER 1 er data-on-file og stammer fra studiets fortrolige *CSR*:

- Data på *andel patienter, der oplever alvorlige bivirkninger* for behandlingsnaive og behandlingserfarne patienter fra DISCOVER 1.
- Den absolutte effektforskel for *SF-36, det fysiske funktion-subdomæne* og *SF-36, det fysiske smerte-subdomæne* fra DISCOVER 1.

5.2.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Vurdering af risikoen for bias ved Cochrane risk of bias tool 2.0 ved de enkelte studier fremgår af bilag 2. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 3).

Indledningsvis blev lægemidlernes direkte sammenligninger med placebo vurderet.

- Overordnet var DISCOVER 1-studiet af guselkumab sammenlignet med placebo af meget lav kvalitet. Evidensen er nedgraderet på baggrund af inkonsistens (kun ét studie), indirekthed (data opgjort som alvorlige uønskede hændelser (SAE) fremfor alvorlige bivirkninger (SAR), og for livskvalitet er data opgjort på ITT, som består både af behandlingsnaive og behandlingserfarne patienter), samt unøjagtighed (konfidensintervallet for SAE indeholder en beslutningsgrænse).
- Overordnet var SPIRIT-P2-studiet af ixekizumab sammenlignet med placebo af meget lav kvalitet. Evidensen er nedgraderet på baggrund af inkonsistens (kun ét studie), indirekthed (data opgjort som alvorlige uønskede hændelser (SAE) fremfor alvorlige bivirkninger (SAR)) samt unøjagtighed (konfidensintervallet for SAE indeholder en beslutningsgrænse).

Da merværdien af guselkumab sammenlignet med ixekizumab er vurderet via indirekte sammenligninger, er der for alle effektmål yderligere nedjusteret for indirekte evidens. Den samlede evidenskvalitet for klinisk spørgsmål 2 er vurderet ud fra det lavest vurderede kritiske effektmål (alvorlige uønskede hændelser ved både DISCOVER 1-SPIRIT-P2-studierne).

Evidensens kvalitet er meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

5.2.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 2.

Tabel 8. Resultater for klinisk spørgsmål 2 - guselkumab sammenlignet med ixekizumab til behandlingserfarne patienter med PsA uden moderat til svær psoriasis

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Sygdomsaktivitet - ledaffektion	Andel patienter, der oplever respons på ACR50 (MKRF: 15 %-point)	Kritisk	-8,6 %-point [-30,2; 104,1]	Kan ikke kategoriseres	RR: 0,75 [0,14-3,95]	Kan ikke kategoriseres	Kan ikke kategoriseres
	Andel patienter uden progression, jf. mTSS (MKRF: 10 %-point)		NA	Kan ikke kategoriseres	NA	Kan ikke kategoriseres	
Bivirkninger	Andel patienter, der oplever alvorlige bivirkninger (MKRF: 5 %-point)	Kritisk	0,8 %-point [-2,1; 24,7]	Kan ikke kategoriseres	RR: 1,31 [0,16-11,06]	Kan ikke kategoriseres	Kan ikke kategoriseres
	Gennemgang af bivirkningsprofil		Se nedenfor				
Livskvalitet	Gennemsnitlig ændring fra baseline på SF-36, det fysiske funktion-subdomæne (MKRF: 7,1 point)*	Kritisk	[redacted] IXE vs. PBO: NA	Kan ikke kategoriseres[§]	NA	Kan ikke kategoriseres[§]	Kan ikke kategoriseres
	Gennemsnitlig ændring fra baseline på SF-36, det fysiske smerte-subdomæne (MKRF: 4,9 point)*		[redacted] IXE vs. PBO: NA	Kan ikke kategoriseres[§]	NA	Kan ikke kategoriseres[§]	

Gennemsnitlig ændring fra baseline på SF-36, den fysiske komponent summary (MKRF: 7,2 point)**	GUS vs. PBO: 4,1 point [2,4; 5,9] IXE vs. PBO: 5,6 point [3,2; 8,0]	Kan ikke kategoriseres§	NA	Kan ikke kategoriseres§
Gennemsnitlig ændring fra baseline på SF-36, den mentale komponent summary (MKRF: 3,1 point)**	GUS vs. PBO: 0,8 point [-1,1; 2,8] IXE vs. PBO: 2,7 point (0,4; 5,0]	Kan ikke kategoriseres§	NA	Kan ikke kategoriseres§

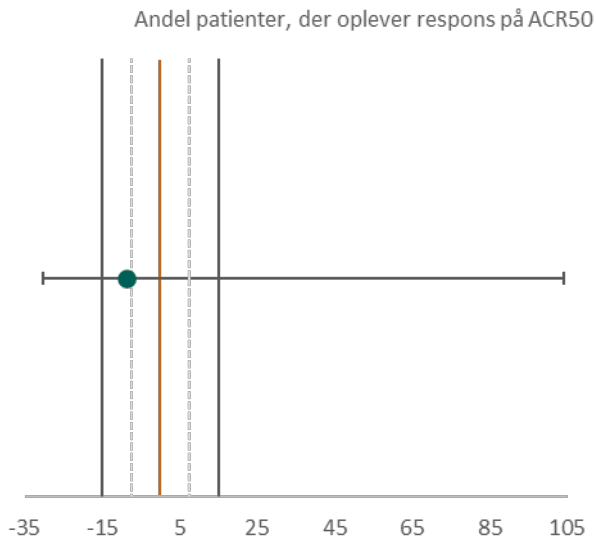
Konklusion	
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres efter Medicinrådets metoder
Kvalitet af den samlede evidens	Meget lav

CI = konfidensinterval, RR = relativ risiko, ACR50 = *American College of Rheumatology 50 % response*, mTSS = *modified Total Sharp Score*, SF-36 = *Short form*-36, GUS = guselkumab, IXE = ixekizumab; PBO = placebo.
***** Data for absolut effekforskel mellem guselkumab og placebo. Data for guselkumab stammer fra DISCOVER 1.
** Data for absolut effekforskel mellem guselkumab eller ixekizumab og placebo. Data for guselkumab stammer fra DISCOVER 1 og for ixekizumab fra SPIRIT-P2.
§ Kategorisering ikke mulig pga. manglende komparative analyser.

Sygdomsaktivitet-ledaffektion
Se afsnit 5.1.4 for definition af effektmålet *Sygdomsaktivitet-ledaffektion*.

ACR50
Efter 24 ugers opfølgning havde 11 ud af 41 patienter (27 %) opnået ACR50 i guselkumab-armen (Q8W) i DISCOVER 1-studiet [19], hvilket var tilfældet for 43 ud af 122 patienter (35 %) i ixekizumab-armen i SPIRIT-P2-studiet [33]. For placeboarmene var andelen 5 % i begge studier.

Den absolutte forskel fra den indirekte sammenligning er vist i figur 4 nedenfor.



Figur 4. Punktestimat og 95 % konfidensinterval for den absolutte forskel for *Andel patienter, der oplever respons på ACR50*. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget har i protokollen defineret MKRF til 15 %-point. Punktestimatet for den absolutte effektforskel på -8,6 %-point afspejler dermed ikke en klinisk relevant effektforskel. Konfidensintervallet er meget bredt, hvilket betyder, at det rummer muligheden for, at guselkumab har en positiv, ingen og negativ værdi. Derfor kan den foreløbige værdi af guselkumab vedr. delmålet *Andel patienter, der oplever respons på ACR50,* ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, opgjort som en relativ risiko på 0,75 [0,14-3,95] (fremgår af tabel 8), har guselkumab foreløbigt en værdi, som ikke kan kategoriseres vedr. delmålet *Andel patienter, der oplever respons på ACR50*, fordi konfidensintervallet inkluderer 1.

mTSS
Ansøger har ikke indsendt en analyse på delmålet, da mTSS ikke indgik i de to studier. Den foreløbige værdi af guselkumab vedr. delmålet kan dermed ikke kategoriseres.

Samlet for effektmålet *Sygdomsaktivitet-ledaffektion*

Baseret på ovenstående gennemgang af effektmålets to delmål vurderer fagudvalget, at guselkumab aggregeret har en værdi, der **ikke kan kategoriseres** efter Medicinrådets metoder vedr. effektmålet *Sygdomsaktivitet-ledaffektion*.

Der foreligger kun data på delmålet ACR50, da mTSS ikke indgik i studierne. For delmålet ACR50 kan hverken den absolutte eller relative effektforskel kategoriseres efter Medicinrådets metoder pga. de brede konfidensintervaller som følge af den indirekte sammenligning. Imidlertid viser data, at effekten af guselkumab peger i negativ retning sammenlignet med ixekizumab, om end den absolutte effektforskel ikke er af klinisk betydning (punktestimat på -8,6 %-point og MKRF er 15 %-point).

På baggrund af det sparsomme datagrundlag, kan fagudvalget ikke konkludere, om der er en klinisk betydende forskel mellem de to lægemidler hvad angår effektmålet *Sygdomsaktivitet-ledaffektion.*

Bivirkninger

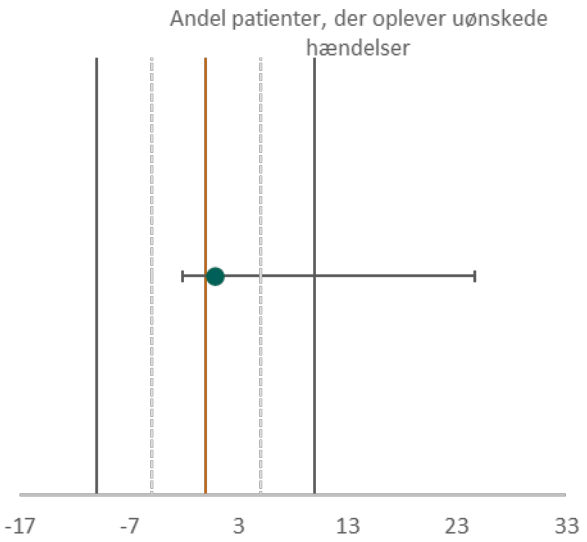
Se afsnit 5.1.4 for definition af effektmålet *Bivirkninger*.

Andel patienter, der oplever alvorlige bivirkninger

Ansøger har indsendt data på andel patienter, der oplever alvorlige uønskede hændelser (SAE), da der ikke foreligger data på SAR fra DISCOVER 1.

Efter 24 ugers opfølgning havde [redacted] oplevet en uønsket hændelse i guselkumab-armen (Q8W) i DISCOVER 1-studiet, hvilket var tilfældet for 3 ud af 122 patienter (2 %) i ixekizumab-armen i SPIRIT-P2-studiet [33]. For placeboarmene var andelen [redacted] og 3 % i hhv. DISCOVER 1- og SPIRIT-P2-studierne.

Den absolutte forskel er vist i figur 5 nedenfor.



Figur 5. Punktestimat og 95 % konfidensinterval for den absolutte forskel for *Andel patienter, der oplever uønskede hændelser*. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget har i protokollen defineret MKRF til 5 %-point. Punktestimatet for den absolutte effektforskel på 0,8 %-point afspejler dermed ikke en klinisk relevant effektforskel. Konfidensintervallet er bredt, hvilket betyder, at det rummer muligheden for, at guselkumab har ingen og negativ værdi. Derfor kan den foreløbige værdi af guselkumab vedr. delmålet *Andel patienter, der oplever alvorlige uønskede hændelser,* ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, opgjort som en relativ risiko på 1,31 [0,16-11,06] (fremgår af tabel 8), har guselkumab foreløbigt en værdi, som ikke kan kategoriseres vedr. delmålet *Andel patienter, der oplever alvorlige uønskede hændelser*, fordi konfidensintervallet inkluderer 1.

Gennemgang af bivirkningsprofil

Gennemgangen af bivirkningsprofilerne for guselkumab og ixekizumab tager udgangspunkt i lægemidlernes produktresuméer [16,37], hvor bivirkningsprofilerne er sammenlagt fra de underliggende kliniske studier. Derudover sammenligner fagudvalget udvalgte bivirkninger mellem de to lægemidler fra de underliggende studier.

Guselkumab

Se gennemgangen af bivirkningsprofilen ved klinisk spørgsmål 1, afsnit 5.1.4.

Ixekizumab

De hyppigst rapporterede bivirkninger er reaktioner på injektionsstedet (udslæt (erytem) og smerte) og øvre luftvejsinfektioner (oftest forkølelse (nasopharyngitis)). Behandling med ixekizumab er forbundet med en øget forekomst af infektioner, f.eks. infektion i øvre luftveje, svamp i munden (oral candidiasis), øjenbetændelse (konjunktivitis) og

svampeinfektioner i huden (dermatofytose). Alvorlige overfølsomhedsreaktioner er rapporteret, og der er blevet rapporteret om tilfælde af nyopstået eller forværret inflammatorisk tarmsygdom ved behandling med ixekizumab, hvilket, fagudvalget bemærker, er alvorligt for patienten [37].

Nedenstående tabel giver et overblik over de rapporterede bivirkninger fra de to studier.

Tabel 9. Oversigt over bivirkninger ved 24 uger fra DISCOVER 1 og SPIRIT-P2

	DISCOVER 1		SPIRIT-P2	
	Placebo	Guselkumab Q8W	Placebo	Ixekizumab Q4W
Uønskede hændelser (AE)	59,5 %	53,5 %	64 %	68 %
Alvorlige uønskede hændelser (SAE)	4,0 %	3,1 %	3 %	2 %
Infektioner	25,4 %	26,0 %	30 %	39 %
Alvorlige infektioner	1,6 %	0 %	0 %	0 %
Behandlingsophør	9,5 %	3,1 %	20,3 %	9,0 %
Grundet AE	1,6 %	2,4 %	5,0 %	4,0 %
Forhøjet alanin aminotransferase	2 %	6 %	NA*	NA*
Forhøjet aspartat aminotransferase	2 %	7 %	NA*	NA*
Nasopharyngitis	6 %	13 %	3 %	7 %
Øvre luftvejsinfektion	6 %	6 %	8 %	9 %

*Hepatic events 2 % i både placebo- og ixekizumab-armene.

Sammenligning af opgørelser over uønskede hændelser i forskellige studier skal tages med forbehold, da der kan være forskel på, hvordan uønskede hændelser bliver opgjort i forskellige studier. Overordnet kan fagudvalget ikke konkludere, at der er forskel i bivirkninger mellem guselkumab og ixekizumab til patienter med PsA på baggrund af ovenstående data.

Samlet vurdering af bivirkningsprofiler

Overordnet finder fagudvalget, at guselkumabs og ixekizumabs bivirkningsprofiler er forskellige, hvor begge lægemidler kan medføre en række uønskede hændelser. Fagudvalget finder dog, at lægemidlerne er sammenlignelige, hvad angår bivirkningernes sværhedsgrad og at potentielle risikofyldte bivirkninger bliver fremhævet i lægemidlernes produktresuméer. Fagudvalget understreger, at den kliniske erfaring med ixekizumab er mere omfattende end med guselkumab.

Samlet for effektmålet *Bivirkninger*

Baseret på ovenstående gennemgang af effektmålets to delmål vurderer fagudvalget, at guselkumab aggregeret har en værdi, som **ikke kan kategoriseres** vedr. effektmålet *Bivirkninger*.

Hverken den absolutte og relative effektforskel for delmålet *Andel patienter, der oplever uønskede hændelser,* kan kategoriseres efter Medicinrådets metoder pga. brede konfidensintervaller. Fagudvalget understreger, at den absolutte effektforskel ikke er af klinisk betydning, da den ligger under den mindste klinisk relevante forskel.

Guselkumabs og ixekizumabs bivirkningsprofiler er forskellige, men lægemidlerne er sammenlignelige, hvad angår bivirkningernes sværhedsgrad. Fagudvalget understreger, at der, grundet den korte opfølgningstid i guselkumab-studierne og den manglende kliniske erfaring med guselkumab, ikke er kendskab til potentielle langtidsbivirkninger, som der er ved ixekizumab.

Livskvalitet

Se afsnit 5.1.4 for definition af effektmålet *Livskvalitet*.

Der foreligger data for guselkumab fra ITT-populationen (30 % behandlingserfarne) i DISCOVER 1 og for ixekizumab fra SPIRIT-P2. På grund af forskelle i dataopgørelse mellem studierne, kan data ikke indgå i en formel indirekte sammenligning. De foreløbige værdier af guselkumab vedr. delmålene kan dermed ikke kategoriseres. Fagudvalget vil kvalitativt gennemgå det data, der foreligger fra de to studier.

Det fysiske funktion-subdomæne

Den gennemsnitlige forbedring i det fysiske funktion-subdomæne var 5,8 point i guselkumab-armen (Q8W) i DISCOVER 1-studiet [32] sammenlignet med 17,1 point i ixekizumab-armen i SPIRIT-P2-studiet [35]. I placeboarmen var den gennemsnitlige forbedring på 1,6 point i DISCOVER 1-studiet. Der foreligger ikke data på placeboarmen fra SPIRIT-P2-studiet. Dermed kan den absolutte effektforskel kun opgøres mellem guselkumab og placebo, hvor den ligger på [redacted]

Fagudvalget bemærker, at data indikerer, at ixekizumab giver patienterne et bedre funktionsniveau end guselkumab. Fordi den absolutte effektforskel ikke kendes fra SPIRIT-P2, er det ikke muligt at konkludere, om der er en klinisk relevant forskel mellem de to lægemidler hvad angår delmålet *Det fysiske funktion-subdomæne*.

Det fysiske smerte-subdomæne

Den gennemsnitlige forbedring i det fysiske smerte-subdomæne var 6,8 point i guselkumab-armen (Q8W) i DISCOVER 1-studiet [32] sammenlignet med 17,1 point i ixekizumab-armen i SPIRIT-P2-studiet [35]. I placeboarmen var den gennemsnitlige forbedring på 2,9 point i DISCOVER 1-studiet. Der foreligger ikke data på placeboarmen fra SPIRIT-P2-studiet. Dermed kan den absolutte effektforskel kun opgøres mellem guselkumab og placebo, hvor den ligger på [redacted]

Fagudvalget bemærker, at data indikerer, at ixekizumab er bedre til at behandle patienternes smerter sammenlignet med guselkumab. Fordi den absolutte effektforskel ikke kendes fra SPIRIT-P2, er det ikke muligt at konkludere, om der er en klinisk relevant forskel mellem de to lægemidler hvad angår delmålet *Det fysiske smerte-subdomæne*.

Den fysiske komponent summary

Efter 24-ugers opfølgning var den gennemsnitlige forbedring i den fysiske komponent summary 6,1 point i guselkumab-armen (Q8W) i DISCOVER 1-studiet [19] sammenlignet med 8,9 point i ixekizumab-armen i SPIRIT-P2-studiet [33]. I placeboarmene var den gennemsnitlige forbedring på 2,0 og 3,3 point i hhv. DISCOVER 1- og SPIRIT-P2-studierne. Den absolutte effektforskel mellem guselkumab og placebo var således 4,1 point [2,4-5,9], mens det for ixekizumab og placebo var 5,6 point [3,2-8,0].

Baseret på ovenstående gennemgang samt klinisk erfaring vurderer fagudvalget, at det er sandsynligt, at der ikke er betydende forskel mellem guselkumab og ixekizumab, hvad angår delmålet *Den fysiske komponent summary*.

Den mentale komponent summary

Efter 24-ugers opfølgning var den gennemsnitlige forbedring i den mentale komponent summary 3,2 point i guselkumab-armen (Q8W) i DISCOVER 1-studiet [19] sammenlignet med 3,6 point i ixekizumab-armen i SPIRIT-P2-studiet [33]. I placeboarmene var den gennemsnitlige forbedring på 2,4 og 0,9 point i hhv. DISCOVER 1- og SPIRIT-P2-studierne. Den absolutte effektforskel mellem guselkumab og placebo var således 0,8 point [-1,1-2,8], mens det for ixekizumab og placebo var 2,7 point [0,4-5,0].

Baseret på ovenstående gennemgang samt klinisk erfaring vurderer fagudvalget, at det er sandsynligt, at der ikke er betydende forskel mellem guselkumab og ixekizumab, hvad angår delmålet *Den mentale komponent summary*.

Samlet for effektmålet *Livskvalitet*

Baseret på ovenstående gennemgang af effektmålets fire delmål vurderer fagudvalget, at guselkumab aggregeret har en værdi, som **ikke kan kategoriseres** vedr. effektmålet *Livskvalitet*.

Det skyldes, at der ikke foreligger komparative analyser for nogen af de fire delmål. Fagudvalget bemærker, at data indikerer, at guselkumabs effekt på patienternes funktions- og smerteniveau er lavere end ixekizumabs. Hvad angår den fysiske og mentale komponent summary, er guselkumabs og adalimumabs effekt sammenlignet med placebo sammenlignelig.

Overordnet vurderer fagudvalget, at på baggrund af det sparsomme datagrundlag, er det ikke muligt at konkludere, om der er en klinisk relevant forskel mellem de to lægemidler hvad angår effektmålet *Livskvalitet*.

5.2.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af guselkumab sammenlignet med ixekizumab til behandlingserfarne patienter med PsA uden moderat til svær plaque psoriasis **ikke kan kategoriseres** efter Medicinrådets metoder.

I den samlede vurdering lægger fagudvalget vægt på, at den absolutte effektforskel ved delmålet ACR50 peger i negativ retning sammenlignet med ixekizumab. Der foreligger ikke data på delmålet mTSS men hos behandlingsnaive patienter (klinisk spørgsmål 1), var der signifikant flere patienter, der havde radiologisk progression efter 24 ugers behandling med guselkumab sammenlignet med adalimumab. Fagudvalget skønner, at evidensen rimeligvis kan ekstrapoleres til de behandlingserfarne patienter.

Overordnet vurderer fagudvalget, at guselkumab er en mindre effektiv behandling til at forebygge kroniske skader i leddene samt kontrollere patienternes sygdomsaktivitet sammenlignet med den behandling, de får i dag.

Fagudvalget fremhæver, at der er usikkerhed forbundet med vurderingen pga. forskelle i de underliggende studier, hvilket betyder, at nye studier med en direkte sammenligning af guselkumab og ixekizumab med høj sandsynlighed kan ændre konklusionen.

5.3 Klinisk spørgsmål 3 og 4

Jf. protokollen er de kliniske spørgsmål:

Hvilken værdi har guselkumab sammenlignet med adalimumab for behandlingsnaive patienter med PsA og moderat til svær plaque psoriasis?

Hvilken værdi har guselkumab sammenlignet med adalimumab for behandlingserfarne patienter med PsA og moderat til svær plaque psoriasis?

Ansøger har ikke søgt ny litteratur til besvarelse af de to kliniske spørgsmål, da patienter med PsA og moderat til svær plaque psoriasis indgår i de studier, der er anvendt til at besvare klinisk spørgsmål 1 og 2 (se yderligere i afsnit 5.1.1 og 5.2.1). Overordnet set har patienterne i studierne imidlertid ikke moderat til svær psoriasis, da deres PASI-score er under 10, hvilket således ikke svarer til den efterspurgte patientpopulation i de kliniske spørgsmål. Dertil foreligger der ikke data på subpopulationsniveau, hvad angår sværhedsgraden af psoriasis. Der er således ikke et solidt datagrundlag til at besvare klinisk spørgsmål 3 og 4.

Fagudvalget påpeger, at Medicinrådet har anbefalet guselkumab til behandling af patienter med moderat til svær plaque psoriasis og ligestillet det til 2. linjebehandling med de øvrige lægemidler [38]. Der er således evidens for, at guselkumab har betydningsfuld effekt på patienternes hudaffektioner, hvilket fagudvalget formoder også vil gælde for patienter med PsA og moderat til svær plaque psoriasis.

5.3.1 Fagudvalgets konklusion vedr. klinisk spørgsmål 3 og 4

Fagudvalget vurderer, at guselkumab til behandlingsnaive og behandlingserfarne patienter med PsA og moderat til svær plaque psoriasis har en værdi, der **ikke kan kategoriseres** efter Medicinrådets metoder sammenlignet med hhv. adalimumab og ixekizumab.

Fagudvalget vurderer, at evidensen ved kliniske spørgsmål 1 og 2 kan ekstrapoleres til patienter med psoriasisartrit og moderat til svær plaque psoriasis, da der ikke er noget biologisk plausibelt rationale, der tilsiger, at guselkumabs effekt adskiller sig mellem de to patientgrupper. Her vurderer fagudvalget overordnet, at guselkumab sandsynligvis er en mindre effektiv behandling til at forebygge kroniske skader i leddene samt kontrollere patienternes sygdomsaktivitet sammenlignet med den behandling, de får i dag. Da det netop er patienternes ledaffektioner, der primært ønskes behandlet, tillægger fagudvalget dette større vægt, end guselkumabs behandlingseffekt på PsA-patienternes hudaffektioner.

Fagudvalget fremhæver, at nye studier med direkte sammenligninger af guselkumab med adalimumab eller ixekizumab med høj sandsynlighed kan ændre konklusionen.

6. Andre overvejelser

Ustekinumab er en IL-12/23 hæmmer, der ikke er ligestillet med de øvrige lægemidler i RADS´ behandlingsvejledning for anvendelse af biologisk behandling af psoriasisartrit [39], da det er mindre effektivt. Ustekinumab er i stedet placeret under *overvej* i anbefalingstabellerne og er dermed indplaceret som sidste valg i den tilhørende lægemiddelrekommandation [18]. Ustekinumab bliver derfor i klinisk praksis kun brugt til de patienter med PsA, hvor andre behandlingsmuligheder er udtømte.

7. Relation til behandlingsvejledning

Fagudvalget har vurderet, at guselkumab ikke har sammenlignelig effekt med adalimumab og ixekizumab. Medicinrådet vil derfor foreløbig placere guselkumab efter adalimumab og ixekizumab i RADS' behandlingsvejledning for anvendelse af biologisk behandling af psoriasisartrit [39]. Det kan få betydning for lægemiddelrekommandationen.

Fagudvalget vurderer, at guselkumab bør have samme placering i behandlingskaskaden (under *overvej*) som ustekinumab.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende gigtsygdomme

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Annemarie Lyng Svensson *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Salome Kristensen *Overlæge*	Region Nordjylland
Lars Erik Bartels *Afdelingslæge*	Region Midtjylland
Hanne M. Lindegaard *Overlæge, klinisk lektor*	Region Syddanmark
Thomas Adelsten *Uddannelsesansvarlig overlæge*	Region Sjælland
Maria Krogstrup *Afdelingslæge*	Region Hovedstaden
Per Damkier *Professor, overlæge*	Dansk Selskab for Klinisk Farmakologi
Ane Hornbæk Mortensen *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Dorte Vendelbo Jensen *Overlæge, sekretariatsleder*	DANBIO
Udpegning i gang	Dansk Reumatologisk Selskab
Annette de Thurah *Klinisk sygeplejespecialist*	Dansk Sygepleje Selskab
Connie Ziegler *Patient/patientrepræsentant*	Danske Patienter

Lene Mandrup Thomsen *Patient/patientrepræsentant*	Danske Patienter
Tidligere medlemmer, som har bidraget til arbejdet	**Udpeget af**
Thomas Loof Hedegård *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse

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10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	23. juni 2021	Godkendt af Medicinrådet

11. Bilag

Bilag 1: Metaanalyser

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Meta-analyses used in the application for the assessment of Tremfya for psoriatic arthritis

1. Meta-analysis of ACR50 response amongst treatment naïve patients receiving guselkumab Q8W

Weights

study names	weights
DISCOVER-2:	78.970%
DISCOVER-1:	21.030%

Summary

Binary Random-Effects Model
Metric: Relative Risk

Model Results

Estimate	Lower bound	Upper bound	p-Value
2.363	1.720	3.247	< 0.001

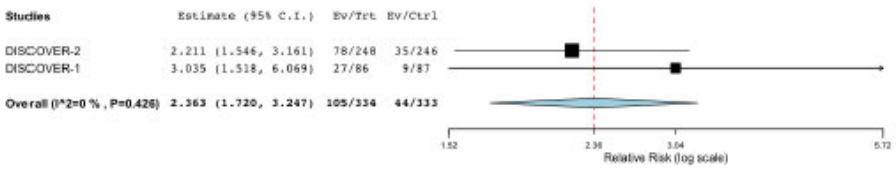
Heterogeneity

tau^2	Q(df=1)	Het. p-Value	I^2
0.000	0.634	0.426	0

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
0.860	0.542	1.178	0.162

Forest plot



2. Meta-analysis of SAE experience amongst treatment naïve patients receiving guselkumab Q8W

Weights

study names	weights
DISCOVER-2:	75.933%
DISCOVER-1:	24.067%

Summary

Binary Random-Effects Model
Metric: Relative Risk

Model Results

Estimate	Lower bound	Upper bound	p-Value
0.443	0.138	1.426	0.172

Heterogeneity

tau^2	Q(df=1)	Het. p-Value	I^2
0.000	0.016	0.901	0

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
-0.814	-1.982	0.355	0.596

4. Meta-analysis of ACR50 response amongst treatment naïve patients receiving adalimumab Q2W

Weights

study names	weights
ADEPT:	47.847%
SPIRIT-1:	52.153%

Summary

Binary Random-Effects Model
Metric: Relative Risk

Model Results

Estimate	Lower bound	Upper bound	p-Value
3.946	1.625	9.581	0.002

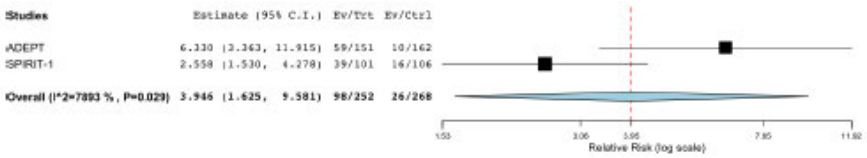
Heterogeneity

tau^2	Q(df=1)	Het. p-Value	I^2
0.324	4.746	0.029	78.928

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
1.373	0.486	2.260	0.453

Forest plot



5. Meta-analysis of SAE experience amongst treatment naïve patients receiving adalimumab Q2W

Weights

study names	weights
ADEPT:	61.573%
SPIRIT-1:	38.427%

Summary

Binary Random-Effects Model
Metric: Relative Risk

Model Results

Estimate	Lower bound	Upper bound	p-Value
1.230	0.380	3.976	0.730

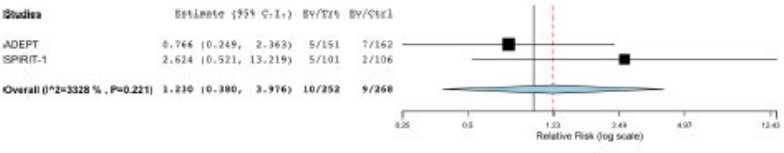
Heterogeneity

tau^2	Q(df=1)	Het. p-Value	I^2
0.252	1.499	0.221	33.276

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
0.207	-0.967	1.380	0.599

Forest plot



7. Meta-analysis of mean change from baseline in SF-36 PCS amongst treatment naïve patients receiving adalimumab Q2W

Weights

study names	weights
SPIRIT-1:	50.275%
ADEPT :	49.725%

Summary
Continuous Random-Effects Model
Metric: Mean Difference

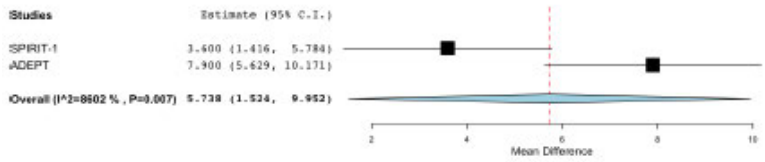
Model Results

Estimate	Lower bound	Upper bound	Std. error	p-Value
5.738	1.524	9.952	2.150	0.008

Heterogeneity

tau^2	Q(df=1)	Het. p-Value	I^2
7.953	7.154	0.007	86.022

Forest plot



8. Meta-analysis of mean change from baseline in SF-36 MCS amongst treatment naïve patients receiving adalimumab Q2W

Weights

study names	weights
SPIRIT-1:	43.241%
ADEPT :	56.759%

Summary
Continuous Random-Effects Model
Metric: Mean Difference

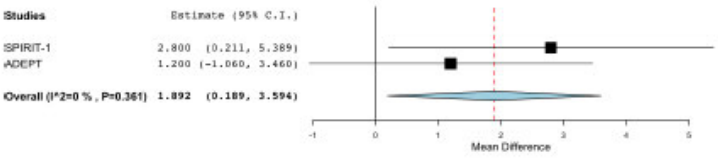
Model Results

Estimate	Lower bound	Upper bound	Std. error	p-Value
1.892	0.189	3.594	0.869	0.029

Heterogeneity

tau^2	Q(df=1)	Het. p-Value	I^2
0.000	0.833	0.361	0

Forest plot



Bilag 2: Cochrane – risiko for bias

Vurdering af risiko for bias ved Cochrane risk of bias tool 2.0.

Tabel 10. Vurdering af risiko for bias Deodhar et al., 2020, DISCOVER 1, NCT03162796

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiseringsprocessen	**Lav**	Randomisering foretaget med et interaktivt web-responssystem ved brug af en computer-genereret permuted-block randomisering. Randomiseringen var stratificeret efter csDMARDs ved baseline (ja eller nej) og seneste måling af høj-sensitivitet CRP før randomisering (< 2,0 mg/dL vs. ≥ 2,0 mg/dL). Patienterne blev randomiseret 1:1:1 til guselkumab 100 mg hver 4. uge, guselkumab 100 mg ved uge 0, 4 og derefter hver 8. uge eller placebo.
Effekt af tildeling til intervention	**Lav**	Dobbeltblindet studie, hvor både investigator, site personale og deltagere var blindede til den allokerede behandling. Guselkumab og placebo blev uddelt i forudfyldte sprøjter, og patienter i hver behandlingsarm modtog samme antal sprøjter på samme tidspunkt for at sikre, at både patienter og site personale forblev blindede. Efter 24-ugers dobbeltblindet periode krydsede patienter i placeboarmen over til guselkumab Q4W. Effektanalyser blev udført efter opfølgningstid på 52 uger, mens sikkerhed havde en opfølgningstid på 60 uger.
Manglende data for effektmål	**Lav**	Data er opgjort på ITT-populationen, og der foreligger data på de effektmål, der er beskrevet i studieprotokollen. Manglende data blev imputeret som non-responder for binære endepunkter. For kontinuerlige endepunkter blev *multiple imputation* brugt ved manglende data.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet, placebo-kontrolleret studie.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Der foreligger data på de effektmål, der er beskrevet i studieprotokollen, og der er ingen indikation om selektiv rapportering.
Overordnet risiko for bias	**Lav**	Den overordnede risiko for bias er lav, da alle domæner har lav risiko for bias.

Tabel 11. Vurdering af risiko for bias Mease et al., 2020, DISCOVER 2, NCT03158285

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiseringsprocessen	**Lav**	Randomisering foretaget med et interaktivt web-responssystem ved brug af en computer-genereret permuted-block randomisering. Randomiseringen var stratificeret efter csDMARDs ved baseline (ja eller nej) og tidligere behandling med TNF-hæmmere (ja eller nej). Patienterne blev randomiseret 1:1:1 til guselkumab 100 mg hver 4. uge, guselkumab 100 mg ved uge 0, 4 og derefter hver 8. uge eller placebo.
Effekt af tildeling til intervention	**Lav**	Dobbeltblindet studie, hvor både investigator, site personale og deltagere var blindede til den allokerede behandling. Guselkumab og placebo blev uddelt i forudfyldte sprøjter, og patienter i hver behandlingsarm modtog samme antal sprøjter på samme tidspunkt for at sikre, at både patienter og site personale forblev blindede. Studiet indeholdt en placebo-kontrolleret periode fra uge 0-24, en aktiv blindet behandlingsperiode fra uge 24-100 efterfulgt af 12 ugers sikkerhedsopfølgningstid efter administration af sidste studiemedicin. Efter 24-ugers dobbeltblindet periode krydsede patienter i placeboarmen over til guselkumab Q4W.
Manglende data for effektmål	**Lav**	Data er opgjort på ITT-populationen, og der foreligger data på de effektmål, der er beskrevet i studieprotokollen. Manglende data blev imputeret som non-responder for binære endepunkter. For kontinuerlige endepunkter blev *multiple imputation* brugt ved manglende data.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet, placebo-kontrolleret studie.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Der foreligger data på de effektmål, der er beskrevet i studieprotokollen, og der er ingen indikation om selektiv rapportering.
Overordnet risiko for bias	**Lav**	Den overordnede risiko for bias er lav, da alle domæner har lav risiko for bias.

Tabel 12. Vurdering af risiko for bias Mease et al., 2005, ADEPT, NCT00195689

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Forbehold**	Der foreligger ikke information om, hvordan randomisering blev foretaget. Randomiseringen var stratificeret efter MTX-behandling ved baseline (ja eller nej) og deres grad af psoriasis involvering (≥ 3 % eller < 3 % af kroppen ved baseline). Patienterne blev randomiseret 1:1 til adalimumab 40 mg hver 2. uge eller placebo. Baselinekarakteristika er sammenlignelige mellem studiearme, hvilket indikerer, at der ikke var bias i randomiseringen.
Effekt af tildeling til intervention	**Lav**	Dobbeltblindet studie, men det er ikke beskrevet, hvordan blinding blev overholdt. Der er dog ikke indikation på, at blinding ikke var overholdt eller brudt (ingen mistænkelige afvigelser fra den allokerede behandling). Studiet havde en 24-ugers dobbeltblindet periode, hvorefter patienter fra begge arme kunne fortsætte i et ublindet ekstension-studie.
Manglende data for effektmål	**Lav**	Data er opgjort på ITT-populationen, og der foreligger data på de effektmål, der er beskrevet i studieprotokollen. Non-responder imputation blev brugt ved manglende data.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet, placebo-kontrolleret studie.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Der foreligger data på de effektmål, der er beskrevet i studieprotokollen, og der er ingen indikation om selektiv rapportering.
Overordnet risiko for bias	**Lav**	Den overordnede risiko for bias er lav.

Tabel 13. Vurdering af risiko for bias Mease et al., 2017, SPIRIT-P1, NCT01695239

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiseringsprocessen	**Lav**	Randomisering foretaget med et interaktivt voice-responssystem ved brug af en computer-genereret randomiseringskode. Randomiseringen var stratificeret efter region og tidligere/nuværende/ingen behandling med csDMARDs. Patienterne blev randomiseret 1:1:1:1 til ixekizumab 80 mg hver 2. uge, ixekizumab 80 mg hver 4. uge, adalimumab 40 mg hver 2. uge eller placebo.
Effekt af tildeling til intervention	**Lav**	Dobbeltblindet studie, hvor både investigator, site personale og deltagere var blindede til den allokerede behandling. Pga. de forskellige behandlinger er blevet administreret på forskellige tidspunkter med forudfyldte sprøjter, der kunne skelnes fra hinanden, samt forskellige tidspunkter for ixekizumab-startdosis, blev der brugt et dobbelt dummy-design med Q2W dosering for at skjule den allokerede behandling. Studiet havde en 24-ugers dobbeltblindet periode, hvorefter patienter fra adalimumab- og placeboarmene blev re-randomiseret til enten IXEQ2W eller IXEQ4W i et ublindet ekstensionsstudie op til uge 52.
Manglende data for effektmål	**Lav**	Data er opgjort på ITT-populationen, og der foreligger data på de effektmål, der er beskrevet i studieprotokollen. Non-responder imputation blev brugt ved manglende data.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet, placebo-kontrolleret studie.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Der foreligger data på de effektmål, der er beskrevet i studieprotokollen, og der er ingen indikation om selektiv rapportering.
Overordnet risiko for bias	**Lav**	Den overordnede risiko for bias er lav, da alle domæner har lav risiko for bias.

Tabel 14. Vurdering af risiko for bias Nash et al., 2017, SPIRIT-P2, NCT02349295

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiseringsprocessen	**Lav**	Randomisering foretaget ved brug af en computer-genereret *random sequence*. Randomiseringen var stratificeret efter region og tidligere behandling med TNF-hæmmere (utilstrækkelig respons efter behandling med én TNF-hæmmer, to TNF-hæmmere eller intolerance overfor TNF-hæmmere). Patienterne blev randomiseret 1:1:1 til ixekizumab 80 mg hver 2. uge, ixekizumab 80 mg hver 4. uge eller placebo.
Effekt af tildeling til intervention	**Lav**	Dobbeltblindet studie, hvor både investigator, site personale og deltagere var blindede til den allokerede behandling. Forudfyldte, identiske sprøjter. Studiet havde en 24-ugers dobbeltblindet periode, hvorefter patienter fra placeboarmene blev re-randomiseret 1:1 til enten IXEQ2W eller IXEQ4W i et ublindet ekstensionsstudie op til uge 156.
Manglende data for effektmål	**Lav**	Data er opgjort på ITT-populationen, og der foreligger data på de effektmål, der er beskrevet i studieprotokollen. Non-responder imputation blev brugt ved manglende data. For kontinuerlige endepunkter blev der anvendt en *mixed-effect model repeated measurement*.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet, placebo-kontrolleret studie.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Der foreligger data på de effektmål, der er beskrevet i studieprotokollen, og der er ingen indikation om selektiv rapportering.
Overordnet risiko for bias	**Lav**	Den overordnede risiko for bias er lav, da alle domæner har lav risiko for bias.

Bilag 3: GRADE

Klinisk spørgsmål 1 – guselkumab sammenlignet med adalimumab til behandling af psoriasisartrit uden moderat til svær psoriasis

Tabel 15. GRADE evidensprofil for klinisk spørgsmål 1, DISCOVER 1 og 2 (metaanalyser og enkelte studier), guselkumab (behandlingsnaive subpopulation) vs. placebo

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Guselkumab Q8W	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
ACR50, 24 uger – metanalyse fra DISCOVER 1 og 2												
2	RCT	Ingen	Ingen	Ingen	Ingen	Ingen	105/334	44/333	RR: 2,36 [1,72-3,25]	18,2 %-point	⨁⨁⨁⨁ HØJ	KRITISK
mTSS, 24 uger – DISCOVER 2												
1	RCT	Ingen	Alvorlig[a]	Ingen	Alvorlig[b]	Ingen	157/248	159/246	RR: 0,98 [0,86-1,12]	-1,2 %-point	⨁⨁◯◯ LAV	KRITISK
SAE, 24 uger– metanalyse fra DISCOVER 1 og 2												
1	RCT	Ingen	Ingen	Alvorlig[c]	Alvorlig[b]	Ingen	[redacted]	[redacted]	[redacted]	[redacted]	⨁⨁◯◯ LAV	KRITISK
SF-36 - det fysiske funktion-subdomæne, 24 uger – DISCOVER 2												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	6,7 point	3,3 point	-	[redacted]	⨁⨁⨁◯ MODERAT	KRITISK

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Guselkumab Q8W	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
SF-36 - det fysiske smerte-subdomæne, 24 uger - DISCOVER 2												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	7,8 point	3,5 point	-	[redacted]	⨁⨁⨁◯ MODERAT	KRITISK
SF-36 - den fysiske komponent summary, 24 uger - DISCOVER 2												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	7,4 point	3,4 point	-	4,0 point [2,8-5,2]	⨁⨁⨁◯ MODERAT	KRITISK
SF-36 - den mentale komponent summary, 24 uger - DISCOVER 2												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	4,2 point	2,1 point	-	2,0 point [0,6-3,5]	⨁⨁⨁◯ MODERAT	KRITISK
Kvalitet af den samlede evidens LAV[d]												

[a] Der er nedgraderet ét niveau, da der kun var ét studie.

[b] Der er nedgraderet ét niveau, da konfidensintervallet indeholder en beslutningsgrænse.

[c] Data opgjort som alvorlige uønskede hændelser (*serious adverse events* (SAE)) fremfor alvorlige bivirkninger (*serious adverse reactions* (SAR)).

[d] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Tabel 16. GRADE evidensprofil for klinisk spørgsmål 1, ADEPT og SPIRIT-P1 (metaanalyser og enkelte studier), adalimumab vs. placebo

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Guselkumab Q8W	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
ACR50, 24 uger – metaanalyse fra ADEPT og SPIRIT-P1												
2	RCT	Ingen	Ingen	Ingen	Ingen	Ingen	98/252	26/268	RR: 3,95 [1,63-9,6]	29,2 %-point	⨁⨁⨁⨁ HØJ	KRITISK
mTSS, 24 uger – SPIRIT-P1												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	93/101	76/106	RR: 1,27 [1,11-1,45]	19,6 %-point	⨁⨁⨁◯ MODERAT	KRITISK
SAE, 24 uger – metaanalyse fra ADEPT og SPIRIT-P1												
1	RCT	Ingen	Ingen	Alvorlig[b]	Alvorlig[c]	Ingen	10/252	9/268	RR: 1,23 [0,38-4,0]	0,6 %-point	⨁⨁◯◯ LAV	KRITISK
SF-36 - det fysiske funktion-subdomæne, 24 uger – SPIRIT-P1												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	14,4 point	5,6 point	-	8,8 point [3,6-14,0]	⨁⨁⨁◯ MODERAT	KRITISK
SF-36 - det smerte funktion-subdomæne, 24 uger – SPIRIT-P1												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	16,8 point	8,3 point	-	8,5 point [2,9-14,1]	⨁⨁⨁◯ MODERAT	KRITISK

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Guselkumab Q8W	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
SF-36 - den fysiske komponent summary, 24 uger - metaanalyse fra ADEPT og SPIRIT-P1												
1	RCT	Ingen	Ingen	Ingen	Ingen	Ingen	-	-	-	5,7 point [1,5-10,0]	⨁⨁⨁⨁ HØJ	KRITISK
SF-36 - den mentale komponent summary, 24 uger - metaanalyse fra ADEPT og SPIRIT-P1												
1	RCT	Ingen	Ingen	Ingen	Ingen	Ingen	-	-	-	1,9 point [0,2-3,6]	⨁⨁⨁⨁ HØJ	KRITISK
Kvalitet af den samlede evidens LAV[d]												

[a] Der er nedgraderet ét niveau, da der kun var ét studie.

[b] Data opgjort som alvorlige uønskede hændelser (*serious adverse events* (SAE)) fremfor alvorlige bivirkninger (*serious adverse reactions* (SAR)).

[c] Der er nedgraderet ét niveau, da konfidensintervallet indeholder en beslutningsgrænse.

[d] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Klinisk spørgsmål 2 - guselkumab sammenlignet med ixekizumab til behandling af psoriasisartrit uden moderat til svær psoriasis

Tabel 17. GRADE evidensprofil for klinisk spørgsmål 2, DISCOVER 1, guselkumab (behandlingserfaren subpopulation) vs. placebo

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Adalimumab	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
ACR50, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	11/41	2/39	RR: 5,23 [1,24-22,11]	22 %-point [7; 37]	⨁⨁⨁◯ MODERAT	KRITISK
mTSS, 24 uger – ingen data												
-	-	-	-	-	-	-	-	-	-	-	-	KRITISK
SAE, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]	Alvorlig[c]	Ingen	[redacted]	[redacted]	[redacted]	[redacted]	⨁◯◯◯ MEGET LAV	KRITISK
SF-36 - det fysiske funktion-subdomæne, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[d]	Ingen	Ingen	5,8 point	1,6 point	-	[redacted]	⨁⨁◯◯ LAV	KRITISK
SF-36 - det fysiske smerte-subdomæne, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[d]	Ingen	Ingen	6,8 point	2,9 point	-	[redacted]	⨁⨁◯◯ LAV	KRITISK

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Adalimumab	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
SF-36 - den fysiske komponent summary, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[d]	Ingen	Ingen	6,1 point	2,0 point	-	4,1 point [2,4-5,9]	⨁⨁◯◯ LAV	KRITISK
SF-36 - den mentale komponent summary, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[d]	Ingen	Ingen	3,2 point	2,4 point	-	0,8 point [-1,1-2,8]	⨁⨁◯◯ LAV	KRITISK
Kvalitet af den samlede evidens	MEGET LAV[e]											

[a] Der er nedgraderet ét niveau, da der kun var ét studie.

[b] Data opgjort som alvorlige uønskede hændelser (*serious adverse events* (SAE)) fremfor alvorlige bivirkninger (*serious adverse reactions* (SAR)).

[c] Der er nedgraderet ét niveau, da konfidensintervallet indeholder en beslutningsgrænse.

[d] Data opgjort på ITT, som består både af behandlingsnaive og behandlingerfarne patienter.

[e] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Tabel 18. GRADE evidensprofil for klinisk spørgsmål 2, SPIRIT-P2, ixekizumab vs. placebo

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Adalimumab	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
ACR50, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	43/122	6/118	RR: 6,93 [3,07-15,67]	30,2 %-point [20,8-39,5]	⊕⊕⊕◯ MODERAT	KRITISK
mTSS, 24 uger – ingen data												
-	-	-	-	-	-	-	-	-	-	-	-	KRITISK
SAE, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]	Alvorlig[c]	Ingen	3/122	4/118	RR: 0,73 [0,17-3,17]	-1,0 %-point	⊕◯◯◯ MEGET LAV	KRITISK
SF-36 - det fysiske funktion-subdomæne, 24 uger – ingen data												
-	-	-	-	-	-	-	-	-	-	-	-	KRITISK
SF-36 - det fysiske smerte-subdomæne, 24 uger – ingen data												
-	-	-	-	-	-	-	-	-	-	-	-	KRITISK

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Adalimumab	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
SF-36 - den fysiske komponent summary, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	8,9 point	3,3 point	-	5,6 point [3,2-8,0]	⨁⨁⨁◯ MODERAT	KRITISK
SF-36 - den mentale komponent summary, 24 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	3,6 point	0,9 point	-	2,7 point [0,4-5,0]	⨁⨁⨁◯ MODERAT	KRITISK
Kvalitet af den samlede evidens	MEGET LAV[d]											

[a] Der er nedgraderet ét niveau, da der kun var ét studie.

[b] Data opgjort som alvorlige uønskede hændelser (*serious adverse events* (SAE)) fremfor alvorlige bivirkninger (*serious adverse reactions* (SAR)).

[c] Der er nedgraderet ét niveau, da konfidensintervallet indeholder en beslutningsgrænse.

[d] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Application for the assessment of Tremfya for psoriatic arthritis

Contents

1. Basic information

Kontaktoplysninger	
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Overview of the pharmaceutical (1)	
Proprietary name	Tremfya
Generic name	Guselkumab
Marketing authorization holder in Denmark	Janssen-Cilag A/S
ATC code	L04AC16
Pharmacotherapeutic group	Immunsuppressiva, interleukinhæmmere
Active substance(s)	Guselkumab, a fully human immunoglobulin G1 lamda (IgG1λ) monoclonal antibody (mAb) to the interleukin (IL)-23 protein,
Pharmaceutical form(s)	Solution for injection in pre-filled syringe or pen
Mechanism of action	Guselkumab is a human IgG1λ mAb that binds selectively to the IL-23 protein with high specificity and affinity. IL-23, a regulatory cytokine, affects the differentiation, expansion, and survival of T cell subsets, (e.g., Th17 cells and Tc17 cells) and innate immune cell subsets, which represent sources of effector cytokines, including IL-17A, IL-17F and IL-22 that drive inflammatory disease. In humans, selective blockade of IL-23 was shown to normalize production of these cytokines. In in vitro models, guselkumab was shown to inhibit the bioactivity of IL-23 by blocking its interaction with cell surface IL-23 receptor, disrupting IL-23-mediated signaling, activation and cytokine cascades. Guselkumab exerts clinical effects in plaque psoriasis and psoriatic arthritis through blockade of the IL-23 cytokine pathway.
Dosage regimen	The recommended dose of Tremfya is 100 mg by subcutaneous injection at weeks 0 and 4, followed by a maintenance dose every 8 weeks. For patients at high risk for joint damage according to clinical judgement, a dose of 100 mg every 4 weeks may be considered
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Psoriatic arthritis Tremfya, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy
Other approved therapeutic indications	Plaque psoriasis Tremfya is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.
Will dispensing be restricted to hospitals?	Yes . dispensing code BEGR
Combination therapy and/or co-medication	Tremfya can be used as monotherapy or in combination with MTX

Overview of the pharmaceutical (1)	
Packaging – types, sizes/number of units, and concentrations	Tremfya is in Denmark available as single pack of 1 pre-filled syringe, 100 mg solution for injection, or as single pack of 1 pre-filled pen 100 mg solution for injection. Each pre-filled syringe or pen contains 100 mg of guselkumab in 1 mL solution.
Orphan drug designation	No

2. Abbrevations

ACR:	American College of Rheumatology
AE:	Adverse event
ALT:	Alanine aminotransferase
AMPAR:	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic receptor
ANCOVA:	analysis of covariance
AST:	Aspartate aminotransferase
bDMARD:	Biologic Disease Modifying Anti-Rheumatic Drug
BSA:	Body surface area
CASPAR:	Classification criteria for Psoriatic Arthritis
CI:	Confidence interval
CRP:	C-Reaktivt Protein
csDMARD:	Conventionel Disease Modifying Anti-Rheumatic Drug
DMARD:	Sygdomsmodificerende antireumatisk lægemiddel (Disease Modifying Anti-Rheumatic Drug)
DIP:	Distal interphalangeal (DIP)
EMA:	European Medicines Agency
EPAR:	European Public Assessment Report
FAS:	Full analyses set
GUS:	Guselkumab
GRADE:	(Grading of Recommendations, Assessment, Development and Evaluation)
HCQ:	hydroxychloroquine
IgG1λ:	Immunoglobulin G1 lamda
IL-17:	Interleukin 17
IL-23:	Interleukin 23
ITT:	Intention-to-treat
JAK:	Janus kinase
LEF:	Leflunomide
LS:	Least squares
LL:	Lower limit
MACE:	major adverse cardiac event (ie, cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke)
MCS:	Mental Component Summary
MKRF:	Mindste klinisk relevante forskel
mTSS:	Modified Total Sharp Score
MTX:	Methotrexat
NCI-CTCAE:	National Cancer Institute common terminology criteria for adverse events
NICE:	The National Institute for Health and Care Excellence
NSAID:	Nonsteroidal anti-inflammatory drug
NRI:	Non-responder imputation

PCS:	Physical Component Summary
PASI:	Psoriasis Area Severity Index
PsA:	Psoriatic arthritis
PsO	Psoriasis
PICO:	Population, intervention, komparator og effektmål (Population, Intervention, Comparison and Outcome)
RA:	Rheumatoid arthritis
RR:	Relative risk
SD:	Standard deviation
SE:	standard error
SAE:	Serious Adverse Event
SF-36:	Short Form 36
SMPC:	Summary of product characteristics
SSZ:	Sulfasalazine
TB:	Tuberculosis
TNF:	Tumor necrosis factor
TNF-i:	Tumor necrosis factor inhibitor
UL:	Upper limit
ULN:	Upper limit of normal
vdH-S:	van der Heijde–Sharp
Q2W, Q4W, Q8W:	Every 2nd, 4th or 8th week

3. Summary

Guselkumab (Tremfya®) is an innovative treatment approved by the European Commission on the 20th of November 2020 for the treatment of adult patients with active psoriatic arthritis. More specifically, Tremfya®, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy.
This application presents the basis for the evaluation of the clinically added value of guselkumab for treatment naive patients with PsA without or with moderate to severe plaque psoriasis compared to adalimumab and treatment experienced patients with PsA without or with moderate to severe plaque psoriasis compared to ixekizumab.
The efficacy measures which the evaluation is based on is ACR50 response, proportion of patients without progression cf. mTSS, serious adverse events, qualitative safety review, PASI90 response and change from baseline in SF-36 PCS, SF-36 MCS, SF-36 the physical functioning subdomain and SF-36 the bodily pain subdomain.

Guselkumab has not been directly compared to either adalimumab or ixekizumab in any published randomized trials. Consequently, an indirect comparison between guselkumab and adalimumab as well as guselkumab and ixekizumab has been performed utilizing Bucher's methodology. The efficacy and safety of guselkumab in the treatment of patients with PsA was demonstrated in the phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies DISCOVER-1 and DISCOVER-2.

Summary of results on the critical efficacy endpoint ACR50 response:

- Results from DISCOVER-2 showed that achievement of an ACR50 response among patients without previous TNFα inhibitor use was significantly greater in the guselkumab Q8W group (31.5%) than in the placebo group (14.2%) at week 24; $P < 0.001$.
- Results from DISCOVER-1 showed that a significantly greater proportion of patients without previous TNFα inhibitor use in the guselkumab Q8W group (31%) achieved an ACR50 response, compared with the placebo group (10%); $P < 0.0007$.
- Results from DISCOVER-1 showed that a significantly greater proportion of patients with previous TNFα inhibitor use in the guselkumab Q8W group (27%) achieved an ACR50 response, compared with patients in the placebo group (5%); $P = 0.0078$.

The safety profile demonstrated in the DISCOVER-1 and DISCOVER-2 trials indicates that Tremfya® for PsA is safe and well-tolerated as the studies found no significant safety issues when comparing Tremfya® to placebo through week 24. Furthermore, Tremfya®- and placebo-treated patients were numerically comparable for the frequency of adverse events, serious adverse events, infections, serious infections, and discontinuations due to adverse events at week 24 of the DISCOVER trials. Consequently, the safety profile demonstrated in PsA is consistent with the safety profile observed in Tremfya® PsO Phase 3 long-term trials.
Results for the indirect comparisons for both the treatment-naïve and treatment-experienced patients showed that guselkumab has comparable efficacy to adalimumab and ixekizumab on joint symptom control, with a great and durable resolution of psoriasis and favorable safety profile. Conclusively, the evaluation of clinically added value presented in this application shows that guselkumab has comparable efficacy to adalimumab and ixekizumab for treatment of both adult treatment naive and treatment experienced patients with PsA without or with moderate to severe plaque psoriasis. The recommendation of Tremfya® will therefore provide PsA patients in Denmark with the possibility to get a new innovative treatment with a different mode of action than currently recommended treatments for PsA.

4. Literature search

Databases and search strategy

A systematic literature search was conducted the 8th of February 2021 according to the search strings and criteria which the secretariat has prepared to be used in MEDLINE (via PubMed) and CENTRAL (via Cochrane Library) as specified in the Medicines Council protocol for evaluation of guselkumab for the treatment of psoriatic arthritis (PsA).(2)

This was done to extract data answering the clinical questions:

1. What is the value of guselkumab compared with adalimumab for treatment naïve patients with PsA without moderate to severe plaque psoriasis?
2. What is the value of guselkumab compared with ixekizumab for treatment experienced patients with PsA without moderate to severe plaque psoriasis?
3. What is the value of guselkumab compared with adalimumab for treatment naive patients with PsA with moderate to severe plaque psoriasis?
4. What is the value of guselkumab compared with ixekizumab for treatment experienced patients with PsA with moderate to severe plaque psoriasis?

The selection of relevant studies was based on the inclusion and exclusion criteria specified by the Medicines Council in the protocol and criteria specified in table A1 in the appendix. Consequently, the included studies had to be phase 3 RCT with a placebo-controlled period of at least 24 weeks and include the relevant populations i.e. treatment-naïve and treatment experienced PsA patients without or with moderate to severe plaque psoriasis (PsO). In addition, the studies had to evaluate guselkumab, adalimumab or ixekizumab and include minimum one of the relevant efficacy endpoints specified in the protocol.
The literature search identified in 197 potentially relevant publications through the search databases PubMed and CENTRAL (via Cochrane library) according to the search strings specified in the protocol. After removing 10 duplicates, the literature search resulted in 187 unique citation. Amongst these, a total of 87 citations were excluded during a title- and abstract-screening because they did not meet the pre-specified inclusion criteria. Among the set of 100 remaining citations, a total of 90 were furthermore excluded at a full text screening phase, leaving 10 citations included addressing the clinical questions for relevant patient populations. The PRISMA flow diagram for the selection of these studies is presented in figure A1 in the appendix. Furthermore, the conducted search strings are available in figure A2 and A3 in the appendix whereas a list of excluded articles including reasons for exclusion are attached to this submission as a separate file.
However, one citation was added to the 10 citations as it was not identified but still relevant for the clinical questions, see table 1 for the relevant studies.
The study added is by Ritchlin CT., et al. 2021 and it investigated the 1-year results of the DISCOVER-1 phase 3 study of patients who were biologic-naïve or tumor necrosis factor (TNF)α inhibitor-experienced.

Furthermore, a poster was included to conduct a scenario analysis on the proportion of patients achieving Psoriasis Area Severity Index (PASI)90 response in the guselkumab Q8W group vs. the adalimumab Q2W group. The poster used presented post-hoc analyses of patients with self-reported PsA in the pivotal VOYAGE-1 and VOYAGE-2 trials of guselkumab conducted in patients with moderate-to-severe plaque PsO including 335 patients (18%) who self-reported having PsA.

4.1 Relevant studies

Table 1 Relevant studies included in the assessment.

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
Deodhar A, Helliwell PS, Boehncke WH, Kollmeier AP, Hsia EC, Subramanian RA, et al. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet (London, England). 2020;395(10230):1115-25.(3)	Discover 1	NCT03162796	August 2017 to March 2019. Study completed results presented	1, 2, 3, 4
Ritchlin CT, Helliwell PS, Boehncke WH, Soriano ER, Hsia EC, Kollmeier AP, et al. Guselkumab, an inhibitor of the IL-23p19 subunit, provides sustained improvement in signs and symptoms of active psoriatic arthritis: 1 year results of a phase III randomised study of patients who were biologic-naïve or TNFα inhibitor-experienced. RMD open. 2021;7(1).(4)				
Mease PJ, Rahman P, Gottlieb AB, Kollmeier AP, Hsia EC, Xu XL, et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2020;395(10230):1126-36.(5)	DISCOVER 2	NCT03158285	May 2017 to Nov 2020. Study completed results presented	1 + 3
McInnes IB, Rahman P, Gottlieb AB, Hsia EC, Kollmeier AP, Chakravarty SD, et al. Efficacy and Safety of Guselkumab, an Interleukin-23p19-Specific Monoclonal Antibody, Through 1 Year in Biologic-naïve Psoriatic Arthritis Patients. Arthritis & rheumatology (Hoboken, NJ). 2020.(6)				

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. Arthritis & Rheumatism. 2005;52(10):3279-89.(7)	ADEPT	NCT00195689	September 2005 to August 2007	1
Mease PJ, Ory P, Sharp JT, Ritchlin CT, Van den Bosch F, Wellborne F, et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). Annals of the rheumatic diseases. 2009;68(5):702-9.(8)				
Mease PJ, Van Der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: Results from the 24-week randomised, double-blind, placebocontrolled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Annals of the Rheumatic Diseases. 2017;76(1):79-87.(9)	SPIRIT P1	NCT01695239	Sep 2012 to Jan 2019. Completed has results	
Gottlieb AB, Strand V, Kishimoto M, Mease P, Thaçi D, Birt J, et al. Ixekizumab improves patient-reported outcomes up to 52 weeks in bDMARD-naïve patients with active psoriatic arthritis (SPIRIT-P1). Rheumatology (Oxford, England). 2018;57(10):1777-88.(10)				

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
Nash P, Kirkham B, Okada M, Rahman P, Combe B, Burmester GR, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet. 2017;389(10086):2317-27.(11)	Spirit P2	NCT02349295	March 2015 – July 2020 Completed has results	2 and 4
Orbai AM, Gratacós J, Turkiewicz A, Hall S, Dokoupilova E, Combe B, et al. Efficacy and Safety of Ixekizumab in Patients with Psoriatic Arthritis and Inadequate Response to TNF Inhibitors: 3-Year Follow-Up (SPIRIT-P2). Rheumatology and therapy. 2020.(12)				
Kavanaugh A, Marzo-Ortega H, Vender R, Wei CC, Birt J, Adams DH, et al. Ixekizumab improves patient-reported outcomes in patients with active psoriatic arthritis and inadequate response to tumour necrosis factor inhibitors: SPIRIT-P2 results to 52 weeks. Clinical and experimental rheumatology. 2019;37(4):566-74.(13)				

*when multiple clinical questions are defined in the protocol

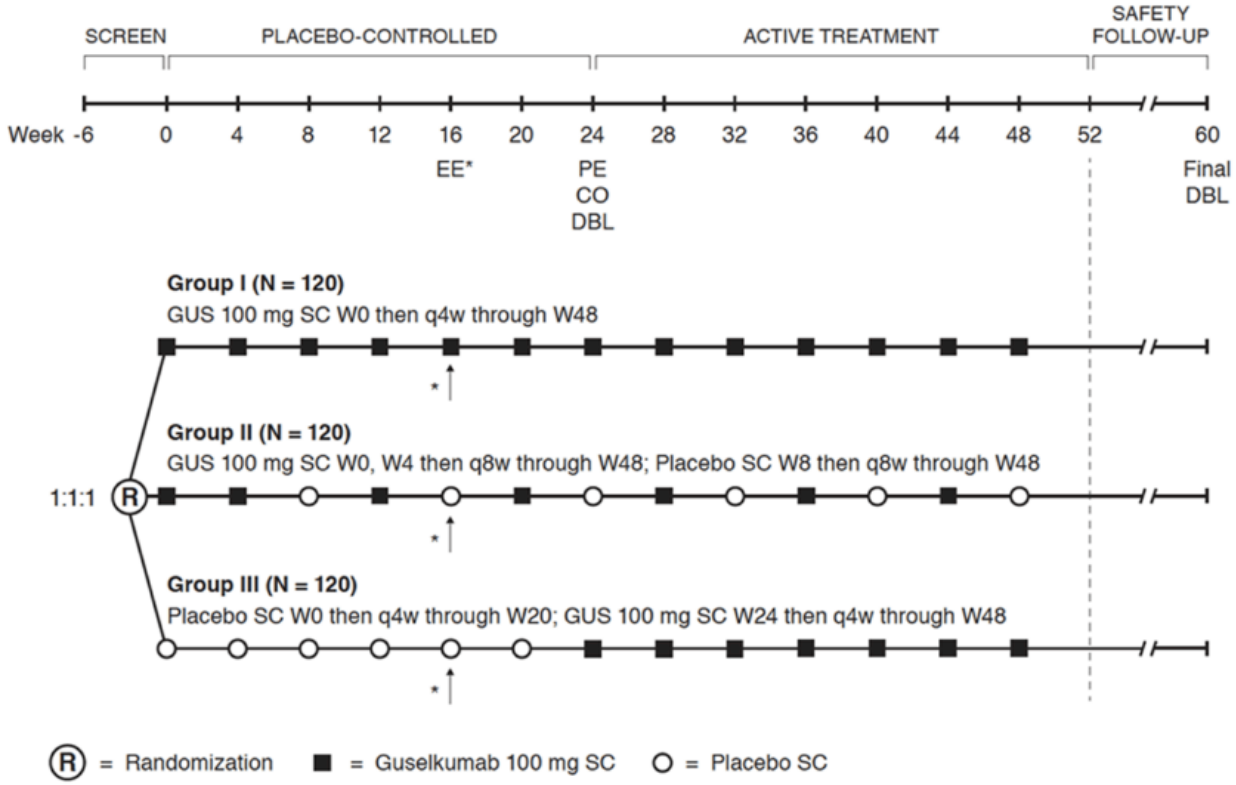
4.2 Main characteristics of included studies

4.2.1 DISCOVER-1

The TREMFYA® (guselkumab) clinical development program for active psoriatic arthritis (PsA) is comprised of two Phase 3, randomized, double-blind, placebo-controlled trials, DISCOVER-1 and DISCOVER-2. Both of these pivotal trials showed that guselkumab was associated with significantly greater efficacy than placebo for PsA rheumatologic domains (ie, joint inflammation, impaired physical function, enthesitis, and dactylitis) and dermatologic domains (ie, plaque PsO).(3, 5) A description of DISCOVER-1 is available in this section whereas a description of DISCOVER-2 is found in the subsequent section.

DISCOVER-1 was a multicenter, Phase 3, randomized, double-blind, placebo-controlled study of biologic-naïve and biologic-experienced adult patients with active PsA. Eligible patients met the Classification criteria for Psoriatic Arthritis (CASPAR) and had active disease, defined as follows: ≥3 swollen joints, ≥3 tender joints, and a C-reactive protein (CRP) level ≥0.3 mg/dL. In addition, patients had ≥1 PsA subtype and current or prior documented plaque PsO (either skin or nail PsO). As per pre-specified eligibility criteria, approximately 70% of patients were to be biologic-naïve, with prior inadequate response or intolerance to conventional disease-modifying antirheumatic drugs (DMARDs; including apremilast) and/or nonsteroidal anti-inflammatory drugs (NSAIDs). The remaining approximately 30% of patients were to have had prior failure on ≤2 anti-TNF-α therapies (ie, lack of benefit, intolerance, or other documented reason for discontinuation). Patients were randomized to one of three parallel treatment arms in a 1:1:1 ratio: guselkumab 100 mg every 4 weeks (ie, Q4W), guselkumab 100 mg at Weeks 0, 4, and then every 8 weeks (Q8W), or placebo Q4W (figure 1). From Week 0 onwards, patients in each treatment group could receive optional concomitant therapy with stable doses of NSAIDs (at approved standard doses), oral corticosteroids (equivalent to ≤10 mg/day of prednisone), and/or a select non-biologic DMARD (methotrexate ≤25 mg/week, sulfasalazine [SSZ] ≤3 g/day, hydroxychloroquine [HCQ] ≤400 mg/day, or leflunomide [LEF] ≤20 mg/day). At Week 24, patients in the placebo group crossed over to the guselkumab Q4W treatment group. Efficacy was evaluated up to 52 weeks of follow-up, whereas safety follow-up extended to 60 weeks.(3, 14)

Figure 1: DISCOVER-1 study design (15)



* Early escape of patients with <5% improvement in tender and swollen joint counts from baseline at Week 16. Note: patients in the guselkumab Q8W group received placebo injections to match the injection frequency of the guselkumab Q4W and placebo groups (ie, at Weeks 8, 16, 24, 32, and 40). KEY: CO = placebo crossover; DBL = database lock; EE = early escape; GUS = guselkumab; PBO = placebo; PE = primary endpoint; q4w = every four weeks; q8w = every eight weeks; R = randomization; SC = subcutaneous; Wk = week.

Patient Selection

To be eligible for DISCOVER-1, patients had to have ≥1 of the following PsA subsets: distal interphalangeal (DIP) joint involvement, polyarticular arthritis with absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis. In addition, patients must have had active plaque PsO with at least 1 psoriatic plaque of ≥2 cm in diameter or nail changes consistent with PsO or documented history of plaque PsO.(3, 14)

Patients were permitted to continue stable doses of non-biologic DMARDs (limited to MTX [≤25 mg/week], SSZ [≤3 g/day], HCQ [≤400 mg/day], or LEF [≤20 mg/day]), low-dose oral corticosteroid (≤10 mg of prednisone per day or equivalent), or NSAIDs and other analgesics treatment during the study. If patients were not using these medications at baseline, these medications must have been stopped ≥4 weeks (for MTX, SSZ, or HCQ), ≥12 weeks (LEF), or ≥2 weeks (for NSAIDs and other analgesics or oral corticosteroid) prior to the first administration of study agent. In addition, patients had to meet criteria for screening laboratory test results and tuberculosis (TB) history and testing results, agree to use adequate birth control measures, avoid prolonged sun exposure, and avoid the use of tanning booths or other ultraviolet light sources during the study.(3, 14)

Patients were not eligible if they had other inflammatory diseases that might confound the evaluations of benefit of guselkumab therapy including but not limited to rheumatoid arthritis (RA), axial spondyloarthritis, system lupus erythematosus, or Lyme disease, or had a form of nonplaque or current drug-induced PsO.(3, 14)

Patients must not have received >2 anti-TNFα agents, biologic treatments other than anti-TNF-α agents (including, but not limited to, guselkumab, ustekinumab, abatacept, secukinumab, tildrakizumab, ixekizumab, brodalumab, risankizumab), or other investigative biologic treatment. Patients who had received the anti-TNF-α agents infliximab or golimumab intravenous (IV) for <8 weeks; golimumab subcutaneous (SC), adalimumab, or certolizumab pegol for <6 weeks; or etanercept for <4 weeks prior to the first study agent administration were not eligible. Patients with prior exposure to Janus kinase (JAK) inhibitors were not eligible. Patients must not have concomitantly used ≥2 permitted DMARDs (MTX, SSZ, HCQ, and LEF) at baseline. Non-biologic DMARDs other than MTX, SSZ, HCQ, and LEF, systemic immunosuppressants, and apremilast were prohibited within 4 weeks before the first study agent administration. Epidural, intra-articular, intramuscular, or IV corticosteroids and lithium were prohibited within 4 weeks prior to the first administration of study agent. Phototherapy and any systemic medications that could affect PsO evaluations were also not allowed within 4 weeks, and topical PsO agents must have been stopped ≥2 weeks before the first study agent administration. Other exclusion criteria related to the mental health of the patients, history or risk of serious infections as well as malignancy or unstable cardiovascular diseases were further applied.(3, 14)

Baseline Patient Characteristics

A total of 381 patients were randomized to the placebo (n = 126), guselkumab Q8W (n = 127), and guselkumab Q4W (n = 128) treatment arms. Baseline demographics and PsA characteristics were generally comparable between treatment arms (see Table A2a in the appendix).(3)

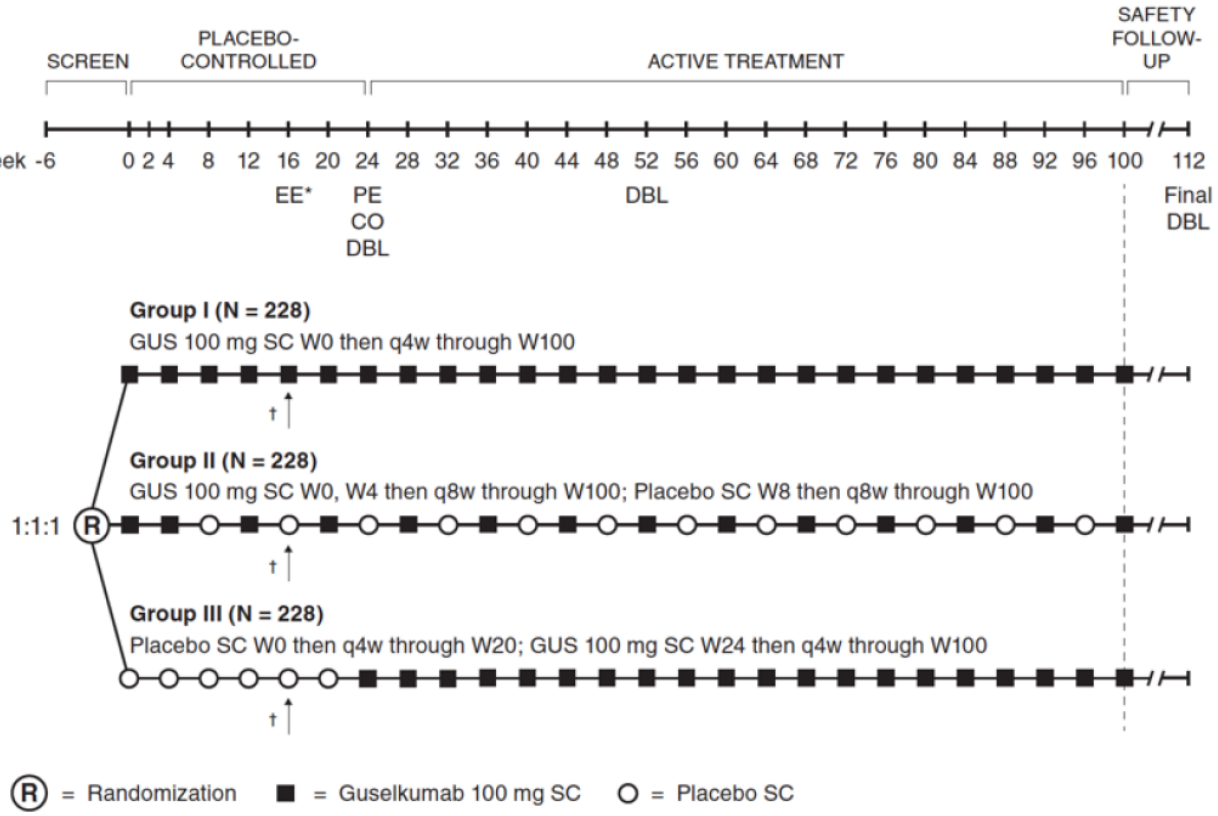
Efficacy Endpoints

The primary efficacy endpoint (*a priori*) of DISCOVER-1 was the proportion of patients who achieved an American College of Rheumatology (ACR)20 response (ie, a ≥20% improvement in ACR score from baseline) at Week 24 of treatment. An overview of the primary and major secondary endpoints and their pre-specified statistical testing procedures is presented in (see Table A2a in the appendix).(3, 14)

4.2.2 DISCOVER-2

DISCOVER-2 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 3-arm study of guselkumab in subjects with active PsA who were biologic naïve and had inadequate response to standard therapies (eg, non-biologic DMARDs, apremilast, or NSAIDs). No previous treatment with TNF agents was permitted. The study consisted of a screening phase of up to 6 weeks, a blinded treatment phase of approximately 2 years (ie, 100 weeks), including a placebo-controlled phase from week 0 to week 24 and an active treatment period from week 24 to week 100, and a safety follow-up phase of 12 weeks after the last administration of study agent, figure 2.
Patients who satisfied all inclusion and exclusion criteria were to be randomly assigned to one of the following three treatment groups, guselkumab 100 mg every 4 weeks (ie, Q4W), guselkumab 100 mg at Weeks 0, 4, and then every 8 weeks (Q8W), or placebo Q4W in a 1:1:1 ratio using permuted block randomization stratified by baseline non-biologic DMARD use (ie, yes or no) and the most recent available CRP level prior to randomization (ie, <2.0 mg/dL or ≥2.0 mg/dL).(5, 16)

Figure 2: DISCOVER-2 study design (15)



* Early escape of patients with <5% improvement in tender and swollen joint counts from baseline at Week 16.
Note: patients in the guselkumab Q8W group received placebo injections to match the injection frequency of the guselkumab Q4W and placebo groups.
KEY: DBL = database lock; EE = early escape; GUS = guselkumab; PBO = placebo; Q4W = every four weeks; Q8W = every eight weeks; R = randomization; SC = subcutaneous; Wk = week.

Patient Selection

To be eligible for DISCOVER-2, patients had to be ≥18 years of age at the time of informed consent, diagnosed with PsA for ≥6 months prior to the first administration of study agent, and meet CASPAR criteria at screening. Patients must have had active PsA as defined by ≥5 tender and ≥5 swollen joints at both screening and baseline and CRP ≥0.6 mg/dL at screening. Patients must have had documented evidence of inadequate response or intolerance to standard PsA therapies, including non-biologic DMARDs (for ≥3 months), apremilast (for ≥4 months), and/or NSAIDs (for ≥4 weeks) prior to the first administration of study agent.(5, 16)

Patients also had to have ≥1 of the following PsA subsets: DIP joint involvement, polyarticular arthritis with absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis. In addition, patients must have had active plaque PsOs, with at least one psoriatic plaque of ≥2 cm diameter or nail changes consistent with PsO or documented history of plaque PsO.(5, 16)

Patients were permitted to continue stable doses of non-biologic DMARDs (limited to MTX [≤25 mg/week], SSZ [≤3 g/day], HCQ [≤400 mg/day], or LEF [≤20 mg/day]), low-dose oral corticosteroids (≤10 mg of prednisone per day or equivalent), or NSAIDs and other analgesics treatment during the study.(5, 16)

Patients were not eligible to be enrolled in the study if they had other inflammatory diseases that might confound the evaluations of benefit of guselkumab therapy, including but not limited to RA, axial spondyloarthritis, system lupus erythematosus, or Lyme disease, or had a form of nonplaque or current drug-induced PsO. Patients must not have received any prior biologic treatments for PsA or PsO, including but not limited to guselkumab, ustekinumab, secukinumab, anti-TNF-α biologic therapies (eg, such as adalimumab, etanercept, infliximab, golimumab SC or IV, certolizumab pegol, or their respective biosimilars) or any other therapeutic agent targeted at IL-12, IL-17, or IL-23. Patients with prior exposure to JAK inhibitors were not eligible.(5, 16)

Baseline Patient Characteristics

A total of 739 patients were randomized to the placebo (n = 246), guselkumab Q8W (n = 248), and guselkumab Q4W (n = 248) treatment arms. Baseline demographics and PsA characteristics were generally consistent between groups (see Table A2b in the appendix).(5)

Efficacy Endpoints

As in DISCOVER-1, the primary efficacy endpoint (*a priori*) was the proportion of patients who achieved an ACR20 response at Week 24 of treatment. Global and US-specific prespecified statistical testing procedures were also used to adjust for secondary endpoint multiplicity if statistical significance was achieved in both guselkumab treatment groups. An overview of major secondary endpoints and pre-specified statistical testing procedures is presented in (see Table A2b in the appendix).(5)

4.2.3 ADEPT

ADEPT was a 24-week, randomized, double-blind, parallel-group, placebo-controlled trial of adalimumab therapy conducted to evaluate the efficacy and safety of adalimumab in treatment naïve patients with moderate to severely active psoriatic arthritis. Patients were randomized in a 1:1 ratio to receive SC injections of placebo or 40 mg adalimumab administered every 2 weeks (i.e., Q2W) after being stratified according to MTX use (yes or no) and degree of PsO involvement (≥3% or <3% of body surface area [BSA]) at baseline.
Study visits were performed at baseline, week 2, week 4 and every 4 weeks in the period from week 4 to 24 and patients who completed the 24 weeks study were eligible for open-label extension study. In addition patients failed to have at least a 20% decrease in both swollen and tender joint counts on 2 consecutive visits aster 12 weeks could receive rescue therapy with corticosteroids or DMARDs.(7)

Patient Selection

To be eligible for ADEPT, patients had to be ≥18 years of age, meet the criteria of moderately to severely active PsA, defined as having ≥3 swollen joints and ≥3 tender or painful joints, and had active psoriatic skin lesions or a documented history of PsO. Furthermore, the patients were required to have a history of an inadequate response or intolerance to nonsteroidal anti-inflammatory drug therapy for PsA. (7)

Baseline Patient Characteristics

A total of 315 patients were randomized to the placebo (n=162) and adalimumab Q2W (n=153) treatment arms. However, two patients randomized to receive adalimumab Q2W did not receive study medication and were therefore excluded from all analyses. The baseline demographics and disease characteristics at baseline were comparable between treatment groups (see Table A2c in the appendix). (7)

Efficacy Endpoints

In ADEPT the primary efficacy endpoints was the proportion of patients who achieved an ACR20 response at Week 12 and change in modified total sharp score of structural damage on radiographs of the hands and feet at week 24. An overview of major secondary endpoints is presented in Table A2c in the appendix. (7)

4.2.4 SPIRIT-P1

SPIRIT-P1 was a phase 3, multicenter, randomized, double-blind, active and placebo-controlled 24-week study followed by long term evaluation of efficacy and safety of ixekizumab in biologic disease-modifying antirheumatic drug-naive patients with active psoriatic arthritis. Patients were randomized with stratification by country and prior/current/no use of non-biologic cDMARDs in a 1:1:1:1 ratio to receive one of four subcutaneous treatments i.e. ixekizumab 80 mg IXEQ2W, ixekizumab 80 mg IXEQ4W, adalimumab 40 mg Q2W, or placebo. Patients with an inadequate response at week 16 irrespectively of treatment group received rescue medication i.e. addition or modification to concomitant medications and remained on their originally assigned dose of ixekizumab or, if receiving adalimumab or placebo, were re-randomized to IXEQ2W or IXEQ4W in a 1:1 ratio.(9, 17)

Patient Selection

To be eligible for SPIRIT-P1, patients had to be ≥18 years of age, having ≥3 tender joints and ≥3 swollen joints; either ≥1 PsA-related hand or foot joint erosion or C-reactive protein >6 mg/L; and current evidence or history of PsO. Furthermore, the patients were biologic naïve i.e. patients were excluded if they had a history of previous anti-TNF therapy.(9, 17)

Baseline Patient Characteristics

A total of 719 were screen of which 417 patients were randomized. The 417 patients were randomized to receive placebo (n=106), adalimumab Q2W (n=101) ixekizumab Q4W (n=107) and ixekizumab Q2W (n=103) treatment arms. Generally, the baseline demographics, disease characteristics and medication usage were comparable between treatment groups (see Table A2d in the appendix).(9, 17)

Efficacy Endpoints

In SPIRIT-P1 the primary efficacy endpoints was the proportion of patients who achieved an ACR20 response at Week 25 and secondary efficacy measures included e.g. ACR50 and PASI90 response. However, an overview of major secondary endpoints is presented in Table A2d in the appendix.(9, 17)

4.2.5 SPIRIT-P2

SPIRIT-P2 was a Phase 3, multicenter, randomized, double-blind, active and placebo-controlled study conducted to evaluate the efficacy and safety of ixekizumab, a monoclonal antibody that inhibits interleukin-17A, in patients with active PsA and an inadequate response to anti-TNF therapy. Patients were randomized in a 1:1:1 ratio to receive SC injections of placebo, 80 mg ixekizumab administered Q2W or 80mg ixekizumab administered Q4W. The starting dose for patients receiving ixekizumab were administered a starting dose of 160 mg as two SC injections at week 0. The study consisted of a 24 weeks double blinded treatment period. Patients with an inadequate response at week 16 were irrespectively of treatment group required to add or modify concomitant drugs. Patients initially randomized to the placebo which demonstrated an inadequate response at week 16 were re-randomized to ixe 80 mg Q2W/Q4W for the remainder of the double blinded treatment period and following period. Patients initially randomized to the ixekizumab treatment arms which demonstrated inadequate response at week 16 continued taking their originally assigned dose of ixekizumab but also received rescue treatment.(11, 18)

Patient Selection

Patients eligible for SPIRIT-P2, were ≥18 years of age, fulfilled the CASPAR criteria, had ≥3 swollen joints and ≥3 tender joints and were previously treated with TNF inhibitors and had an inadequate response to one or two TNF inhibitors or were intolerant to TNF inhibitors. Furthermore, the patients must have had a documented history of cDMARDs and must have had active plaque PsO or a documented history of plaque psoriasis.(11, 18)

Baseline Patient Characteristics

A total of 363 patients were randomized to receive placebo (n=118), ixekizumab Q4W (n=122) and ixekizumab Q2W (n=123) treatment arms. Of the 363 patients, 204 (56%) had Inadequate response to one TNFi, 128 (35%) had Inadequate response to two TNFi and 31 (9%) had intolerance to a TNFi. Furthermore, the baseline demographics and disease characteristics were comparable between the treatment groups with the exception for imbalances in concomitant methotrexate use and swollen joint counts at baseline (see Table A2e in the appendix).(11, 18)

Efficacy Endpoints

In SPIRIT-P2 the primary efficacy endpoints was the proportion of patients who achieved an ACR20 response at week 24 versus placebo. The major secondary consisted e.g. proportion of patients who achieved an ACR50 response and PASI-90, however a full overview is presented in Table A2e in the appendix.(11, 18)

5. Clinical questions

5.1 What is the value of guselkumab compared with adalimumab for treatment naive patients with PsA without moderate to severe plaque psoriasis?

5.1.1 Presentation of relevant studies

The studies used in the assessment of the added clinical value of guselkumab for treatment naive patients compared to adalimumab consist of DISCOVER-1 and DISCOVER-2, as well as ADEPT and SPIRIT-P1 for guselkumab and adalimumab, respectively.(3, 5, 7, 9) Furthermore, the EMA European Public Assessment Report (EPAR) of Guselkumab® will be consulted.(15)

Overall, DISCOVER-1 and DISCOVER-2 evaluating guselkumab, and ADEPT as well as SPIRIT-P1 evaluating adalimumab as therapy for patients with PsA without moderately to severe plaque PsO have certain important characteristics in common.

The studies were published between 2004 and 2018. Baseline characteristics across studies are summarized in table 2. Mean age across the studies ranged from 45.7 to 49.1 years. The percentage of males ranged from 46.0% to 55.6% across studies. The duration of PsA ranged from 5.5 years to 9.5 years. The percentage of Caucasian patients ranged from 91.6% to 98.0% across RCTs. Across studies, the mean number of swollen and tender joints at baseline ranged from 9.9 to 14.3 and 19.2 to 24.9, respectively. Baseline PASI score ranged from 6.1 to 9.9.(3, 5, 7, 9)

Table 2: Summary of Baseline Characteristics from Randomized Controlled Trials

Author, Publication Date	Trial Name	Primary Timepoint (weeks)	Treatment[a]				Sample Size (N)	Mean Age (years)	Male (%)	Race (% Caucasian)	Body Weight (kg)	Duration of PsA (years)	Prior Biologic Use (%)	No. of swollen joints (mean)	No. of tender joints (mean)	BL PASI Score (mean)	PsO BSA >3% (%)	BL HAQ-DI score
			1	2	3	4												
Mease 2005(7)	ADEPT	12	PBO	ADA 40 mg	NA	NA	313	48.9	55.6	95.5	85.7	9.5	0.0	14.3	24.9	7.9	NR	1.0
Mease 2017(9)	SPIRIT-P1	24	PBO	IXE 80 Q2W	IXE 80 Q4W	ADA 40 mg	417	49.5	46.0	94.0	85.6	6.7	0.0	11.0	20.1	6.1	69.5	1.2
Deodhar 2020 (3)	DISCOVER-1	24	PBO	GUS 100 mg Q8W	GUS 100 mg Q4W	NA	381	48.4	51.2	91.6	86.0	6.8	31.0	9.9	19.2	8.5	65.4	1.2
Mease 2020 (5)	DISCOVER-2	24	PBO	GUS 100 mg Q8W	GUS 100 mg Q4W	NA	739	45.7	52.5	98.0	84.3	5.5	0.0	12.3	21.3	9.9	73.5	1.3

KEY: ADA = adalimumab; BL = baseline; BSA = body surface area; GUS = guselkumab; HAQ-DI = Health Assessment Questionnaire Disability Index; NA = not available; N = number; PASI = Psoriasis Area and Severity Index; PBO = placebo; PsA = psoriatic arthritis; PsO = psoriasis; Q2W = every two weeks; Q4W = every four weeks; Q8W = every eight weeks

However, small difference between the studies were found. The two studies i.e. ADEPT and SPIRIT-P1 for adalimumab and DISCOVER-2 for guselkumab were only conducted in biologic-naïve patients, whereas the DISCOVER-1 study of guselkumab were conducted in a mixed population consisting 31% biologic-experienced patients and 69% treatment naive patients. Furthermore, the studies differed as patients in ADEPT as well as DISCOVER-1 and DISCOVER-2 were

required to have had an inadequate response to previous non-biologic DMARD therapy whereas 85%.3 of patients in SPIRIT-P1 were cDMARD experienced.
For the SF-36 PCS, SF-36 MCS outcomes

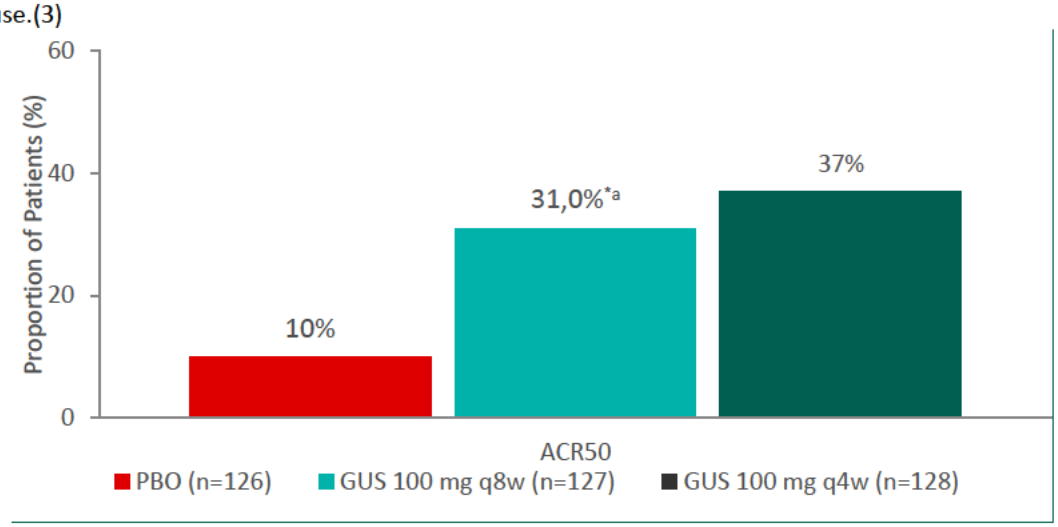
5.1.2 Results per study

5.1.2.1 DISCOVER-1

Guselkumab efficacy results from DISCOVER-1 for treatment naive patients with PsA without moderate to severe plaque PsO defined in the Medicines Council protocol is presented in the following section. Overview of the results is available in table A3a in the appendix. Some of the endpoints defined in the Medicines Council protocol are not published and therefore not presented. Serious adverse reactions which is an endpoint requested in the Medicines Councils protocol for this evaluation is not available neither in the published study, the EPAR or on clinicaltrials.gov. Thus, SAE are presented instead to give the Medicines Council a relevant safety endpoint to evaluate.
Furthermore, safety data besides unpublished SAE results are not stratified on treatment naive and treatment experienced patients and the safety results are therefore presented for total patient population.

Proportion of patients experiencing response to ACR50
At Week 24, a significantly greater proportion of patients among the 86 patients without previous TNF inhibitor use in the guselkumab Q8W group achieved an ACR50 response, compared with patients without previous TNF inhibitor use in the placebo group, 31% (27 of 86) vs. 10% (9 of 87) , respectively; $P < 0.0007$), see figure 3. Similarly, achievement of an ACR50 response was significantly greater in the guselkumab Q4W group 37% (33 of 90) than in the placebo group (37% vs. 10%; $P < 0.0001$).(3)

Figure 3: Proportion of patients with an ACR50 or at Week 24 in DISCOVER-1 amongst patients without previous TNF inhibitor use.(3)



*[a] Unadjusted $P < 0.0007$ vs. PBO
KEY: ACR = American College of Rheumatology; GUS = guselkumab; PBO = placebo; Q8W = every eight weeks.

Achievement of ACR50 response continued to improve between Weeks 24 and 52 in patients without previous TNF inhibitor use. Based on non-responder imputation (NRI) analyses both the guselkumab Q8W and Q4W groups increased over time to 38.4% and 56.7%, respectively. ACR50 response rates also increased after Week 24 in the placebo → guselkumab Q4W group, reaching 33.3% at Week 52.(4)

Proportion of patients without progression, cf. Modified Total Sharp Score (mTSS)

Unfortunately results on the proportion of patients without progression are not available from the DISCOVER-1 study neither for the treatment naive or full patient population.

In this submission, it is stated that data is not available for the proportion of patients without progressions, cf. mTSS on several pages i.e., page 21, 28, 41, 46 and 49.
The data is not available for guselkumab as mTSS was not included as a secondary endpoint in the DISCOVER-1 study. Thus, the outcome has not been analyzed and is therefore not available for bio-experienced population or the full population in DISCOVER-1. The reason regarding data not being available for Ixekizumab in SPIRIT-2 is that we have not been able to identify it in the study article. Furthermore. as for the DISCOVER-1 study, mTSS was not included as a secondary endpoint in the SPIRIT-2 study. Regarding the data being missing for adalimumab in the ADEPT study, the reason is that we have not been able to identify it in the study article. However, mTSS data for adalimumab is available in the SPIRIT-1 study, thus this is being used in the submission.

Proportion of patients who experience serious adverse events

Unfortunately results on the proportion of patients who experienced Serious Adverse Event (SAE) is not publicly availble seperately for the treatment naive patients and treatment experienced population. However, data on file results show that serious AEs were uncommon as the proportions of treatment naive patients who experienced ≥1 or more SAEs through Week 24 were [redacted] in the guselkumab Q8W group and [redacted] in the placebo group.(19) In addition, all SAEs were singular in occurrence.

Qualitative review of safety profile

A qualitative review of the safety profile based on DISCOVER-1 is available in clinical question 2.

Mean change from baseline on Short Form 36 (SF-36), the physical function subdomain

Unfortunately results on the mean change from baseline of SF-36, the physical function subdomain are not available seperately for the treatment naive patients and treatment experienced population. Data for the full patient population consisting of both treatment naive and treatment experienced patients is available, however the results for full patient population will be presented in clinical question two and used to reflect the efficacy in treatment experienced patients.(3) As DISCOVER-2 has efficacy data entirely on treatment naive patients and therefore deemed more relevant for clinical question 1.

Mean change from baseline on SF-36, the bodily pain subdomain

Unfortunately results on the mean change from baseline of SF-36, the bodily pain subdomain are not available seperately for the treatment naive patients and treatment experienced population. Data for the full patient population consisting of both treatment naive and treatment experienced patients is available, however the results for full patient population will be presented in clinical question two and used to reflect the efficacy in treatment experienced patients.(3) As DISCOVER-2 has efficacy data entirely on treatment naive patients and therefore deemed more relevant for clinical question 1.

Mean change from baseline on SF-36, the physical component summary

Unfortunately results on the mean change from baseline of SF-36, the physical component summary, are not available seperately for the treatment naive patients and treatment experienced population. Data for the full patient population consisting of both treatment naive and treatment experienced patients is available, however the results for the full patient population will be presented in clinical question two and used to reflect the efficacy in treatment

experienced patients.(3) As DISCOVER-2 has efficacy results on SF-36 Physical Component Summary (PCS) entirely on treatment naive patients the study is deemed more relevant for clinical question 1.

Average change from baseline on SF-36, the mental component summary

Unfortunately results on the mean change from baseline of SF-36, the physical component summary, are not available seperately for the treatment naive patients and treatment experienced population. Data for the full patient population consisting of both treatment naive and treatment experienced patients is available, however the results for the full patient population will be presented in clinical question two and used to reflect the efficacy in treatment experienced patients.(3) As DISCOVER-2 has efficacy results on SF-36 Mental Component Summary (MCS) entirely for treatment naive patients the study is deemed more relevant for clinical question 1.

Proportion of patients experiencing PASI90 response

Not relevant for clinical question 1.

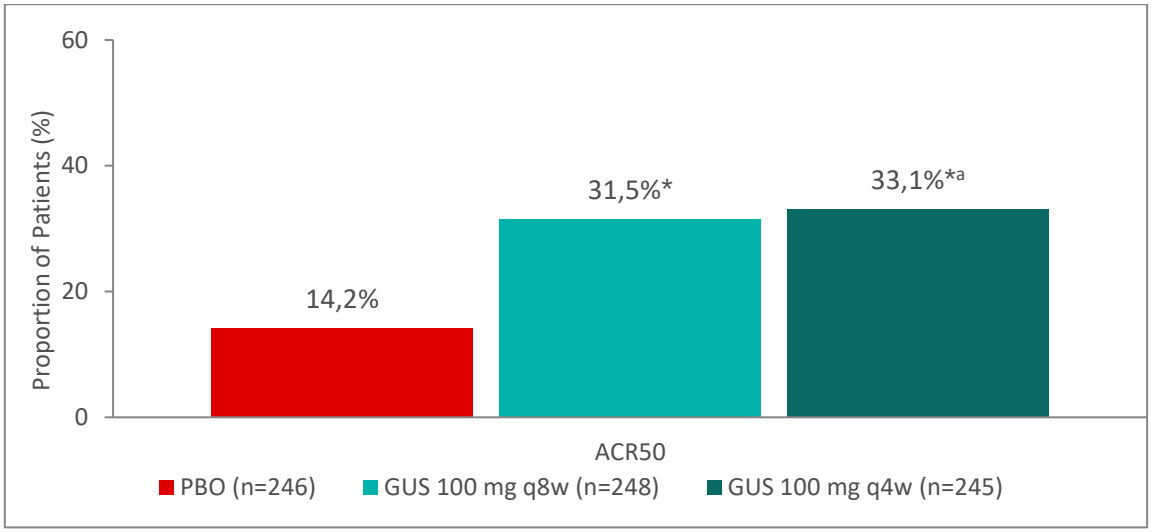
5.1.2.2 DISCOVER-2

Guselkumab efficacy results from DISCOVER-2 for treatment naive patients with PsA without moderate to severe plaque PsO defined in the Medicine Council protocol is presented in the following section. Serious adverse reactions which is an endpoint requested in the Medicines Councils protocol for this evaluation is not available neither in the published study, the EPAR or on clinicaltrials.gov. Thus, SAE are presented instead to give the Medicines Council a relevant safety endpoint to evaluate. Overview of the results is available in table A3c in the appendix.

Proportion of patients experiencing response to ACR50

At Week 24, achievement of an ACR50 response was significantly greater in the guselkumab Q8W group 31.5% (78 of 248) than in the placebo group 14.2% (35 of246) (unadjusted $P < 0.001$ vs. placebo), see figure 4. Similarly, achievement of an ACR50 response was significantly greater in the guselkumab Q4W group 33.1% (81 of 245) than in the placebo group as per the global statistical analysis plan (33.1% vs. 14.2%; $P < 0.001$).(5)

Figure 4: Proportion of patients with an ACR50 response at Week 24 in DISCOVER-2.(5)



*[a] $P < 0.001$ vs. placebo and statistical significance was achieved as per the global statistical testing plan. As per the US statistical testing plan, ACR50; unadjusted *P*-value was < 0.001 for GUS q8w vs. PBO.
KEY: ACR = American College of Rheumatology; GUS = guselkumab; PBO = placebo; q4w = every four weeks; q8w = every eight weeks; US = United States. Source: DISCOVER-2

Achievement of ACR50 response continued to improve between Weeks 24 and 52. Based on NRI analyses both the guselkumab Q8W and Q4W groups, increasing to 48.4% and 45.7%, respectively. ACR50 response rates also increased after Week 24 in the placebo → guselkumab Q4W group, reaching 41.1% at Week 52. Furthermore, based on observed cases ACR50 response continued to improve between Weeks 24 and 52 in both the guselkumab Q8W and Q4W groups, increasing to 51.3% and 49.1%, respectively. ACR50 response rates also increased after Week 24 in the placebo → guselkumab Q4W group, reaching 43.7% at Week 52.(6)

Proportion of patients without progression, cf. mTSS

The proportion og patient without porgression is reflected by the percentage of patients with a change of ≤0 from baseline in modified van der Heijde–Sharp (vdH-S) score at week 24. The percentage were 63.5% in the guselkumab Q8W group, 67.3% in the guselkumab Q4W group and 64.7% in the placebo group. In addition, when looking at the percentage of patients with a change of ≤0.5 from baseline in modified vdH-S score at week 24 were 74.4% in the guselkumab Q8W group, 78.0% in the guselkumab Q4W group and 72.1% in the placebo group.(16)

Proportion of patients who experience serious adverse events

The proportions of patients who experienced ≥1 or more SAEs through Week 24 were 1.2% (3 of 248) in the guselkumab Q8W group, 3.3% (8 of 245) in the guselkumab Q4W group and 2.8% (7 of 246) in the placebo group. All events were singular in occurrence and no specific pattern of SAEs was identified. In the guselkumab q8w group one patient each had a SAE with ankle fracture, coronary artery disease, and pyrexia, whereas one patient each in the placebo group had cell renal cell carcinoma, isoniazidinduced liver injury, inflammatory bowel disease (suspected), obesity, post-procedural fistula, tubulointerstitial nephritis, and unstable angina.(5, 16)

Qualitative review of safety profile

The proportions of patients experiencing ≥1 AEs through Week 24 were slightly higher in the guselkumab groups compared with the placebo group: 46.0% in the guselkumab Q8W group, 46.1% in the guselkumab mg Q4W group, and 40.7% in the placebo group (table 3).(5)

Infections and infestations were comparable across treatment groups: 20% in the guselkumab Q4W group, 16% in the guselkumab Q8W group, and 18% in the placebo group. The most common AEs reported were alanine aminotransferase (ALT) increased (10.2% in the guselkumab Q4W group, 6.0% in the guselkumab Q8W group, and 4.5% in the placebo group), followed by aspartate aminotransferase (AST) increased (4.5% in the guselkumab Q4W group, 5.6% in the guselkumab Q8W group, and 2.4% in the placebo group). One case (0.4%) of malignant melanoma was reported in the guselkumab Q8W group; this event was considered unrelated to guselkumab therapy and was resolved by Week 24.(5)

Table 3: Summary of treatment-emergent AEs through Week 24 in DISCOVER-2.(5)

Characteristics	Placebo (n = 246)	Guselkumab Q8W (n = 248)	Guselkumab Q4W (n = 245)
Number of patients with ≥1 AE			
Any AE (%)	40.7%	46.0%	46.1%
SAE (%)	2.8%	1.2%	3.3%
AE leading to treatment discontinuation (%)	1.6%	0.8%	2.4%
Infections (%)	18.3%	16.1%	20.0%
Serious infections (%)	0.4%	0.4%	1.2%
Opportunistic infections (%)	0%	0%	0%
Injection site reactions (%)	0.4%	1.2%	1.2%
MACE (%)	0%	0%	0.4%
Malignancies (%)	0.4%	0.4%[a]	0%
AEs leading to death (%)	0%	0%	0%

[a] Malignant melanoma in situ that was considered severe, not related to study agent, and was resolved by Week 24.
KEY: AE = adverse event; MACE = major adverse cardiac event (ie, cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke); Q4W = every four weeks; Q8W = every eight weeks; SAE = serious adverse event.
Source: DISCOVER-2

Through Week 24, 23 (3.1%) patients discontinued treatment: 9 (3.7%) patients in the guselkumab Q4W group, 8 (3.2%) patients in the guselkumab Q8W group, and 6 (2.4%) patients in the placebo group, see table 4. The most common reasons for treatment discontinuation were AEs (n = 12) followed by lack of efficacy (n = 6). Through Week 24, the number of patients who discontinued due to an AE was low and no specific pattern was noted; 6 (2.4%) patients discontinued due to AEs in the guselkumab Q4W group, 2 (0.8%) patients in the guselkumab Q8W group, and 4 (1.6%) patients in the placebo group.(5)

Table 4: Summary of treatment discontinuation through Week 24 in DISCOVER-2.(5)

Characteristics	Placebo (n = 246)	Guselkumab Q8W (n = 248)	Guselkumab Q4W (n = 245)
Discontinued study treatment	2.4%	3.2%	3.7%
Because of AEs	1.6%	0.8%	2.4%
AEs caused by worsening of PsA	0%	0%	0%
Other AEs	1.6%	0.8%	2.4%
Lack of efficacy	0%	1.2%	1.2%
Initiation of protocol-prohibited medications	0%	0%	0%
Withdrawal of consent	0.4%	0.4%	0%
Lost to follow-up	0%	0.4%	0%
Pregnancy	0%	0%	0%
Death	0%	0%	0%
Other	0.4%	0.4%	0%

KEY: AE = adverse event; FAS = full analysis set; PsA = psoriatic arthritis; Q4W = every four weeks; Q8W = every eight weeks.

Active Treatment Period (Weeks 24-52)

During Weeks 24-52 of the Active Treatment Period, safety outcomes remained generally consistent with earlier Week 1-24 results in the guselkumab Q8W and Q4W groups. As a result, the proportion of patients with ≥1 AE during Weeks 1-52 remained similar between the guselkumab Q8W group (62.5%) and the Q4W group (62.0%) (table 5). Safety outcomes are not directly comparable between the placebo group before and after crossover to guselkumab Q4W at Week 24, although fewer patients reported ≥1 AE during Weeks 24-60 of guselkumab treatment (36.6%; table 5) than during Weeks 1-24 of placebo therapy (40.7%; see table 3). Infections continued to be the most common AE type (guselkumab Q8W: 28.6% of patients; guselkumab Q4W: 27.3%; placebo → guselkumab Q4W: 17.2%), although few serious infections were reported (1.2%, 1.2%, and 1.3%, respectively). More specifically, the most commonly reported

AEs (>5% of patients in any guselkumab group) through Week52 included upper respiratory tract infection, nasopharyngitis and bronchitis.(6)

Few patients reported SAEs (4.0%, 4.5%, and 4.2%) with no deaths occurring through week 52 and only a small proportion discontinued because of AEs (1.2%, 3.7%, and 1.7%).(6) Overall, 4% (31/731) of guselkumab-treated patients had SAEs, with similar proportions observed in the guselkumab Q4W and Q8W groups. Lower limb fracture, goiter, pneumonia/pneumonia influenza, and pulmonary embolism each occurred in two guselkumab-treated patients. Other SAEs were singular events. No patient had active TB or an opportunistic infection through Week52.Among 75 (10%) patients who were required to start treatment for latent TB prior to the first study agent administration, to (1 placebo, 1 guselkumab Q4W [see below]) were reported to have isoniazid-induced liver injury. No AEs of inflammatory bowel disease were reported in a guselkumab treated patient.(6)
No malignancies were reported during Week24–52, while two were reported during Week 0–24 (guselkumab Q8W: melanoma in situ; placebo: renal clear cell cancer). No major adverse cardiac event (MACE) occurred during Week 24–52; one event (guselkumab Q4W: ischemic stroke) was reported prior to Week24. One patient, who received guselkumab Q8W, reported suicidal ideation during Week24–52; two patients (one in each of the placebo and guselkumab Q4W groups) did so during Week 0–24. Through Week52, National Cancer Institute common terminology criteria for adverse events (NCI-CTCAE) Grade ≥2 decreased neutrophil counts (<1.5×109/L) were infrequent, occurring in 3.7% (9/243) and 3.6% (9/247), respectively, of patients who received guselkumab Q4W and Q8W from Week0. Fewer than 1% (5/731) of guselkumab-treated patients had Grade≥3 decreased neutrophil counts, including four with Grade-3 (<1.0 to 0.5×109/L) and one with Grade-4 (<0.5×109/L) values. These findings were generally transient and reversible, resolved spontaneously without treatment, and did not require discontinuation. Through Week 52, NCI-CTCAE Grade ≥2 elevated ALT and/or AST concentrations (>3x upper limit of normal [ULN]) occurred in 7.4% and 6.6%, respectively, of 243 patients receiving guselkumab Q4W and 2.0% and 3.2%, respectively, of 247 patients receiving guselkumab Q8W from Week 0. No additional Grade-3 (>5 to 20×ULN) ALT or AST values, which were uncommon during Week0–24 (1.4% and 1.2%, respectively, of 493 guselkumab-randomized patients),19 occurred post-Week 24. No Grade-4 ALT or AST value (>20x ULN) occurred through Week 52.(6)

Table 5: Summary of treatment-emergent AEs through Week 52 in DISCOVER-2.(6)

Characteristics	GUS Q8W Weeks 1-52 (n = 248)	GUS Q4W Weeks 1-52 (n = 245)	Placebo → GUS Q4W Weeks 24-52[a] (n = 238)
Number of patients with ≥1 AE			
Any AE (%)	62.5%	62.0%	36.6%
SAE (%)	4.0%	4.5%	4.2%
AE leading to treatment discontinuation (%)	1.2%	3.7%	1.7%
AE with severe intensity (%)	1.6%	2.0%	2.9%
Infections (%)	28.6%	27.3%	17.2%
Serious infections (%)	1.2%	1.2%	1.3%
Opportunistic infections (%)	0%	0%	0%
Injection site reactions (%)	1.6%	2.0%	0.8%
Suicidal ideation or behavior	0.4%	0%	0.2%
MACE (%)	0%	0.4%	0%
Malignancies (%)	0.4%[b]	0%	0%
AEs leading to death (%)	0%	0%	0%

a Note: all AEs in the placebo → guselkumab Q4W group are reported *after* crossover to guselkumab at Week 24 (ie, from Weeks 24-52); see table 3 above for AEs reported in the placebo group during Weeks 1-24 (before crossover).
[b] One patient in the guselkumab Q8W group had malignant melanoma in situ. This event was considered unrelated to study treatment and was resolved after discontinuation.

KEY: AE = adverse event; GUS = guselkumab; MACE = major adverse cardiac event (ie, cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke); Q4W = every four weeks; Q8W = every eight weeks; SAE = serious adverse event.

Treatment discontinuation remained low throughout Weeks 1-52 among patients who were originally assigned to guselkumab Q8W (5.6%) or Q4W (7.3%) table 6. Treatment discontinuation remained similar in the placebo → guselkumab Q4W group during Weeks 24-52 of guselkumab treatment (4.2%, Table 6) as during Weeks 1-24 of placebo therapy (2.4%; see table 4).

Table 6. Summary of treatment discontinuation through Week 52 in DISCOVER-2.(6)

Characteristics	GUS Q8W Weeks 1-52 (n = 248)	GUS Q4W Weeks 1-52 (n = 245)	Placebo → GUS Q4W Weeks 24-52[a] (n = 238)
Discontinued study treatment	5.6%	7.3%	4.2%
Because of AEs	0.8%	3.3%	1.3%
AEs caused by worsening of PsA	0%	0%	0.4%
Other AEs	0.8%	3.3%	0.8%
Lack of efficacy	2.4%	2.9%	2.1%
Initiation of protocol-prohibited medications	0%	0%	0%
Withdrawal of consent	1.2%	0.4%	0.4%
Lost to follow-up	0.4%	0%	0%
Pregnancy	0%	0.4%	0%
Death	0%	0%	0%
Other	0.8%	0.4%	0.4%

[a] Note: all discontinuations in the placebo → guselkumab Q4W group are reported *after* crossover to guselkumab at Week 24 (ie, from Weeks 24-48); see table 4 above discontinuation Weeks 1-24 (prior to crossover).
KEY: AE = adverse event; FAS = full analysis set; GUS = guselkumab; PsA = psoriatic arthritis; Q4W = every four weeks; Q8W = every eight weeks

Mean change from baseline on Short Form 36 (SF-36), the physical function subdomain

A significantly greater improvement in the least squares mean change from baseline in SF-36, the physical function subdomain was observed in both the guselkumab Q4W (least squares [LS] mean: 6.624, CI:5.680-7.567) and Q8W groups (6.703, confidence interval [CI]:5.764-7.642) compared with the placebo group (3.254, CI:2.310-4.197).(16) The LS mean difference when comparing Guselkumab Q8W with placebo was [redacted] and guselkumab Q4W compared with placebo was [redacted] (20)

Mean change from baseline on SF-36, the bodily pain subdomain

A significantly greater improvement in the least squares mean change from baseline in SF-36, the bodily pain subdomain was observed in both the guselkumab Q4W (LS mean: 7.739, CI:6.813-8.664) and Q8W groups (7.811, CI:6.890-8.733) compared with the placebo group (3.482, CI:2.556-4.408).(16) The LS mean difference when comparing Guselkumab Q8W with placebo was [redacted] and for guselkumab Q4W compared with placebo was [redacted] (20)

Mean change from baseline on SF-36, the physical component summary

A numerically and significantly greater improvement from baseline in SF-36 PCS scores at Week 24 was observed in both the guselkumab Q4W (LS mean: 7.04, CI:6.14-7.94) and Q8W groups (7.39, CI:6.50-8.29) compared with the placebo group (3.42, CI:2.53-4.32), see figure 5.(5) The LS mean difference when comparing guselkumab Q8W with placebo was 3.97 (2.75-5.20) and for guselkumab Q4W compared with placebo was 3.62 (2.39-4.85) and based on the US analysis the mean difference was statistically significant in both the guselkumab Q4W and Q8W groups ($P = 0.011$ vs. placebo for both comparisons).(5) Furthermore, based on the global analysis, the mean change was statistically

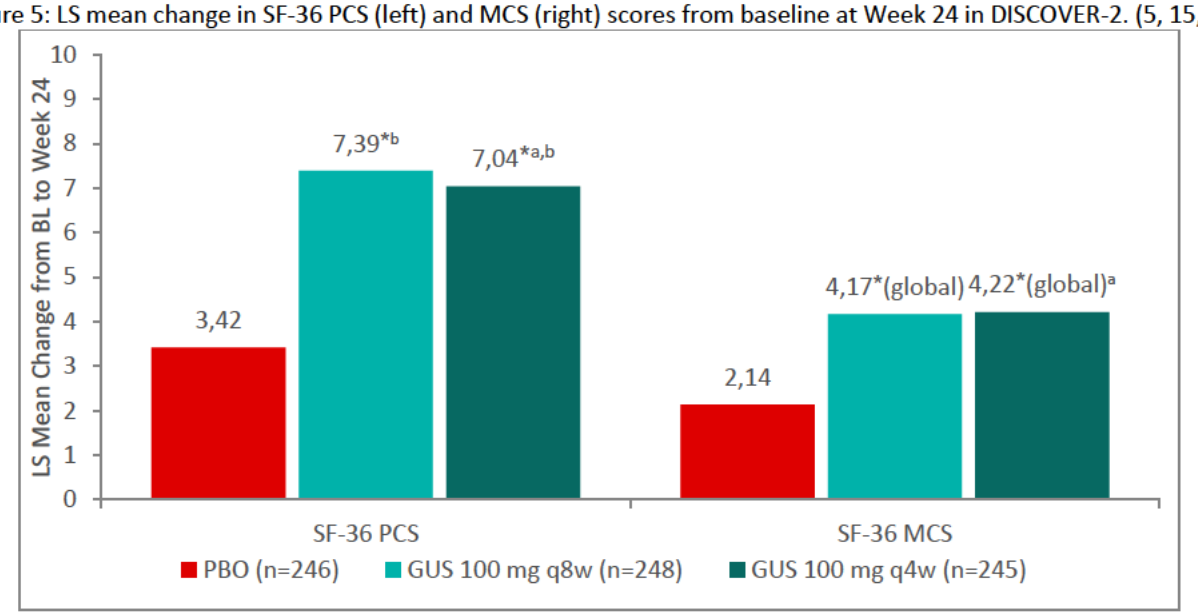
significant in the guselkumab Q4W group ($P = 0.006$ vs. placebo) and was not formally tested in the guselkumab Q8W group (unadjusted $P < 0.001$).(15)

SF-36 PCS scores improved from Week 24 to Week 52 across each treatment group. At Week 52, the mean improvement in SF-36 PCS scores from baseline was 8.64 (CI:7.60-9.68) points in the guselkumab Q4W group, 8.97 (CI:7.94-10.00) points in the guselkumab Q8W group, and 7.53 (CI:6.49-8.56) points in the placebo → guselkumab Q4W group.(6) In addition, most patients in the guselkumab Q4W (55.9%) and Q8W (60.1%) groups achieved a clinically meaningful ≥5-point improvement in SF-36 PCS scores at Week 24 compared with 40.2% of patients in the placebo group (other secondary endpoint; unadjusted $P < 0.001$ for both comparisons).(5, 15, 16)

Average change from baseline on SF-36, the mental component summary

A numerically greater improvement from baseline in SF-36 MCS score at Week 24 was observed in both the guselkumab Q4W (LS mean: 4.22, CI:3.14-4.85) and Q8W groups (4.17, CI:3.10-5.23) compared with the placebo group (2.14, CI:1.07-3.22). The LS mean difference when comparing guselkumab Q8W with placebo was 2.02 (0.56-3.49) and for guselkumab Q4W compared with placebo was 2.07 (0.60-3.54) DISCOVER-2. Based on the global analysis, the mean change was statistically significant in the guselkumab Q4W group ($P = 0.006$ vs. placebo) and was not formally tested in the guselkumab Q8W group (unadjusted $P = 0.007$) (5, 15) Based on the US analysis, the mean change was not statistically significant in either the guselkumab Q4W or Q8W groups ($P = 0.072$ for both comparisons vs. placebo).(5)

Figure 5: LS mean change in SF-36 PCS (left) and MCS (right) scores from baseline at Week 24 in DISCOVER-2. (5, 15, 16)



* $P < 0.05$ vs. placebo in both global and US statistical analyses, unless otherwise specified; [a] statistical significance was achieved as per the global statistical testing plan (for GUS qw4 group only; unadjusted P-values were < 0.05 for the GUS q8w group vs. PBO for both SF-36 PCS and MCS); [b] statistical significance was achieved as per the US statistical testing plan.
KEY: BL = baseline; FAS = full analysis set; GUS = guselkumab; LS = least squares; MCS = Mental Component Summary; PBO = placebo; PCS = Physical Component Summary; q4w = every four weeks; q8w = every eight weeks; SF-36 = Short Form 36 Health Survey.

SF-36 MCS scores improved from Week 24 to Week 52 across each treatment group. The mean improvement in SF-36 MCS scores from baseline was 4.43 points in the guselkumab Q4W group at Week 52, 4.31 points in the guselkumab

Q8W group, and 4.04 points in the placebo → guselkumab Q4W group.(6)
In addition, a clinically meaningful ≥5-point improvement in SF-36 MCS scores was achieved by approximately one-third of patients in the guselkumab Q4W group (34.3%), the Q8W group (37.5%), and the placebo group (30.9%; other secondary endpoint; unadjusted *P* > 0.05 for both comparisons). (5, 15, 16)

Proportion of patients experiencing PASI90 response
Not relevant for clinical question 2.

5.1.2.3 ADEPT

Adalimumab efficacy results from ADEPT for treatment naive patients with PsA without moderate to severe plaque PsO defined in the Medicine Council protocol is presented in the following section. Overview of the results is available in table A3d in the appendix. Some of the endpoints defined in the Medicines Council protocol are not published and therefore not presented. SAE are presented to enable a comparative analysis with data from the DISCOVER-1 and DISCOVER-2 studies for guselkumab.

Proportion of patients experiencing response to ACR50
At Week 24, a significantly greater proportion of patients without previous TNF inhibitor use in the adalimumab Q2W group achieved an ACR50 response, compared with patients in the placebo group, 39% (59 of 151) vs. 6% (10 of 162), p<0.001.(7)

Proportion of patients without progression, cf. mTSS
Unfortunately results on the proportion of patients without progression are not available from the ADEPT study.

Proportion of patients who experience serious side effects
The proportions of patients who experienced SAEs through Week 24 were 3.31% (5 of 151) in the adalimumab Q2W group and 4.32% (7 of 162) in the placebo group. In the adalimumab Q2W group the SAE were nasal septum disorder, toe arthrodesis, aggravation of convulsions, viral meningitis and renal calculus whereas the reported for the placebo group were cerebrovascular accident, pericarditis and hand fracture in the same patient, muscle weakness, deep venous thrombosis, and pulmonary embolism in the same patient, depression, 2 events of hyperglycemia in the same patient, cellulitis, and aggravation of coronary artery disease.(7)

Qualitative review of safety profile
The proportions of patients experiencing any AEs through Week 24 were slightly higher in the adalimumab group compared with the placebo group: 80.8% in the adalimumab Q2W group and 80.2% in the placebo group (Table 7).(8)

Infections were comparable across treatment groups: 45% in the adalimumab Q2W group and 39.5% in the placebo group. The most common AEs reported were upper respiratory tract infection (12.6% in the adalimumab Q4W group and 14.8% in the placebo group), followed by nasopharyngitis (9.9% in the adalimumab Q2W group and 9.3% in the placebo group) and injection site reaction (6.6% in the adalimumab Q2W group and 3.1% in the placebo group).

Table 7: Summary of treatment-emergent AEs through Week 24 in ADEPT. (7, 8)

Characteristics	Placebo (n = 162)	Adalimumab (n = 151)
Number of patients with ≥1 AE		
Any AE (%)	80.2%	80.8%
SAE (%)	4.3%	3.3%
AE leading to treatment discontinuation (%)	3.1%	4.0%
Infections (%)	39.5%	45.0%
Serious infections (%)	0.6%	0.7%
Opportunistic infections (%)	0%	0%
Injection site reactions (%)	3.1%	6.6%
MACE (%)	0%	0%
Malignancies (%)	0%	0%
AEs leading to death (%)	0%	0%

KEY: AE = adverse event; SAE: serious adverse events; MACE: major adverse cardiac event

Through Week 24, 11 (7.3%) patients discontinued treatment in the adalimumab Q2W group and 13 (8.0%) patients in the placebo group. The most common reasons for treatment discontinuation in the adalimumab Q2W group were AEs and withdrawal of consent, see table 8. (8)

Table 8: Summary of treatment discontinuation through Week 24 in ADEPT. (7, 8)

Characteristics	Placebo (n = 162)	Adalimumab (n = 151)
Discontinued study treatment	8.0%	7.3%
Because of AEs	0.6%	2.0%
Lack of efficacy	2.5%	0.7%
Abnormal laboratory value	0%	1.3%
Withdrawal of consent	3.1%	2.0%
Lost to follow-up	0.6%	0%
Protocol violation	0.6%	0%
Administrative problems	0%	0.7%
Other	0.6%	0.7%

KEY: AE = adverse event

The proportion of patients with any AE throughout 2 years of open-label adalimumab exposure was 91.6% (table 9). Infections continued to be the most common AE type with 69.5% of adalimumab patients experiencing an infection with 5% having a serious infection. In addition, injection-site reaction (14.4%) remained the second most commonly reported AE throughout 2 years of open-label adalimumab exposure.(8)
Few patients reported SAEs (5.0%) but 3 deaths (2%) occurred through 2 years. Only a small proportion discontinued because of AEs (6.7%). One patient (0.1%) had TB and 1.3% had an opportunistic infection through 2 years.(8)

Table 9: Summary of treatment-emergent AEs throughout 2 years of open-lab adalimumab exposure. (8)

Characteristics	Adalimumab (n = 298)
Number of patients with ≥1 AE	
Any AE (%)	91.6%
SAE (%)	16.8%
AE leading to treatment discontinuation (%)	6.7%
Infections (%)	69.5%
Serious infections (%)	5.0%
Opportunistic infections (%)	1.3%
Injection site reactions (%)	14.4%%
MACE (%)	0%
Malignancies (%)	1.3%
Death (%)	1%

KEY: AE = adverse event; SAE: serious adverse events; MACE: major adverse cardiac event

Mean change from baseline on Short Form 36 (SF-36), the physical function subdomain

Unfortunately results for adalimumab Q2W on the mean change from baseline on Short Form 36 (SF-36), the physical function subdomain are mot from the ADEPT study.

Mean change from baseline on SF-36, the bodily pain subdomain

Unfortunately results for adalimumab Q2W on the mean change from baseline on Short Form 36 (SF-36), the bodily subdomain are not available from the ADEPT study.

Mean change from baseline on SF-36, the physical component summary

At Week 24, the adalimumab Q2W group had a mean change from baseline, by last observation carried forward, of 9.3 (standard deviation [SD]:10.1) which was a significantly greater improvement in Short Form 36 Health Survey (SF-36) Physical Component Summary (PCS) scores than the placebo group with a mean change of 1.4 (SD:9.6), $P < 0.001$.(7)

Average change from baseline on SF-36, the mental component summary

At Week 24, the adalimumab Q2W group had a mean change from baseline, by last observation carried forward, of 1.8 (SD:9.3) which was a numerically greater improvement in Short Form 36 Health Survey (SF-36) Mental Component Summary (MCS) scores than the placebo group with a mean change of 0.6 (SD:10.4), $P = 0.288$.(7)

5.1.2.4 SPIRIT-P1

Adalimumab efficacy results from SPIRIT-P1 for treatment naive patients with PsA without moderate to severe plaque PsO defined in the Medicines Council protocol is presented in the following section. SAE are presented to enable a comparative analysis with data from the DISCOVER-1 and DISCOVER-2 studies for guselkumab. Overview of the results is available in table A3e in the appendix.

Proportion of patients experiencing response to ACR50

At Week 24, a significantly greater proportion of patients without previous TNF inhibitor use in the adalimumab Q2W group achieved an ACR50 response, compared with patients in the placebo group, 38.7% (39 of 101) vs. 15.1% (16 of 106), p≤0.001.(9)

Proportion of patients without progression, cf. mTSS

The proportion of patient without porgression is reflected by the percentage of patients with a change of ≤0 from baseline in modified vdH-S score at week 24. The percentage were 91.6% (93/101) in the adalimumab Q2W group and 72% (76/196) in the placebo group.(9)

Proportion of patients who experience serious side effects

The proportions of patients who experienced SAEs through Week 24 were 5% (5 of 101) in the adalimumab Q2W group and 2% (2 of 106) in the placebo group. In the adalimumab Q2W group the SAE were gastric ulcer, oesophagitis, cellulitis, pneumonia mycoplasmal, carotid artery occlusion and metrorrhagia, whereas the reported for the placebo group were hepatic enzyme increase and Bartholin's cyst. In addition, all SAEs of infection resolved with treatment and did not lead to study discontinuation.(9)

Qualitative review of safety profile

The proportions of patients experiencing any AEs through Week 24 were higher in the adalimumab group compared with the placebo group: 64.4% in the adalimumab Q2W group and 47.2% in the placebo group (Table 10).(9) Infections were comparable across treatment groups: 25.7% in the adalimumab Q2W group and 25.5% in the placebo group. The most common AEs reported were nasopharyngitis (6.9% in the adalimumab Q2W group and 4.7% in the placebo group) followed by upper respiratory tract infection (5.0% in the adalimumab Q2W group and 6.6% in the placebo group).(9)

Table 10: Summary of treatment-emergent AEs through Week 24 in SPIRIT-P1 .(9)

Characteristics	Placebo (n = 106)	Adalimumab (n = 101)
Number of patients with ≥1 AE		
Any AE (%)	47.2%	64.4%
SAE (%)	1.9%	5.0%
AE leading to treatment discontinuation (%)	1.9%	2.0%
Infections (%)	25.5%	25.7%
Serious infections (%)	0%	2.0%
Opportunistic infections (%)	0%	0%
Injection site reactions (%)	0%	2%
MACE (%)	0%	0%
Malignancies (%)	0.9%	1%
AEs leading to death (%)	0%	0%

KEY: AE = adverse event; SAE: serious adverse events; MACE: major adverse cardiac event

Through Week 24, 4 (4.0%) patients discontinued treatment in the adalimumab Q2W group and 13 (14.2%) patients in the placebo group. The most common reasons for treatment discontinuation in the adalimumab Q2W group were AEs and withdrawal of consent, see table 11.(9)

Table 11: Summary of treatment discontinuation through Week 24 in SPIRIT-P1.(9)

Characteristics	Placebo (n = 106)	Adalimumab (n = 101)
Discontinued study treatment	14.2%	4.0%
Because of AEs	1.9%	2.0%
Lack of efficacy	3.8%	0%
Entry criteria not met	0.9%	1%
Patient decision	2.8%%	1%
Lost to follow-up	0.9%	0%
Protocol violation	0.9%	0%
Administrative problems	0%	0%
Other	0%	0%

KEY: AE = adverse event

Mean change from baseline on Short Form 36 (SF-36), the physical function subdomain

A significantly greater improvement in the least squares mean change from baseline in SF-36, the physical function subdomain was observed in the adalimumab Q2W 14.4 (SD:19.9) compared with the placebo group 5.6 (SD:18.4), P=0.002.(10)

Mean change from baseline on SF-36, the bodily pain subdomain

A significantly greater improvement in the least squares mean change from baseline in SF-36, the bodily pain subdomain was observed in the adalimumab Q2W 16.8 (SD:21.3) compared with the placebo group 8.3 (SD:19.8), P=0.002.(10)

Mean change from baseline on SF-36, the physical component summary

A significantly greater improvement in the least squares mean change from baseline in SF-36, the physical component summary was observed in the adalimumab Q2W 6.3 (SD:8.3) compared with the placebo group 2.7 (SD:7.7), P=0.002.(10)

Average change from baseline on SF-36, the mental component summary

A nummerically but not significantly greater improvement in the least squares mean change from baseline in SF-36, the mental component summary was observed in the adalimumab Q2W 4.6 (SD:9.5) compared with the placebo group 1.8 (SD:9.5), P=0.055.(10)

5.1.3 Comparative analyses of guselkumab vs. adalimumab

Guselkumab has not been directly compared to adalimumab for the treatment of PsA in any published randomized trials. Consequently, an indirect comparison between guselkumab and adalimumab has been performed utilizing Bucher's methodology with the results available in table A4a in the appendix. Furthermore, meta-analysis was used to combine the results of the DISCOVER-1 and DISCOVER-2 studies for guselkumab as well as the results of the ADEPT and SPIRIT-P1 study for adalimumab using random effect models. The relevant meta-analyses are attached to this submission as a separate file. Indirect comparison between guselkumab and adalimumab has been performed based on Bucher´s methodology using the results from the meta-analyses. Absolute difference in effect were calculated using the estimated risk ratio (RR) from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies.
For the efficacy endpoints, SF-36 PCS, SF-36 MCS, SF-36 the physical functioning subdomain and SF-36 the bodily pain subdomain, an indirect comparison has not been done as the mean change from baseline and mean differences between respective comparison e.g. guselkumab vs. PBO and adalimumab vs. PBO are analyzed with different methodologies. This is will evidently limit the comparability of the outcomes and therefor a narrative review has been conducted instead. The different methodologies are described the sections beneath.

For guselkumab in both DISCOVER-1 and DISCOVER-2 the continuous endpoints of least squares mean change from baseline in SF-36 PCS, and SF-36 MCS, treatment comparisons were performed using an analysis of covariance (ANCOVA) model based on multiple imputation (MI) data. The MI method was applied to impute the missing value(s) under the assumption of missing at random (MAR). For the SF- 36 subdomains, bodily pain and physical functioning, treatment comparisons and LS means were performed using a Mixed-Effect Model Repeated Measures (MMRM) model.
For adalimumab the analyses of mean change from baseline in SF-36 PCS and SF-36 MCS differs as the mean is estimated by last observation carried forward analysis and not least squares mean as for guselkumab. Furthermore, the comparisons of adalimumab vs PBO were done using analysis of variance (ANOVA). For the mean change in baseline in SF- 36 subdomains, bodily pain and physical functioning, also differs at the mean is estimated by last observation carried forward. Furthermore, the treatment comparisons were performed using an ANCOVA model which differs from the MMRM analyses used for Guselkumab.

Proportion of patients experiencing response to ACR50

The relative difference in RR between guselkumab Q8W and adalimumab Q2W in the proportion of patients achieving ACR50 response at week 24 is 0.60 (0.23-1.54) when utilizing the meta-analysis results of DISCOVER-1 and DISCOVER-2 for guselkumab as well as ADEPT and SPIRIT-P1 for adalimumab, see table A4a in the appendix. As the confidence interval of the relative difference does not correspond to any of the specified confidence limits as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions, the preliminary clinically added value cannot be categorized, see table 12.(21) In addition, the absolute difference in effect is -15.6% (-29.8%-20.9%) Thus, the preliminary added value cannot be categorized. This is evident when the confidence interval around the absolute effect difference is compared with the least clinically relevant difference of 15%-point and the criteria for the different preliminary categorize. This is evident when the confidence interval around the absolute effect difference is compared with the least clinically relevant difference of 15%-point and the criteria for the different preliminary categorize. More specifically the upper bound of 20.9% is neither equal to; upper limit (UL) < -15%-point and the lower limit (LL) is not equal to; LL > -15%-point nor equal to; LL ≥ 15%-point.

Table 12: Clinically added value of guselkumab comparted to adalimumab in regards to ACR50 response at week 24.

Clinically added value – ACR50		
Absolute difference – ACR50	**Least clinically relevant difference – 15%**	**Estimated absolute difference (CI)**
Merværdi af ukendt størrelse	LL ≥ MKRF	
Ingen dokumenteret merværdi	LL > -MKRF	
Negativ merværdi	UL < -MKRF	
Kan ikke kategoriseres		-15.6% (-29.8%-20.9%)
Relative difference - ACR50	**Specified confidence limit - ACR50**	**RR (CI)**
Stor merværdi	LL>1.33	
Moderat merværdi	1.33 ≥ LL > 1.11	
Lille merværdi	1.11 ≥ LL > 1.00 og UL ≤ 1.33	
Merværdi af ukendt størrelse	1.11 ≥ LL > 1.00 og UL > 1.33	
Ingen dokumenteret merværdi	0.90<LL=<1.00 og UL>=1.00	
Negativ merværdi	UL<1.00	
Kan ikke kategoriseres		0.60 (0.23-1.54

KEY: ACR=American College of Rheumatology; CI = confidence interval; Upper limit = UL; LL= lower limit; MKRF = Mindste klinisk relevante forskel

Proportion of patients without progression, cf. mTSS

The relative difference in RR between guselkumab Q8W and adalimumab Q2W in the proportion of patients without progression at week 24 is 0.77 (0.64-0.93) when utilizing the results of DISCOVER-2 for guselkumab and SPIRIT-P1 for adalimumab. As the upper confidence interval of the relative difference is below 1 it corresponds to negative added value as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions, see table 13. (21)

However, the absolute difference in effect is -20.9% (-33.0% to -6.3%) Thus, the absolute difference does not indicate negative added value but instead the preliminary added value cannot be categorized. This is evident when the confidence interval around the absolute effect difference is compared with the least clinically relevant difference of 10%-point and the criteria for the different preliminary categorizations. More specifically the upper bound of -6.3% is not equal to; upper limit (UL) < -10%-point and the lower limit (LL) is not equal to; LL > -10%-point nor equal to; LL ≥ 10%-point.

Table 13: Clinically added value of guselkumab comparted to adalimumab in regard to patients without progression, cf. mTSS at week 24.

Clinically added value – patients without progression, cf. mTSS		
Absolute difference – mTSS	**Least clinically relevant difference – 10%**	**Estimated absolute difference (CI)**
Merværdi af ukendt størrelse	LL ≥ MKRF	
Ingen dokumenteret merværdi	LL > -MKRF	
Negativ merværdi	UL < -MKRF	
Kan ikke kategoriseres		-20.9% (-33% to -6.3%)
Relative difference - mTSS	**Specified confidence limit - mTSS**	**RR (CI)**
Stor merværdi	LL>1.33	
Moderat merværdi	1.33 ≥ LL > 1.11	
Lille merværdi	1.11 ≥ LL > 1.00 og UL ≤ 1.33	
Merværdi af ukendt størrelse	1.11 ≥ LL > 1.00 og UL > 1.33	
Ingen dokumenteret merværdi	0.90<LL=<1.00 og UL>=1.00	
Negativ merværdi	UL<1.00	0.77 (0.64-0.93)
Kan ikke kategoriseres		

KEY: CI = confidence interval; Upper limit = UL; LL= lower limit; MKRF = Mindste klinisk relevante forskel

Proportion of patients who experience serious side effects

The relative difference in RR between guselkumab Q8W and adalimumab Q2W in the proportion of patients experiencing a SAE at week 24 is 0.36 (0.07-1.89). As the confidence interval of the relative difference does not correspond to any of the specified confidence limits as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions, the preliminary clinically added value cannot be categorized, see table 14. (21)

In addition, the estimated difference on absolute effect is -2.5% (-3.7%-3.52%). Thus, the preliminary added value corresponds to no documented added value. This is evident when the confidence interval around the absolute effect difference is compared with the least clinically relevant difference of 5%-point and the criteria for the different preliminary categorize. More specifically the upper bound of 3.52% is not equal to; upper limit (UL) ≤ -5%-point but it is equal to; UL < 5%-point and the lower bound of -3.7% is not equal to; LL > 5%-point.

Table 14: Clinically added value of guselkumab in regards to SAEs at week 24.

Clinically added value – Serious adverse events		
Absolute difference - SAE	**Least clinically relevant difference -** 5%	**Estimated CI**
Merværdi af ukendt størrelse	UL ≤ -MKRF	
Ingen dokumenteret merværdi	UL < MKRF	
Negativ merværdi	LL > MKRF	
Kan ikke kategoriseres		-2.5% (-3.7%-3.52%)
Relative difference - SAE	**Specified confidence limit - SAE**	**RR (CI)**
Stor merværdi	UL<0.75 og risiko >05%	
Moderat merværdi	0.75 ≤ UL < 0.90 eller (UL < 0.75 og risiko < 5%)	
Lille merværdi	0.90 ≤ UL < 1.00 og LL ≤ 0.75	
Merværdi af ukendt størrelse	0.90 ≤ UL < 1.00 og LL< 0.75	
Ingen dokumenteret merværdi	1.00 ≤ UL < 1.11 og LL ≤ 1.00	
Negativ merværdi	LL > 1.00	
Kan ikke kategoriseres		0.36 (0.07-1.89)

KEY: CI = confidence interval; Upper limit = UL; LL= lower limit; MKRF = Mindste klinisk relevante forskel

Comparative qualitative review of safety profile

The proportion of patients experiencing any AEs through week 24 is noticeably higher among patients treated with adalimumab with a narratively reviewed difference of 34.8% and 18.4% comparing to the data reported from ADEPT and SPIRIT-P1, respectively (table 15). In addition, the proportion of patients experiencing infections are also noticeably higher among adalimumab treated patients compared to guselkumab Q8W treated patients. More specifically the narratively reviewed increased proportions is of 28.9% and 9.6% comparing to the data reported from ADEPT and SPIRIT-P1, respectively. For the rest of the safety outcomes the frequencies were comparable across the guselkumab treatment group and the two adalimumab treatment groups although the frequency in all cases were slightly higher for adalimumab.(5, 7, 9) Thus, the safety profile of guselkumab is considered to be superior to adalimumab at week 24.

Table 15: comparison of treatment-emergent AEs through Week 24 reported in DISCOVER-2, ADEPT and SPIRIT-P1. (5, 7, 9)

Characteristics	Guselkumab Q8W (n = 248)	Adalimumab Q2W ADEPT (n=151)	Adalimumab Q2W SPIRIT-P1 (n=101)
Number of patients with ≥1 AE			
Any AE (%)	46.0%	80.8%	64.4%
SAE (%)	1.2%	3.3%	5.0%
AE leading to treatment discontinuation (%)	0.8%	4.0%	2.0%
Infections (%)	16.1%	45.0%	25.7%
Serious infections (%)	0.4%	0.7%	2.0%
Opportunistic infections (%)	0%	0%	0%
Injection site reactions (%)	1.2%	6.6%	2%
MACE (%)	0%	0%	0%
Malignancies (%)	0.4%[a]	0%	1%
AEs leading to death (%)	0%	0%	0%

KEY: AE = adverse event; SAE: serious adverse events; MACE: major adverse cardiac event

Furthermore, long-term safety of guselkumab is superior to adalimumab when doing a narrative review of the 1 year safety data reported for guselkumab and 2 year open label safety data for adalimumab.
The proportion of guselkumab Q8W patients experiencing any AEs through weeks 1-52 is noticeably lower than patients treated with adalimumab through 2 years with a narratively reviewed difference of 29.1% when data reported from DISCOVER-2 is compared with data from ADEPT, see table 16. In addition, the proportion of patients experiencing infections are also noticeably higher among adalimumab treated patients compared to guselkumab Q8W treated patients. More specifically the narratively reviewed increased proportions is of 40.9% comparing to the data reported. For the rest of the safety outcomes the long-term frequencies were comparable across the guselkumab treatment group and the adalimumab treatment group although the frequency in all cases were slightly higher for adalimumab. However, 1% died in the adalimumab group whereas 0% died in the guselkumab group. Thus, the long-term safety profile of guselkumab is considered to be superior to adalimumab.

Table 16: Comparison of treatment-emergent AEs through Week 52 in DISCOVER-2 and 2 years of open-lab adalimumab exposure in ADEPT. (6, 8)

Characteristics	GUS Q8W Weeks 1-52 (n = 248)	Adalimumab Q2W 2 years (n = 298)
Number of patients with ≥1 AE		
Any AE (%)	62.5%	91.6%
SAE (%)	4.0%	16.8%
AE leading to treatment discontinuation (%)	1.2%	6.7%
AE with severe intensity (%)	1.6%	n/a
Infections (%)	28.6%	69.5%
Serious infections (%)	1.2%	5.0%
Opportunistic infections (%)	0%	1.3%
Injection site reactions (%)	1.6%	14.4%
Suicidal ideation or behavior	0.4%	n/a
MACE (%)	0%	0%
Malignancies (%)	0.4%	1.3%
AEs leading to death (%)	0%	1%

KEY: AE = adverse event; SAE: serious adverse events; MACE: major adverse cardiac event

In addition to the comparative qualitative review based on safety data reported in the DISOVER-1 and SPIRIT-P2 study a qualitative review of safety based on the Summary of product characteristics (SMPC)s for guselkumab and adalimumab is provided in the following section.

Based on the SMPC, guselkumab has the following contraindications 1) serious hypersensitivity to the active substance or to any of the excipients; histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose and water for injections, 2) clinically important active infections (e.g., active tuberculosis). In contrary, adalimumab has the following contraindications 1) serious hypersensitivity to the active substance or to any of the excipients; mannitol, polysorbate 80 and water for injections, 2) Active tuberculosis or other severe infections such as sepsis and opportunistic infections, 3) Moderate to severe heart failure e (NYHA class III/IV). Consequently, more contraindication are stated for adalimumab compared to guselkumab which underlines the beneficial safety profile of guselkumab.(1, 22)
In addition, when comparing the special warning and precautions for use some differences appears, see table A5 in the appendix. For example, adalimumab has special warning and precautions for, hepatitis B reactivation, neurological events, allergic reactions, malignancies and lympho-proliferative disorders, haematologic reactions, congestive heart failure, autoimmune processes, opportunistic infection and serious infection which is not the case for guselkumab.(1, 22) Furthermore, adalimumab has more common adverse reactions compared to guselkumab according to the SMPCs listing adverse reactions linked to infection and infestations for guselkumab and adalimumab. For guselkumab respiratory tract infections are very common whereas herpes simplex infection, tinea infections and gastroenteritis are uncommon.(1, 22)

In contrary, respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral) are very common for adalimumab. Furthermore, the following infections are listed as common: Systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including gastroenteritis viral), skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotising fasciitis and herpes zoster), ear infections, oral infections (including herpes simplex, oral herpes and tooth infections), reproductive tract infections (including vulvovaginal mycotic infection), urinary tract infections (including pyelonephritis), fungal infections and joint infections. More uncommon adverse reaction are also reported for adalimumab compared to guselkumab with the following listed in the SMPC: Neurological infections (including viral meningitis), opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection), bacterial infections, eye infections and diverticulitis.(1, 22)

Conclusively, the safety profile of guselkumab is superior to that of adalimumab based on a comparison of the adverse reactions related to infection and infestations.

Mean change from baseline on SF-36, the physical function subdomain
A narrative comparison between guselkumab Q8W and adalimumab Q4W on SF-36, the physical function subdomain will be conducted in following section. Data for guselkumab Q8W is based on the DISCOVER-2 study whereas data for adalimumab Q2W is based on the SPIRIT-P1 study.
Guselkumab Q8W demonstrated a significantly greater improvement in SF-36, the physical function subdomain compared the to the placebo group with a LS mean difference of [redacted] Similarly, adalimumab Q2W demonstrated a significantly greater improvement compared the to the placebo group with a with a calculated mean difference of 8.8 (3.572-14.028).

A narratively reviewed difference of the points estimates show a [redacted] difference and for the lower confidence interval the difference is [redacted]. Consequently, it is deemed that guselkumab Q8W and adalimumab Q2W

presents similar efficacy as the narratively reviewed difference in the point estimates and lower confidence intervals does not exceed the least clinically relevant difference of 7.1 points. Furthermore, the comparison of guselkumab Q8W and adalimumab Q4W on mean change from baseline in SF-36, the physical function subdomain is believed to result in no documented added value.

Mean change from baseline on SF-36, the bodily pain subdomain

A narrative comparison between guselkumab Q8W and adalimumab Q4W on SF-36, the bodily pain subdomain will be conducted in following section. Data for guselkumab Q8W is based on the DISCOVER-2 study whereas data for adalimumab Q2W is based on the SPIRIT-P1 study.

Guselkumab Q8W demonstrated a significantly greater improvement in SF-36, the bodily pain subdomain compared to the placebo group with a LS mean difference of [redacted] Similarly, adalimumab Q2W demonstrated a significantly greater improvement compared the to the placebo group with a with a calculated mean difference of 8.5 (2.891-14.109).

A narratively reviewed difference of the points estimates show a [redacted] difference in favor of adalimumab and for the lower confidence interval the difference is [redacted] in favor of guselkumab. Consequently, it is deemed that guselkumab Q8W and adalimumab Q2W presents similar efficacy as the narratively reviewed difference in the point estimates and lower confidence intervals does not exceed the least clinically relevant difference of 4.9 points. Furthermore, the comparison of guselkumab Q8W and adalimumab Q4W on mean change from baseline in SF-36, the bodily pain subdomain is believed to result in no documented added value.

Mean change from baseline on SF-36, the physical component summary

A narrative comparison between guselkumab Q8W and adalimumab Q2W will be conducted in following section. Data for guselkumab Q8W is based on the DISCOVER-2 study whereas data for adalimumab Q2W is based on a random effects meta-analysis of ADEPT and the SPIRIT-P1 study.

As described guselkumab Q8W demonstrated a significantly greater improvement in SF-36 (PCS) scores compared the to the placebo group with a LS mean difference of 3.97 (2.75-5.20, p=0.011).(5) Similarly, the results from the meta-analyses showed that adalimumab Q2W demonstrated a significantly greater improvement in SF-36 (PCS) scores compared the to the placebo group with a mean difference of (5.738; CI:1.524-9.952, $P = 0.008$), see table A4a in the appendix. The mean differences vs. placebo are at the same level with a narrative reviewed difference on the point estimate of 1.768 points in favor of adalimumab and for the lower confidence interval the difference is 1.226 points in favor of guselkumab. However, the clinically added value of both guselkumab Q8W and adalimumab Q4W compared to placebo results in no documented added value based on the medicine council least clinically relevant difference of 7.2 points. This is shown when the confidence interval around the absolute effect difference is compared with the least clinically relevant difference of 7.2 points and the criteria for the different preliminary categorize. More specifically the upper bound of 5.20 for guselkumab Q8W and 9.9 for adalimumab Q2W is not equal to; upper limit (UL) < -7.2-point, and the lower limit (LL) of 2.75 for guselkumab Q8W and 1.524 for adalimumab Q2W is equal to; LL > -7.2-point but not equal to; LL ≥ 7.2-point.

Furthermore, the comparison of guselkumab Q8W and adalimumab Q2W on mean change from baseline in SF-36 (PCS) is deemed to also result in no documented added value as the narratively reviewed difference in the point estimates and lower confidence intervals does not exceed the least clinically relevant difference of 7.2-points.

Mean change from baseline on SF-36, the mental component summary

A narrative comparison between guselkumab Q8W and adalimumab Q2W will be conducted in following section. Data for guselkumab Q8W is based on the DISCOVER-2 study whereas data for adalimumab Q2W is based on a random effects meta-analysis of ADEPT and the SPIRIT-P1 study.

As described guselkumab Q8W demonstrated a greater improvement in SF-36 (MCS) scores compared the to the placebo group with a LS mean difference of 2.02 (0.56-3.49, unadjusted p=0.007).(5) Similarly, the results from the meta-analyses showed that adalimumab Q2W demonstrated a significantly greater improvement in SF-36 (MCS) scores compared the to the placebo group with a mean difference of 1.892 (0.189-3.594, *P* = 0.029), see table A4a in the appendix. The mean differences vs. placebo are at the same level with a narrative reviewed difference on the point estimate of 0.128 points in favor of guselkumab and for the lower confidence interval the difference is 0.371 points in favor of guselkumab. However, the clinically added value of both guselkumab Q8W and adalimumab Q2W compared to placebo results in no documented added value based on the Medicines Council´s least clinically relevant difference of 3.1 points. This is shown when the confidence interval around the absolute effect difference is compared with the least clinically relevant difference of 3.1 points and the criteria for the different preliminary categorize. More specifically the upper bound of 3.49 for guselkumab Q8W and 3.594 for adalimumab Q2W is not equal to; upper limit (UL) < -7.2-point, and the lower limit (LL) of 0.56 for guselkumab Q8W and 0.189 for adalimumab Q2W is equal to; LL > -3.1-point but not equal to; LL ≥ 3.1-point. Furthermore, the comparison of guselkumab Q8W and adalimumab Q2W on mean change from baseline in SF-36 (MCS) is deemed to also result in no documented added value as the narratively reviewed difference in the point estimates and lower confidence intervals does not exceed the least clinically relevant difference of 3.1-points.

5.2 What is the value of guselkumab compared with ixekizumab for treatment experienced patients with PsA without moderate to severe plaque psoriasis?

5.2.1 Presentation of relevant studies

The studies used in the assessment of the added clinical value of guselkumab for treatment experienced patients compared to ixekizumab consist of DISCOVER-1 and SPIRIT-P2 for guselkumab and ixekizumab, respectively.(3, 11) Furthermore, the EPAR of Guselkumab® will be consulted.(15)
Overall, DISCOVER-1 evaluating guselkumab, and SPIRIT-P2 evaluating ixekizuamb as therapy for patients with PsA without moderately to severe plaque PsO have certain important characteristics in common.

The studies were published between 2017 and 2019. Baseline characteristics across studies are summarized in table 17. Mean age across the studies ranged from 48.4 to 51.9 years. The percentage of males ranged from 46.6% to 51.2% across studies. The duration of PsA ranged from 6.8 years to 10.0 years. The percentage of Caucasian patients ranged from 91.6% to 92.0% across RCTs. Across studies, the mean number of swollen and tender joints at baseline ranged from 9.9 to 12.3 and 19.2 to 23.3, respectively. Baseline PASI score ranged from 7.9 to 9.9. (3, 11)

Table 17: Summary of Baseline Characteristics from Randomized Controlled Trials (3, 11)

Author, Publication Date	Trial Name	Primary Timepoint (weeks)	Treatment[a]				Sample Size (N)	Mean Age (years)	Male (%)	Race (% Caucasian)	Body Weight (kg)	Duration of PsA (years)	Prior Biologic Use (%)	No. of swollen joints (mean)	No. of tender joints (mean)	BL PASI Score (mean)	PsO BSA >3% (%)	BL HAQ-DI score
			1	2	3	4												
Nash 2017(11)	SPIRIT-P2	24	PBO	IXE 80 Q2W	IXE 80 Q4W	NA	363	51 9	46.6	92.0	88.7	10.0	100.0	12.3	23.3	5.9	56.0	1.2
Deodhar 2020 (3)	DISCOVER-1	24	PBO	GUS 100 mg Q8W	GUS 100 mg Q4W	NA	381	48.4	51.2	91.6	86.0	6.8	31.0	9.9	19.2	8.5	65.4	1.2

KEY: BL = baseline; BSA = body surface area; GUS = guselkumab; HAQ-DI = Health Assessment Questionnaire Disability Index; IXE =ixekizumab; NA = not available; N = number; PASI = Psoriasis Area and Severity Index; PBO = placebo; PsA = psoriatic arthritis; PsO = psoriasis; Q2W = every two weeks; Q4W = every four weeks; Q8W = every eight weeks

However, small difference between the studies were found. The SPIRIT-P2 were only conducted in biologic-experienced patients, whereas the DISCOVER-1 study of Guselkumab were conducted in a mixed population consisting 31% biologic-experienced patients and 69% treatment naive patients. (3, 11)

5.2.2 Results per study

5.2.2.1 DISCOVER-1

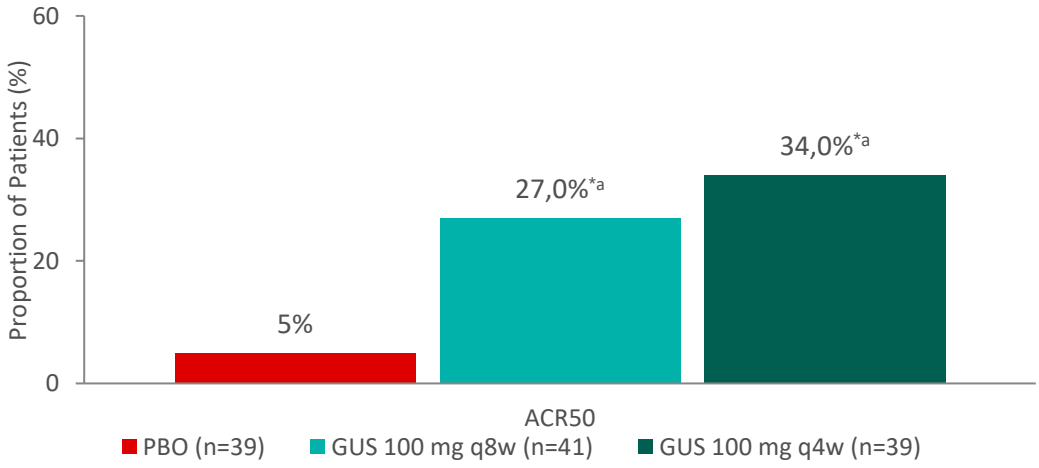
Guselkumab efficacy results from DISCOVER-1 for treatment experienced patients with PsA without moderate to severe plaque PsO defined in the Medicines Council protocol is presented in the following section. Overview of the results is available in table A3b in the appendix. Some of the endpoints defined in the Medicines Council´s protocol are not published and therefore not presented. Serious adverse reactions which is an endpoint requested in the Medicines Councils protocol for this evaluation is not available neither in the published study, the EPAR or on clinicaltrials.gov. Thus, SAE are presented instead to give the Medicines Council a relevant safety endpoint to evaluate. Furthermore, safety data, aside unpublished SAE results, is not stratified on treatment naive and treatment experienced patients and the safety results are therefore presented for total patient population.

Some of the endpoints defined in the Medicines Council´s protocol are not published for the treatment experienced patient population. However, published data based on the primary efficacy analysis set which consist of both treatment naive and treatment experienced patients are available. Results and analyses are therefore presented for the total patient population where data is missing for the defined sub-populations.

Proportion of patients experiencing response to ACR50

At Week 24, a significantly greater proportion of patients among the 41 patients with previous TNF inhibitor use in the guselkumab Q8W group achieved an ACR50 response, compared with patients with previous TNF inhibitor use in the placebo group, 27% (11 of 41) vs. 5% (2 of 39) , respectively; unadjusted *P* = 0.0078), see figure 6. Similarly, achievement of an ACR50 response was significantly greater in the guselkumab Q4W group 34% (13/38) than in the placebo group (34% vs. 5%; *P* = 0.0015).(3)

Figure 6: Proportion of patients with an ACR50 or at Week 24 in DISCOVER-1 amongst patients with previous TNF inhibitor use. (3)



*[a] Unadjusted *P* = 0.0078 for GUS Q8W vs. PBO and *P* = 0.0015 for GUS Q4W vs. PBO
KEY: ACR = American College of Rheumatology; GUS = guselkumab; PBO = placebo; Q8W = every eight weeks; Q4W = every four weeks.

Achievement of ACR50 response continued to improve between Weeks 24 and 52 in patients with previous TNF inhibitor use. Based on NRI analyses both the guselkumab Q8W and Q4W groups increased over time to 39.0% and

47.4%, respectively. ACR50 response rates also increased after Week 24 in the placebo → guselkumab Q4W group, reaching 23.1% at Week 52. (4)

Proportion of patients without progression, cf. mTSS

Unfortunately results on the proportion of patients without progression are not available from the DISCOVER-1 study neither for the treatment experienced or full patient population.

Proportion of patients who experience serious adverse events

Unfortunately results on the proportion of patients who experienced SAE is not publicly availble seperately for the treatment naive patients and treatment experienced population.
However, data on file results show that serious AEs were uncommon as the proportions of treatment experienced patients who experienced ≥1 or more SAEs through Week 24 were [redacted] in the guselkumab Q8W group and [redacted] in the placebo group. In addition, all SAEs were singular in occurrence.

Additionally data for the full patient population consisting of both treatment naive and treatment experienced patients is available. Results are presented for the full patient population to elaborate on SAE type. Serious AEs results for the full population consisting of treatment naive and treatment experienced patients at week 24 showed that 3.1% (4 of 127), 0% (0 of 128), and 4.0% (5 of 126) of patients in the guselkumab q8w, guselkumab q4w, and placebo groups had a SAE, respectively. In the guselkumab q8w group one patient each had a SAE with cervical dysplasia, ileus, plasma cell myeloma, and supraventricular arrhythmia, whereas one patient each in the placebo group had cardiac failure, chronic obstructive pulmonary disease, limb abscess, pain, upper respiratory tract infection. All SAEs were singular in occurrence. (3)

Qualitative review of safety profile

Placebo-controlled Period (Weeks 1-24)
Through Week 24, the proportions of patients experiencing ≥1 adverse event (AE) were generally comparable across the treatment groups (guselkumab Q8W: 53.5%; guselkumab Q4W: 55.5%; placebo: 59.5%) (Table 18).
Infections and infestations were reported in 26.8%, 22.7% and 25.4% in the guselkumab Q8W, guselkumab Q4W, and placebo groups, respectively. However, no serious infections were reported for the guselkumab treatment arms through week 24 whereas 1.6% reported serious infection in the placebo group.(3)

The most common (reported in ≥5% of patients) AEs were nasopharyngitis (12.6%, 5.5%, and 6.3% in the guselkumab Q8W, guselkumab 100 mg Q4W, and placebo groups, respectively) and upper respiratory tract infection (URTI; 5.5%, 8.6%, and 6.3%, respectively).(3)
Elevated liver enzyme levels were reported more frequently in the guselkumab Q8W group (alanine aminotransferase [ALT]: 6.3%; aspartate aminotransferase [AST]: 7.1%) and the Q4W group (3.9% and 2.3%, respectively) than in the placebo group (2.4% for both); however, these events were predominantly low-grade and no dose-dependent trend was observed. Overall, the safety and tolerability profile of guselkumab was consistent with that observed in pivotal studies of patients with moderate-to-severe PsO (VOYAGE studier). As in psoriasis, safety results were generally consistent across all patient subgroups evaluated, including age (ie, <45, 45-64, or ≥65 years), prior use of non-biologic DMARDs, and prior use of anti-TNF-α biologic therapies. Furthermore, no clinically meaningful differences in safety were observed between the guselkumab Q8W and Q4W dosing regimens or between patients with or without previous TNF inhibitor use.(3)

Table 18: Summary of treatment-emergent AEs through Week 24 in DISCOVER-1 (3)

Characteristics	Placebo (n = 126)	Guselkumab Q8W (n = 127)	Guselkumab Q4W (n = 128)
Number of patients with ≥1 AE			
Any AE (%)	59.5%	53.5%	55.5%
SAE (%)	4.0%	3.1%	0%
AE leading to treatment discontinuation (%)	2.4%	2.4%	0.8%
Infections (%)	25.4%	26.0%	24.2%
Serious infections (%)	1.6%	0%	0%
Opportunistic infections (%)	0%	0%	0%
Injection site reactions (%)	0%	1.6%	0.8%
MACE (%)	0.8%	0%	0%
Malignancies (%)	0%	0.8%[a]	0%
AEs leading to death (%)	0.8%	0%	0%

[a] Serum samples obtained prior to the first dose of guselkumab indicated the presence of pre-existing malignancy (ie, elevated level of gamma globulin and M protein, excess free kappa light chain production, and a marked abnormal kappa/lambda ratio).
KEY: AE = adverse event; MACE = major adverse cardiac event (ie, cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke); Q4W = every four weeks; Q8W = every eight weeks; SAE = serious adverse event.

Through Week 24, fewer patients discontinued treatment in the guselkumab Q8W (3.1%) and Q4W (2.3%) groups than in the placebo group (9.5%) table 19. Lack of efficacy was the most common reason for discontinuation in the placebo group (3.2% of patients); in contrast, no patients in either of the guselkumab treatment groups discontinued because of lack of efficacy.(3)

Table 19: Summary of treatment discontinuation through Week 24 in DISCOVER-1 (3)

Characteristics	Placebo (n = 126)	Guselkumab Q8W (n = 127)	Guselkumab Q4W (n = 128)
Discontinued study treatment	9.5%	3.1%	2.3%
Because of AEs	1.6%	2.4%	0.8%
AEs caused by worsening of PsA	1.6%	0.8%	0%
Other AEs	0%	1.6%	0.8%
Lack of efficacy	3.2%	0%	0%
Initiation of protocol-prohibited medications	0.8%	0%	0%
Withdrawal of consent	2.4%	0%	0.8%
Lost to follow-up	0.8%	0%	0%
Pregnancy	0%	0%	0%
Death	1.8%	0%	0%
Other	0%	0.8%	0.8%

KEY: AE = adverse event; FAS = full analysis set; PsA = psoriatic arthritis; Q4W = every four weeks; Q8W = every eight weeks.
Source: DISCOVER-1

Active Treatment and Safety Follow-up Periods (Weeks 24-60)

During Weeks 24 to 60 safety outcomes remained generally consistent with earlier Week 1 to 24 results among patients who were originally assigned to guselkumab Q8W or Q4W. As a result, the proportion of patients with ≥1 AE during Weeks 1 to 60 remained similar between the guselkumab Q8W group (68.5%) and the Q4W group (69.5%) (table 20).(4) Safety outcomes are not directly comparable between the placebo group before and after crossover to guselkumab Q4W at Week 24, although fewer patients reported ≥1 AE during Weeks 24 to 60 of guselkumab treatment (48.2%; table 20) than during Weeks 1 to 24 of placebo therapy (59.5%; see table 18).(3, 4) Infections continued to be the most common AE type (guselkumab Q8W: 42.5% of patients; guselkumab Q4W: 38.3%; placebo → guselkumab Q4W: 26.3%), although few serious infections were reported (1.6%, 0%, and 1.8%, respectively). As in

earlier safety follow-up, few patients reported SAEs (6.3%, 3.1%, and 3.5%) or discontinued because of AEs (3.9%, 0.8%, and 2.6%).(4)

Adverse events from DISCOVER 1 study has not been divided into treatment experienced and treatment naive, however the results from the first 60 weeks of treatment for the combined patient group is reported here. Consistent with the placebo-controlled period, the most commonly reported AEs through Week 60 were nasopharyngitis (11% and 16%, respectively, in Q4W-randomised and Q8W-randomised patients), upper respiratory tract infection (12% and 8%), increased alanine aminotransferase (ALT) (both 7%) and increased aspartate aminotransferase (AST) (5% and 9%). No guselkumab-treated patient died or had a MACE.(14)

The frequency of serious infections continued to be low (guselkumab Q8W: 1.6% of patients; guselkumab Q4W: 0%; placebo → guselkumab Q4W: 1.8%). Furthermore, all serious infections resolved, and none necessitated study agent discontinuation. No patient had uveitis, active tuberculosis, or an opportunistic infection. One guselkumab-treated patient, with a history of asthma and concomitant inhaled corticosteroid use, had a mild, non-serious case of oral thrush. No AE of inflammatory bowel disease was reported in a guselkumab-treated patient, and no events of suicidal behaviour or self-injurious behaviour without suicidal intent were reported. Relatively few patients had clinically meaningful postbaseline abnormalities in laboratory values through Week60. For neutrophil, leucocyte and platelet counts, no further mean decreases after Week24 and no dose-related trends were observed through 1 year of guselkumab. The majority of ALT and AST elevations were transient, resolved and did not require study agent discontinuation. Among patients with baseline values at or below the ULN, ALT and AST concentrations increased to above the ULN in 32% (64/200) and 27% (54/200), respectively, of guselkumab-treated patients receiving methotrexate and in 26% (43/167) and 24% (40/166), respectively, of those not receiving methotrexate, at baseline.(4)

Table 20: Summary of treatment-emergent AEs through Week 60 in DISCOVER-1.(4)

Characteristics	GUS Q8W Weeks 1-60 (n = 127)	GUS Q4W Weeks 1-60 (n = 128)	Placebo → GUS Q4W Weeks 24-60[a] (n = 114)
Number of patients with ≥1 AE			
Any AE (%)	68.5%	69.5%	48.2%
SAE (%)	6.3%	3.1%	3.5%
AE leading to treatment discontinuation (%)	3.9%	0.8%	2.6%
Infections (%)	42.5%	38.3%	26.3%
Serious infections (%)	1.6%	0%	1.8%
Opportunistic infections (%)	0%	0%	0%
Injection site reactions (%)	1.6%	3.1%	1.8%
Suicidal ideation or behavior	1.6%	0.8%	0.9%
MACE (%)	0%	0%	0%
Malignancies (%)	0.8%[b]	0%	0.9%[c]
AEs leading to death (%)	0%	0%	0%

[a] Note: all AEs in the placebo → guselkumab Q4W group are reported *after* crossover to guselkumab at Week 24 (ie, from Weeks 24-60); see table 18 above for AEs reported in the placebo group during Weeks 1-24 (prior to crossover).
[b] Serum samples obtained prior to the first dose of guselkumab indicated the presence of pre-existing malignancy (ie, elevated level of gamma globulin and M protein, excess free kappa light chain production, and a marked abnormal kappa/lambda ratio).
[c] One patient in the placebo → guselkumab Q4W group had squamous cell carcinoma (mild) and malignant melanoma (moderate). Neither event was considered related to study treatment, as per the patient narrative. The patient had a prior squamous cell carcinoma in a similar location before enrollment and had a maternal history of melanoma. Both events were resolved after discontinuation.
KEY: AE = adverse event; GUS = guselkumab; MACE = major adverse cardiac event (ie, cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke); Q4W = every four weeks; Q8W = every eight weeks; SAE = serious adverse event.

Treatment discontinuation remained low throughout Weeks 1 to 60 among patients who were originally assigned to guselkumab Q8W (8.7%) or Q4W (3.1%) (table 21). Treatment discontinuation was also lower in the placebo → guselkumab Q4W group during Weeks 24 to 60 of guselkumab treatment (6.1%; table 19) than during Weeks 1 to 24 of placebo therapy (9.5%; see table 19).(4)

Table 21: Summary of treatment discontinuation through Week 48 in DISCOVER-1.(4)

Characteristics	GUS Q8W Weeks 1-48 (n = 127)	GUS Q4W Weeks 1-48 (n = 128)	Placebo → GUS Q4W Weeks 24-48[a] (n = 114)
Discontinued study treatment	8.7%	3.1%	6.1%
Because of AEs	3.9%	0.8%	2.6%
AEs caused by worsening of PsA	0.8%	0%	0.9%
Other AEs	3.1%	0.8%	1.8%
Lack of efficacy	2.4%	0.8%	3.5%
Initiation of protocol-prohibited medications	0%	0%	0%
Withdrawal of consent	1.6%	0.8%	0%
Lost to follow-up	0%	0%	0%
Pregnancy	0%	0%	0%
Death	0%	0%	0%
Other	0%	0.8%	0%

[a] Note: all discontinuations in the placebo → guselkumab Q4W group are reported *after* crossover to guselkumab at Week 24 (ie, from Weeks 24-48); see table 19 above discontinuation Weeks 1-24 (prior to crossover).
KEY: AE = adverse event; FAS = full analysis set; GUS = guselkumab; PsA = psoriatic arthritis; Q4W = every four weeks; Q8W = every eight weeks.

Mean change from baseline on Short Form 36 (SF-36), the physical function subdomain

At week 24, a significantly greater improvement in the least squares mean change from baseline in SF-36, the physical function subdomain was observed in both the guselkumab Q4W (LS mean: 6.952, CI: 5.571-8.333) and Q8W groups (5.776, CI: 4.394-7.158) compared with the placebo group (1.636, CI: 0.249-3.023).(14) The LS mean difference when comparing Guselkumab Q8W with placebo was [redacted] and guselkumab Q4W compared with placebo was [redacted] (19)

Mean change from baseline on SF-36, the bodily pain subdomain

At week 24, a significantly greater improvement in the least squares mean change from baseline in SF-36, the bodily pain subdomain was observed in both the guselkumab Q4W (LS mean: 7.490, CI: 6.110 to 8.871) and Q8W groups (6.840, CI: 5.459 to 8.221) compared with the placebo group (2.854, CI: 1.468 to 4.240). (14) The LS mean difference when comparing Guselkumab Q8W with placebo was [redacted] and for guselkumab Q4W compared with placebo was [redacted] (19)

Mean change from baseline on SF-36, the physical component summary

At Week 24, both the guselkumab Q4W (LS mean: 6.87, CI:5.60-8.14) and guselkumab Q8W (LS mean: 6.10, CI:4..83-7.37) group achieved a significantly greater improvement in SF-36 Physical Component Summary (PCS) scores than the placebo group (LS mean: 1.96, CI:0.69-3.24), see figure 7. The LS mean difference when comparing guselkumab Q8W with placebo was 4.14 (2.42-5.85, p<0.0001) and for guselkumab Q4W compared with placebo was 4.91 (3.19-6.63, p<0.0001) (3)

Most patients in the guselkumab Q4W (53.9%) and Q8W (51.2%) groups achieved a clinically meaningful ≥5-point improvement in SF-36 PCS scores, compared with 28.6% of patients in the placebo group (other secondary endpoint; unadjusted $P < 0.001$ for both comparisons). (14)

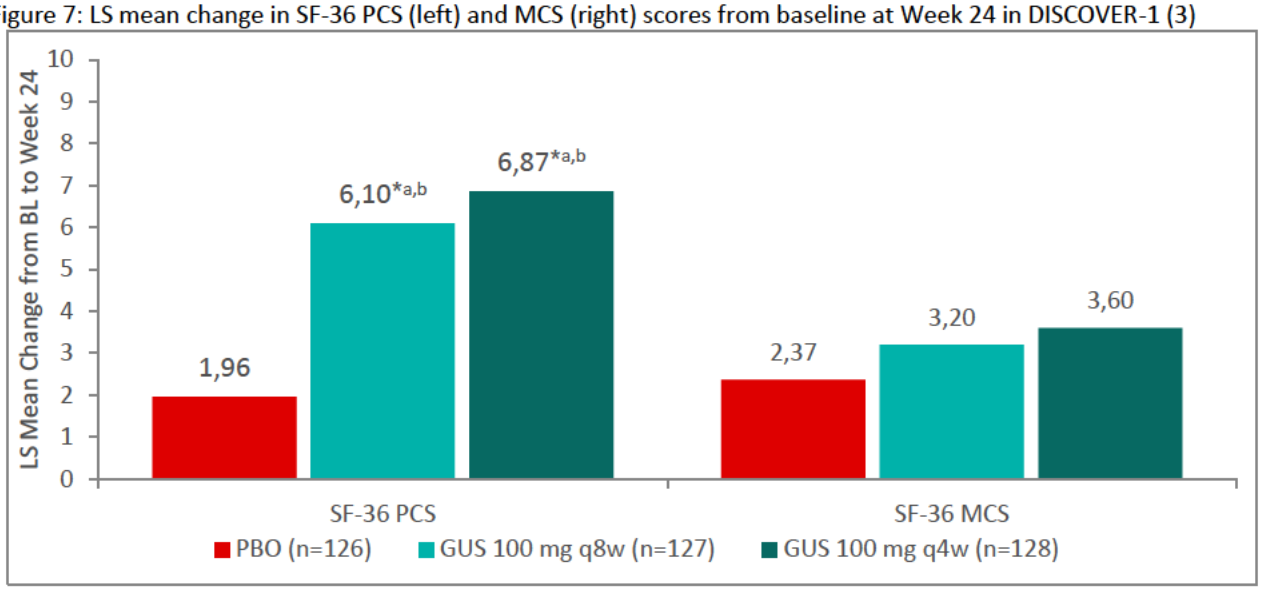
In addition SF-36 PCS scores, analysed with imputation of missing data, improved from Week 24 to Week 52 across each treatment group. At Week 52, the mean improvement in SF-36 PCS scores from baseline was 8.6 points in the guselkumab Q4W group, 6.6 points in the guselkumab Q8W group, and 5.5 points in the placebo → guselkumab Q4W group.(4)

Average change from baseline on SF-36, the mental component summary

The mean improvement in SF-36 Mental Component Summary (MCS) scores was numerically similar between each treatment group at Week 24[1] with guselkumab Q4W (LS mean: 3.60, CI:2.17-5.02) and Q8W groups (3.20, CI:1.78-4.63) compared with the placebo group (2.37, CI:0.93-3.81).The LS mean difference when comparing Guselkumab Q8W with placebo was 0.83 (-1.10-2.77, p=0.40) and for guselkumab Q4W compared with placebo was 1.23 (-0.71-3.16, p=0.21).(3)

However, more patients in the guselkumab Q4W (43.0%) and Q8W (37.8%) groups achieved a clinically meaningful ≥5-point improvement in SF-36 MCS scores than in the placebo group (25.4%; other secondary endpoint; unadjusted *P* < 0.05 for both comparisons).(14)

Figure 7: LS mean change in SF-36 PCS (left) and MCS (right) scores from baseline at Week 24 in DISCOVER-1 (3)



* *P* < 0.001 vs. placebo; [a] statistical significance was achieved for SF-36 PCS as per the global statistical testing plan; [b] statistical significance was achieved for SF-36 PCS as per the US statistical testing plan. SF-36 MCS was not multiplicity controlled as per the global and US statistical testing plans; unadjusted *P*-values were 0.214 for GUS q4w, and 0.398 for GUS q8w, vs. placebo.
KEY: BL = baseline; FAS = full analysis set; GUS = guselkumab; LS = least squares; MCS = Mental Component Summary; PBO = placebo; PCS = Physical Component Summary; q4w = every four weeks; q8w = every eight weeks; SF-36 = Short Form 36 Health Survey; US = United States.

In addition SF-36 MCS scores, analysed with imputation of missing data, improved from Week 24 to Week 52 across each treatment group. The mean improvement in SF-36 MCS scores from baseline was 4.3 points in the guselkumab Q4W group at Week 52, 4.4 points in the guselkumab Q8W group, and 4.1 points in the placebo → guselkumab Q4W group.(4)

Proportion of patients experiencing PASI90 response

Not relevant for clinical question 1.

[1] Note: SF-36 MCS was not multiplicity controlled in either the global or US statistical testing plans.

5.2.2.2 SPIRIT-P2

Ixekizumab efficacy results from SPIRIT-P2 for treatment experienced patients with PsA without moderate to severe plaque PsO defined in the Medicine Council protocol is presented in the following section. SAE are presented to enable a comparative analysis with data from the DISCOVER-1 study for guselkumab. Overview of the results is available in table A3e in the appendix.

Proportion of patients experiencing response to ACR50

At Week 24, a significantly greater proportion of patients with previous TNF inhibitor use in the Ixekizumab Q4W group achieved an ACR50 response, compared with patients in the placebo group, 35% (43 of 122) vs. 5% (6 of 118), p<0.0001.(11)

Proportion of patients without progression, cf. mTSS

Unfortunately results for ixekizumab Q4W on the proportion of patients without progression are not available from the SPIRIT-P2 study.

Proportion of patients who experience serious side effects

The proportions of patients who experienced SAEs through Week 24 were 2% (3 of 122) in the ixekizumab Q4W group and 3% (4 of 118) in the placebo group. In the ixekizumab Q4W group one of the SAE was reported as prostate cancer and led to study discontinuation. (11)

Qualitative review of safety profile

The proportions of patients experiencing treatment-emergent AEs through Week 24 were higher in the ixekizumab Q4W group compared with the placebo group: 68% in the ixekizumab Q4W group and 64% in the placebo group (Table 22).(11)

The proportion of patients with infections were also higher in the in the ixekizumab Q4W group (39%) compared to the placebo group (30%). The most common AEs reported were upper respiratory tract infection (9% in the ixekizumab Q4W group and 8% in the placebo group) followed by nasopharyngitis (7% in the ixekizumab Q4W group and 3% in the placebo group) and injection site reaction (7% in the ixekizumab Q4W group and 1% in the placebo group). Through Week 24, 5 (4.0%) patients discontinued treatment in the ixekizumab Q4W group and 6 (5%) patients in the placebo group.(11)

Table 22: Summary of treatment-emergent AEs through Week 24 in SPIRIT-P2 (11)

Characteristics	Placebo (n = 118)	Ixekizumab (n = 122)
Number of patients with ≥1 AE		
Any AE (%)	64%	68%
SAE (%)	3%	2%
AE leading to treatment discontinuation (%)	5%	4%
Infections (%)	30%	39%
Serious infections (%)	0%	0%
Candida infections (%)	0%	2%
Injection site reactions (%)	1%	7%
Cerebro-cardiovascular events (%)	2%%	0%
Malignancies (%)	0%	2%

KEY: AE = adverse event; MACE = major adverse cardiac event; SAE = serious adverse event.

The proportion of patients with any AE amongst the 168 ixekizumab Q4W patient included through the 3 years extension period of SPIRIT-P2 study was 83.9% and in the 1. Year the proportion was 79.2% (table 23). Infections continued to be the most common AE type with 66.7% of ixekizumab Q4W patients experiencing an infection over the 3-year period and 54.2% within the first year. Few were experiencing a serious infection (3%) at 3 years and 1.2% at year 1. In addition, injection-site reaction (14.9%) at 3 years and 13.7% at year 1 remained the second most commonly reported AE.(12)

Few patients reported SAEs at 1 year (4.2%) compared to the overall 3-year period (11.3%). Furthermore, lower proportion discontinued because of AEs (4.1%) at 1 year compared to the 3-year period 10.1%.(12)

Table 23: Summary of treatment-emergent AEs throughout the 3 years extension period of SPIRIT-P2.(12)

Characteristics	Ixekizumab Q4W (3 years period) (n = 168)	Ixekizumab Q4W (years 0-1) (n = 168)
Number of patients with ≥1 AE		
Any AE (%)	83.9%	79.2%
SAE (%)	11.3%	4.2%
AE leading to treatment discontinuation (%)	10.1%	4.2%
Infections (%)	66.7%	54.2%
Serious infections (%)	3.0%	1.2%
Injection site reactions (%)	14.9%	13.7%
Cerebro-cardiovascular events (%)	2%	0%
Malignancies (%)	4.2%	1.8%
Death (%)	0.6%	0%

KEY: AE = adverse event; MACE = major adverse cardiac event; SAE = serious adverse event.

Mean change from baseline on Short Form 36 (SF-36), the physical function subdomain

Mean SF-36 domain scores i.e. the physical function subdomain was analysed by imputating missing data using the the modified baseline observation carried forward method. Results are only available for the ixekizumab Q4W group (n=122) and the not placebo group. At Week 24, the ixekizumab Q4W mean change from baseline was 17.1 (standard error [SE]:2.3) which increased to 18.8 (2.3) at week 52.(13)

Mean change from baseline on SF-36, the bodily pain subdomain

Mean SF-36 domain scores i.e. the bodily pain subdomain was analysed by imputating missing data using the modified baseline observation carried forward method. Results are only available for the ixekizumab Q4W group (n=122) and the not placebo group. At Week 24, the ixekizumab Q4W mean change from baseline was 17.1 (SE:2.2) which increased to 19.6 (2.1) at week 52.(13)

Mean change from baseline on SF-36, the physical component summary

At Week 24, the ixekizumab Q4W (LS mean: 8.9, SE:1.3) group achieved a significantly greater improvement in SF-36 Physical Component Summary (PCS) scores than the placebo group (LS mean: 3.3, SE:1.4) with a LS mean difference (5.6; CI:3.2-8.0, $P < 0.0001$).(13)

Average change from baseline on SF-36, the mental component summary

At Week 24, the ixekizumab Q4W (LS mean: 3.6, SE:1.2) group achieved a significant greater improvement in SF-36 Mental Component Summary (MCS) scores than the placebo group (LS mean: 0.9, SE:1.3) with a LS mean difference (2.7; CI:0.4-5.0, $P = 0.02$).(13)

Proportion of patients experiencing PASI90 response

Not relevant for clinical question 1.

5.2.3 Comparative analyses of guselkumab vs. ixekizumab

Gusekumab has not been directly compared to ixekizumab for the treatment of PsA in any published randomized trials. Consequently, an indirect comparison between guselkumab and ixekizumab has been performed utilizing Bucher's methodology with the results available in table A4b in the appendix. Indirect comparison between guselkumab and ixekizumab has been performed based on Bucher´s. Absolute difference in effect were calculated using the estimated risk ratio and the formula provided in the Handbook of the Medicines Council's process and methodologies.

Proportion of patients experiencing response to ACR50

The relative difference in RR between guselkumab Q8W and ixekizumab Q4W in the proportion of patients achieving ACR50 response at week 24 is 0.75 (0.14-3.95). As the confidence interval of the relative difference does not correspond to any of the specified confidence limits as per the Handbook of the Medicines Council´s process and methodologies for new pharmaceuticals and indication expansions, the preliminary clinically added value cannot be categorized, see table 24.(21)

In addition, the absolute difference in effect is -8.6% (-30.2%-104.1%) Thus, the preliminary added value cannot be categorized. This is evident when the confidence interval around the absolute effect difference is compared with the least clinically relevant difference of 15%-point and the criteria for the different preliminary categorize. This is evident when the confidence interval around the absolute effect difference is compared with the least clinically relevant difference of 5%-point and the criteria for the different preliminary categorize. More specifically the upper bound of 104.1% is neither equal to; upper limit (UL) < -15%-point and the lower limit (LL) is not equal to; LL > -15%-point nor equal to; LL ≥ 15%-point.

Table 24: Clinically added value of guselkumab comparted to ixekizumab in regard to ACR50 response at week 24.

Clinically added value – ACR50		
Absolute difference – ACR50	**Least clinically relevant difference – 15%**	**Estimated absolute difference (CI)**
Merværdi af ukendt størrelse	LL ≥ MKRF	
Ingen dokumenteret merværdi	LL > -MKRF	
Negativ merværdi	UL < -MKRF	
Kan ikke kategoriseres		-8.6% (-30.2%-104.1%)
Relative difference - ACR50	**Specified confidence limit - ACR50**	**RR (CI)**
Stor merværdi	LL>1.33	
Moderat merværdi	1.33 ≥ LL > 1.11	
Lille merværdi	1.11 ≥ LL > 1.00 og UL ≤ 1.33	
Merværdi af ukendt størrelse	1.11 ≥ LL > 1.00 og UL > 1.33	
Ingen dokumenteret merværdi	0.90<LL=<1.00 og UL>=1.00	
Negativ merværdi	UL<1.00	
Kan ikke kategoriseres		0.75 (0.14-3.95)

KEY: ACR = American College of Rheumatology; CI = confidence interval; Upper limit = UL; LL= lower limit; MKRF = Mindste klinisk relevante forskel; RR = relative risk

Proportion of patients without progression, cf. mTSS

Unfortunately a comparative analysis of guselkumab Q8W and ixekizumab Q4W on the proportion of patients without progression is not possible as data is not available for ixekizumab.

Proportion of patients who experience serious side effects

The relative difference in RR between guselkumab Q8W and ixekizumab Q4W in the proportion of patients experiencing a SAE at week 24 is 1.31 (0.16-11.06). As the confidence interval of the relative difference does not correspond to any of the specified confidence limits as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions, the preliminary clinically added value cannot be categorized, see table 25. (21)

In addition, the estimated difference on absolute effect is 0.8% (-2.1%- 24.7%). Thus, the preliminary added value cannot be categorized. This is evident when the confidence interval around the absolute effect difference is compared with the least clinically relevant difference of 5%-point and the criteria for the different preliminary categorize. More specifically the upper bound of 24.7% is neither equal to; upper limit (UL) ≤ -5%-point nor is it equal to; UL < 5%-point and the lower bound of -2.1% is not equal to; LL > MKRF 5%-point.

Table 25: Clinically added value of guselkumab in regards to SAEs at week 24.

Clinically added value – Serious adverse events		
Absolute difference - SAE	**Least clinically relevant difference** - 5%	**Estimated CI**
Merværdi af ukendt størrelse	UL ≤ -MKRF	
Ingen dokumenteret merværdi	UL < MKRF	
Negativ merværdi	LL > MKRF	
Kan ikke kategoriseres		0.8% (-2.1%- 24.7%)
Relative difference - SAE	**Specified confidence limit - SAE**	**RR (CI)**
Stor merværdi	UL<0.75 og risiko >05%	
Moderat merværdi	0.75 ≤ UL < 0.90 eller (UL < 0.75 og risiko < 5%)	
Lille merværdi	0.90 ≤ UL < 1.00 og LL ≤ 0.75	
Merværdi af ukendt størrelse	0.90 ≤ UL < 1.00 og LL< 0.75	
Ingen dokumenteret merværdi	1.00 ≤ UL < 1.11 og LL ≤ 1.00	
Negativ merværdi	LL > 1.00	
Kan ikke kategoriseres		1.31 (0.16-11.06)

KEY: CI = confidence interval; Upper limit = UL; LL= lower limit; MKRF = Mindste klinisk relevante forskel; RR = relative risk; SAE = serious adverse event

Comparative Qualitative review of safety profile

Unfortunately DISCOVER-1 safety results for guselkumab Q8W are not available seperately for the treatment experienced population. However, data for the full patient population consisting of both treatment naive and treatment experienced patients is available and will be used in this comparative qualitative review of guselkumab Q8W and Ixekizumab Q4W safety profile for treatment experienced patients.

The proportion of patients experiencing any AEs through week 24 is noticeably higher among patients treated with ixekizumab with a narratively reviewed difference of 14.5% comparing the data reported from DISCOVER-1 with data reported from SPIRIT-P2, see table 26. In addition, the proportion of patients experiencing infections are also noticeably higher among ixekizumab Q4W treated patients compared to guselkumab Q8W treated patients. More specifically the narratively reviewed increased proportion is of 13%. For the rest of the safety outcomes the frequencies were comparable across the guselkumab treatment group and the ixekizumab treatment group although

the frequency in all cases were higher for ixekizumab. Thus, the safety profile of guselkumab is considered to be superior to ixekizumab at week 24.

Table 26: Comparison of treatment-emergent AEs through Week 24 in DISCOVER-1 and SPIRIT-P2.(3, 11)

Characteristics	Guselkumab Q8W (n = 127)	Ixekizumab Q4W (n = 122)
Number of patients with ≥1 AE		
Any AE (%)	53.5%	68%
SAE (%)	3.1%	2%
AE leading to treatment discontinuation (%)	2.4%	4%
Infections (%)	26.0%	39%
Serious infections (%)	0%	0%
Opportunistic infections (%)	0%	2%*
Injection site reactions (%)	1.6%	7%
MACE (%)	0%	0%
Malignancies (%)	0.8%	2%
AEs leading to death (%)	0%	0%

*candida infections KEY: AE = adverse events; SAE = serious adverse events; MACE = major adverse cardiac event (ie, cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke)

Furthermore, long-term safety of guselkumab is superior to ixekizumab when conducting a narrative review of the week 1-60 safety data reported for guselkumab in DISCOVER-1 and 1 year as well as 3 years safety data for ixekizumab.

The proportion of guselkumab Q8W patients experiencing any AEs through weeks 1-60 is noticeably lower than patients treated with ixekizumab through 1 year with a narratively reviewed difference of 10.7% when data reported from DISCOVER-1 is compared with data from SPIRIT-P2, see table 27. However, the difference is 15.4% when comparing the 1-60 weeks safety data for guselkumab with the 3-year safety data for ixekizumab. **(4, 12)**
In addition, the proportion of patients experiencing infections are also noticeably higher among ixekizumab treated patients compared to guselkumab Q8W treated patients. More specifically the narratively reviewed increased proportions is of 11.7% when comparing the 1-60 weeks safety data for guselkumab with the 1-year safety data for ixekizumab and 24.2% when comparing with the 3-year safety data for ixekizumab. Injection site reactions were also more frequent in patients treated with ixekizumab Q4W compared to patients treated with guselkumab Q8W with a difference of 12.1% at 1-year and 13.3% when comparing to the 3-years data. For the rest of the safety outcomes the long-term frequencies were comparable across the guselkumab treatment group and the ixekizumab treatment group. **(4, 12)** Thus, the long-term safety profile of guselkumab is considered to be superior to ixekizumab.
table 27: Comparison of treatment-emergent AEs through Week 60 in DISCOVER-1 and through 1 year and 3 years in SPIRIT-P2. (4, 12)

Table 27: Comparison of treatment-emergent AEs through Week 60 in DISCOVER-1 and through 1 year and 3 years in SPIRIT-P2.

Characteristics	GUS Q8W Weeks 1-60 (n = 127)	Ixekizumab Q4W (3 years period) (n = 168)	Ixekizumab Q4W (years 0-1) (n = 168)
Number of patients with ≥1 AE			
Any AE (%)	68.5%	83.9%	79.2%
SAE (%)	6.3%	11.3%	4.2%
AE leading to treatment discontinuation (%)	3.9%	10.1%	4.2%
Infections (%)	42.5%	66.7%	54.2%
Serious infections (%)	1.6%	3.0%	1.2%
Opportunistic infections (%)	0%	n/a	n/a
Injection site reactions (%)	1.6%	14.9%	13.7%
Suicidal ideation or behavior	1.6%	n/a	n/a
MACE (%)	0%	2%	0%
Malignancies (%)	0.8%	4.2%	1.8%
AEs leading to death (%)	0%	0.6%	0%

KEY: AE = adverse events; SAE = serious adverse events; MACE = major adverse cardiac event (ie, cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke)

In addition to the comparative qualitative review based on safety data reported in the DISOVER-1 and SPIRIT-P2 study a qualitative review of safety based on the SMPCs for guselkumab and ixekizumab is provided in the following section.

Based on the SMPC, guselkumab has the following contraindications 1) serious hypersensitivity to the active substance or to any of the excipients; histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose and water for injections and 2) cinically important active infections (e.g., active tuberculosis). Similarly, ixekizumab has the following contraindications 1) serious hypersensitivity to the active substance or to any of the excipients; sodium citrate, citric acid, anhydrous, sodium chloride, polysorbate 80 and water for injections and 2) cinically important active infections (e.g., active tuberculosis).(1, 23)
However, when comparing the special warning and precautions for use some differences appears, see table A5 in the appendix. For example, ixekizumab has special warning for Inflammatory bowel disease (including Crohn's disease and ulcerative colitis) which is not the case for guselkumab. (1, 23)
Furthermore, ixekizumab has more common adverse reactions compared to guselkumab according to the SMPCs listing adverse reactions linked to infection and infestations for guselkumab and ixekizumab. For guselkumab respiratory tract infections are very common where herpes simplex infection, tinea infections and gastroenteritis are uncommon. In contrary, upper respiratory tract infection are very common for ixekizumab whereas tinea infection and herpes simplex infection are common. Furthermore, influenza, rhinitis, oral candidiasis, conjunctivitis and cellulitis are reported to be uncommon. (1, 23)

Mean change from baseline on Short Form 36 (SF-36), the physical function subdomain
A narrative comparison between guselkumab Q8W and ixekizumab Q4W on SF-36, the physical function subdomain will be conducted in following section. However, data for the ixekizumab Q4W group vs. placebo is not reported, whereas guselkumab Q8W has reported data vs. placebo

It should be noticed that guselkumab Q8W demonstrated a significantly greater improvement in SF-36, the physical function subdomain compared the to the placebo group with a LS mean difference of [redacted] and whether that is the case for ixekuzmab Q4W is not possible to estimate. Consequently, guselkumab Q8W has in contrast to ixekizumab Q4W shown to have a significant clinical benefit in SF-36, the physical function subdomain for patients with PsA.

Mean change from baseline on SF-36, the bodily pain subdomain

A narrative comparison between guselkumab Q8W and ixekizumab Q4W will be conducted in following section. However, data for the ixekizumab Q4W group vs. placebo is not reported, whereas guselkumab Q8W has reported data vs. placebo.

It should be noticed that guselkumab Q8W demonstrated a significantly greater improvement in SF-36, the bodily pain score compared the to the placebo group with a LS mean difference of [redacted] and whether that is the case for ixekizumab Q4W is not possible to estimate. Consequently, guselkumab Q8W has in contrast to ixekizumab Q4W shown to have a significant clinical benefit in SF-36, the bodily pain subdomain for patients with PsA.

Mean change from baseline on SF-36, the physical component summary

A narrative comparison between guselkumab Q8W and ixekizumab Q4W will be conducted in following section.
As described guselkumab Q8W demonstrated a significantly greater improvement in SF-36 (PCS) scores compared to the placebo group with a LS mean difference of 4.14 (2.42-5.85, p<0.0001).(3) Similarly, the mean ixekizumab Q4W demonstrated a significantly greater improvement in SF-36 (PCS) scores compared the to the placebo group with a LS mean difference of (5.6; CI:3.2-8.0, *P* < 0.0001).(13) The two LS mean differences vs. placebo are at the same level with a narrative reviewed difference on the point estimate of only 1.46 points. However, the clinically added value of both guselkumab Q8W and ixekizumab Q4W compared to placebo results in no documented added value based on the Medicines Council´s least clinically relevant difference of 7.2 points. This is shown when the confidence interval around the absolute effect difference is compared with the least clinically relevant difference of 7.2 points and the criteria for the different preliminary categorize. More specifically the upper bound of 5.85 for guselkumab Q8W and 8.0 for Ixekizumab Q4W is not equal to; upper limit (UL) < -7.2-point, however the lower limit (LL) of 2.42 for guselkumab Q8W and 3.2 for ixekizumab is equal to; LL > -7.2-point but not equal to; LL ≥ 7.2-point.

Consequently, the comparison of guselkumab Q8W and ixekizumab Q4W on mean change from baseline in SF-36 (PCS) is deemed to also result in no documented added value.

Mean change from baseline on SF-36, the mental component summary

A narrative comparison between guselkumab Q8W and ixekizumab Q4W will be conducted in following section.
As described guselkumab Q8W demonstrated a numerically greater improvement in SF-36 (MCS) scores compared the to the placebo group with a LS mean difference of 0.83 (-1.10-2.77, p=0.40). (3) In comparison ixekizumab Q4W demonstrated a significantly greater improvement in SF-36 (MCS) scores compared the to the placebo group with a LS mean difference of (2.7; CI:0.4-5.0, *P* = 0.02). (3) The LS mean differences vs. placebo is greater for ixekizumab Q4W with a narrative reviewed difference on the point estimate of only 1.87 points. However, the clinically added value of both guselkumab Q8W and ixekizumab Q4W compared to placebo results in no documented added value based on the Medicines Council´s least clinically relevant difference of 3.1 points. This is shown when the confidence interval around the absolute effect difference is compared with the least clinically relevant difference of 3.1 points and the criteria for the different preliminary categorize. More specifically the upper bound of 2.77 for guselkumab Q8W and 5.0 for Ixekizumab Q4W is not equal to; upper limit (UL) < -3.1-point, however the lower limit (LL) of -1.10 for guselkumab Q8W and 0.4 for ixekizumab Q4W is equal to; LL > -3.1-point but not equal to; LL ≥ 3.1-point.
Consequently, the comparison of guselkumab Q8W and ixekizumab Q4W on mean change from baseline in SF-36 (MCS) is deemed to also result in no documented added value.

Proportion of patients experiencing response to PASI90

Not relevant for clinical question 1.

5.3 What is the value of guselkumab compared with adalimumab for treatment naive patients with PsA with moderate to severe plaque psoriasis?

5.3.1 Presentation of relevant studies

The studies used in the assessment of the added clinical value of guselkumab for treatment naive patients compared to adalimumab consist of DISCOVER-1 and DISCOVER-2, and ADEPT as well as SPIRIT-P1 for guselkumab and adalimumab, respectively.
As mentioned in the main characteristics of included studies, the patient population in the DISCOVER-1 and DISCOVER-2 trials included patients which have active plaque PsO, with at least one psoriatic plaque of >= 2 centimeter (cm) diameter or nail changes consistent with PsO or documented history of plaque PsO. Similarly, the patient population in ADEPT included patients which have presence of active psoriatic skin lesions or a history of plaque PsO and SPIRIT-P1 included patients with presence of active psoriatic skin lesion or a history of plaque PsO.(3, 5, 7, 9)

Consequently, the results presented in clinical question 1 are also representative for clinical question 3 concerning treatment naive patients with PsA with moderate to severe plaque PsO. However, PASI 90 results from DISCOVER-1, DISCOVER-2, ADEPT and SPIRIT-P1 are only for patients with PsA with moderate to severe plaque PsO and therefore presented here in section 5.3

5.3.2 Results per study

5.3.2.1 DISCOVER-1

Proportion of patients experiencing PASI90 response
In DISCOVER-1, improvement in PASI scores of at least 90% (PASI90) were reported among patients with mild-to-severe PsO at baseline i.e. patients with at least 3% body surface area affected by PsO and investigator's global assessment score of at least 2 at week 0. 82 patients in the guselkumab Q8W group were assessed of which 53 were treatment naive.(3)
Unfortunately results on the proportion of patients who achieved PASI90 response is not publicly availble seperately for the treatment naive patients and treatment experienced population. However data on file show that at week 24, a significantly greater proportion of the patients without previous TNF inhibitor use in the guselkumab Q8W group achieved an PASI90 response, compared with patients in the placebo group, [redacted]

5.3.2.2 DISCOVER-2

Proportion of patients experiencing PASI90 response
In DISCOVER-2, improvement in PASI scores of at least 90% (PASI90) were reported among patients with mild-to-severe psoriasis at baseline i.e. patients with at least 3% body surface area affected by PsO and investigator's global assessment score of at least 2 at week 0. At Week 24, a significantly greater proportion of the patients without previous TNF inhibitor use in the guselkumab Q8W group achieved an PASI90 response, compared with patients in the placebo group, 69% (121 of 176) vs. 10% (18 of 183), p<0.0001.(5)

5.3.2.3 ADEPT

Proportion of patients experiencing PASI90 response

At Week 24, a significantly greater proportion of patients without previous TNF inhibitor use in the adalimumab Q2W group achieved an PASI90 response, compared with patients in the placebo group, 42% (29 of 69) vs. 0% (0 of 69), p<0.001.(7)

5.3.2.4 SPIRIT-P1

Proportion of patients experiencing PASI90 response

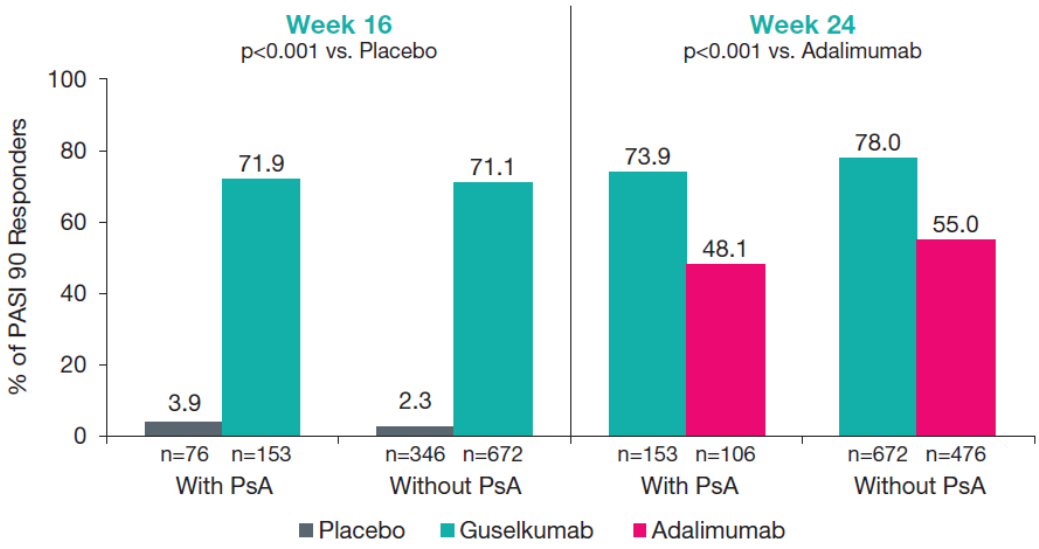
At Week 24, a significantly greater proportion of patients without previous TNF inhibitor use in the adalimumab Q2W group achieved an PASI90 response, compared with patients in the placebo group, 36.8% (37 of 101) vs. 6% (6 of 106), p≤0.001.(9)

5.3.2.5 Post-hoc analyses of patients with self-reported PsA in the voyage-1 and voyage-2 trials

Proportion of patients experiencing PASI90 response

The VOYAGE-1 and VOYAGE-2 trials were conducted in patients with moderate-to-severe PsO (N = 1.829) including 335 patients (18%) who self-reported having PsA of which 76 patients were in the placebo group, 153 in the guselkumab Q8W group and 106 patients in the adalimumab Q2W group. (24). A post-hoc pooled analysis of the VOYAGE trials found that 73.9% (113 of 153) of guselkumab-treated patients with PsA had a PASI 90 response at Week 24, compared with 48.1% (51 of 106) of adalimumab-treated patients (unadjusted *P* < 0.001) (figure 8).(24)

Figure 8: Achievement of a PASI 90 response at Weeks 16 and 24, stratified by self-reported PsA status, pooled analysis of VOYAGE-1 and VOYAGE-2 (24)



KEY: PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis.

5.3.3 Comparative analyses of guselkumab vs. adalimumab

Guselkumab has not been directly compared to adalimumab for the treatment of PsA in any published randomized trials. Consequently, an indirect comparison between guselkumab and adalimumab has been performed utilizing Bucher's methodology with the results available in table A4a in the appendix. Furthermore, meta-analysis was used to combine the results of the DISCOVER-1 and DISCOVER-2 studies for guselkumab as well as the results of the ADEPT and SPIRIT-P1 study for adalimumab using random effect models. The relevant meta-analyses are attached to this submission as a separate file. Indirect comparison between guselkumab and adalimumab has been performed based on Bucher´s methodology using the results from the meta-analyses. Absolute difference in effect were calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies.(21)

Proportion of patients experiencing response to PASI90

The relative difference in RR between guselkumab Q8W and adalimumab Q2W in the proportion of patients achieving PASI90 response at week 24 is 0.45 (0.06-3.55) when utilizing the meta-analysis results of DISCOVER-1 and DISCOVER-2 for guselkumab as well as ADEPT and SPIRIT-P1 for adalimumab. As the confidence interval of the relative difference does not correspond to any of the specified confidence limits as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions, the preliminary clinically added value cannot be categorized, see table 28.(21)

In addition, the absolute difference in effect is -21.5% (-36.6%-98.9%). Thus, the preliminary added value cannot be categorized. This is evident when the confidence interval around the absolute effect difference is compared with the least clinically relevant difference of 10%-point and the criteria for the different preliminary categorize. More specifically the upper bound of 98.9% is not equal to; upper limit (UL) < -10%-point and the lower limit (LL) of -36.6% is not equal to; LL > -10%-point nor equal to; LL ≥ 10%-point.

Table 28: Clinically added value of guselkumab comparted to adalimumab in regards to PASI90 response at week 24.

Clinically added value – PASI90		
Absolute difference – PASI90	**Least clinically relevant difference – 10%**	**Estimated absolute difference (CI)**
Merværdi af ukendt størrelse	LL ≥ MKRF	
Ingen dokumenteret merværdi	LL > -MKRF	
Negativ merværdi	UL < -MKRF	
Kan ikke kategoriseres		-21.5% (-36.6%-98.9%)
Relative difference – PASI90	**Specified confidence limit – PASI90**	**RR (CI)**
Stor merværdi	LL>1.33	
Moderat merværdi	1.33 ≥ LL > 1.11	
Lille merværdi	1.11 ≥ LL > 1.00 og UL ≤ 1.33	
Merværdi af ukendt størrelse	1.11 ≥ LL > 1.00 og UL > 1.33	
Ingen dokumenteret merværdi	0.90<LL=<1.00 og UL>=1.00	
Negativ merværdi	UL<1.00	
Kan ikke kategoriseres		0.45 (0.06-3.55)

KEY: CI = confidence interval; PASI = Psoriasis Area Severity Index; LL= lower limit; MKRF = Mindste klinisk relevante forskel; RR = relative risk; UL = upper limit

Scenario analysis on the proportion of patients experiencing PASI 90 response

A sensitivity analysis using results from the post-hoc analyses of patients with self-reported PsA in voyage-1 and voyage-2 trials is presented in following section as it reflects a direct comparison of guselkumab Q8W vs. adalimumab Q2W.

The relative difference in RR between guselkumab Q8W and adalimumab Q2W in the proportion of patients achieving PASI90 response at week 24 is 1.54 (1.23-1.91) when utilizing the post-hoc analysis results of patients with self-reported PsA in voyage-1 and voyage-2 trials. The confidence interval of the relative difference corresponds to a moderate added value categorization as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions, see table 29.(21)
In addition, the absolute difference in effect is 25.8% (11.3%-43.9%). Thus, the preliminary categorization is added value of unknown size. This is evident when the confidence interval around the absolute effect difference is compared with the least clinically relevant difference of 10%-point and the criteria for the different preliminary categorize. More specifically the upper bound of 43.9% is not equal to; upper limit (UL) < -10%-point and the lower limit (LL) of 11.3% is not equal to; LL > -10%-point but equal to; LL ≥ 10%-point.

Table 29: Clinically added value of guselkumab compared to adalimumab in regards to PASI90 response at week 24 when utilizing the post-hoc analysis results of patients with self-reported PsA in voyage-1 and voyage-2 trials.

Clinically added value – PASI90		
Absolute difference – PASI90	**Least clinically relevant difference – 10%**	**Estimated absolute difference (CI)**
Merværdi af ukendt størrelse	LL ≥ MKRF	25.8% (11.3%-43.9%)
Ingen dokumenteret merværdi	LL > -MKRF	
Negativ merværdi	UL < -MKRF	
Kan ikke kategoriseres		
Relative difference – PASI90	**Specified confidence limit – PASI90**	**RR (CI)**
Stor merværdi	LL>1.33	
Moderat merværdi	1.33 ≥ LL > 1.11	1.54 (1.23-1.91)
Lille merværdi	1.11 ≥ LL > 1.00 og UL ≤ 1.33	
Merværdi af ukendt størrelse	1.11 ≥ LL > 1.00 og UL > 1.33	
Ingen dokumenteret merværdi	0.90<LL=<1.00 og UL>=1.00	
Negativ merværdi	UL<1.00	
Kan ikke kategoriseres		

KEY: CI = confidence interval; PASI = Psoriasis Area Severity Index; LL= lower limit; MKRF = Mindste klinisk relevante forskel; RR = relative risk; UL = upper limit

5.4 What is the value of guselkumab compared with ixekizumab for treatment experienced patients with PsA with moderate to severe plaque psoriasis?

5.4.1 Presentation of relevant studies

The studies used in the assessment of the added clinical value of guselkumab for treatment experienced patients compared to ixekizumab consist of DISCOVER-1 and SPIRIT-P2 for guselkumab and ixekizumab, respectively. As mentioned in the main characteristics of included studies, the patient population in the DISCOVER-1 trial included patients which have active plaque PsO, with at least one psoriatic plaque of >= 2 centimeter (cm) diameter or nail

changes consistent with PsO or documented history of plaque PsO. Similarly, the patient population is SPIRIT-P2 included patients which have presence of active psoriatic skin lesion or a history of plaque PsO.(3, 11)

Consequently, the results presented in clinical question 2 are also representative for clinical question 4 concerning treatment experienced patients with PsA with moderate to severe plaque PsO. However, PASI 90 results from DISCOVER-1 and SPIRIT-P2 are only for patients with PsA with moderate to severe plaque PsO and therefore presented here in section 5.4

5.4.2 Results per study

5.4.2.1 DISCOVER-1

Proportion of patients experiencing response to PASI90

In DISCOVER-1, improvement in PASI scores of at least 90% (PASI90) were reported among patients with mild-to-severe PsO at baseline i.e. patients with at least 3% body surface area affected by PsO and investigator's global assessment score of at least 2 at week 0. 82 patients were assessed of which 29 were treatment experienced.(3)

Unfortunately results on the proportion of patients who achieved PASI90 response is not publicly availble seperately for the treatment naive patients and treatment experienced population. However data on file show that at week 24, a significantly greater proportion of the patients with previous TNF inhibitor use in the guselkumab Q8W group achieved an PASI90 response, compared with patients in the placebo group, [redacted]

5.4.2.2 SPIRIT-P2

Proportion of patients experiencing response to PASI90

In SPIRIT-P2, 68 (56%) patients in the ixekizumab Q4W group had PsO ≥3% of body surface area compared to 67 (56%) patients in the placebo group. At Week 24, a significantly greater proportion of the patients with previous TNF inhibitor use in the ixekizumab Q4W group achieved an PASI90 response, compared with patients in the placebo group, 44% (30 of 68) vs. 12% (8 of 67), p<0.0001.(11)

5.4.3 Comparative analyses of guselkumab vs. ixekizumab

Guselkumab has not been directly compared to ixekizumab for the treatment of PsA in any published randomized trials. Consequently, an indirect comparison between guselkumab and ixekizumab has been performed utilizing Bucher's methodology with the results available in table A4b in the appendix. The studies used in the assessment of the added clinical value of guselkumab for treatment experienced patients compared to ixekizumab consist of DISCOVER-1 and SPIRIT-P2 for guselkumab and ixekizumab, respectively.

For the efficacy endpoints, SF-36 PCS, SF-36 MCS, SF-36 the physical functioning subdomain and SF-36 the bodily pain subdomain, an indirect comparison has not been done as the mean change from baseline and mean differences between respective comparison e.g. guselkumab vs. PBO and ixekizumab vs. PBO are analyzed with different methodologies. This is will evidently limit the comparability of the outcomes and therefor a narrative review has been conducted instead. The different methodologies are described the sections beneath.

For guselkumab in both DISCOVER-1 and DISCOVER-2 the continuous endpoints of least squares mean change from baseline in SF-36 PCS, and SF-36 MCS, treatment comparisons were performed using an analysis of covariance (ANCOVA) model based on multiple imputation (MI) data. The MI method was applied to impute the missing value(s) under the assumption of missing at random (MAR). For the SF- 36 subdomains, bodily pain and physical functioning,

treatment comparisons and LS means were performed using a Mixed-Effect Model Repeated Measures (MMRM) model.

For Ixekizxumab the analyses of mean change from baseline in SF-36 PCS and SF-36 MCS differs as the mean is estimated by last observation carried forward analysis. The mean change in baseline in SF- 36 subdomains, bodily pain and physical functioning, also differs at the mean is estimated by last observation
carried forward. Furthermore. the treatment comparisons were performed using an ANCOVA model which differs from the MMRM analyses used for Guselkumab.
In addition, SF-36 PCS and SF-36 MCS for treatment experienced patients treated with ixekizumab in SPIRIT-2, treatment comparisons and LS means were performed using a Mixed-Effect Model Repeated Measures (MMRM) model. Whereas the SF-36 subdomains, bodily pain and physical functioning are analyzed using MMRM for LS mean however data are not available for the PBO population as common comparator.

Proportion of patients experiencing response to PASI90

The relative difference in RR between guselkumab Q8W and ixekizumab Q4W in the proportion of patients achieving PASI90 response at week 24 is 1.46 (0.30-6.98). As the confidence interval of the relative difference does not correspond to any of the specified confidence limits as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions, the preliminary clinically added value cannot be categorized, see table 30.
In addition, the absolute difference in effect is 20.1% (-30.7%-263.7%). Thus, the preliminary added value cannot be categorized. This is evident when the confidence interval around the absolute effect difference is compared with the least clinically relevant difference of 10%-point and the criteria for the different preliminary categorize. This is evident when the confidence interval around the absolute effect difference is compared with the least clinically relevant difference of 10%-point and the criteria for the different preliminary categorize. More specifically the upper bound of 263,7% is not equal to; upper limit (UL) < -10%-point and the lower limit (LL) of -30.7% is not equal to; LL > -10%-point nor equal to; LL ≥ 10%-point.

Table 30: Clinically added value of guselkumab comparted to ixekizumab in regards to PASI90 response at week 24.

Clinically added value – PASI90		
Absolute difference – PASI90	**Least clinically relevant difference – 10%**	**Estimated absolute difference (CI)**
Merværdi af ukendt størrelse	LL ≥ MKRF	
Ingen dokumenteret merværdi	LL > -MKRF	
Negativ merværdi	UL < -MKRF	
Kan ikke kategoriseres		20.1% (-30.7%-263.7%)
Relative difference – PASI90	**Specified confidence limit – PASI90**	**RR (CI)**
Stor merværdi	LL>1.33	
Moderat merværdi	1.33 ≥ LL > 1.11	
Lille merværdi	1.11 ≥ LL > 1.00 og UL ≤ 1.33	
Merværdi af ukendt størrelse	1.11 ≥ LL > 1.00 og UL > 1.33	
Ingen dokumenteret merværdi	0.90<LL=<1.00 og UL>=1.00	
Negativ merværdi	UL<1.00	
Kan ikke kategoriseres		1.46 (0.30-6.98)

KEY: CI = confidence interval; PASI = Psoriasis Area Severity Index; LL= lower limit; MKRF = Mindste klinisk relevante forskel; RR = relative risk; UL = upper limit

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7. Appendices

7.1 Literature search

Table A1 Inclusion and exclusion criteria

Item	Inclusion criteria	Exclusion criteria
Population	• Active psoriatic arthritis with or without moderate to severe psoriasis • ≥18 years of age	• <18 years of age
Interventions/ Comparators	• Anti-TNF agents and their biosimilars: adalimumab, • Anti-IL-23 agents: guselkumab, • Anti-IL-17 agents: ixekizumab • Placebo	• All other treatments than the ones specified in the inclusion criteria • Non-pharmacologic treatments
Outcomes	• At least one of the outcomes specified in the protocol	• NA
Study design	• Published phase III RCTs	• Non-randomized, single-arm, or observational studies • Pre-clinical studies, case reports, expert opinion articles, letters, narrative (non-systematic) reviews • Conference abstracts and posters • Phase I and Phase I/II RCTs • Pilot studies • Phase IV studies • Published phase II, II/III
Study Duration	≥24 weeks	<24 weeks
Study Language	English	Non-English

Figure A1: PRISMA Flow Diagram of Study Selection for Systematic Review

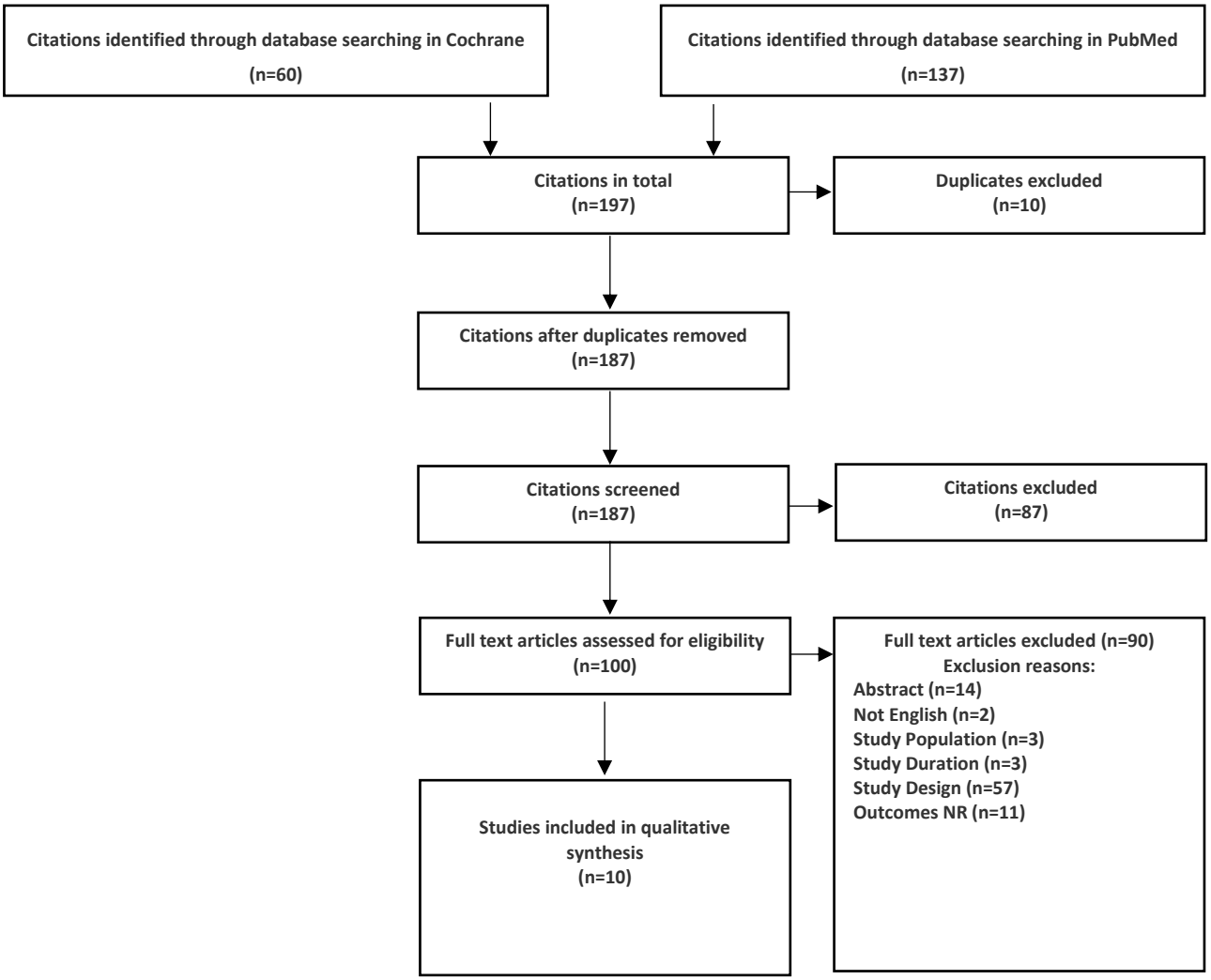

Figure A2: Screenshot of literature search conducted in Cochrane Library

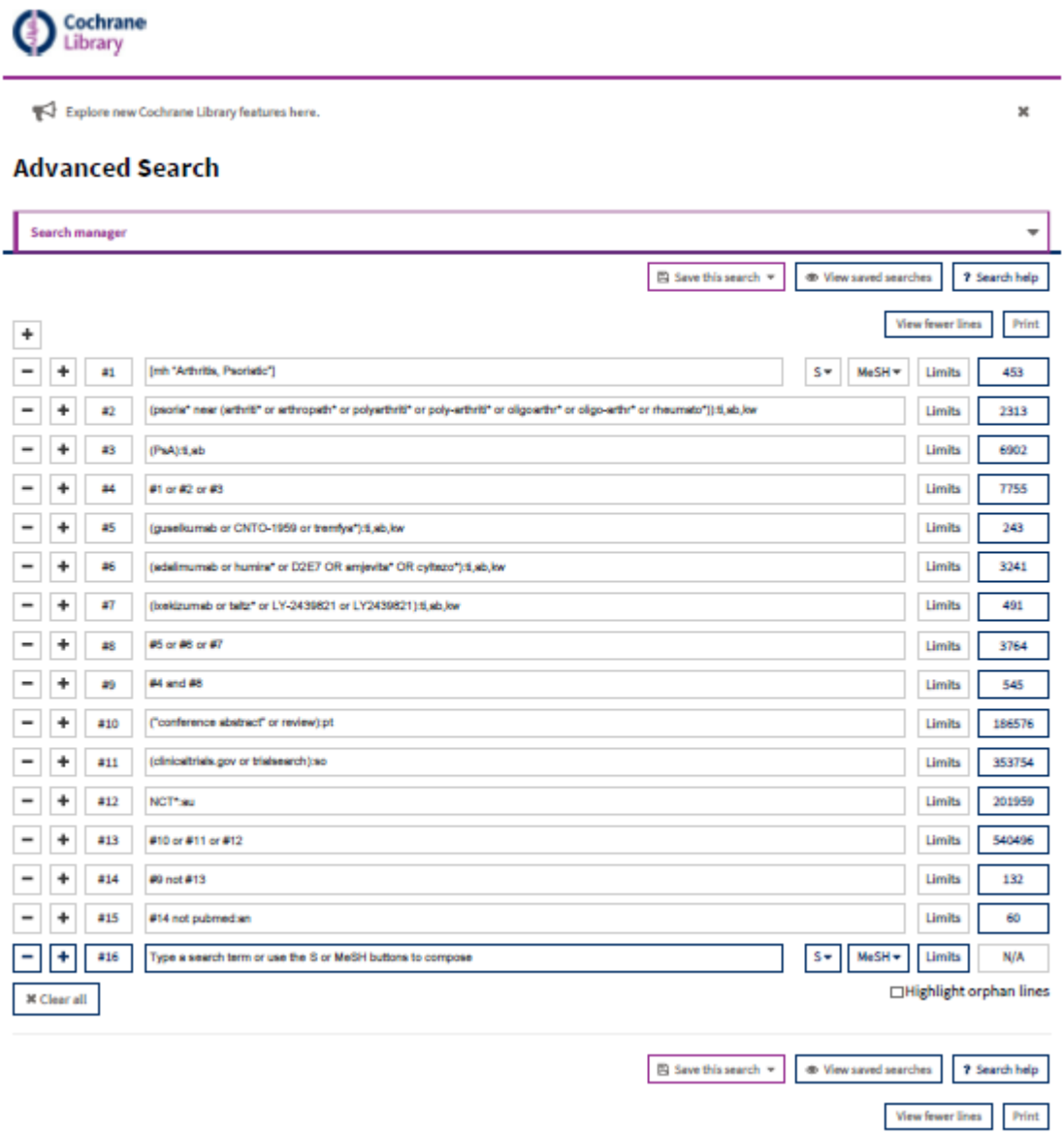

Figure A3: Screenshot of literature search conducted in Pubmed

History and Search Details

Search	Actions	Details	Query	Results	Time
#15	•••		Search: **#3 AND #10 AND #11 NOT #14**	137	09:41:06
#14	•••		Search: **#12 OR #13**	8,036,404	09:40:55
#13	•••		Search: **animal*[ti] OR murine[ti] OR mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti] OR rodent[ti]**	1,554,887	09:40:39
#12	•••		Search: **Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Guideline[pt] OR Review[pt] OR case report[ti]**	6,533,905	09:40:24
#11	•••		Search: **randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals [mh] NOT humans [mh])**	1,286,915	09:40:04
#10	•••		Search: **#4 OR #5 OR #6 OR #7 OR #8 OR #9**	9,633	09:39:46
#9	•••		Search: **ixekizumab[tiab] OR taltz*[tiab] OR LY-2439821[tiab] OR LY2439821[tiab]**	603	09:39:22
#8	•••		Search: **ixekizumab[nm]**	275	09:39:06
#7	•••		Search: **adalimumab[tiab] OR humira*[tiab] OR D2E7[tiab] OR amjevita* [tiab] OR cyltezo*[tiab]**	7,442	09:38:49
#6	•••		Search: **adalimumab[mh]**	5,550	09:38:28
#5	•••		Search: **guselkumab[tiab] OR CNTO-1959[tiab] OR tremfya*[tiab]**	266	09:38:08
#4	•••		Search: **guselkumab[nm]**	113	09:37:56
#3	•••		Search: **#1 OR #2**	47,151	09:37:35
#2	•••		Search: **PsA[tiab] OR (psoria*[tiab] AND (arthriti*[tiab] OR arthropath* [tiab] OR polyarthriti*[tiab] OR poly-arthriti*[tiab] OR oligoarthr*[tiab] OR oligo-arthr*[tiab] OR rheumato*[tiab]))**	46,236	09:37:08
#1	•••		Search: **"Arthritis, Psoriatic"[mh]**	6,395	09:36:37

7.2 Main characteristics of included studies

Table A2a Main study characteristics of DISCOVER-1 (3, 14)	
Trial name	DISCOVER-1
NCT number	NCT03162796
Objective	Establish the Efficacy and safety of guselkumab in patients with moderate to severe PsA both treatment naive and TNF experienced
Publications – title, author, journal, year	Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. Deodhar, A et al on behalf of the DISCOVER-1 Study Group Lancet, The.2020;395(10230):1115-1125
Study type and design	The study is a interventional, phase 3, randomized, double blind placebo controlled, parallel study testing the safety and efficacy of two different dosing intervals of guselkumab vs placebo in subjects with active PsA who have had inadequate response to standard therapies (eg, non-biologic DMARDs, apremilast or NSAIDs). In addition, approximately 30% of the study population could have been previously exposed to up to 2 anti-TNFα agents.
Follow-up time	The study consisted of 4 phases: a screening phase of up to 6 weeks, a blinded treatment phase of approximately 1 year (that is, 52 weeks), including a placebo controlled period from Week 0 to Week 24 and double-blind active treatment period from Week 24 to Week 52, and a safety follow-up phase of 8 weeks after Week 52 (Week 52 to 60) and will be 12 weeks from the last administration of study agent (at Week 48) to the final safety follow-up visit
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** • Have a diagnosis of Psoriatic Arthritis (PsA) for at least 6 months before the first administration of study agent and meet Classification criteria for Psoriatic Arthritis (CASPAR) at screening • Have active PsA as defined by: at least 3 swollen joints and at least 3 tender joints at screening and at baseline; and C-reactive protein (CRP) greater than or equal to (>=) 0.3 milligram per deciLitre (mg/dL) at screening from the central laboratory • Have at least 1 of the PsA subsets: distal interphalangeal joint involvement, polyarticular arthritis with absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis • Have active plaque psoriasis, with at least one psoriatic plaque of >= 2 centimeter (cm) diameter or nail changes consistent with psoriasis or documented history of plaque psoriasis • Have active PsA despite previous non-biologic DMARD, apremilast, and/or NSAID therapy : Non-biologic DMARD therapy is defined as taking a non-biologic DMARD for at least 3 months or evidence of intolerance; Apremilast therapy is defined as taking apremilast at the marketed dose approved in the country where the study is being conducted for at least 4 months or evidence of intolerance; NSAID therapy is defined as taking an NSAID for at least 4 weeks or evidence of intolerance

Table A2a Main study characteristics of DISCOVER-1 (3, 14)

	• Participants may have been previously treated with up to 2 anti-TNF (tumor necrosis factor) alpha agents (approximately 30 percent [%] of the overall study population), and must document the reason for discontinuation **Exclusion Criteria:** • Has other inflammatory diseases that might confound the evaluations of benefit of guselkumab therapy, including but not limited to RA, axial spondyloarthritis (this does not include a primary diagnosis of PsA with spondylitis), systemic lupus erythematosus, or Lyme disease • Has ever received more than 2 anti-TNFalpha agents • Has previously received any biologic treatment (other than anti-TNF alpha agents), including, but not limited to ustekinumab, abatacept, secukinumab, tildrakizumab, ixekizumab, brodalumab, risankizumab, or other investigative biologic treatment • Has previously received any systemic immunosuppressants (for example, azathioprine, cyclosporine, 6 thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, tacrolimus) within 4 weeks of the first administration of study agent • Has received apremilast within 4 weeks prior to the first administration of study agent Has previously received tofacitinib, baricitinib, filgotinib, peficitinib (ASP015K), decernotinib (VX-509), or any other JAK inhibitor
Intervention	• Group I (n=128): Guselkumab subcutaneously (SC) 100 mg every 4 weeks (q4w) from Week 0 through Week 48. • Group II (n=127): Guselkumab SC 100 mg at Weeks 0 and 4, then every 8 weeks (q8w; Weeks 12, 20, 28, 36, and 44) and placebo injections at other visits (Weeks 8, 16, 24, 32, 40, and 48) to maintain the blind; hereafter referred to as the guselkumab 100 mg q8w group. • Group III (n=126): Placebo SC q4w from Week 0 to Week 20 and crossed over at Week 24 to receive guselkumab 100 mg q4w through Week 48.
Baseline characteristics	Biologic-naive (69%) or biologic-experienced (31%) adult patients with active PsA[b]; biologic experience included prior failure on ≤2 anti-TNF-α therapies. Baseline demographics and PsA characteristics were generally comparable between treatment arms

Characteristics	Placebo (n = 126)	Guselkumab Q8W (n = 127)	Guselkumab Q4W (n = 128)
Age (years, mean)	49.0	48.9	47.4
Male (%)	48.4%	53.5%	51.6%
Weight (kg, mean)	85.2	86.3	86.7
BMI (mean)	29.6	29.9	29.9
PsA/PsO characteristics			
Mean PsA duration, years (SD)	7.2 (7.6)	6.4 (5.9)	6.6 (6.3)
Number of swollen joints 0-66 (mean)	10.1	10.9	8.6
Number of tender joints 0-68 (mean)	19.8	20.2	17.7

Table A2a Main study characteristics of DISCOVER-1 (3, 14)

DAS28-CRP (mean)	4.94	4.92	4.65
HAQ-DI score (mean)	1.1	1.2	1.1
CRP level (mean, mg/dL)	1.44	1.56	1.14
BSA (mean, %)	12%	13.1%	15.0%
IGA score of ≥2 (ie, mild-to-severe PsO; %)	73.0%	78.7%	85.9%
PASI score (mean)	7.7	8.4	9.5
Proportion with dactylitis (%)	43.7%	38.9%	29.7%
Proportion with enthesitis (LEI; %)	61.1%	57.1%	57.0%
BASDAI score[a] (mean)	6.2	6.2	5.6
Prior PsA/PsO therapies			
Anti-TNF-α biologic (%)	31%	32.3%	29.7%
Any conventional DMARDs (%)	89.7%	91.3%	89.8%
MTX (%)	80.2%	80.3%	82.0%
Baseline PsA/PsO therapies			
Non-biologic DMARDs (MTX, HCQ, SSZ, and LEF) (%)	65.1%	65.4%	64.1%
MTX (%)	56.3%	53.5%	56.3%
Oral corticosteroids (%)	15.9%	14.2%	12.5%
NSAIDs (%)	61.1%	55.9%	53.9%

[a] In patients with spondylitis and peripheral arthritis and BASDAI score >0 at baseline (n placebo = 23; n guselkumab Q8W = 24; n guselkumab Q4W = 20).

KEY: BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BMI = body mass index; BSA = body surface area; CRP = C-reactive protein; DAS-28 CRP = Disease Activity Score 28 C-reactive protein; DMARD = disease-modifying antirheumatic drug; FAS = full analysis set; HAQ-DI = Health Assessment Questionnaire Disability Index; HCQ = hydroxychloroquine; LEF = leflunomide; LEI = Leeds Enthesitis Index; MTX = methotrexate; NSAIDs = nonsteroidal anti-inflammatory drugs, PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; PsO = psoriasis; Q4W = every four weeks; Q8W = every eight weeks; SD = standard deviation; SSZ = sulfasalazine.

Primary and secondary endpoints	**Primary endpoint:** • Percentage of Participants who Achieve an American College of Rheumatology (ACR) 20 Response at Week 24 [Time Frame: Week 24] **Secondary Endpoints:** • Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Week 24 [Time Frame: Baseline and Week 24] • Percentage of Participants who Achieve an ACR 50 Response at Week 24 [Time Frame: Week 24] • Percentage of Participants With a Psoriasis Response of IGA (Score of 0 [Cleared] or 1 [Minimal]) at Week 24 Among the Participants With >=3% (percentage) BSA Psoriatic Involvement and an IGA Score of >=2 (Mild) at Baseline [Time Frame: Week 24]

Table A2a Main study characteristics of DISCOVER-1 (3, 14)	
	• Percentage of Participants who Achieve an ACR 20 Response at Week 16 [Time Frame: Week 16] • Change From Baseline in Disease Activity Score (DAS28) (C-reactive Protein [CRP]) at Week 24 [Time Frame: Baseline and Week 24] • Percentage of Participants who Achieve an ACR 70 Response at Week 24 [Time Frame: Week 24] • Percentage of Participants who Achieve an ACR 50 Response at Week 16 [Time Frame: Week 16] • Change From Baseline in 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS) at Week 24 [Time Frame: Baseline and Week 24] • Percentage of Participants With Resolution of Enthesitis at Week 24 Among the Participants With Enthesitis at Baseline [Time Frame: Week 24] • Change From Baseline in Enthesitis Score (Based on Leeds Enthesitis Index [LEI]) at Week 24 Among the Participants with Enthesitis at Baseline [Time Frame: Baseline and Week 24] • Change From Baseline in SF-36 Mental Component Summary (MCS) at Week 24 [Time Frame: Baseline and Week 24] • Percentage of Participants With Resolution of Dactylitis at Week 24 Among the Participants with Dactylitis at Baseline [Time Frame: Week 24] • Change From Baseline in Dactylitis Scores at Week 24 Among the Participants with Dactylitis at Baseline [Time Frame: Baseline and Week 24]
Method of analysis	Treatment differences were assessed via Cochran- Mntel-Haenszel testing for binary endpoints and analyses of covariance for continuous endpoints Because of differing regional health authority requirements for the multiplicity control of endpoints, two prespecified statistical testing procedures were used. For both approaches, the primary endpoint was first tested for every 4 weeks group and then for the every 8th weeks group (each at the 0·05 level).
Subgroup analyses	Subgroup analyses of the primary endpoint included establishing the proportions of patients achieving ACR20 response at week 24 by previous TNF inhibitor use and by methotrexate use.

Table A2b Main study characteristics of DISCOVER-2 (5, 16)	
Trial name	DISCOVER 2
NCT number	NCT03158285
Objective	Establish the Efficacy and safety of guselkumab in treatment naive patients with moderate to severe PsA
Publications – title, author, journal, year	Mease PJ, Rahman P et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2020 Apr 4;395(10230):1126-1136. doi: 10.1016/S0140-6736(20)30263-4.
Study type and design	DISCOVER-2 is a Phase 3 randomized, double-blind, placebo-controlled, multicenter, three-arm study of guselkumab in patients with active PsA who were biologic naïve and had an inadequate response to standard therapies (eg, non-biologic DMARDs, apremilast, NSAIDs). Eligible patients were distributed into three treatment groups in a 1:1:1 ratio using permuted block randomization stratified by baseline non-biologic DMARD use (ie, yes or no) and the most recent available CRP level prior to randomization
Follow-up time	The study consisted of a screening phase of up to 6 weeks, a blinded treatment phase of approximately 2 years (ie, 100 weeks) including a placebo-controlled period from Week 0 to Week 24 and an active treatment phase from Week 24 to Week 100, and a safety follow-up phase of 12 weeks after the last administration of study agent
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** • Have a diagnosis of Psoriatic Arthritis (PsA) for at least 6 months before the first administration of study agent and meet Classification criteria for Psoriatic Arthritis (CASPAR) at screening • Have active PsA as defined by: at least 5 swollen joints and at least 5 tender joints at screening and at baseline, and CRP greater than or equal to (>=) 0.6 milligram per deciLitre (mg/dL) at screening from the central laboratory • Have at least 1 of the PsA subsets: distal interphalangeal joint involvement, polyarticular arthritis with absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis (confirmation of sacroiliitis should be performed at the screening visit by a locally performed pelvic x-ray [single anterior-posterior view] unless a pelvic or SI joint x-ray or pelvic magnetic resonance imaging (MRI) has been previously performed. Results must be documented) • Have active plaque psoriasis, with at least one psoriatic plaque of >= 2 centimeter (cm) diameter or nail changes consistent with psoriasis or documented history of plaque psoriasis • Have active PsA despite previous non-biologic DMARD, apremilast, and/or NSAID therapy **Exclusion Criteria**: • Has other inflammatory diseases that might confound the evaluations or benefit of guselkumab therapy, including but not limited to RA, axial

Table A2b Main study characteristics of DISCOVER-2 (5, 16)

	spondyloarthritis (this does not include a primary diagnosis of PsA with spondylitis), systemic lupus erythematosus, or Lyme disease • Has previously received any biologic treatment • Has ever received tofacitinib, baricitinib, filgotinib, peficitinib (ASP015K), decernotinib (VX-509), or any other JAK inhibitor • Has received any systemic immunosuppressants (eg, azathioprine, cyclosporine, 6 thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, tacrolimus) within 4 weeks of the first administration of study agent • Is currently receiving 2 or more non-biologic DMARDs (other than MTX, SSZ, HCQ, LEF) including, but not limited to chloroquine, gold preparations, and penicillamine within 4 weeks before the first administration of study agent • Has received apremilast within 4 weeks prior to the first administration of study agent
Intervention	• Group I (n=246): Guselkumab 100 mg subcutaneously (SC) every 4 weeks (q4w) from Week 0 through Week 100. • Group II (n=248): Guselkumab 100 mg SC at Weeks 0 and 4 then q8w (Weeks 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, and 100) and placebo injections at other visits (Weeks 8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, and 96) to maintain the blind; hereafter referred to as the guselkumab 100 mg q8w group. • Group III (n=247): Placebo SC q4w from Week 0 to Week 20 and crossed over at Week 24 to receive guselkumab 100 mg SC q4w from Week 24 through Week 100.
Baseline characteristics	

Characteristics	Placebo (n = 246)	Guselkumab Q8W (n = 248)	Guselkumab Q4W (n = 245)
Age (years, mean)	46.3	44.9	45.9
Male (%)	47.6%	52.0%	58.0%
Weight (kg, mean)	84.0	83.0	85.8
BMI (mean)	29.0	28.7	29.1
PsA/psoriasis characteristics			
Mean PsA duration, years (SD)	5.8 (5.6)	5.1 (5.5)	5.5 (5.9)
Number of swollen joints 0-66 (mean)	12.3	11.7	12.9
Number of tender joints 0-68 (mean)	21.6	19.8	22.4
HAQ-DI score (mean)	1.3	1.3	1.2
CRP level (mean, mg/dL)	1.2	1.3	1.2
BSA (mean)	17.1	17.0	18.2
IGA score of 4 (ie, severe psoriasis; %)	5.7%	9.3%	11.0%
PASI score (mean)	9.3	9.7	10.8
DLQI scores (mean)	9.9	9.7	10.1

Table A2b Main study characteristics of DISCOVER-2 (5, 16)

Proportion with dactylitis (%)	40.4%	44.8%	49.4%
Proportion with enthesitis (LEI; %)	72.7%	63.7%	69.4%
Prior PsA/PsO therapies			
Any conventional DMARDs	93.1%	89.1%	90.2%
MTX	87.4%	80.2%	87.3%
Baseline PsA/PsO therapies			
Non-biologic DMARDs (MTX, HCQ, SSZ, and LEF)	69.9%	68.5%	69.4%
MTX	63.4%	56.9%	59.6%
Oral corticosteroids	19.9%	20.2%	18.8%
NSAIDs	68.3%	66.5%	69.8%

KEY: BMI = body mass index; BSA = body surface area; CRP = C-reactive protein; DLQI = Dermatology Life Quality Index; DMARD = disease-modifying antirheumatic drug; FAS = full analysis set; HAQ-DI = Health Assessment Questionnaire Disability Index; HCQ = hydroxychloroquine; LEF = leflunomide; LEI = Leeds Enthesitis Index MTX = methotrexate; NSAIDs = nonsteroidal anti-inflammatory drugs, PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; PsO = psoriasis; Q4W = every four weeks; Q8W = every eight weeks; SD = standard deviation; SSZ = sulfasalazine.

Primary and secondary endpoints	The primary endpoint was the ACR20 response rate at week 24. • Major secondary endpoints at week 24 were ACR50 and ACR70 responses; changes from baseline in DAS28-CRP scores; IGA skin response (score 0 or 1 and ≥2-grade improvement from baseline) among patients with at least 3% body surface area of psoriasis and IGA score of at least 2 (mild-to-severe psoriasis) at baseline; changes from baseline in HAQ-DI and psoriatic arthritis modified vdHS scores; changes from baseline in, and resolution of, enthesitis and dactylitis pooled across DISCOVER-1 and DISCOVER-2; changes in the SF-36 physical component summary (PCS) and mental component summary (MCS) scores; and at week 16, ACR20 and ACR50 response rates. • Other selected key secondary outcomes were clinically meaningful improvement (≥0·35) in HAQ-DI scores in patients with baseline HAQ-DI scores of at least 0·35; improvement in PASI of at least 75% (PASI75), 90% (PASI90), and 100% (PASI100) in patients with mild-to-severe psoriasis at baseline; and minimal disease activity, all at week 24. • Safety outcomes included adverse events, serious adverse events, adverse events resulting in discontinuation of study drug, infections, injection-site reactions, malignancies, major adverse cardiovascular events, suicidal ideation or behaviour and clinical laboratory abnormalities classified by National Cancer Institute common terminology criteria for adverse events (NCI-CTCAE) grades
Method of analysis	Treatment differences were assessed via Cochran- Mntel-Haenszel testing for binary endpoints and analyses of covariance for continuous endpoints Because of differing regional health authority requirements for the multiplicity control of endpoints, two prespecified statistical testing procedures were used. For

Table A2b Main study characteristics of DISCOVER-2 (5, 16)	
	both approaches, the primary endpoint was first tested for every 4 weeks group and then for the every 8th weeks group (each at the 0·05 level). Data handling rules were applied to all clinical efficacy analyses. Patients who met treatment-failure criteria (discontinued study treatment, terminated study participation, initiated or increased DMARD or oral corticosteroid doses, or initiated protocol-prohibited psoriatic arthritis treatment) were considered non-responders for binary endpoints and as having no improvement from baseline for continuous endpoints. Missing data, assumed to be missing at random, were imputed as non-responders for binary endpoints and using multiple imputation for continuous endpoints assuming they were missing at random and using the predicted value from the full conditional specification regression method (requiring 200 successful imputations) for any missing pattern
Subgroup analyses	Subgroup analyses has been conducted in PsA patients with moderate to severe psoriasis to evaluate PASI-90.

Table A2c Main study characteristics of ADEPT (7)	
Trial name	ADEPT
NCT number	NCT00195689
Objective	Efficacy and safety for adalimumab for the treatment of moderately to severely active PsA in bio naïve patients
Publications – title, author, journal, year	Adalimumab for the Treatment of Patients with Moderately to Severely Active Psoriatic Arthritis Mease PJ et al. Arthritis Rheum . 2005 Oct;52(10):3279-89. doi: 10.1002/art.21306
Study type and design	The study was a 24-week, randomized, double-blind, parallel-group, placebo-controlled trial of adalimumab therapy. Patients were stratified according to MTX use (yes or no) and degree of psoriasis involvement (≥3% or <3% of BSA) at baseline, and then randomized in a 1:1 ratio by site to receive either adalimumab or placebo.
Follow-up time	Up to 2 years
Population (inclusion and exclusion criteria)	**Inclusion criteria** • At least 18 years old, • Moderately to severely active PsA (defined as having at least 3 swollen joints and 3 tender or painful joints) • Either active psoriatic skin lesions or a documented history of psoriasis. • A history of an inadequate response or intolerance to nonsteroidal antiinflammatory drug therapy for PsA. **Exclusion criteria** • included the following: 1) treatment within 4 weeks of the baseline visit with cyclosporine, tacrolimus, DMARDs other than MTX, or oral retinoids; 2) topical treatments for psoriasis within 2 weeks of baseline, other than medicated shampoos or low-potency topical steroids; 3) concurrent treatment with MTX at dosages _30 mg/week and/or corticosteroids in a prednisone-equivalent dosage of _10 mg/day; and 4) anti-TNF therapy at any time.
Intervention	40 mg adalimumab or placebo subcutaneously every other week for 24 weeks, followed with open-label long term extension

Baseline characteristics

Characteristic	Placebo every other week (n = 162)	Adalimumab 40 mg every other week (n = 151)
Age, years	49.2 ± 11.1	48.6 ± 12.5
Sex, % male	54.9	56.3
Race, % white	93.8	97.4
Weight, kg	85.5 ± 16.5†	86.0 ± 20.6
Psoriatic arthritis duration, years	9.2 ± 8.7	9.8 ± 8.3
Psoriasis duration, years	17.1 ± 12.6†	17.2 ± 12.0
Rheumatoid factor negative, %	90.1	89.4
C-reactive protein, mg/dl (normal <0.287)	1.4 ± 1.7	1.4 ± 2.1
Subtype of PsA, no. (%)		
Symmetric polyarthritis	113 (69.8)	97 (64.2)
Asymmetric oligoarthritis	40 (24.7)	37 (24.5)
Distal interphalangeal arthropathy	8 (4.9)	15 (9.9)
Arthritis mutilans	0 (0)	1 (0.7)
Spondylitis	0 (0)	1 (0.7)
Number of previous DMARDs	1.5 ± 1.2	1.5 ± 1.2
Patients taking MTX at baseline, %	50	51
Tender joint count (0–78 joints)	25.8 ± 18.0	23.9 ± 17.3
Swollen joint count (0–76 joints)	14.3 ± 11.1	14.3 ± 12.2
Modified total Sharp score‡	19.1 ± 35.5	22.7 ± 46.0
Erosion score‡	9.2 ± 16.9	11.2 ± 21.9
Joint space narrowing score‡	10.0 ± 19.7	11.4 ± 25.5
HAQ DI (range 0–3)	1.0 ± 0.7	1.0 ± 0.6
Physician's global assessment of disease activity (0–100-mm VAS)§	53.5 ± 15.7	53.8 ± 15.7
Patient's global assessment of disease activity (0–100-mm VAS)¶	48.1 ± 21.2	47.1 ± 23.2
Patient's assessment of pain (0–100-mm VAS)¶	48.8 ± 21.7	51.1 ± 21.4
BSA ≥3% skin involvement, no.	70	70
PASI (range 0–72)#	8.3 ± 7.2	7.4 ± 6.0
Physician's global assessment of psoriasis, % "clear" or "almost clear"**	1.4	1.4

* Except where indicated otherwise, values are the mean ± SD. There were no significant differences between treatment groups at baseline. Higher scores reflect more severe disease. PsA = psoriatic arthritis; DMARDs = disease-modifying antirheumatic drugs; MTX = methotrexate; HAQ DI = Health Assessment Questionnaire disability index; VAS = visual analog scale; BSA = body surface area; PASI = Psoriasis Area and Severity Index.
† n = 161.
‡ n = 161 for placebo, n = 150 for adalimumab.
§ n = 161 for placebo, n = 149 for adalimumab.
¶ n = 161 for placebo, n = 151 for adalimumab.
# n = 69 for both placebo and adalimumab.
** n = 70 for both placebo and adalimumab.

Primary and secondary endpoints

The primary efficacy end points were the American College of Rheumatology 20% improvement (ACR20) response (27) at week 12 and the change in modified total Sharp score of structural damage on radiographs of the hands and feet at week 24

Secondary efficacy end points included the ACR20 response rate at week 24, as well as the ACR 50% and 70% (ACR50 and ACR70, respectively) response rates (27) at weeks 12 and 24.

Other secondary end points included response rates on the modified Psoriatic Arthritis Response the disability index of the Health Assessment Questionnaire (HAQ DI) and the Short Form 36 (SF-36) health survey at weeks 12 and 24. Additional

	assessments included an evaluation of dactylitis and enthesitis .Scores on the fatigue scale of the Functional Assessment of Chronic Illness Therapy (FACIT-F) For patients with psoriasis involving at least 3% of BSA at study entry, secondary end points at weeks 12 and 24 included the following measures. PASI50 and PASI75. The physician's global assessment psoriasis (PGA), the dermatology life quality index (DLQI). Safety was evaluated in terms of adverse events reported by the patients. In addition, the results of physical examinations and laboratory evaluations, which included standard chemistry, hematology, and urinalysis measures, were considered in the safety assessments.
Method of analysis	All patients who received at least 1 dose of study treatment were included in the data analysis (intention-to-treat analysis). The percentages of patients achieving ACR20, ACR50, ACR70, or PsARC responses were assessed for treatment group differences, using the Cochran-Mantel-Haenszel (CMH) mean score test adjusted for MTX use and extent of psoriasis at baseline. The PASI response was determined using the CMH mean score test adjusted for baseline MTX use. Nonresponder imputation was used, in which patients who discontinued participation in the study or had missing data were counted as nonresponders.
Subgroup analyses	NA

Table A2d Main study characteristics of SPIRIT-P1 (9, 17)	
Trial name	Spirit P1
NCT number	NCT01695239
Objective	Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in Biologic Disease-Modifying Antirheumatic Drug-Naive Patients With Active Psoriatic Arthritis
Publications – title, author, journal, year	Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naïve patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebocontrolled and active (adalimumab)-controlledperiod of the phase III trial SPIRIT-P1. Mease et al. Ann Rheum Dis 2017;76:79-87
Study type and design	A Multicenter, Randomized, Double-Blind, Active and Placebo-Controlled 24-Week Study Followed by Long Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in Biologic Disease-Modifying Antirheumatic Drug-Naive Patients With Active Psoriatic Arthritis
Follow-up time	3 years follow-up
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Presents with established diagnosis of active psoriatic arthritis for at least 6 months, and currently meets Classification for Psoriatic Arthritis (CASPAR) criteria • Active psoriatic arthritis (PsA) defined as the presence of at least 3 tender and at least 3 swollen joints • Presence of active psoriatic skin lesion or a personal history of plaque psoriasis (Ps) • Men must agree to use a reliable method of birth control or remain abstinent during the study • Women must agree to use reliable birth control or remain abstinent during the study and for at least 12 weeks after stopping treatment Exclusion Criteria: • Current or prior use of biologic agents for treatment of Ps or PsA • Inadequate response to greater than or equal to 4 conventional disease-modifying antirheumatic drugs (DMARDs) • Current use of more than one conventional DMARD • Evidence of active inflammatory arthritic syndromes or spondyloarthropathies other than PsA • Have participated in any study with interleukin 17 (IL-17) antagonists, including ixekizumab • Serious disorder or illness other than psoriatic arthritis • Serious infection within the last 3 months • Breastfeeding or nursing (lactating) women
Intervention	• Ixekizumab Q2W administered by 80 milligram (mg) subcutaneous (SC) injection every 2 weeks (Q2W). • Ixekizumab Q4W administered by 80 mg SC injection every 4 weeks (Q4W).

Table A2d Main study characteristics of SPIRIT-P1 (9, 17)

- Placebo for ixekizumab and placebo for adalimumab administered by SC injection
- Adalimumab Q2W administered by 40 mg SC injection Q2W.

Baseline characteristics

	Placebo N=106	IXEQ4W N=107	IXEQ2W N=103	Adalimumab 40 mg Q2W* N=101	Total N=417
Age (years), mean (SD)	50.6 (12.3)	49.1 (10.1)	49.8 (12.6)	48.6 (12.4)	49.5 (11.9)
Male, n (%)	48 (45.3)	45 (42.1)	48 (46.6)	51 (50.5)	192 (46.0)
Weight (kg), mean (SD)	83.8 (19.6)	85.5 (23.0)	81.6 (17.5)	91.6 (21.5)†	85.6 (20.9)
BMI (kg/m²), mean (SD)	29.2 (6.3)	30.2 (8.4)	28.6 (6.6)	32.1 (11.4)‡	30 (8.5)
Race, n (%)					
White	99 (93.4)	102 (95.3)	96 (93.2)	95 (94.1)	392 (94.0)
Asian	5 (4.7)	2 (1.9)	5 (4.9)	3 (3.0)	15 (3.6)
American Indian or Alaska native	2 (1.9)	2 (1.9)	2 (1.9)	3 (3.0)	9 (2.2)
Other	0	1 (0.9)	0	0	1 (0.2)
Time since psoriatic arthritis diagnosis (years), mean (SD)	6.3 (6.9)	6.2 (6.4)	7.2 (8.0)	6.9 (7.5)	6.7 (7.2)
Time since psoriasis diagnosis (years), mean (SD)	16.0 (13.8)	16.5 (13.8)	17.0 (14.0)	15.7 (12.7)	16.3 (13.5)
Background cDMARD therapy, n (%)					
Naive	13 (12.3)	17 (15.9)	17 (16.5)	14 (13.9)	61 (14.6)
Past use	24 (22.6)	22 (20.6)	23 (22.3)	20 (19.8)	89 (21.3)
Current use	69 (65.1)	68 (63.6)	63 (61.2)	67 (66.3)	267 (64.0)
Methotrexate current use, n (%)	59 (55.7)	57 (53.3)	53 (51.5)	57 (56.4)	226 (54.2)
Patients with specific disease characteristics, n (%)					
Current psoriasis§	102 (96.2)	100 (93.5)	95 (92.2)	97 (96.0)	394 (94.5)
Psoriasis BSA ≥3%¶	67 (67.7)	73 (73.0)	59 (64.8)	68 (72.3)	267 (69.5)
Fingernail psoriasis§	74 (69.8)	70 (65.4)	74 (71.8)	71 (70.3)	289 (69.3)
Dactylitis§	39 (36.8)	54 (50.5)	41 (39.8)	23 (22.8)‡	157 (37.6)
Enthesitis§	57 (53.8)	70 (65.4)	59 (57.3)	56 (55.4)	242 (58.0)
Baseline disease and quality of life scores, mean (SD)					
Tender joint count (68 joints)	19.2 (13.0)	20.5 (13.7)	21.5 (14.1)	19.3 (13.0)	20.1 (13.4)
Swollen joint count (66 joints)	10.6 (7.3)	11.4 (8.2)	12.1 (7.2)	9.9 (6.5)	11.0 (7.4)
HAQ-DI	1.2 (0.60)	1.2 (0.54)	1.2 (0.57)	1.1 (0.59)	1.2 (0.58)
Patient-reported pain VAS 0–100	58.5 (23.0)	60.1 (19.4)	58.4 (21.7)	58.7 (19.7)	58.9 (20.9)
Patient-assessed global disease activity VAS 0–100	61.1 (22.7)	62.7 (19.1)	62.5 (19.9)	59.1 (19.1)	61.4 (20.2)
Physician-assessed global disease activity VAS 0–100	55.9 (19.3)	57.6 (18.7)	58.5 (19.0)	55.4 (18.7)	56.9 (18.9)
CRP (mg/L)	15.1 (23.6)	12.8 (16.4)	15.1 (25.9)	13.2 (19.1)	14.1 (21.5)
mTSS	17.6 (28.6)	19.2 (32.7)	15.2 (28.9)	15.9 (27.4)	17.0 (29.4)
DAS28-CRP	4.9 (1.0)	5.0 (1.0)	5.0 (1.1)	4.9 (1.0)	4.9 (1.0)
LEI**	2.9 (1.7)	2.7 (1.6)	3.1 (1.8)	3.0 (1.6)	2.9 (1.7)
LDI-B††	46.2 (65.5)	58.1 (96.7)	40.6 (54.6)	93.9 (111.9)‡	55.8 (83.6)
LDI-B‡‡	62.7 (69.3)	73.0 (103.4)	64.0 (56.6)	119.9 (113.5)‡	75.9 (89.4)
% Psoriasis BSA involved¶	14.4 (20.2)	15.1 (16.3)	12.0 (15.6)	14.8 (19.2)	14.1 (17.9)
PASI total score¶	6.2 (7.5)	6.9 (6.6)	6.0 (7.0)	5.5 (6.5)	6.1 (6.9)
NAPSI§§	19.8 (17.2)	21.3 (18.9)	25.0 (21.2)	20.9 (17.5)	21.8 (18.8)
SF-36 PCS	34.0 (8.3)	32.4 (10.1)	34.2 (8.7)	33.9 (8.8)	33.6 (9.0)

*The adalimumab 40 mg Q2W treatment arm served as active reference for comparison with placebo. The study was not powered to test equivalence or non-inferiority of ixekizumab versus adalimumab.
†p≤0.01 vs placebo.
‡p<0.05 vs placebo.
§Presence or absence, as qualitatively assessed by the investigator.
¶Evaluated in patients with psoriasis, as qualitatively assessed by the investigator, at baseline.
**Evaluated in patients with enthesitis, as qualitatively assessed by the investigator, at baseline.
††Evaluated in patients with dactylitis, as qualitatively assessed by the investigator, at baseline.
‡‡Evaluated in patients with baseline LDI-B score >0; post hoc analysis.
§§Evaluated in patients with fingernail psoriasis, as qualitatively assessed by the investigator, at baseline.
BMI, body mass index; BSA, body surface area; cDMARD, conventional disease-modifying antirheumatic drug; CRP, C reactive protein; DAS28-CRP, 28-joint Disease Activity Score using C reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index; IXEQ2W, 80 mg ixekizumab once every 2 weeks; IXEQ4W, 80 mg ixekizumab once every 4 weeks; LDI-B, Leeds Dactylitis Index-Basic; LEI, Leeds Enthesitis Index; mTSS, van der Heijde modified total Sharp score; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; SF-36 PCS, Short Form (36 Items) Health Survey Physical Component Score; VAS, visual analogue scale.

Primary and secondary endpoints

Primary endpoints

- Percentage of Participants Achieving American College of Rheumatology 20 (ACR20) Response at Week 24 (Efficacy of Ixekizumab in Participants With Active Psoriatic Arthritis. Measure: American College of Rheumatology 20 Index [ACR20]) [Time Frame: Week 24]

Secondary endpoints

- Percentage of Participants Achieving ACR20 Response [Time Frame: Week 12]
- Percentage of Participants Achieving American College of Rheumatology 50 (ACR50) Response [Time Frame: Week 24]
- Percentage of Participants Achieving American College of Rheumatology 70 (ACR70) Score [Time Frame: Week 24]

Table A2d Main study characteristics of SPIRIT-P1 (9, 17)

- Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Scores (Quality of Life and Outcome Assessments Measures: Participant Reported Outcomes [PRO]) [Time Frame: Baseline, Week 24]
- Change From Baseline in Modified Total Sharp Score (mTSS) (Efficacy of Ixekizumab in Participants With Active Psoriatic Arthritis. Measure: Modified Total Sharp Score [mTSS]) [Time Frame: Baseline, Week 24]
- Percentage of Participants Achieving Psoriasis Area and Severity Index 75%, 90%, 100% (PASI 75, 90, 100) [Time Frame: Week 12]
- Change From Baseline in Leeds Enthesitis Index (LEI) [Time Frame: Baseline, Week 12]
- Change From Baseline in Itching Severity Using the Itch Numeric Rating Scale (NRS) (Quality of Life and Outcome Assessments Measures: Participant Reported Outcomes [PRO]) [Time Frame: Baseline, Week 12]
- Change From Baseline in Fatigue Severity NRS Score (Quality of Life and Outcome Assessments Measures: Participant Reported Outcomes [PRO]) [Time Frame: Baseline, Week 24]
- Change From Baseline in Joint Space Narrowing Score (JSN) And Bone Erosion Score (BES) [Time Frame: Baseline, Week 24]
- Change From Baseline in Medical Outcomes Study 36-item Short Form Health Survey (SF-36): Physical Component Summary (PCS) and Mental Component Summary (MCS) (Quality of Life and Outcome Assessments Measures: Participant Reported Outcomes [PRO]) [Time Frame: Baseline, Week 24]
- Change From Baseline in Quick Inventory of Depressive Symptomatology-Self Reported 16 Items (QIDS-SR16) (Quality of Life and Outcome Assessments. Measures: Patient Reported Outcomes [PRO]) [Time Frame: Baseline, Week 24]
- Change From Baseline in Disease Activity Score (28 Diarthrodial Joint Count) Based on C-ReactiveProtein (DAS28-CRP) Measure: Non-Arthritic Disease [Time Frame: Baseline, Week 24]
- Percentage of Participants Meeting the Psoriatic Arthritis Response Criteria (PsARC Modified) [Time Frame: Week 24]
- Percentage of Participants Achieving Static Physician Global Assessment (sPGA) of 0 or 1 and With at Least a 2-point Improvement From Baseline [Time Frame: Week 24]
- Percent Change From Baseline in BSA [Time Frame: Baseline, Week 24]
- Change From Baseline in the Nail Psoriasis Severity Index (NAPSI) Score Fingernail Involvement at Baseline [Time Frame: Baseline, Week 24]
- Change From Baseline in Leeds Dactylitis Index-Basic (LDI-B) [Time Frame: Baseline, Week 24]
- Change From Baseline in in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [Time Frame: Baseline, Week 24]
- Number of Participants With Treatment Emergent Anti-Ixekizumab Antibodies (TE-ADA) and Neutralizing Antibodies (NAb) [Time Frame: Baseline to Week 24]
- Percent Change in American College of Rheumatology-N (ACR-N) Score [Time Frame: Baseline, 24 Weeks]
- Change From Baseline in Tender Joint Counts (TJC) [Time Frame: Baseline, Week 24]
- Change From Baseline in Swollen Joint Counts (SJC) [Time Frame: Baseline, Week 24]
- Change From Baseline in Patient's Assessment of Pain VAS [Time Frame: Baseline, Week 24]
- Change From Baseline in Patient's Global Assessment of Disease Severity (PatGA) VAS [Time Frame: Baseline, Week 24]

Table A2d Main study characteristics of SPIRIT-P1 (9, 17)	
	• Change From Baseline in Physician's Global Assessment of Disease Activity VAS [Time Frame: Baseline, 24 Weeks] • Change From Baseline in C-Reactive Protein (CRP) [Time Frame: Baseline, Week 24] • Change From Baseline in Leeds Enthesitis Index (LEI) [Time Frame: Baseline, Week 24] • Percentage of Participants Achieving Psoriasis Area and Severity Index 75%, 90%, 100% (PASI 75, 90, 100) [Time Frame: Week 24] • Change From Baseline in Itching Severity Using the Itch NRS [Time Frame: Baseline, Week 24]
Method of analysis	Efficacy analyses were conducted on the intent-to-treat population (all randomised patients). Primary analyses of categorical variables were based on a logistic regression analysis with treatment, geographical region and baseline cDMARD experience in the model. Missing data were imputed using a non-responder imputation method, in which patients who were Inadequate Responders, or who discontinued treatment before week 24, were defined as non-responders.
Subgroup analyses	NA

Table A2e Main study characteristics of SPIRIT-P2 (11, 18)	
Trial name	SPIRIT-P2
NCT number	NCT02349295
Objective	Efficacy and safety of the treatment of ixekizumab in treatment experienced patients with active psoriatic arthritis.
Publications – title, author, journal, year	Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Nash, P *et al* Lancet 2017; 389: 2317–27
Study type and design	A Multicenter, Randomized, Double-Blind, Placebo Controlled. Patients were randomly assigned (1:1:1) by a computer-generated random sequence to receive a subcutaneous injection of 80 mg ixekizumab every 4 weeks or every 2 weeks after a 160 mg starting dose or placebo for 24 weeks.
Follow-up time	The placebo controlle time was 24 weeks. The ixekizumab treated patients were pooled with patients from SPIRIT P1 and followed in an open label extension study up to week 156
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Presents with established diagnosis of active psoriatic arthritis (PsA) for at least 6 months, and currently meets Classification for Psoriatic Arthritis (CASPAR) criteria • Active PsA defined as the presence of at least 3 tender and at least 3 swollen joints • Presence of active psoriatic skin lesion or a history of plaque psoriasis (Ps)

Table A2e Main study characteristics of SPIRIT-P2 (11, 18)	
	• Men must agree to use a reliable method of birth control or remain abstinent during the study • Women must agree to use reliable birth control or remain abstinent during the study and for at least 12 weeks after stopping treatment • Have been treated with 1 or more conventional disease-modifying antirheumatic drugs (cDMARDs) • Have had prior treatment with at least 1 and not more than 2 tumor necrosis factor (TNF) inhibitors. The participant must have discontinued at least 1 TNF inhibitor due to either an inadequate response (based on a minimum of 12 weeks on therapy) or documented intolerance. Exclusion Criteria: • Current use of biologic agents for treatment of Ps or PsA • Inadequate response to greater than 2 biologic DMARDs • Current use of more than one cDMARDs • Diagnosis of active inflammatory arthritic syndromes or spondyloarthropathies other than PsA • Have received treatment with interleukin (IL) -17 or IL12/23 targeted monoclonal antibody (MAb) therapy • Serious disorder or illness other than psoriatic arthritis • Serious infection within the last 3 months • Breastfeeding or nursing (lactating) women
Intervention	Patients were randomized at a 1:1:1 ratio to one of three treatment groups ixekizumab 80 mg every 4 weeks (n=122), ixekizumab 80 mg every 2 weeks (n=123), or placebo (n=118), all administered via subcutaneous injection. Patients randomised to ixekizumab every 4 weeks or every 2 weeks were administered a starting dose of 160 mg given as two injections at week 0.

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Table A2e Main study characteristics of SPIRIT-P2 (11, 18)

Baseline characteristics

	Placebo (n=118)	Ixekizumab every 4 weeks (n=122)	Ixekizumab every 2 weeks (n=123)
Age (years)	51·5 (10·4)	52·6 (13·6)	51·7 (11·9)
Sex			
Male	56 (47%)	63 (52%)	50 (41%)
Female	62 (53%)	59 (48%)	73 (59%)
Weight (kg)	91·0 (22·1)	89·9 (22·0)	85·2 (20·7)
BMI (kg/m²)	31·6 (7·6)	30·9 (7·1)	30·1 (6·8)
Race			
White	108 (92%)	111 (91%)	113 (93%)
Asian	7 (6%)	7 (6%)	7 (6%)
Other	3 (3%)	4 (3%)	2 (2%)
Time since psoriatic arthritis diagnosis (years)	9·2 (7·3)	11·0 (9·6)	9·9 (7·4)
Time since psoriasis diagnosis (years)	15·3 (12·6)	15·7 (12·3)	16·5 (13·0)
Present use of cDMARD	52 (44%)	60 (49%)	73 (59%)
Present use of methotrexate	40 (34%)	48 (39%)	61 (50%)
Previous TNFi treatment			
Inadequate response to one TNFi	68 (58%)	71 (58%)	65 (53%)
Inadequate response to two TNFi	41 (35%)	41 (34%)	46 (37%)
Intolerance to a TNFi*	9 (8%)	10 (8%)	12 (10%)
Patients with specific disease characteristics			
Present psoriasis†	108 (92%)	118 (97%)	113 (92%)
Psoriasis ≥3% of body surface area†	67 (57%)	68 (56%)	68 (55%)
Fingernail psoriasis†	73 (62%)	89 (73%)	74 (60%)
Dactylitis‡	14 (12%)	28 (23%)	20 (16%)
Enthesitis§	69 (58%)	68 (56%)	84 (68%)
Baseline disease and quality of life scores			
Tender joint count (68 joints)	23·0 (16·2)	22·0 (14·1)	25·0 (17·3)
Swollen joint count (66 joints)	10·3 (7·4)	13·1 (11·2)	13·5 (11·5)
HAQ-DI	1·2 (0·7)	1·2 (0·6)	1·2 (0·6)
Patient-reported pain¶	63·9 (20·1)	63·9 (21·4)	62·7 (20·9)
Patient-assessed global disease¶	64·1 (21·5)	66·4 (20·5)	66·0 (20·5)
Physician-assessed global disease¶	58·9 (20·7)	60·3 (20·9)	64·6 (16·8)
C-reactive protein (mg/L)	12·1 (19·6)	17·0 (27·5)	13·5 (26·1)
28-joint Disease Activity Score with C-reactive protein	5·0 (1·1)	5·1 (1·1)	5·1 (1·1)
LEI§	2·9 (1·7)	2·9 (1·4)	3·0 (1·7)
LDI Basic‡	37·3 (25·2)	31·5 (33·8)	53·9 (37·6)
Psoriasis body surface area involved (%)||	9·0 (13%)	12·5 (17%)	11·6 (19%)
PASI total score||	5·2 (6·3)	6·4 (7·9)	6·2 (8·7)
NAPSI**	18·7 (18·8)	20·5 (20·0)	21·0 (22·0)
SF-36 physical component summary score	33·9 (9·0)	34·8 (8·8)	34·3 (9·1)
SF-36 mental component summary score	48·0 (13·1)	49·6 (11·3)	49·1 (11·5)

Data are mean (SD) or n (%). BMI=body-mass index. cDMARD=conventional disease-modifying antirheumatic drug. TNFi=tumour necrosis factor inhibitor. HAQ-DI=Health Assessment Questionnaire-Disability Index. LDI=Leeds Dactylitis Index. LEI=Leeds Enthesitis Index. PASI=Psoriasis Area and Severity Index Improvement. NAPSI=Nail Psoriasis Severity Index. SF-36=Short Form (36 Items) Health Survey. *Patients had previously received a TNFi and had discontinued. †Qualitatively assessed by the investigator at baseline. ‡Defined as LDI>0. §Defined as LEI>0. ¶Visual analogue scale 0–100. ||Assessed only in patients with psoriasis. **Assessed only in patients with fingernail psoriasis.

Primary and secondary endpoints

The primary endpoint:

Table A2e Main study characteristics of SPIRIT-P2 (11, 18)	
	• Percentage of Participants Achieving American College of Rheumatology 20 Index (ACR20) [Time Frame: Week 24] Secondary Endpoints: • Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score [Time Frame: Baseline, Week 24], • Percentage of Participants Achieving ACR20 [Time Frame: Week 12], • Percentage of Participants Achieving American College of Rheumatology 50 Index (ACR50) [Time Frame: Week 24] • Percentage of Participants Achieving American College of Rheumatology 70 Index (ACR70) [Time Frame: Week 24], • Percentage of Participants With Psoriasis Area and Severity Index (PASI) 75 [Time Frame: Week 12], • Percentage of Patients Achieving Minimal Disease Activity (MDA) [Time Frame: Week 24], • Percentage of Patients Achieving Complete Resolution in Enthesitis as Assessed by the Leeds Enthesitis Index (LEI) [Time Frame: Week 24] • Change From Baseline in Itch Numeric Rating Scale (NRS) [Time Frame: Baseline, Week 12] • Change From Baseline in Tender Joint Count (TJC) and Swollen Joint Count (SJC) [Time Frame: Baseline, Week 24] • Change From Baseline in Participants Assessment of Pain Visual Analog Scale (VAS) [Time Frame: Baseline, Week 24] • Change From Baseline in Patients Global Assessment of Disease Activity VAS [Time Frame: Baseline, Week 24] • Change From Baseline in Physicians Global Assessment of Disease Activity VAS [Time Frame: Baseline, Week 24] • Change From Baseline in C-Reactive Protein (CRP) [Time Frame: Baseline, Week 24] • Change From Baseline in Disease Activity Score-CRP (DAS28-CRP) [Time Frame: Baseline, Week 24] • Change From Baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) Score [Time Frame: Baseline, Week 24] • Change From Baseline in Fatigue Severity Numeric Rating Scale (NRS) Score [Time Frame: Baseline, Week 24] • Change From Baseline in 36-Item Short-Form Health Survey (SF-36) Scores: Physical Component Summary (PCS) [Time Frame: Baseline, Week 24] • Change From Baseline in 36-Item Short-Form Health Survey (SF-36) Scores: Mental Component Summary (MCS) [Time Frame: Baseline, Week 24] • Number of Participants With Treatment Emergent Anti-Drug Antibodies (TE-ADA) [Time Frame: Week 24] • Number of participants with positive treatment emergent anti-ixekizumab antibodies was summarized by treatment group. • Percentage of Participants Achieving ACR 20, ACR 50 and ACR 70 [Time Frame: Week 52 and Week 156]
Method of analysis	Efficacy and health outcomes were analysed with the intention-to-treat population defined as all patients who were randomly assigned. For categorical data, a logistic regression model (with Wald's test with treatment, geographical region, and previous TNF inhibitor use incorporated into the model) was used for comparisons

Table A2e Main study characteristics of SPIRIT-P2 (11, 18)	
	unless otherwise noted. Patients who had missing data, who were deemed inadequate responders at week 16, or who discontinued treatment early were imputed as nonresponders. A graphical approach to multiplicity control that used a sequentially rejective Bonferroni multiple testing procedure (for each ixekizumab dose compared with placebo) was implemented in this study to control the family-wise error rate of 0·05. Initially, all the primary and major secondary endpoints within an ixekizumab dose regimen were tested in a sequential manner. If all the hypotheses for the dose regimen were rejected at the 0·025 level then the hypotheses related to the other dose regimen was tested at the 0·05 level. Analyses within a dose regimen were completed in the following sequence: ACR-20 at week 24; HAQ-DI change from baseline at week 24; ACR-20 at week 12; PASI-75 at week 12; minimal disease activity at week 24; and resolution of enthesitis at week 24.
Subgroup analyses	NA

7.3 Results per study

Table A3a Results of study DISCOVER-1 treatment naive									
Trial name:	DISCOVER-1								
NCT number:	NCT03162796								
					Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**n/N**	**Result**	**Measurement**	**Difference**	**95% CI**	***P* value**		
ACR50 at week 24	GUS Q8W	27/86	31%	Relative	3.03	1.52-6.07	n/a	*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(3)
	PBO	9/87	10%						
Pt. without progression, cf. mTSS	GUS Q8W	n/a	n/a		n/a	n/a	n/a		
	PBO	n/a	n/a						
SAE	GUS Q8W	[redacted]	[redacted]	Relative	[redacted]	[redacted]	n/a	*Data on file is extracted as stated in the Clinical Study Report for DISCOVER-1 and relative difference is provided as unadjusted risk ratio*	(19)
	PBO	[redacted]	[redacted]						
SF-36, the physical function subdomain	GUS Q8W	n/a	n/a		n/a	n/a	n/a		
	PBO	n/a	n/a						

Table A3a Results of study DISCOVER-1 treatment naive									
SF-36, the bodily pain subdomain	GUS Q8W PBO	n/a n/a	n/a n/a		n/a	n/a	n/a		
SF-36, the physical component summary	GUS Q8W PBO	n/a n/a	n/a n/a		n/a	n/a	n/a		
SF-36, the mental component summary	GUS Q8W PBO	n/a n/a	n/a n/a		n/a	n/a	n/a		
PASI90	GUS Q8W PBO	[redacted] [redacted]	[redacted] [redacted]	Relative	[redacted]	[redacted]	n/a	*Data on file is extracted as stated in the Clinical Study Report for DISCOVER-1 and relative difference is provided as unadjusted risk ratio*	(19)

Table A3b Results of study DISCOVER-1 bio-experience/full population									
Trial name:	DISCOVER-1								
NCT number:	NCT03162796								
					Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**n/N**	**Result (CI)**	**Measurement**	**Difference**	**95% CI**	***P* value**		
ACR50 at week 24	GUS Q8W PBO	11/41 2/39	27% 5%	Relative	5.23	1.24-22.11	n/a	*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(3)
Pt. without progression, cf. mTSS	GUS Q8W PBO	n/a n/a	n/a n/a		n/a	n/a	n/a		
SAE	GUS Q8W PBO	[redacted] [redacted]	[redacted] [redacted]	Relative	[redacted]	[redacted]		*Data on file is extracted as stated in the Clinical Study Report for DISCOVER-1 and relative difference is provided as unadjusted risk ratio*	(19)
SF-36, the physical function subdomain	GUS Q8W PBO	N=127 N=126	5.776 (4.394-7.158) 1.636 (0.249-3.023)	Absolute	[redacted]	[redacted]	[redacted]	*Data extracted from clinicaltrials.gov and LS mean difference between GUS Q8W and PBO is data on file extracted as stated in the Clinical Study Report for DISCOVER-1*	(14, 19)

Table A3b Results of study DISCOVER-1 bio-experience/full population									
SF-36, the bodily pain subdomain	GUS Q8W PBO	N=127 N=126	6.840 (5.459-8.221) 2.854 (1.468-4.240)	Absolute	[redacted]	[redacted]	[redacted]	*Data extracted from clinicaltrials.gov and LS mean difference between GUS Q8W and PBO is extracted as stated in the Clinical Study Report for DISCOVER-1*	(14, 19)
SF-36, the physical component summary	GUS Q8W PBO	N=127 N=126	6.10 (4.83-7.37) 1.96 (0.69-3.24)	Absolute	4.14	2.42-5.85	p<0.0001	*Least squares mean data extracted as stated in the study*	(3)
SF-36, the mental component summary	GUS Q8W PBO	N=127 N=126	3.20 (1.78-4.63) 2.37 (0.93-3.81)	Absolute	0.83	-1.10-2.77	P=0.40	*Least squares mean data extracted as stated in the study*	(3)
PASI90	GUS Q8W PBO	[redacted] [redacted]	[redacted] [redacted]	Relative	[redacted]	[redacted]	[redacted]	*Data on file is extracted as stated in the Clinical Study Report for DISCOVER-1 and relative difference is provided as unadjusted risk ratio*	(14, 19)

Table A3c Results of study DISCOVER-2 treatment naive									
Trial name:	DISCOVER-2								
NCT number:	NCT03158285								
					Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**n/N**	**Result (CI)**	**Measurement**	**Difference**	**95% CI**	***P* value**		
ACR50 at week 24	GUS Q8W PBO	78/248 35/246	31.5% 14.2%	Relative	2.21	1.55-3.16	n/a	*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(5)
Pt. without progression, cf. mTSS	GUS Q8W PBO	157/248 159/246	63.5% 64.7%	Relative	0.98	0.86-1.12	n/a	*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(5)
SAE	GUS Q8W PBO	3/248 7/246	1.2% 2.8%	Relative	0.43	0.11-1.61	n/a	*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(5)
	GUS Q8W	N=248	6.703 (5.764-7.642)	Absolute	[redacted]	[redacted]	[redacted]		

Table A3c Results of study DISCOVER-2 treatment naive									
SF-36, the physical function subdomain	PBO	N=246	3.254 (2.310-4.197)					*Data extracted from clinicaltrials.gov and LS mean difference between GUS Q8W and PBO is extracted as stated in the Clinical Study Report for DISCOVER-2*	(16, 20)
SF-36, the bodily pain subdomain	GUS Q8W PBO	N=248 N=246	7.811 (6.890-8.733) 3.482 (2.556-4.408)	Absolute	[redacted]	[redacted]	[redacted]	*Data extracted from clinicaltrials.gov and LS mean difference between GUS Q8W and PBO is extracted as stated in the Clinical Study Report for DISCOVER-2*	(16, 20)
SF-36, the physical component summary	GUS Q8W PBO	N=248 N=246	7.39 (6.50-8.29) 3.42 (2.53-4.32)	Absolute	3.97	2.75-5.20	P=0.011	*Least squares mean data extracted as stated in the study*	(5)
SF-36, the mental component summary	GUS Q8W PBO	N=248 N=246	4.17 (3.10-5.23) 2.14 (1.07-3.22)	Absolute	2.02	0.56-3.49	unadjusted *P* = 0.007 US analysis P=0.072	*Least squares mean data extracted as stated in the study*	(5)
PASI90	GUS Q8W PBO	121/176 18/183	69% 10%	Relative	6.99	4.46-10.96	n/a	*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(5)

Table A3d Results of study ADEPT treatment naive									
Trial name:	ADEPT								
NCT number:	NCT00195689								
					Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**n/N**	**Result (CI)**	**Measurement**	**Difference**	**95% CI**	***P* value**		
ACR50 at week 24	ADA Q2W	59/151	39%	Relative	6.33	3.36-11.92	n/a	*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(7)
	PBO	10/162	6%						
Pt. without progression, cf. mTSS	ADA Q2W	n/a	n/a	Relative	n/a	n/a	n/a		
	PBO	n/a	n/a						
SAE	ADA Q2W	5/151	3.31%	Relative	0.77	0.25-2.36	n/a	*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(7)
	PBO	7/162	4.32%						
SF-36, the physical function subdomain	ADA Q2W	n/a	n/a		n/a	n/a	n/a		
	PBO	n/a	n/a						

Table A3d Results of study ADEPT treatment naive									
SF-36, the bodily pain subdomain	ADA Q2W PBO	n/a n/a	n/a n/a		n/a	n/a	n/a		
SF-36, the physical component summary	ADA Q2W PBO	140 150	9.3 (SD:10.1) 1.4 (SD:9.6)	Absolute	7.9	5.63-10.17	n/a	*Data extracted as stated in the study and difference between means was calculated using following formula: 1) Mean difference = Mean1 – Mean2, 2) Standard error of the mean difference (SE) = $\sqrt{(SD_1^2/N_1 + SD_2^2/N_2)}$, 3) 95% CI = mean difference ± 1.96 × SE*	(7)
SF-36, the mental component summary	ADA Q2W PBO	140 152	1.8 (SD:9.3) 0.6 (SD:10.4)	Absolute	1.2	-1.06-3.46		*Data extracted as stated in the study and difference between means was calculated using following formula: 1) Mean difference = Mean1 – Mean2, 2) Standard error of the mean difference (SE) = $\sqrt{(SD_1^2/N_1 + SD_2^2/N_2)}$, 3) 95% CI = mean difference ± 1.96 × SE*	(7)
PASI90	ADA Q2W PBO	29/69 0/69	42% 0%	Relative	59	3.68-946.80		*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(7)

Table A3e Results of study SPIRIT-P1 treatment naive									
Trial name:	SPIRIT-P1								
NCT number:	NCT01695239								
					Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**n/N**	**Result (CI)**	**Measurement**	**Difference**	**95% CI**	***P* value**		
ACR50 at week 24	ADA Q2W PBO	39/101 16/106	38.6% 15.1%	Relative	2.56	1.53-4.27	n/a	*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(9)
Pt. without progression, cf. mTSS	ADA Q2W PBO	93/101 76/106	91.6% 72%	Relative	1.27	1.11-1.45	n/a	*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(9)
SAE	ADA Q2W PBO	5/101 2/106	5% 2%	Relative	2.62	0.52-13.22	n/a	*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(9)
	ADA Q2W	N=101	14.4 (SD:19.9)	Absolute	8.8	3.572-14.028			

Table A3e Results of study SPIRIT-P1 treatment naive								
SF-36, the physical function subdomain	PBO	N=106	5.6 (SD:18.4)				*Data extracted as stated in the study and difference between means was calculated using following formula (25): 1) Mean difference = Mean1 – Mean2, 2) Standard error of the mean difference (SE) = $\sqrt{(SD_1^2/N_1 + SD_2^2/N_2)}$, 3) 95% CI = mean difference ± 1.96 × SE*	(9)
SF-36, the bodily pain subdomain	ADA Q2W	N=101	16.8 (SD:21.3)	Absolute	8.5	2.891-14.109	*Data extracted as stated in the study and difference between means was calculated using following formula (25): 1) Mean difference = Mean1 – Mean2, 2) Standard error of the mean difference (SE) = $\sqrt{(SD_1^2/N_1 + SD_2^2/N_2)}$, 3) 95% CI = mean difference ± 1.96 × SE*	(9)
	PBO	N=106	8.3 (SD:19.8)					
SF-36, the physical component summary	ADA Q2W	N=101	6.3 (SD:8.3)	Absolute	3.6	1.416-5.784	*Data extracted as stated in the study and difference between means was calculated using following formula (25): 1) Mean difference = Mean1 – Mean2, 2) Standard error of the mean difference (SE) = $\sqrt{(SD_1^2/N_1 + SD_2^2/N_2)}$, 3) 95% CI = mean difference ± 1.96 × SE*	(9)
	PBO	N=106	2.7 (SD:7.7)					
	ADA Q2W	N=101	4.6 (SD:9.5)	Absolute	2.8	0.211-5.389		

Table A3e Results of study SPIRIT-P1 treatment naive								
SF-36, the mental component summary	PBO	N=106	1.8 (SD:9.5)				*Data extracted as stated in the study and difference between means was calculated using following formula (25): 1) Mean difference = Mean1 – Mean2, 2) Standard error of the mean difference (SE) = $\sqrt{(SD_1^2 / N_1 + SD_2^2 / N_2)}$, 3) 95% CI = mean difference ± 1.96 × SE*	(9)
PASI90	ADA Q2W	37/101	36.8%	Relative	6.13	2.77-13.59	*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(9)
	PBO	6/106	6%					

Table A3f Results of study SPIRIT-P2 treatment experienced									
Trial name:	SPIRIT-P2								
NCT number:	NCT02349295								
					Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**n/N**	**Result (CI)**	**Measurement**	**Difference**	**95% CI**	***P* value**		
ACR50 at week 24	IXE Q4W PBO	43/122 6/118	35% 5%	Relative	6.93	3.07-15.67	n/a	*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(11)
Pt. without progression, cf. mTSS	IXE Q4W PBO	n/a n/a	n/a n/a		n/a	n/a	n/a		
SAE	IXE Q4W PBO	3/122 4/118	2% 3%	Relative	0.73	0.17-3.17	n/a	*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(11)
SF-36, the physical function subdomain	IXE Q4W PBO	N=122 n/a	17.1 (SE:2.3) n/a		n/a	n/a	n/a	*Mean change from baseline extracted as stated in the study but only available for IXE Q4W Data*	(11)
SF-36, the bodily pain subdomain	IXE Q4W PBO	N=122 n/a	17.1 (SE:2.2) n/a		n/a	n/a	n/a	*Mean change from baseline extracted as stated in the study but only available for IXE Q4W Data*	(11)

Table A3f Results of study SPIRIT-P2 treatment experienced									
SF-36, the physical component summary	IXE Q4W PBO	N=122 N=118	8.9 (SE:1.3) 3.3 (SE:1.4)	Absolute	5.6	3.2-8.0	$P < 0.0001$	*Least squares mean data extracted as stated in the study*	(11)
SF-36, the mental component summary	IXE Q4W PBO	N=122 N=118	3.6 (SE:1.2) 0.9 (SE:1.3)	Absolute	2.7	0.4-5.0	$P = 0.02$	*Least squares mean data extracted as stated in the study*	(11)
PASI90	IXE Q4W PBO	30/68 8/67	44% 12%	Relative	3.39	1.83-7.46		*Data extracted as stated in the study and relative difference is provided as unadjusted risk ratio*	(11)

7.4 Results per PICO (clinical question)

Table A4a Results referring to <clinical question 1 and clinical question 3> comparing guselkumab Q8W to adalimumab Q2W								
Results per outcome:	*The relevant meta-analyses are attached to this submission as a separate file*							
		Absolute difference in effect			**Relative difference in effect**			**Methods used for quantitative synthesis**
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
ACR50 at week 24	DISCOVER-2, DISCOVER-1, ADEPT, SPIRIT-P1	-15.6%	-29.8%-20.9%	n/a	0.60	0.23-1.54	n/a	*Meta-analysis was used to combine the results of the DISCOVER-1 and DISCOVER-2 studies for guselkumab as well as ADEPT and SPIRIT-P1 for adalimumab using random effects model. Indirect comparison between guselkumab and adalimumab has been performed based on Bucher´s methodology using the results from the meta-analyses. Absolute difference in effect was calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies. The event rate of 38.9% for adalimumab based on meta-analysis of ACR50 was utilized.*

Table A4a Results referring to <clinical question 1 and clinical question 3> comparing guselkumab Q8W to adalimumab Q2W								
Pt. without progression, cf. mTSS	DISCOVER-2, SPIRIT-P1	-20.9%	-33.0% to -6.3%	n/a	0.77	0.64-0.93	n/a	*Indirect comparison between guselkumab and adalimumab has been performed based on Bucher´s methodology. Absolute difference in effect was calculated using the estimated risk ratio and the formula provided in the Handbook of the Medicines Council's process and methodologies. The event rate of 91.6% for adalimumab was utilized.*
SAE	DISCOVER-2, DISCOVER-1, ADEPT, SPIRIT-P1	-2.5%	-3.7%-3.52%	n/a	0.36	0.07-1-89	n/a	*Meta-analysis was used to combine the results of the DISCOVER-1 and DISCOVER-2 studies for guselkumab as well as ADEPT and SPIRIT-P1 for adalimumab using random effects model. Indirect comparison between guselkumab and adalimumab has been performed based on Bucher´s methodology using the results from the meta-analyses. Absolute difference in effect was calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies. The event rate of 4.0% for adalimumab based on meta-analysis of SAE was utilized.*
SF-36, the physical function subdomain	DISCOVER-2, SPIRIT-P1	n/a	n/a	n/a	n/a	n/a	n/a	Narrative review

Table A4a Results referring to <clinical question 1 and clinical question 3> comparing guselkumab Q8W to adalimumab Q2W							
SF-36, the bodily pain subdomain	DISCOVER-2, SPIRIT-P1	n/a	n/a	n/a	n/a	n/a	Narrative review
SF-36, the physical component summary	DISCOVER-2, ADEPT, SPIRIT-P1	n/a	n/a	n/a	n/a	n/a	Narrative review
SF-36, the mental component summary	DISCOVER-2, ADEPT, SPIRIT-P1	n/a	n/a	n/a	n/a	n/a	Narrative review
PASI90	DISCOVER-2, DISCOVER-1, ADEPT, SPIRIT-P1	-21.5%	-36.6%-98.9%		0.45	0.06-3.55	n/a	*Meta-analysis was used to combine the results of the DISCOVER-1 and DISCOVER-2 studies for guselkumab as well as ADEPT and SPIRIT-P1 for adalimumab using random effects model. Indirect comparison between guselkumab and adalimumab has been performed based on Bucher´s methodology using the results from the meta-analyses. Absolute difference in effect was calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies. The event rate of 38.8% for adalimumab based on meta-analysis of PASI90 was utilized.*

Table A4a Results referring to <clinical question 1 and clinical question 3> comparing guselkumab Q8W to adalimumab Q2W							
	Post-hoc analysis of Voyage-1 and Voyage-2	25.8%	11.3%-43.9%	1.54	1.23-1.91	n/a	*A scenario analysis using H2H data of GUS Q8W vs. adalimumab Q2W based on the post-hoc analyses of patients with self-reported PsA in voyage-1 and voyage-2 trials. The risk ratio was calculated based on data extracted from the post-hoc analysis. Absolute difference in effect was calculated using the estimated risk ratio and the formula provided in the Handbook of the Medicines Council's process and methodologies. The event rate of 48.1% for adalimumab was utilized.*

Table A4b Results referring to <clinical question 2 and clinical question 4> comparing guselkumab Q8W to ixekizumab Q4W								
Results per outcome:	*The relevant meta-analyses are attached to this submission as a separate file*							
		Absolute difference in effect			**Relative difference in effect**			**Methods used for quantitative synthesis**
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
ACR50 at week 24	DISCOVER-1, SPIRIT-P2	-8.6	-30.2%-104-1%		0.75	0.14-3.95	n/a	*The risk ratio was calculated based on data extracted from the studies. Absolute difference in effect was calculated using the estimated risk ratio and the formula provided in the Handbook of the Medicines Council's process and methodologies. The event rate of 35% for ixekizumab was utilized.*
Pt. without progression, cf. mTSS	DISCOVER-1, SPIRIT-P2	n/a	n/a	n/a	n/a	n/a	n/a	
SAE	DISCOVER-1, SPIRIT-P2	0.8%	-2.1%-24.7%		1.31	0.16-11.06	n/a	*The risk ratio was calculated based on data extracted from the studies. Absolute difference in effect was calculated using the estimated risk ratio and the formula provided in the Handbook of the Medicines Council's process and methodologies. The event rate of 2% for ixekizumab was utilized.*

Table A4b Results referring to <clinical question 2 and clinical question 4> comparing guselkumab Q8W to ixekizumab Q4W								
SF-36, the physical function subdomain	DISCOVER-1, SPIRIT-P2	n/a	n/a	n/a	n/a	n/a	n/a	Narrative review
SF-36, the bodily pain subdomain	DISCOVER-1, SPIRIT-P2	n/a	n/a	n/a	n/a	n/a	n/a	Narrative review
SF-36, the physical component summary	DISCOVER-1, SPIRIT-P2	n/a	n/a	n/a	n/a	n/a	n/a	Narrative review
SF-36, the mental component summary	DISCOVER-1, SPIRIT-P2	n/a	n/a	n/a	n/a	n/a	n/a	Narrative review
PASI90	DISCOVER-1, SPIRIT-P2	20.1%	-30.7%-263.7%	n/a	1.46	0.30-6.98	n/a	*The risk ratio was calculated based on data extracted from the studies. Absolute difference in effect was calculated using the estimated risk ratio and the formula provided in the Handbook of the Medicines Council's process and methodologies. The event rate of 44% for ixekizumab was utilized.*

7.5 Qualitative review of safety – special warnings and precautions for use

Table A5: Comparison of special warnings and precautions for use stated in the SMPCs for guselkumab, adalimumab and ixekizumab.(1, 22, 23)

	Guselkumab	Adalimumab	Ixekizumab
Infections	Tremfya may increase the risk of infection. Treatment with Tremfya should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. 4 Patients treated with Tremfya 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 should be monitored closely and Tremfya should be discontinued until the infection resolves.	Patients taking TNF -antagonists are more susceptible to serious infections. Impaired lung function may increase the risk for developing infections. Patients must therefore be monitored closely for infections, including tuberculosis, before, during and after treatment with Humira. Because the elimination of adalimumab may take up to four months, monitoring should be continued throughout this period. Treatment with Humira should not be initiated in patients with active infections including chronic or localised infections until infections are controlled. In patients who have been exposed to tuberculosis and patients who have travelled in areas of high risk of tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, the risk and benefits of treatment with Humira should be considered prior to initiating therapy. Patients who develop a new infection while undergoing treatment with Humira should be monitored closely and undergo a complete diagnostic evaluation. Administration of Humira should be discontinued if a patient develops a new serious infection or sepsis and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. Physicians should exercise caution when considering the use of Humira in patients with a history of recurring infection or with underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications.	Treatment with Taltz is associated with an increased rate of infections such as upper respiratory tract infection, oral candidiasis, conjunctivitis, and tinea infections. Taltz should be used with caution in patients with clinically important chronic infection or a history of recurrent infection. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If an infection develops, patients should be carefully monitored and Taltz discontinued if the patient is not responding to standard therapy or if the infection becomes serious. Taltz should not be resumed until the infection resolves. Taltz must not be given to patients with active TB. Anti-TB therapy prior to initiation of Taltz in patients with latent TB should be considered.
Serious infections	n/a	Serious infections, including sepsis, due to bacterial, mycobacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis have been reported in patients receiving Humira. Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicaemia. Hospitalisation or fatal outcomes associated with infections have been reported.	n/a
Opportinistic infections	n/a	Opportunistic infections, including invasive fungal infections have been observed in patients receiving Humira. These infections have not consistently been recognised in patients taking TNF-antagonists and this has resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes. 8 For patients who develop the signs and symptoms such as fever, malaise, weight	n/a

		loss, sweats, cough, dyspnoea, and/or pulmonary infiltrates or other serious systemic illness with or without concomitant shock an invasive fungal infection should be suspected and administration of Humira should be promptly discontinued. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections.	
Pre-treatment evaluation for tuberculosis	Prior to initiating treatment with Tremfya, patients should be evaluated for TB infection. Patients receiving Tremfya should be monitored for signs and symptoms of active TB during and after treatment. Anti-TB therapy should be considered prior to initiating Tremfya in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.	Before initiation of therapy with Humira, all patients must be evaluated for both active or inactive ("latent") tuberculosis infection. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests (i.e. tuberculin skin test and chest X-ray) should be performed in all patients (local recommendations may apply). It is recommended that the conduct and results of these tests are recorded in the Patient Reminder Card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. If active tuberculosis is diagnosed, Humira therapy must not be initiated. If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted.	n/a
Hypersensitivity	Serious hypersensitivity reactions, including anaphylaxis, have been reported in the post-marketing setting. Some serious hypersensitivity reactions occurred several days after treatment with guselkumab, including cases with urticaria and dyspnoea. If a serious hypersensitivity reaction occurs, administration of Tremfya should be discontinued immediately and appropriate therapy initiated.	n/a	Serious hypersensitivity reactions, including some cases of anaphylaxis, angioedema, urticaria and, rarely, late (10-14 days following injection) serious hypersensitivity reactions including widespread urticaria, dyspnea and high antibody titres have been reported. If a serious hypersensitivity reaction occurs, administration of Taltz should be discontinued immediately and appropriate therapy initiated.
Hepatic Trans-aminase Elevations	In psoriatic arthritis clinical studies, an increased incidence of liver enzyme elevations was observed in patients treated with Tremfya q4w compared to patients treated with Tremfya q8w or	n/a	n/a

	placebo. When prescribing Tremfya q4w in psoriatic arthritis, it is recommended to evaluate liver enzymes at baseline and thereafter according to routine patient management. If increases in ALT or AST are observed and drug-induced liver injury is suspected, Tremfya should be temporarily interrupted until this diagnosis is excluded.		
Immunisations	Prior to initiating therapy with Tremfya, completion of all appropriate immunisations should be considered according to current immunisation guidelines. Live vaccines should not be used concurrently in patients treated with Tremfya. No data are available on the response to live or inactive vaccines. Before live viral or live bacterial vaccination, treatment with Tremfya should be withheld for at least 12 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Prescribers should consult the Summary of Product Characteristics of the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.	Patients on Humira may receive concurrent vaccinations, except for live vaccines.	Taltz should not be used with live vaccines. No data are available on the response to live vaccines; there are insufficient data on response to inactive vaccine
Hepatitis B reactivation	n/a	Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including Humira, who are chronic carriers of this virus (i.e. surface antigen positive). Some cases have had a fatal outcome. Patients should be tested for HBV infection before initiating treatment with Humira. For patients who test positive for hepatitis B infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.	n/a

Neurological events	n/a	TNF-antagonists including Humira have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including GuillainBarré syndrome.	n/a
Allergic reactions	n/a	Serious allergic reactions associated with Humira were rare during clinical trials. Non-serious allergic reactions associated with Humira were uncommon during clinical trials. Reports of serious allergic reactions including anaphylaxis have been received following Humira administration. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Humira should be discontinued immediately and appropriate therapy initiated.	n/a
Malignancies and lympho-proliferative disorders	n/a	In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare. In the post marketing setting, cases of leukaemia have been reported in patients treated with a TNF-antagonist.	n/a
Haematologic reactions	n/a	Rare reports of pancytopenia including aplastic anaemia have been reported with TNF-antagonists. Adverse events of the haematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been reported with Humira. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor) while on Humira. Discontinuation of Humira therapy should be considered in patients with confirmed significant haematologic abnormalities.	n/a
Congestive heart failure	n/a	In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of worsening congestive heart failure have also been reported in patients receiving Humira. Humira should be used with caution in patients with mild heart failure (NYHA class I/II). Humira is contraindicated in moderate to severe heart failure. Treatment with Humira must be discontinued in patients who develop new or worsening symptoms of congestive heart failure	n/a
Autoimmune processes	n/a	Treatment with Humira may result in the formation of autoimmune antibodies. The impact of long-term treatment with Humira on the development of autoimmune diseases is unknown. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Humira and is positive for	n/a

		antibodies against double-stranded DNA, further treatment with Humira should not be given (	
Inflammatory bowel disease (including Crohn's disease and ulcerative colitis)			Cases of new or exacerbations of inflammatory bowel disease have been reported with ixekizumab. Ixekizumab is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, ixekizumab should be discontinued and appropriate medical management should be initiated.

Application for the assessment of cost-analysis and budget impact of Tremfya® (guselkumab) for psoriatic arthritis

Contents

1 Basic information

Table 1: Contact information	
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2 Background

Guselkumab (Tremfya®) is a first-in class human monoclonal antibody approved for by the European Commission on November 20, 2020 for the treatment of active psoriatic arthritis. According to the label, Tremfya, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy. Janssen has requested the Medicines Council to evaluate guselkumab as standard treatment for this indication in Denmark.

Psoriasis arthritis (PsA) is a clinically heterogeneous, progressive, and chronic inflammatory condition that causes irreversible joint damage. The disease can lead to impaired physical functioning, and a decreased quality of life. The classical manifestation of PsA include swelling, tenderness, stiffness and pain of the joints and surrounding tissues. Tactylitis is a hallmark feature of PsA that involves swelling of the joints, tendons and ligaments, and synovial tissue in the hands and/or feet. Tenderness and swelling where tendon, ligaments, or joint capsule fibers insert into the bone are common; it is particularly prominent within the plantar fascia, achilles tendon, ribs, spine and pelvics. Most patients with PsA have peripheral arthritis (~96%) and skin or nail PsO (85%-100%); involvement of other domains varies considerably between patients. (1, 2)

Patients with PsA experience substantial impairment of general physical and mental HRQoL. Compared with the normative population, patients have significantly poorer HRQoL across all dimensions of the SF-36, including physical and mental component summary scores (3, 4). Additionally, they report a considerable psychosocial burden that includes persistent low-level stress, depression, mood/behavioral changes, and poor body image (5). As patients often experience joint, skin, and psychological symptoms, an interdisciplinary team of clinicians may be needed to fully manage PsA symptom burden.

Despite available therapies, real-world data show variable treatment response rates and poor long-term persistence (6). This failure to achieve effective relief of PsA signs and symptoms leads to impaired work productivity and high rates of unemployment for patients, causing substantial societal and economic burden.(7, 8) This highlights the need for a new effective treatment options, such as guselkumab, that demonstrate efficacy across several domains, including joint signs and symptoms, physical function, skin disease, enthesitis, dactylitis and health-related quality of life (HRQoL)(9, 10).

3 Purpose

The purpose of the analyses presented in this application is to estimate the costs associated with the treatment of adult treatment naive patients with PsA without or with moderate to severe plaque psoriasis as well as the costs associated with the treatment of adult treatment experienced patients with PsA without or with moderate to severe plaque psoriasis.
The populations have not been split up in the four clinical questions defined by the Medicines Council but solely treatment naïve and treatment experienced as we assume that the resource consumption associated with the population in clinical questions 1 and 3 is the same, and correspondingly for the population in clinical questions 2 and 4. This is due to the fact that the treatment naïve patients having PsA without PsO is managed the same way as PsA with PsO, meaning that the primary diagnosis which both populations are treated for is PsA. This is substantiated by RADS´s treatment guideline and background document which

does not highlight any difference in the disease management between the two population other than available treatments. Furthermore, same conclusion can be made regarding the population in clinical question 2 and 4 as the treatment experienced patients having PsA without PsO is managed the same way as PsA with PsO, meaning that the primary diagnosis which both populations are treated for is PsA.(11, 12)

The analyses will result in the average cost per patient and the overall budgetary consequences of using guselkumab as standard treatment. In the cost analyses, treatment with guselkumab is compared with adalimumab and ixekizumab, as requested in the Medicines Council protocol for evaluation of guselkumab for the treatment of PsA.(13) However, for the budgetary consequences of using guselkumab as standard treatment for treatment experienced patients, secukinumab has been included. This is due to the secukinumab being used for a significant proportion of treatment experienced patients and the expectation that guselkumab will take market shares from secukinumab.(14, 15)

4 Patient population

The prevalence of patients with PsA is difficult to estimate, however the Medicines Council estimated it to be between 6.000 and 25.000 patients as per stated in the Medicines Council protocol for evaluation of guselkumab for the treatment of PsA.(13)

No precise estimation of the amount of patient with PsA without or with moderate to severe plaque psoriasis is available. However, some useful estimations are available in RADS´ background document for biological and synthetic targeted drugs for treatment of PsA.(12)

More specifically, guselkumab is expected to be used in the PsA populations P1 and P4 described in the RADS´ background document. The P1 population corresponds to adult treatment naïve and treatment experienced patients with PsA without moderate to severe plaque psoriasis whereas the P4 population corresponds to adult treatment naïve and treatment experienced patients with PsA with moderate to severe plaque psoriasis. The incident number of biologic treatment-demanding patients in P1 and P4 who could potentially benefit from guselkumab is 200 patients per year. In addition, out of the approx. 200 biologically treatment demanding patients there are approx. 80 treatment naive and 120 treatment experienced patients per year.(12) As there is no evidence on the distribution of bio-naïve patients between the patients which have PsA without moderate to severe plaque psoriasis and the patients which have PsA with moderate to severe plaque psoriasis, we have assumed an even split. The same assumption is done for the bio-experienced patients, as evidence for the distribution of that population between the PsA patients without and with PsO is lacking too. Thus, this will be the base case assumption for the budget impact results, however a different distribution can be selected in the model.

5 Intervention

Guselkumab is a first-in class human monoclonal antibody binds to the p19-subunit of IL-23 with high specificity and affinity. Interleukin-23 (IL-23) is a heterodimer composed of both p19- and p40-subunits, and evidence indicate that the IL-23/T-helper-17 cell pathway is pivotal in the development of both skin and joint manifestation of psoriasis arthritis.

In 2018, guselkumab received marketing approval for the treatment of moderate to severe plaque PsO in adults who are candidates for systemic therapy. As of 20th of November 2020, guselkumab also received European Commission approval for the treatment of active PsA. The efficacy in PsA has been established in the two pivotal trials, DISCOVER-1 and DISCOVER-2 (9, 10). The clinical evidence for guselkumab in the treatment of patients with active PsA shows robust improvements across key disease outcomes, including joint signs and symptoms, skin involvement, structural damage, and other common disease domains such as enthesitis, dactylitis, and axial inflammation. Further, guselkumab therapy was safe and well tolerated and provided meaningful improvements to patient quality of life.(9, 10)

The recommended dose of Tremfya is 100 mg by subcutaneous injection at weeks 0 and 4, followed by a maintenance dose every 8 weeks. For patients at high risk for joint damage according to clinical judgement, a dose of 100 mg every 4 weeks may be considered.(16) The treatment duration of Tremfya, is of lifelong duration as PsA is a chronic non-curable disease and thus treatment is continued until either primary or secondary failure which is in accordance to Danish clinical practice.(12, 16)

6 Comparators

The comparators specified in the protocol by the Medicines Council for evaluation of guselkumab for the treatment of active PsA, is adalimumab and ixekizumab in the treatment naïve and treatment experienced patients, respectively (13). The cost-analysis will be conducted comparing guselkumab with adalimumab and ixekizumab whereas secukinumab is only included in the budget impact analysis for treatment experienced patients. Further reasoning for these comparisons is stated in section 9.1.

The posology in PsA for the comparators are outlined below as per the Medicine Council´s protocol and SMPCs. The treatment duration of the adalimumab, ixekizumab and secukinumab is equal to that of Tremfya, thus being of lifelong duration or until either primary or secondary failure in Danish clinical practice.(17-19)

Adalimumab
The recommended dose for patients with psoriatic arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection.(13, 18)

Ixekizumab, Taltz®
The recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) every 4 weeks thereafter.(13, 19)

Secukinumab, Cosentyx®
For patients with concomitant moderate to severe plaque psoriasis or who are anti-TNFα inadequate responders (IR), the recommended dose is 300 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Each 300 mg dose is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg.(17)

7 Model and cost-analysis perspective

A simple cost-analysis model, which means that the model only estimates costs associated to treatment with guselkumab, adalimumab and ixekizumab, was conducted using a restricted societal perspective, as

advised by the Medicines Council. Consequently, irrespectively of whom the treatment associated expense was carried by, it was included in the analysis with the exception for productivity losses.(20) Basic assumptions for the cost-analysis model as well as the budget impact model is available in table A1 in the appendix. The simple cost-analysis model was used with the assumption that the effect of the three treatment is similar which is shown by the comparative analyses in the clinical submission. To summarize the conclusion of the clinical comparison regarding ACR50 and PASI90, which would otherwise drive an advanced health economic model, is for both the comparison of guselkumab vs. adalimumab and guselkumab vs. ixekizumab that the confidence intervals of the relative difference does not correspond to any of the specified confidence limits as per the Handbook of the Medicines Council´s process and methodologies for new pharmaceuticals and indication expansions. Thus, the preliminary clinically added value cannot be categorized and the same conclusion is done for the absolute difference outcomes. Consequently, as there is no difference in effect between the drugs, a simple cost analysis is utilized, which has also been the case in previous evaluations of treatments for PsA.

The base case analysis assumptions and results, as well as sensitivity analyses are presented in section 8 and section 11, respectively.

7.1 Time horizon

The time horizon of the cost-analysis was 5 years, which is considered long enough to even out the induction doses difference and capture the additional main differences with regards to costs such as treatment administration and patients costs associated with the treatments. Consequently a 5 year treatment comparison is deemed sufficient and is in accordance with the time horizon of the budget impact model (21, 22) However, the model includes the possibility to vary the time horizon from 1 to 5 years. The costs occurring after the first initial year are discounted using a rate of 3.5% in accordance with the Ministry of Finance´s recommendation.

7.2 Cost

The following costs were included in the analyses:

- Medicine cost
- Treatment administration cost
- Patient cost (Transportation and time spent on treatment)

Costs in the healthcare sector outside the hospital, including municipal costs, are not included.
This is due to the drugs in the analysis are not affect the municipal costs as they don´t present any burden on home care or visits to general practitioner due to treatment being provided at hospitals and patients getting consultations at the hospitals in association with administrations. Thus, these municipal costs are not included in the analysis. This approach is furthermore in accordance with previous evaluation of treatments for PsA.

Serious adverse event costs were considered but not included in the analysis, as no significant difference has been reported between the treatments in the pivotal trials.(9, 10, 23-27). Further substantiation of the assumption that the side effect profile of the three treatment is similar is shown by the comparative analyses in the clinical submission. The conclusion of the comparison regarding the proportion of patients who experience serious adverse events for both the comparison of guselkumab vs. adalimumab and guselkumab vs. ixekizumab is that the confidence intervals of the relative difference does not correspond

to any of the specified confidence limits as per the Handbook of the Medicines Council´s process and methodologies for new pharmaceuticals and indication expansions. Thus, the preliminary clinically added value cannot be categorized and the same conclusion is done for the absolute difference outcomes.

The included costs were, if possible, based on the 2021 diagnosis related groups (DRG) rates reported by Sundhedsdatastyrelsen. The DRG rates was found using an online program, Interactive DRG, provided by Sundhedsdatastyrelsen, which allowed to specify patients characteristics i.e. age and gender, and a type of patient i.e. elective or acute. Furthermore, specification of procedures, treatments and diagnoses could be done. When running the program with a specified combination of choices it reported the DRG associated with the specific combination.

7.2.1 Medicine cost

The per unit treatment cost of guselkumab, adalimumab biosimilar (average of Hyrimoz and Amgevita), ixekizumab, and secukinumab was based on the Danish Medicines Agency´s reported AIP prices on medicinpriser.dk. The average of Hyrimoz and Amgevita prices is used as the tender recommendations state that Hyrimoz must be used in region Syddanmark, Midtjylland and Nordjylland whereas Amgevita must the used in region Sjælland and Hovedstaden.(11) Table 2 shows the price, units, strength, and ATC code.

Table 2: AIP price of guselkumab, adalimumab, and ixekizumab

Product	Units	Strength	ATC	Price
Guselkumab, Tremfya®	1	100 mg	L04AC16	15.987,88 DKK
Adalimumab biosimilar, Hyrimoz®	2	40 mg	L04AB04	7151,09 DKK
Adalimumab biosimilar, Amgevita®	2	40 mg	L04AB04	4770,74 DKK
Ixekizumab, Taltz®	1	80 mg	L04AC13	7565,49 DKK
Secukinumab, Cosentyx®	2	150	L04AC10	7908,00 DKK

The recommended standard posology in PsA, described above in section 6, constituted the basis for calculating the cost of the respective treatments included in the cost-analysis. For secukinumab the 300 mg dosing regimen was applied, as that is the recommended dosing in treatment experienced patients. The number of administrations and units administered over 5 years in the analyses are accounted for in Table 3. Furthermore, the excel model contains the possibility of having dose escalation of guselkumab as patients at high risk for joint damage according to clinical judgement, a dose of 100 mg every 4 weeks may be considered. However, as there are no specific definition of these high risk patients and as the smpc states that the patient´s doctor will decide on the dosing schedule we have not included the scenario in our analyses. Furthermore, the Medicines Council´s protocol for the evaluation of guselkumab has not defined the need for comparison of the guselkumab Q4W dosing for patients at high risk for joint damage to neither ixekizumab nor adalimumab.
Consequently, the possibility for dose escalation in the model is solely to accommodate potential interest on treatment cost of patients at high risk for joint damage from the scientific committee.

Table 3: Dosing and number of administrations over 5 years

Product	Strength	Units administered over 5 year	Number of administrations
Guselkumab, Tremfya®	100 mg	33	33
Adalimumab biosimilars, Hyrimoz® and Amgevita®	40 mg	130	130
Ixekizumab, Taltz®	80 mg	66	65
Secukinumab, Cosentyx®	150 mg	126	63

7.2.2 Treatment administration cost

Treatment administration cost, i.e. the cost of providing a SC injection including time used by health care personal was incorporated in the cost analyses and budget impact analyses. The cost per SC administration was estimated to 1.658 DKK based on DRG 08MA98 which specifies the cost of a SC administration for patients with psoriatic arthritis and assumed to be equal for all products (Table 4) (28). The DRG tariff system is one tool to group patient care into clinically meaningful and resource homogeneous groups. This means that patients' treatment grouped by diagnosis, treatment, age, etc. in such a way, that those grouped into the same DRG group are treated for approximately the same - and costs roughly the same. To each DRG group is associated with a DRG value / DRG rate. This is calculated as the national average of the associated costs patients who are grouped into the given DRG group treated on public Danish hospitals. The average cost includes diverse services, outpatient assistance in connection with hospitalization, special investigations, etc.
Consequently, by using DRG rate, the treatment administration, monitoring, and time used by healthcare personal has been taken into account. This is substantiated by the Medicines Council´s method guide for cost-analyses of new medicines and indications in the hospital sector. Here following is stated: Similarly, DRG tariffs can also be used as average estimates for costs rather than a breakdown on sub-elements.

In relation to monitoring, all patients should be monitored for tuberculosis before initiation with any of the treatments included in the analysis. This is stated in the summary of product characteristics and also detailed in the clinical part of this submission. Consequently, the associated cost has not been included as the monitoring for tuberculosis is equal for all of the treatments, the cost difference between the treatments would therefore be zero.

Table 4: Cost per treatment administration used in base case analysis

Treatment cost per	Guselkumab	Adalimumab	Ixekizumab	Secukinumab
SC administration	1.658 DKK	1.658 DKK	1.658 DKK	1.658 DKK

7.2.3 Patient cost

To estimate the patient cost associated with guselkumab, adalimumab, ixekizumab, and secukinumab SC treatment administration, the Medicines Council guidance regarding valuation of unit costs was applied. According to this guidance, the recommended transportation cost associated with a hospital visit is 100 DKK and the recommended cost for 1 h spent in the hospital to receive treatment equals 179 DKK (29).

These same per administration patient costs were assumed across all treatments since all share the same route of administration (Table 5).

Table 5: Patient cost per treatment administration used in base case analysis

	Cost per administration
Patient time, 1h	179 DKK
Transport	100 DKK

8 Cost analysis results

The base case cost analysis in the treatment naïve population resulted in a total treatment cost of 553.431 DKK for guselkumab, whereas ixekizumab and adalimumab had a total treatment cost of 584.812 DKK and 597.471 DKK over 5 years, respectively. Consequently, the incremental cost saving of guselkumab compared to ixekizumab was estimated to be 31.381 DKK and 44.040 DKK compared to adalimumab, see Table 6.

Table 6: Results of the base case cost-analysis over 5 years of treatment for treatment naïve patients (discounted)

Regimen	Patient	Administration	Drug	Total	Incremental cost
Guselkumab	kr 8.614	kr 51.191	kr 493.626	kr 553.431	
Ixekizumab	kr 16.949	kr 100.724	kr 467.139	kr 584.812	-kr 31.381
Adalimumab	kr 33.899	kr 201.447	kr 362.126	kr 597.471	-kr 44.040

The base case cost analysis in the treatment experienced population resulted in a total treatment cost of 553.431 DKK for guselkumab, whereas ixekizumab and secukinumab had a total treatment cost of 584.812 DKK and 619.707 DKK over 5 years, respectively. Consequently, the incremental cost saving of guselkumab compared to ixekizumab was estimated to 31.381 DKK and 66.276 DKK compared to secukinumab, see Table 7.

Table 7: Results of the base case cost-analysis over 5 years of treatment for treatment experienced patients (discounted)

Regimen	Patient	Administration	Drug	Total	Incremental cost
Guselkumab	kr 8.614	kr 51.191	kr 493.626	kr 553.431	
Ixekizumab	kr 16.949	kr 100.724	kr 467.139	kr 584.812	-kr 31.381
Secukinumab	kr 33.899	kr 117.411	kr 468.397	kr 619.707	-kr 66.276

The base case results from this cost analysis indicates that guselkumab treatment is associated with cost savings compared to the comparative treatments if considering drug and administration cost, as well as patient costs. Thus, the recommendation of guselkumab as standard treatment for adult treatment naïve and treatment experienced patients with active PsA will not only provide a valuable addition to the treatment arsenal by being a proven safe and first in class drug with demonstrated robust improvements across key disease outcomes, including joint signs and symptoms, skin involvement, and structural damage, but also lower the total expense related with PsA treatment if used instead of the comparators.(9, 10) Furthermore, the introduction of guselkumab to the market will likely increase the competitiveness between approved standard treatments.

9 Budget impact perspective

The budget impact analysis was conducted for a period of 5 years and based on the same costs as described above for the cost analysis, with the exception for patient costs. Specifically, the cost of incident patients entering the budget impact model in year 1 will have costs assigned for a total of 5 years, incident patient entering in year 2 will have costs assigned for a total of 4 years, and so forth. Furthermore, the costs are not discounted as advised by the Medicines Council.(20)

9.1 Assumption of market share

Estimation of patients eligible for treatment with guselkumab is based on, first and foremost, how many treatment naïve patients start biological treatment annually and how many treatment-experienced change treatments. As described in section 4, there are approx. 80 treatment-naive and 120 treatment-experienced patients per year.(12) In the protocol from the Medicines Council, Janssen has been given adalimumab and ixekizumab as comparators.(13) Consequently, the number of patients which will receive guselkumab is based on the proportion of treatment naïve and treatment experienced patients currently treated with adalimumab and ixekizumab. However, secukinumab has also been included for the budgetary consequence analyses of using guselkumab as standard treatment for treatment experienced patients, as secukinumab is being used for a significant proportion of treatment experienced patients and the expectation that guselkumab will take market shares from secukinumab.(14, 15)

In the treatment guidelines incl. drug recommendation for use of biological treatment of psoriatic arthritis it is for P1 and P4 stated that the 1st line treatment must be used for at least 90% of the populations. Furthermore, it appears that at least 1 TNF-α inhibitor must be included as the 1st or 2nd line for the individual patient. Adalimumab is the current TNF-α inhibitor used as first-line treatment in treatment-naive patients in both population P1 and P4. This is stated in the latest drug recommendation from January 2021, where it is specified that the 1st choice for at least 90% of the populations must be treated with the generic adalimumab products, Hyrimoz® and Amgevita®.(11) The fact that adalimumab is the most widely used standard treatment for treatment naive patients and should be used for 90% of the patients is further reflected in DANBIO reports covering the year of 2020. The remaining 10% of the treatment-naïve patients should receive treatments according to the drug recommendation where secukinumab 150mg and ixekizumab 300mg is listed at the 4. and 5. treatments choice but 1. and 2. choice not being a TNF-α inhibitor. However, when looking at data from the DANBIO reports ixekizumab is the most used treatment for treatment-naïve patients aside of adalimumab whereas the use of secukinumab is very limited.(14, 15)

Thus, only adalimumab and ixekizumab is included in the budgetary consequences analysis for treatment-naïve patients and it was assumed that 90% of the 80 treatment-naïve patients available each year will receive adalimumab and 10% will receive ixekizumab. This corresponds to 72 patients starting on adalimumab and 8 patients starting on ixekizumab each year.

The treatment guidelines incl. drug recommendation for use of biological treatment of psoriatic arthritis shows that ixekizumab is recommended as the 1st line for treatment-experienced patients in populations P1 and P4 i.e. the 2nd line treatment after prior use of the TNF-α inhibitor.(11) Although this conclusion regarding ixekizumab has been made and that ixekizumab is currently ranked just above secukinumab in the drug recommendation, secukinumab is still a widely used treatment for treatment experienced patients in population P1 and P4. Based on data from the DANBIO reports covering 2020, the split in proportions of treatment-experienced patients receiving ixekizumab and secukinumab after TNF- α failure is estimated to be 62% and 38%, respectively.(14, 15) Consequently, applying these percentages to the 120 treatment-

experienced patients available each year results in 74 patients receiving ixekizumab and 46 patients starting on secukinumab each year.

To summarize the market share inputs for the budgetary consequence analyses it was assumed that 72 treatment naïve patients would start on adalimumab and 8 patients start on ixekizumab each year whereas 74 treatment experienced patients would start on ixekizumab and 46 patients would start on secukinumab each year. Furthermore, incident patients starting treatment each year are included the following years getting maintenance treatment. Discontinuation rates has not been applied as there are no evidence available on the discontinuation rates for the different treatments i.e. guselkumab, adalimumab, ixekizumab and secukinumab in psoriatic arthritis. Consequently, 100% of the incident patients in year one will continue to year 2 and so forth.

In the base case estimation, it is assumed that guselkumab will take 3% of ixekizumab´s market share in year 1 in the treatment-naïve population which will increase to 5% in year 5 resulting in having an equal market share split between ixekizumab and guselkumab. Additionally, 0% will be taken of adalimumab´s market share as it is assumed that 90% of treatment naïve patients must be treated with adalimumab as first line treatment throughout the period. Table 8 and 9 shows the market share in number of treatment naïve patients in the current market and number of treatment naïve patients in the new market with guselkumab, respectively.

Regarding the market share of treatment-experienced patients, it is assumed that guselkumab will take 20% of consentyx´ market share in year 1 which will increase to 27.5% in year 5, whereas guselkumab will take 10% of ixekizumab´s market share in year 1 which will increase to 17.5% in year 5. This forecast is based on internal expectations as well as the historic uptake when a new treatment is introduced. Table 10 and 11 shows the market share in number of treatment experienced patients in the current market and number of treatment experienced patients in the new market with guselkumab, respectively. As there is no evidence on the percentage split of bio-naïve patients between patients which have PsA without moderate to severe plaque psoriasis and patients which with PsA with moderate to severe plaque psoriasis, we have assumed an even split. This will be the base case assumption for the budget impact results related to each clinical question/population which is presented in section 10. The same assumption is done for the results related to the bio-experienced patients, also presented in section 10.

Table 8: Number of treatment naïve patients in current market without guselkumab recommended as standard treatment

Regimen	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Guselkumab	0	0	0	0	0
Ixekizumab	8	16	24	32	40
Adalimumab	72	144	216	288	360
Total	80	160	240	320	400

Table 9: Number of treatment naïve patients in new market with guselkumab recommended as standard treatment

Regimen	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Guselkumab	2	6	10	14	20
Ixekizumab	6	10	14	18	20
Adalimumab	72	144	216	288	360
Total	80	160	240	320	400

Table 10: Number of treatment experienced patients in current market without guselkumab recommended as standard treatment

Regimen	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Guselkumab	0	0	0	0	0
Ixekizumab	74	149	223	298	372
Secukinumab	46	91	137	182	228
Total	120	240	360	480	600

Table 11: Number of treatment experienced patients in new market with guselkumab recommended as standard treatment

Regimen	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Guselkumab	36	84	144	204	270
Ixekizumab	62	119	169	220	267
Secukinumab	22	37	47	56	63
Total	120	240	360	480	600

10 Budget impact results

Base case budget impact results exclude patient costs, i.e. transport and time used, as per the Medicines Council´s methodology. The total cost per year of treatment for the full treatment naïve patient population in current market scenario without guselkumab is shown in table 12 whereas the scenario with guselkumab is shown in table 13. Furthermore, the results of the base case budget impact analysis for treatment naïve patients are shown in Table 14. The total cost per year for treatment of the full treatment experienced patient population in current market scenario without guselkumab is shown in table 15 whereas the scenario with guselkumab is shown in table 16. The results of the base case budget impact analysis for the full treatment experienced patient population are shown in table 17.

Table 12: Total cost per year for treatment of the full treatment naïve patient population in current market scenario without guselkumab

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 9.702.904	kr 19.345.289	kr 28.987.673	kr 38.630.058	kr 48.272.442
Drug cost	kr 6.426.696	kr 12.792.873	kr 19.159.049	kr 25.525.226	kr 31.891.402
Administration cost	kr 3.276.208	kr 6.552.416	kr 9.828.624	kr 13.104.832	kr 16.381.040

Table 13: Total cost per year for treatment of the full treatment naïve patient population in new market scenario with guselkumab

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 9.693.442	kr 19.320.190	kr 28.942.778	kr 38.561.205	kr 48.175.471
Drug cost	kr 6.441.109	kr 12.825.472	kr 19.214.297	kr 25.607.582	kr 32.005.329
Administration cost	kr 3.252.333	kr 6.494.718	kr 9.728.481	kr 12.953.622	kr 16.170.142

Table 14: Results of the base case budget impact analysis for treatment of the full treatment naïve patient population

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 9.463	-kr 25.099	-kr 44.896	-kr 68.853	-kr 96.971
Drug cost	kr 14.412	kr 32.599	kr 55.247	kr 82.356	kr 113.926
Administration cost	-kr 23.875	-kr 57.698	-kr 100.143	-kr 151.210	-kr 210.898

Table 15: Total cost per year for treatment of the full treatment experienced patient population in current market scenario without guselkumab

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 16.093.575	kr 30.487.021	kr 44.880.468	kr 59.273.915	kr 73.667.362
Drug cost	kr 13.344.254	kr 24.988.379	kr 36.632.505	kr 48.276.630	kr 59.920.756
Administration cost	kr 2.749.321	kr 5.498.642	kr 8.247.963	kr 10.997.284	kr 13.746.606

Table 16: Total cost per year for treatment of the full treatment experienced patient population in new market scenario with guselkumab

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 15.531.688	kr 29.582.676	kr 43.570.523	kr 57.647.528	kr 71.648.383
Drug cost	kr 13.226.201	kr 25.142.348	kr 37.146.105	kr 49.248.968	kr 61.346.082
Administration cost	kr 2.305.487	kr 4.440.328	kr 6.424.418	kr 8.398.561	kr 10.302.302

Table 17: Results of the base case budget impact analysis for treatment of the full treatment experienced patient population

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 561.887	-kr 904.345	-kr 1.309.945	-kr 1.626.387	-kr 2.018.978
Drug cost	-kr 118.053	kr 153.969	kr 513.600	kr 972.337	kr 1.425.325
Administration cost	-kr 443.834	-kr 1.058.314	-kr 1.823.545	-kr 2.598.724	-kr 3.444.304

In the base case budget impact analyses for both the treatment naïve and treatment experienced patients, the adaption of guselkumab as standard treatment to the market is associated with cost savings already from year 2021 and onwards. In 2021, a budgetary saving of 9.463 DKK will occur in the treatment of treatment naïve patient, which continue to increase each year ending with a saving of 96.971 DKK in 2025. Equal important a budgetary saving of 561.887 DKK will occur in 2021 in the treatment experienced patient population, which continue to increase each year ending with a saving of 2.018.978 DKK in 2025. In addition, this is estimated to give a cumulative budget saving of 245.282 DKK in the treatment of treatment naïve patients, whereas a cumulative budgetary saving of 6.421.542 DKK is estimated to occur in the treatment of treatment experienced patients.

In addition to the budget impact results for the full treatment naïve population presented above, the budget impact results are also presented separately for treatment naïve patients which have PsA without moderate to severe plaque psoriasis and treatment naïve patients which have PsA with moderate to severe plaque psoriasis. These results are presented in section 10.1 and 10.2, respectively. Furthermore, the budget impact results are also presented separately for treatment experienced patients which have PsA

without moderate to severe plaque psoriasis and treatment experienced patients which have PsA with moderate to severe plaque psoriasis. These results are presented in section 10.3 and 10.4, respectively.

10.1 Budget impact results for treatment naïve patients which have PsA without moderate to severe plaque psoriasis

The total cost per year of treatment for treatment naïve patients which have PsA without moderate to severe plaque psoriasis in current market scenario without guselkumab is shown in table 18 whereas the scenario with guselkumab is shown in table 19. Furthermore, the results of the base case budget impact analysis for treatment naïve patients which have PsA without moderate to severe plaque psoriasis are shown in Table 20. The patients which have PsA without moderate to severe plaque psoriasis is assumed to constitute half of the bio-naïve population and thus the results constitute half of the budget impact for the bio-naïve population.

Table 18: Total cost per year for treatment of treatment naïve patients which have PsA without moderate to severe plaque psoriasis in current market scenario without guselkumab

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 4.851.452	kr 9.672.644	kr 14.493.837	kr 19.315.029	kr 24.136.221
Drug cost	kr 3.213.348	kr 6.396.436	kr 9.579.525	kr 12.762.613	kr 15.945.701
Administration cost	kr 1.638.104	kr 3.276.208	kr 4.914.312	kr 6.552.416	kr 8.190.520

Table 19: Total cost per year for treatment of treatment naïve patients which have PsA without moderate to severe plaque psoriasis in new market scenario with guselkumab

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 4.846.721	kr 9.660.095	kr 14.471.389	kr 19.280.602	kr 24.087.736
Drug cost	kr 3.220.554	kr 6.412.736	kr 9.607.148	kr 12.803.791	kr 16.002.664
Administration cost	kr 1.626.166	kr 3.247.359	kr 4.864.240	kr 6.476.811	kr 8.085.071

Table 20: Results of the base case budget impact analysis for treatment of treatment naïve patients which have PsA without moderate to severe plaque psoriasis

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 4.731	-kr 12.549	-kr 22.448	-kr 34.427	-kr 48.486
Drug cost	kr 7.206	kr 16.300	kr 27.624	kr 41.178	kr 56.963
Administration cost	-kr 11.938	-kr 28.849	-kr 50.072	-kr 75.605	-kr 105.449

10.2 Budget impact results for treatment naïve patients which have PsA with moderate to severe plaque psoriasis

The total cost per year of treatment for treatment naïve patients which have PsA with moderate to severe plaque psoriasis in current market scenario without guselkumab is shown in table 21 whereas the scenario with guselkumab is shown in table 22. Furthermore, the results of the base case budget impact analysis for treatment naïve patients which have PsA with moderate to severe plaque psoriasis are shown in Table 23. The patients which have PsA with moderate to severe plaque psoriasis is assumed to constitute half of the bio-naïve population and thus the results constitute half of the budget impact for the bio-naïve population.

Table 21: Total cost per year for treatment of treatment naïve patients which have PsA with moderate to severe plaque psoriasis in current market scenario without guselkumab

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 4.851.452	kr 9.672.644	kr 14.493.837	kr 19.315.029	kr 24.136.221
Drug cost	kr 3.213.348	kr 6.396.436	kr 9.579.525	kr 12.762.613	kr 15.945.701
Administration cost	kr 1.638.104	kr 3.276.208	kr 4.914.312	kr 6.552.416	kr 8.190.520

Table 22: Total cost per year for treatment of treatment naïve patients which have PsA with moderate to severe plaque psoriasis in new market scenario with guselkumab

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 4.846.721	kr 9.660.095	kr 14.471.389	kr 19.280.602	kr 24.087.736
Drug cost	kr 3.220.554	kr 6.412.736	kr 9.607.148	kr 12.803.791	kr 16.002.664
Administration cost	kr 1.626.166	kr 3.247.359	kr 4.864.240	kr 6.476.811	kr 8.085.071

Table 23: Results of the base case budget impact analysis for treatment of treatment naïve patients which have PsA with moderate to severe plaque psoriasis

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 4.731	-kr 12.549	-kr 22.448	-kr 34.427	-kr 48.486
Drug cost	kr 7.206	kr 16.300	kr 27.624	kr 41.178	kr 56.963
Administration cost	-kr 11.938	-kr 28.849	-kr 50.072	-kr 75.605	-kr 105.449

10.3 Budget impact results for treatment experienced patients which have PsA without moderate to severe plaque psoriasis

The total cost per year for treatment of treatment experienced patients which have PsA without moderate to severe plaque psoriasis in current market scenario without guselkumab is shown in table 24 whereas the scenario with guselkumab is shown in table 25. The results of the base case budget impact analysis for treatment experienced patients which have PsA without moderate to severe plaque psoriasis are shown in table 26. The patients which have PsA without moderate to severe plaque psoriasis is assumed to constitute half of the bio-experienced population and thus the results constitute half of the budget impact for the bio-experienced population.

Table 24: Total cost per year for treatment of treatment experienced patients which have PsA without moderate to severe plaque psoriasis in current market scenario without guselkumab

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 8.046.787	kr 15.243.511	kr 22.440.234	kr 29.636.957	kr 36.833.681
Drug cost	kr 6.672.127	kr 12.494.190	kr 18.316.252	kr 24.138.315	kr 29.960.378
Administration cost	kr 1.374.661	kr 2.749.321	kr 4.123.982	kr 5.498.642	kr 6.873.303

Table 25: Total cost per year for treatment of treatment experienced patients which have PsA without moderate to severe plaque psoriasis in new market scenario with guselkumab

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 7.765.844	kr 14.791.338	kr 21.785.262	kr 28.823.764	kr 35.824.192
Drug cost	kr 6.613.100	kr 12.571.174	kr 18.573.052	kr 24.624.484	kr 30.673.041
Administration cost	kr 1.152.744	kr 2.220.164	kr 3.212.209	kr 4.199.280	kr 5.151.151

Table 26: Results of the base case budget impact analysis for treatment of treatment experienced patients which have PsA without moderate to severe plaque psoriasis

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 280.943	-kr 452.173	-kr 654.972	-kr 813.193	-kr 1.009.489
Drug cost	-kr 59.027	kr 76.985	kr 256.800	kr 486.169	kr 712.663
Administration cost	-kr 221.917	-kr 529.157	-kr 911.772	-kr 1.299.362	-kr 1.722.152

10.4 Budget impact results for treatment experienced patients which have PsA with moderate to severe plaque psoriasis

The total cost per year for treatment of treatment experienced patients which have PsA with moderate to severe plaque psoriasis in current market scenario without guselkumab is shown in table 27 whereas the scenario with guselkumab is shown in table 28. The results of the base case budget impact analysis for treatment experienced patients which have PsA with moderate to severe plaque psoriasis are shown in table 29. The patients which have PsA with moderate to severe plaque psoriasis is assumed to constitute half of the bio-experienced population and thus the results constitute half of the budget impact for the bio-experienced population.

Table 27: Total cost per year for treatment of treatment experienced patients which have PsA without moderate to severe plaque psoriasis in current market scenario without guselkumab

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 8.046.787	kr 15.243.511	kr 22.440.234	kr 29.636.957	kr 36.833.681
Drug cost	kr 6.672.127	kr 12.494.190	kr 18.316.252	kr 24.138.315	kr 29.960.378
Administration cost	kr 1.374.661	kr 2.749.321	kr 4.123.982	kr 5.498.642	kr 6.873.303

Table 28: Total cost per year for treatment of treatment experienced patients which have PsA without moderate to severe plaque psoriasis in new market scenario with guselkumab

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 7.765.844	kr 14.791.338	kr 21.785.262	kr 28.823.764	kr 35.824.192
Drug cost	kr 6.613.100	kr 12.571.174	kr 18.573.052	kr 24.624.484	kr 30.673.041
Administration cost	kr 1.152.744	kr 2.220.164	kr 3.212.209	kr 4.199.280	kr 5.151.151

Table 29: Results of the base case budget impact analysis for treatment of treatment experienced patients which have PsA without moderate to severe plaque psoriasis

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 280.943	-kr 452.173	-kr 654.972	-kr 813.193	-kr 1.009.489
Drug cost	-kr 59.027	kr 76.985	kr 256.800	kr 486.169	kr 712.663
Administration cost	-kr 221.917	-kr 529.157	-kr 911.772	-kr 1.299.362	-kr 1.722.152

11 Deterministic sensitivity analyses – cost analyses

A deterministic sensitivity analysis (DSA) was conducted by varying parameters from their base-case value, one parameter at a time. The analysis evaluated lower and upper bounds for each model parameter considered. The bounds were assumed ±10% from the parameter's mean value. The alternative input values used in the DSA is summarized in Table 30.

Table 30: Alternative input values used in the DSA

Parameters	Base Case	Lower Bound	Upper Bound	Source
Costs Inputs				
Unit cost - Guselkumab	DKK 15.987,88	DKK 14.389,09	DKK 17.586,67	Assumption (±10%)
Unit cost – Adalimumab Biosimilar*	DKK 5.960,92	DKK 5.364,83	DKK 6.557,01	Assumption (±10%)
Unit cost - Ixekizumab	DKK 7.565,49	DKK 6.808,94	DKK 8.322,04	Assumption (±10%)
Unit cost - Secukinumab	DKK7.908,00	DKK 7.117,20	DKK 8.698,80	Assumption (±10%)
SC administration cost	DKK 1.658,00	DKK 1.492,20	DKK 1.823,80	Assumption (±10%)
Patient time cost	DKK 179,00	DKK 161,10	DKK 196,90	Assumption (±10%)
Transport cost	DKK 100,00	DKK 90,00	DKK 110,00	Assumption (±10%)

*(average of Hyrimoz and Amgevita)

11.1 Results of the One-way Sensitivity Analyses for treatment naïve patients

The results of the one-way sensitivity analyses for treatment naïve patients are presented for guselkumab versus the referent therapy, adalimumab, in Table 31. Results are also presented versus ixekizumab because it is one of the most relevant comparators for guselkumab also in the treatment naïve population Table 32.

11.1.1 Results of One-way Sensitivity Analyses treatment naïve patients Versus Adalimumab and Ixekizumab

The one-way sensitivity analyses for guselkumab versus adalimumab suggest the top three model drivers were guselkumab and adalimumab unit costs, as well as the SC administration cost.
A similar pattern was seen for the one-way sensitivity analyses for guselkumab versus ixekizumab, which suggest that the three top model drivers were guselkumab and ixekizumab unit costs, along with the SC administration cost.

Table 31: Results of one-way sensitivity analyses for guselkumab vs. adalimumab for treatment naïve patients

Parameters	Lower bound Incremental cost	Upper bound Incremental cost	Incremental LB vs. UB
Costs Inputs			
Unit cost – Guselkumab	DKK -93.403	DKK 5.322	DKK -98.725
Unit cost – Adalimumab Biosimilar*	DKK -80.253	DKK -7.828	DKK 72.425
Unit cost - Ixekizumab	n/a	n/a	n/a
Unit cost - Secukinumab	n/a	n/a	n/a
SC administration cost	DKK -29.015	DKK -59.066	DKK 30.051
Patient time cost	DKK -42.418	DKK -45.663	DKK 3.245
Transport cost	DKK -43.134	DKK -44.947	DKK 1.813

Table 32: Results of one-way sensitivity analyses for guselkumab vs. ixekizumab for treatment naïve patients

Parameters	Lower bound Incremental cost	Upper bound Incremental cost	Incremental LB vs. UB
Costs Inputs			
Unit cost – Guselkumab	DKK -80.744	DKK 17.982	DKK -98.726
Unit cost – Adalimumab Biosimilar*	n/a	n/a	n/a
Unit cost - Ixekizumab	DKK 15.302	DKK -78.126	DKK -93.428
Unit cost - Secukinumab	n/a.	n/a	n/a
SC administration cost	DKK -26.428	DKK -36.344	DKK 9.916
Patient time cost	DKK -30.846	DKK -31.916	DKK 1.070
Transport cost	DKK -31.082	DKK -31.680	DKK 598

11.2 Results of the One-way Sensitivity Analyses for treatment experienced patients

The results of the one-way sensitivity analyses for treatment experienced patients are presented for guselkumab versus the referent therapy, Ixekizumab, in Table 33. Results are also presented versus secukinumab because it is one of the most relevant comparators for guselkumab also in the treatment experienced population Table 34.

11.2.1 Results of One-way Sensitivity Analyses treatment experienced patients Versus Ixekizumab and Secukinumab

The one-way sensitivity analyses for guselkumab versus ixekizumab suggest the top three model drivers were guselkumab and ixekizumab unit costs, as well as SC administration cost.
A similar pattern was seen for the one-way sensitivity analyses for guselkumab versus secukinumab, which suggests the that top three model drivers were guselkumab and secukinumab unit costs, as well as the SC administration cost.

Table 33: Results of one-way sensitivity analyses for guselkumab vs. ixekizumab for treatment experienced patients

Parameters	Lower bound Incremental cost	Upper bound Incremental cost	Incremental LB vs. UB
Costs Inputs			
Unit cost – Guselkumab	DKK -80.744	DKK 17.982	DKK 98.726
Unit cost – Adalimumab Biosimilar*	n/a	n/a	n/a
Unit cost - Ixekizumab	DKK 15.302	DKK -78.126	DKK -93.428
Unit cost - Secukinumab	n/a	n/a	n/a
SC administration cost	DKK -26.428	DKK -36.344	DKK 9.916
Patient time cost	DKK -30.846	DKK -31.916	DKK 1.070
Transport cost	DKK -31.082	DKK -31.680	DKK 598

Table 34: Results of one-way sensitivity analyses for guselkumab vs. secukinumab for treatment experienced patients

Parameters	Lower bound Incremental cost	Upper bound Incremental cost	Incremental LB vs. UB
Costs Inputs			
Unit cost – Guselkumab	DKK -115.639	DKK -16.914	DKK 98.275
Unit cost – Adalimumab Biosimilar*	n/a	n/a	n/a
Unit cost - Ixekizumab	n/a	n/a	n/a
Unit cost - Secukinumab	DKK -19.436	DKK -113.116	DKK 93.680
SC administration cost	DKK -59.654	DKK -72.898	DKK 13.244
Patient time cost	DKK -64.654	DKK -67.898	DKK 3.224
Transport cost	DKK -63.370	DKK -67.182	DKK 3.812

12 Deterministic sensitivity analyses – budget impact analyses

As described for the cost-analysis in section 11, variation of the unit cost of guselkumab and comparators has a notable impact on the incremental cost comparisons. Consequently, the impact on the budget of varying the unit costs for the different treatments were explored in sensitivity analyses.

12.1 Results of DSA for budget impact analysis in treatment naïve population

12.1.1 Sensitivity analysis of varying guselkumab unit cost with ±10% presented for the full the treatment naïve population

The result of the budget impact sensitivity analysis if varying guselkumab unit cost with ±10% in the full treatment naïve population is provided in Table 35 and Table 36, respectively.

Table 35: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients when decreasing the unit cost of Guselkumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 36.322	-kr 85.853	-kr 147.858	-kr 222.337	-kr 309.290
Drug cost	-kr 12.447	-kr 28.155	-kr 47.715	-kr 71.127	-kr 98.393
Administration cost	-kr 23.875	-kr 57.698	-kr 100.143	-kr 151.210	-kr 210.898

Table 36: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients when increasing the unit cost of Guselkumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 17.397	kr 35.655	kr 58.066	kr 84.631	kr 115.348
Drug cost	kr 41.272	kr 93.353	kr 158.210	kr 235.840	kr 326.246
Administration cost	-kr 23.875	-kr 57.698	-kr 100.143	-kr 151.210	-kr 210.898

In addition to the sensitivity analysis of varying guselkumab unit cost with ±10% for the full treatment naïve population presented above, the budget impact sensitivity results are also presented separately for treatment naïve patients which have PsA without moderate to severe plaque psoriasis and treatment naïve patients which have PsA with moderate to severe plaque psoriasis. These results are presented in section 12.1.2 and 12.1.3.

12.1.2 Sensitivity analysis of decreasing guselkumab unit cost with 10% presented separately for the treatment naïve population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis

The result of the budget impact sensitivity analysis if decreasing guselkumab unit cost with 10% in the treatment naïve populations are provided in Table 37 and Table 38, respectively. The results in Table 37 and Table 38 are equal due to the assumption of an even distribution of bio-naïve patients between the population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis.

Table 37: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients which have PsA without moderate to severe plaque psoriasis when decreasing the unit cost of Guselkumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 18.161	-kr 42.926	-kr 73.929	-kr 111.168	-kr 154.645
Drug cost	-kr 6.224	-kr 14.077	-kr 23.857	-kr 35.564	-kr 49.196
Administration cost	-kr 11.938	-kr 28.849	-kr 50.072	-kr 75.605	-kr 105.449

Table 38: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients which have PsA with moderate to severe plaque psoriasis when decreasing the unit cost of Guselkumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 18.161	-kr 42.926	-kr 73.929	-kr 111.168	-kr 154.645
Drug cost	-kr 6.224	-kr 14.077	-kr 23.857	-kr 35.564	-kr 49.196
Administration cost	-kr 11.938	-kr 28.849	-kr 50.072	-kr 75.605	-kr 105.449

12.1.3 Sensitivity analysis of increasing guselkumab unit cost with 10% presented separately for the treatment naïve population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis

The result of the budget impact sensitivity analysis if increasing guselkumab unit cost with 10% in the treatment naïve populations are provided in Table 39 and Table 40, respectively. The results in Table 39 and Table 40 are equal due to the assumption of an even distribution of bio-naïve patients between the population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis.

Table 39: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients which have PsA without moderate to severe plaque psoriasis when increasing the unit cost of Guselkumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 8.698	kr 17.828	kr 29.033	kr 42.315	kr 57.674
Drug cost	kr 20.636	kr 46.677	kr 79.105	kr 117.920	kr 163.123
Administration cost	-kr 11.938	-kr 28.849	-kr 50.072	-kr 75.605	-kr 105.449

Table 40: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients which have PsA with moderate to severe plaque psoriasis when increasing the unit cost of Guselkumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 8.698	kr 17.828	kr 29.033	kr 42.315	kr 57.674
Drug cost	kr 20.636	kr 46.677	kr 79.105	kr 117.920	kr 163.123
Administration cost	-kr 11.938	-kr 28.849	-kr 50.072	-kr 75.605	-kr 105.449

12.1.4 Sensitivity analysis of varying adalimumab unit cost with ±10% presented for the full the treatment naïve population

The result of the budget impact sensitivity analysis if varying adalimumab unit cost with ±10% in the full treatment naïve population is provided in Table 41 and Table 42, respectively. As evident from the results, adalimumab unit cost has no impact on the budget impact result in full treatment naïve population, as guselkumab is not expected to take any market share from adalimumab.

Table 41: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients when decreasing the unit cost of adalimumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 9.463	-kr 25.099	-kr 44.896	-kr 68.853	-kr 96.971
Drug cost	kr 14.412	kr 32.599	kr 55.247	kr 82.356	kr 113.926
Administration cost	-kr 23.875	-kr 57.698	-kr 100.143	-kr 151.210	-kr 210.898

Table 42: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients when increasing the unit cost of adalimumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 9.463	-kr 25.099	-kr 44.896	-kr 68.853	-kr 96.971
Drug cost	kr 14.412	kr 32.599	kr 55.247	kr 82.356	kr 113.926
Administration cost	-kr 23.875	-kr 57.698	-kr 100.143	-kr 151.210	-kr 210.898

In addition to the sensitivity analysis of varying adalimumab unit cost with ±10% for the full treatment naïve population presented above, the budget impact sensitivity results are also presented separately for treatment naïve patients which have PsA without moderate to severe plaque psoriasis and treatment naïve patients which have PsA with moderate to severe plaque psoriasis. These results are presented in section 12.1.5 and 12.1.6.

12.1.5 Sensitivity analysis of decreasing adalimumab unit cost with 10% presented separately for the treatment naïve population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis

The result of the budget impact sensitivity analysis if decreasing adalimumab unit cost with 10% in the treatment naïve populations are provided in Table 43 and Table 44, respectively. As evident from the results, adalimumab unit cost has no impact on the budget impact result in treatment naïve populations, as guselkumab is not expected to take any market share from adalimumab. The results in Table 43 and Table 44 are equal due to the assumption of an even distribution of bio-naïve patients between the population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis.

Table 43: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients which have PsA without moderate to severe plaque psoriasis when decreasing the unit cost of adalimumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 4.731	-kr 12.549	-kr 22.448	-kr 34.427	-kr 48.486
Drug cost	kr 7.206	kr 16.300	kr 27.624	kr 41.178	kr 56.963
Administration cost	-kr 11.938	-kr 28.849	-kr 50.072	-kr 75.605	-kr 105.449

Table 44: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients which have PsA with moderate to severe plaque psoriasis when decreasing the unit cost of adalimumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 4.731	-kr 12.549	-kr 22.448	-kr 34.427	-kr 48.486
Drug cost	kr 7.206	kr 16.300	kr 27.624	kr 41.178	kr 56.963
Administration cost	-kr 11.938	-kr 28.849	-kr 50.072	-kr 75.605	-kr 105.449

12.1.6 Sensitivity analysis of increasing adalimumab unit cost with 10% presented separately for the treatment naïve population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis

The result of the budget impact sensitivity analysis if increasing adalimumab unit cost with 10% in the treatment naïve populations are provided in Table 45 and Table 46, respectively. As evident from the results, adalimumab unit cost has no impact on the budget impact result in treatment naïve populations, as guselkumab is not expected to take any market share from adalimumab. The results in Table 45 and Table 46 are equal due to the assumption of an even distribution of bio-naïve patients between the population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis.

Table 45: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients which have PsA without moderate to severe plaque psoriasis when increasing the unit cost of adalimumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 4.731	-kr 12.549	-kr 22.448	-kr 34.427	-kr 48.486
Drug cost	kr 7.206	kr 16.300	kr 27.624	kr 41.178	kr 56.963
Administration cost	-kr 11.938	-kr 28.849	-kr 50.072	-kr 75.605	-kr 105.449

Table 46: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients which have PsA with moderate to severe plaque psoriasis when increasing the unit cost of adalimumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 4.731	-kr 12.549	-kr 22.448	-kr 34.427	-kr 48.486
Drug cost	kr 7.206	kr 16.300	kr 27.624	kr 41.178	kr 56.963
Administration cost	-kr 11.938	-kr 28.849	-kr 50.072	-kr 75.605	-kr 105.449

12.1.7 Sensitivity analysis of varying ixekizumab unit cost with ±10% presented for the full the treatment naïve population

The result of the budget impact sensitivity analysis if varying ixekizumab unit cost with ±10% in the full treatment naïve population is provided in Table 47 and Table 48, respectively.

Table 47: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients when decreasing the unit cost of ixekizumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 15.939	kr 32.357	kr 52.477	kr 76.299	kr 103.822
Drug cost	kr 39.814	kr 90.055	kr 152.620	kr 227.508	kr 314.720
Administration cost	-kr 23.875	-kr 57.698	-kr 100.143	-kr 151.210	-kr 210.898

Table 48: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients when increasing the unit cost of ixekizumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 34.898	-kr 82.631	-kr 142.397	-kr 214.197	-kr 298.030
Drug cost	-kr 11.023	-kr 24.933	-kr 42.254	-kr 62.988	-kr 87.133
Administration cost	-kr 23.875	-kr 57.698	-kr 100.143	-kr 151.210	-kr 210.898

In addition to the sensitivity analysis of varying ixekizumab unit cost with ±10% for the full treatment naïve population presented above, the budget impact sensitivity results are also presented separately for treatment naïve patients which have PsA without moderate to severe plaque psoriasis and treatment naïve patients which have PsA with moderate to severe plaque psoriasis. These results are presented in section 12.1.8 and 12.1.9.

12.1.8 Sensitivity analysis of decreasing ixekizumab unit cost with 10% presented separately for the treatment naïve population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis

The result of the budget impact sensitivity analysis if decreasing ixekizumab unit cost with 10% in the treatment naïve populations are provided in Table 49 and Table 50, respectively. The results in Table 49 and Table 50 are equal due to the assumption of an even distribution of bio-naïve patients between the population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis.

Table 49: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients which have PsA without moderate to severe plaque psoriasis when decreasing the unit cost of ixekizumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 7.969	kr 16.179	kr 26.239	kr 38.149	kr 51.911
Drug cost	kr 19.907	kr 45.028	kr 76.310	kr 113.754	kr 157.360
Administration cost	-kr 11.938	-kr 28.849	-kr 50.072	-kr 75.605	-kr 105.449

Table 50: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients which have PsA with moderate to severe plaque psoriasis when decreasing the unit cost of ixekizumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	kr 7.969	kr 16.179	kr 26.239	kr 38.149	kr 51.911
Drug cost	kr 19.907	kr 45.028	kr 76.310	kr 113.754	kr 157.360
Administration cost	-kr 11.938	-kr 28.849	-kr 50.072	-kr 75.605	-kr 105.449

12.1.9 Sensitivity analysis of increasing ixekizumab unit cost with 10% presented separately for the treatment naïve population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis

The result of the budget impact sensitivity analysis if increasing ixekizumab unit cost with 10% in the treatment naïve populations are provided in Table 51 and Table 52, respectively. The results in Table 51 and Table 52 are equal due to the assumption of an even distribution of bio-naïve patients between the population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis.

Table 51: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients which have PsA without moderate to severe plaque psoriasis when increasing the unit cost of ixekizumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 17.449	-kr 41.315	-kr 71.199	-kr 107.099	-kr 149.015
Drug cost	-kr 5.511	-kr 12.466	-kr 21.127	-kr 31.494	-kr 43.566
Administration cost	-kr 11.938	-kr 28.849	-kr 50.072	-kr 75.605	-kr 105.449

Table 52: Results of the budget impact sensitivity analysis for treatment of treatment naïve patients which have PsA with moderate to severe plaque psoriasis when increasing the unit cost of ixekizumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 17.449	-kr 41.315	-kr 71.199	-kr 107.099	-kr 149.015
Drug cost	-kr 5.511	-kr 12.466	-kr 21.127	-kr 31.494	-kr 43.566
Administration cost	-kr 11.938	-kr 28.849	-kr 50.072	-kr 75.605	-kr 105.449

12.2 Results of DSA for budget impact analysis in treatment experienced population

12.2.1 Sensitivity analysis of varying guselkumab unit cost with ±10% presented for the full the treatment experienced population

The result of the budget impact sensitivity analysis if varying guselkumab unit cost with ±10% in the full treatment experienced population is provided in Table 53 and Table 54, respectively.

Table 53: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients when decreasing the unit cost of guselkumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 964.782	-kr 1.815.655	-kr 2.854.376	-kr 3.794.346	-kr 4.877.615
Drug cost	-kr 520.948	-kr 757.341	-kr 1.030.831	-kr 1.195.622	-kr 1.433.311
Administration cost	-kr 443.834	-kr 1.058.314	-kr 1.823.545	-kr 2.598.724	-kr 3.444.304

Table 54: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients when increasing the unit cost of guselkumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 158.992	kr 6.965	kr 234.486	kr 541.573	kr 839.658
Drug cost	kr 284.842	kr 1.065.279	kr 2.058.031	kr 3.140.296	kr 4.283.962
Administration cost	-kr 443.834	-kr 1.058.314	-kr 1.823.545	-kr 2.598.724	-kr 3.444.304

In addition to the sensitivity analysis of varying guselkumab unit cost with ±10% for the full treatment experienced population presented above, the budget impact sensitivity results are also presented separately for treatment experienced patients which have PsA without moderate to severe plaque psoriasis and treatment experienced patients which have PsA with moderate to severe plaque psoriasis. These results are presented in section 12.2.2 and 12.2.3.

12.2.2 Sensitivity analysis of decreasing guselkumab unit cost with 10% presented separately for the treatment experienced population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis

The result of the budget impact sensitivity analysis if decreasing guselkumab unit cost with 10% in the treatment experienced populations are provided in Table 55 and Table 56, respectively. The results in Table 55 and Table 56 are equal due to the assumption of an even distribution of bio-experienced patients between the population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis.

Table 55: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients which have PsA without moderate to severe plaque psoriasis when decreasing the unit cost of guselkumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 482.391	-kr 907.828	-kr 1.427.188	-kr 1.897.173	-kr 2.438.807
Drug cost	-kr 260.474	-kr 378.671	-kr 515.416	-kr 597.811	-kr 716.656
Administration cost	-kr 221.917	-kr 529.157	-kr 911.772	-kr 1.299.362	-kr 1.722.152

Table 56: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients which have PsA with moderate to severe plaque psoriasis when decreasing the unit cost of guselkumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 482.391	-kr 907.828	-kr 1.427.188	-kr 1.897.173	-kr 2.438.807
Drug cost	-kr 260.474	-kr 378.671	-kr 515.416	-kr 597.811	-kr 716.656
Administration cost	-kr 221.917	-kr 529.157	-kr 911.772	-kr 1.299.362	-kr 1.722.152

12.2.3 Sensitivity analysis of increasing guselkumab unit cost with 10% presented separately for the treatment experienced population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis

The result of the budget impact sensitivity analysis if increasing guselkumab unit cost with 10% in the treatment experienced populations are provided in Table 57 and Table 58, respectively. The results in Table 57 and Table 58 are equal due to the assumption of an even distribution of bio-experienced patients between the population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis.

Table 57: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients which have PsA without moderate to severe plaque psoriasis when increasing the unit cost of guselkumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 79.496	kr 3.483	kr 117.243	kr 270.786	kr 419.829
Drug cost	kr 142.421	kr 532.640	kr 1.029.016	kr 1.570.148	kr 2.141.981
Administration cost	-kr 221.917	-kr 529.157	-kr 911.772	-kr 1.299.362	-kr 1.722.152

Table 58: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients which have PsA with moderate to severe plaque psoriasis when increasing the unit cost of guselkumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 79.496	kr 3.483	kr 117.243	kr 270.786	kr 419.829
Drug cost	kr 142.421	kr 532.640	kr 1.029.016	kr 1.570.148	kr 2.141.981
Administration cost	-kr 221.917	-kr 529.157	-kr 911.772	-kr 1.299.362	-kr 1.722.152

12.2.4 Sensitivity analysis of varying ixekizumab unit cost with ±10% presented for the full the treatment experienced population

The result of the budget impact sensitivity analysis if varying ixekizumab unit cost with ±10% in the full treatment experienced population is provided in Table 59 and Table 60, respectively.

Table 59: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients when decreasing the unit cost of ixekizumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 434.879	-kr 595.897	-kr 761.089	-kr 841.659	-kr 966.626
Drug cost	kr 8.955	kr 462.417	kr 1.062.456	kr 1.757.065	kr 2.477.677
Administration cost	-kr 443.834	-kr 1.058.314	-kr 1.823.545	-kr 2.598.724	-kr 3.444.304

Table 60: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients when increasing the unit cost of ixekizumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 689.063	-kr 1.213.201	-kr 1.859.527	-kr 2.412.153	-kr 3.072.722
Drug cost	-kr 245.229	-kr 154.887	-kr 35.982	kr 186.571	kr 371.581
Administration cost	-kr 443.834	-kr 1.058.314	-kr 1.823.545	-kr 2.598.724	-kr 3.444.304

In addition to the sensitivity analysis of varying ixekizumab unit cost with ±10% for the full treatment experienced population presented above, the budget impact sensitivity results are also presented separately for treatment experienced patients which have PsA without moderate to severe plaque psoriasis and treatment experienced patients which have PsA with moderate to severe plaque psoriasis. These results are presented in section 12.2.5 and 12.2.6.

12.2.5 Sensitivity analysis of decreasing ixekizumab unit cost with 10% presented separately for the treatment experienced population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis

The result of the budget impact sensitivity analysis if decreasing ixekizumab unit cost with 10% in the treatment experienced populations are provided in Table 61 and Table 62, respectively. The results in Table 61 and Table 62 are equal due to the assumption of an even distribution of bio-experienced patients between the population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis.

Table 61: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients which have PsA without moderate to severe plaque psoriasis when decreasing the unit cost of ixekizumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 217.439	-kr 297.949	-kr 380.544	-kr 420.829	-kr 483.313
Drug cost	kr 4.477	kr 231.209	kr 531.228	kr 878.533	kr 1.238.839
Administration cost	-kr 221.917	-kr 529.157	-kr 911.772	-kr 1.299.362	-kr 1.722.152

Table 62: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients which have PsA with moderate to severe plaque psoriasis when decreasing the unit cost of ixekizumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 217.439	-kr 297.949	-kr 380.544	-kr 420.829	-kr 483.313
Drug cost	kr 4.477	kr 231.209	kr 531.228	kr 878.533	kr 1.238.839
Administration cost	-kr 221.917	-kr 529.157	-kr 911.772	-kr 1.299.362	-kr 1.722.152

12.2.6 Sensitivity analysis of increasing ixekizumab unit cost with 10% presented separately for the treatment experienced population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis

The result of the budget impact sensitivity analysis if increasing ixekizumab unit cost with 10% in the treatment experienced populations are provided in Table 63 and Table 64, respectively. The results in Table 63 and Table 64 are equal due to the assumption of an even distribution of bio-experienced patients between the population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis.

Table 63: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients which have PsA without moderate to severe plaque psoriasis when increasing the unit cost of ixekizumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 344.531	-kr 606.601	-kr 929.763	-kr 1.206.076	-kr 1.536.361
Drug cost	-kr 122.615	-kr 77.443	-kr 17.991	kr 93.286	kr 185.791
Administration cost	-kr 221.917	-kr 529.157	-kr 911.772	-kr 1.299.362	-kr 1.722.152

Table 64: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients which have PsA with moderate to severe plaque psoriasis when increasing the unit cost of ixekizumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 344.531	-kr 606.601	-kr 929.763	-kr 1.206.076	-kr 1.536.361
Drug cost	-kr 122.615	-kr 77.443	-kr 17.991	kr 93.286	kr 185.791
Administration cost	-kr 221.917	-kr 529.157	-kr 911.772	-kr 1.299.362	-kr 1.722.152

12.2.7 Sensitivity analysis of varying secukinumab unit cost with ±10% presented for the full the treatment experienced population

The result of the budget impact sensitivity analysis if varying secukinumab unit cost with ±10% in the full treatment experienced population is provided in Table 65 and Table 66, respectively.

Table 65: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients when decreasing the unit cost of secukinumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 274.279	-kr 317.085	-kr 366.095	-kr 340.911	-kr 355.926
Drug cost	kr 169.555	kr 741.229	kr 1.457.450	kr 2.257.813	kr 3.088.378
Administration cost	-kr 443.834	-kr 1.058.314	-kr 1.823.545	-kr 2.598.724	-kr 3.444.304

Table 66: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients when increasing the unit cost of secukinumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 849.495	-kr 1.491.605	-kr 2.253.795	-kr 2.911.862	-kr 3.682.031
Drug cost	-kr 405.661	-kr 433.291	-kr 430.250	-kr 313.139	-kr 237.727
Administration cost	-kr 443.834	-kr 1.058.314	-kr 1.823.545	-kr 2.598.724	-kr 3.444.304

In addition to the sensitivity analysis of varying secukinumab unit cost with ±10% for the full treatment experienced population presented above, the budget impact sensitivity results are also presented separately for treatment experienced patients which have PsA without moderate to severe plaque psoriasis and treatment experienced patients which have PsA with moderate to severe plaque psoriasis. These results are presented in section 12.2.8 and 12.2.9.

12.2.8 Sensitivity analysis of decreasing secukinumab unit cost with 10% presented separately for the treatment experienced population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis

The result of the budget impact sensitivity analysis if decreasing secukinumab unit cost with 10% in the treatment experienced populations are provided in Table 67 and Table 68, respectively. The results in Table 67 and Table 68 are equal due to the assumption of an even distribution of bio-experienced patients between the population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis.

Table 67: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients which have PsA without moderate to severe plaque when decreasing the unit cost of secukinumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 137.139	-kr 158.542	-kr 183.047	-kr 170.455	-kr 177.963
Drug cost	kr 84.777	kr 370.615	kr 728.725	kr 1.128.906	kr 1.544.189
Administration cost	-kr 221.917	-kr 529.157	-kr 911.772	-kr 1.299.362	-kr 1.722.152

Table 68: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients which have PsA with moderate to severe plaque when decreasing the unit cost of secukinumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 137.139	-kr 158.542	-kr 183.047	-kr 170.455	-kr 177.963
Drug cost	kr 84.777	kr 370.615	kr 728.725	kr 1.128.906	kr 1.544.189
Administration cost	-kr 221.917	-kr 529.157	-kr 911.772	-kr 1.299.362	-kr 1.722.152

12.2.9 Sensitivity analysis of increasing secukinumab unit cost with 10% presented separately for the treatment experienced population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis

The result of the budget impact sensitivity analysis if increasing secukinumab unit cost with 10% in the treatment experienced populations are provided in Table 69 and Table 70, respectively. The results in Table 69 and Table 70 are equal due to the assumption of an even distribution of bio-experienced patients between the population which have PsA without moderate to severe plaque psoriasis and the population which have PsA with moderate to severe plaque psoriasis.

Table 69: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients which have PsA without moderate to severe plaque when increasing the unit cost of secukinumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 424.747	-kr 745.803	-kr 1.126.898	-kr 1.455.931	-kr 1.841.015
Drug cost	-kr 202.830	-kr 216.646	-kr 215.125	-kr 156.569	-kr 118.863
Administration cost	-kr 221.917	-kr 529.157	-kr 911.772	-kr 1.299.362	-kr 1.722.152

Table 70: Results of the budget impact sensitivity analysis for treatment of treatment experienced patients which have PsA with moderate to severe plaque when increasing the unit cost of secukinumab with 10%

	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-kr 424.747	-kr 745.803	-kr 1.126.898	-kr 1.455.931	-kr 1.841.015
Drug cost	-kr 202.830	-kr 216.646	-kr 215.125	-kr 156.569	-kr 118.863
Administration cost	-kr 221.917	-kr 529.157	-kr 911.772	-kr 1.299.362	-kr 1.722.152

13 Appendix

Table A1: Model assumptions for the cost-analysis and budget impact model.

Parameter	Model assumptions
Comparator	Adalimumab and Ixekizumab
Model type	Simple cost-analysis
Perspective	Restricted societal perspective
Time horizon cost analysis	5 years
Time horizon budget impact analysis	5 years
Discounting rate	3.5%
Included costs	Medicine costs Treatment administration costs Patient costs
Patient number	80 treatment naïve* 120 treatment experienced*
Handling of uncertainty	One-way sensitivity analyses

*See section 9.1

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Medicinrådet

Medicinrådets protokol for vurdering vedrørende guselkumab til behandling af psoriasisartrit

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i sin endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel, Medicinrådet undersøger, den behandling, Medicinrådet sammenligner med, og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil den ansøgende virksomhed få besked.

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1. Begreber og forkortelser

ACR50: *American College of Rheumatology 50 % response*

bDMARD: Biologisk *Disease Modifying Anti-Rheumatic Drug*

CRP: C-Reaktivt Protein

csDMARD: Konventionel *Disease Modifying Anti-Rheumatic Drug*

DANBIO Dansk Reumatologisk Database

DMARD: Sygdomsmodificerende antireumatisk lægemiddel (*Disease Modifying Anti-Rheumatic Drug)*

EMA: Det Europæiske Lægemiddelagentur (*European Medicines Agency*)

EPAR: *European Public Assessment Report*

EUnetHTA: *European Network for Health Technology Assessment*

FDA: *The Food and Drug Administration*

FINOSE: Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger

GRADE: System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)

HTA: Medicinsk teknologivurdering (*Health Technology Assessment)*

IL-17: Interleukin 17

IL-23: Interleukin 23

IQWIG: *The Institute for Quality and Efficiency in Healthcare*

ITT: *Intention-to-treat*

MKRF: Mindste klinisk relevante forskel

mTSS: *Modified Total Sharp Score*

MTX: Methotrexat

NICE: *The National Institute for Health and Care Excellence*

PASI: *Psoriasis Area Severity Index*

PICO: Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*

PsA: Psoriasisartrit

SF-36: Short Form 36

SMD: *Standardized Mean Difference*

tsDMARD: Targeteret syntetisk *Disease Modifying Anti-Rheumatic Drug*

VAS: *Visual Assessment Scale*

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Janssen-Cilag A/S, som ønsker, at Medicinrådet vurderer guselkumab til psoriasisartrit. Medicinrådet modtog den foreløbige ansøgning den 20. oktober 2020.

2.1 Psoriasisartrit

Psoriasisartrit (PsA) er en kronisk inflammatorisk ledsygdom, der ofte (men ikke nødvendigvis) optræder sammen med den kroniske hudsygdom psoriasis [1,2]. Patogenesen er en T-celle-medieret inflammation og involverer en kompleks række interaktioner mellem immunceller og proinflammatoriske cytokiner, hvor T-celler og makrofager rekrutteres til led- og hudvæv [3]. Disse immunceller fremmer derefter inflammatoriske processer involveret i sygdommen, hvoraf inflammation medieret af det ekstracellulære interleukin 17 og 23 (IL-17 og IL-23) ser ud til at spille en nøglerolle [3–6]. Sygdommen er multifaktoriel og betinget af både genetiske og miljømæssige faktorer [7].

PsA kan både manifestere sig ved inflammation i perifere led og i rygsøjlen, og der kan desuden optræde ekstraartikulære symptomer som inflammation i senetilhæftninger (entesit), hævede fingre eller tæer (daktylit) og negledystrofi [8]. Patienterne kan også have betændelse i øjets regnbue- og årehinde (uveitis) eller have kronisk inflammatorisk tarmsygdom. Det kan være vanskeligt at skelne diagnostisk mellem PsA med aksial involvering og rygsøjlegigt (spondylartrit) af anden art. De kliniske manifestationer varierer betydeligt mellem patienter [9–11] og har stor betydning for patienternes liv. PsA-patienter rapporterer ofte om smerter, nedsat fysisk funktion, træthed og vanskeligheder med daglige aktiviteter [12,13].

I den nationale behandlingsvejledning for PsA fra Dansk Reumatologisk Selskab fremgår det, at der mangler validerede kliniske diagnosekriterier for PsA, men at der er udviklet klassifikationskriterier, som kan benyttes som støtte. Diagnosen stilles på baggrund af en objektiv undersøgelse af bevægeapparat og hud sammen med serologi og biokemi [8].

Prævalensen er svær at estimere grundet manglen på klare diagnostiske kriterier. Baseret på estimater fra et studie fra 2008 og beregninger fra Gigtforeningen finder Medicinrådet, at prævalensen formentlig er mellem 6.000 og 25.000 personer [14,15]. Det skønnes desuden, at op til ca. 15 % af patienter med psoriasis udvikler PsA [8]. Sygdommen debuterer oftest i alderen 40-50 år, og prævalensen er ens for mænd og kvinder.

2.2 Guselkumab

Guselkumab (Tremfya) er en systemisk biologisk antistofbehandling, der virker ved, at det aktive stof binder sig til IL-23. Herved bliver IL-23 forhindret i at bidrage til immunaktivering, og den inflammatoriske reaktion, der spiller en central rolle i udviklingen af PsA, begrænses.

Guselkumab forventes at få følgende indikation til PsA hos Det Europæiske Lægemiddelagentur (*European Medicines Agency* (EMA)):

> *Tremfya® alene eller i kombination med methotrexat (MTX) er indiceret til behandling af aktiv psoriasisartrit hos voksne patienter, som har haft et utilstrækkeligt respons på, eller som har været intolerante over for, en forudgående behandling med et sygdomsmodificerende antireumatisk lægemiddel (DMARD).*

Guselkumab gives som subkutan injektion à 100 mg i uge 0 og 4 samt herefter hver 8. uge. For patienter med høj risiko for ledskade, i henhold til klinisk vurdering, kan der overvejes en dosis på 100 mg hver 4. uge.

Guselkumab er desuden indiceret til behandling af moderat til svær plaque psoriasis [16].

2.3 Nuværende behandling

Der findes ingen behandling, som kan kurere PsA. Den nuværende behandling er i stedet målrettet patienternes smerter og symptomer, som beskrevet i afsnit 2.1. Behandlingsmålet er, at patienterne opnår så lav sygdomsaktivitet som muligt og helst remission, så symptomer og inflammation er kontrollerede. Dette er blandt andet for at optimere patientens livskvalitet og sociale liv, forhindre progredierende strukturelle ledskader og bevare funktionsevne.

Sygdomsmodificerende behandling (*disease modifying antirheumatic drugs* (DMARDs)) gives ved betydelig affektion af led. Til patienter med lav sygdomsaktivitet og lav risiko for progressiv ledsygdom (ledaffektion i mindre end fem led) anvendes monoterapi med lægemidler af typen konventionelle DMARDs (csDMARDs), hvor MTX sædvanligvis er førstevalg i dansk klinisk praksis [8].

Hos patienter med betydelig ledaffektion (mere end fire led) eller ved utilstrækkelig effekt af csDMARDs, eventuelt i kombination med lokale steroidinjektioner [17], kan biologisk behandling med antistoffer (bDMARDs) eller targeteret syntetisk behandling med små molekyler (tsDMARDs) indledes. Kriterierne for at indlede b/tsDMARD-behandling omfatter sygdomsaktivitet, fravær af kontraindikationer, og at beslutningen træffes på konference med speciallæger i reumatologi [8]. Af b/tsDMARDs-behandling benyttes på nuværende tidspunkt forskellige TNF-alfa-hæmmere, monoklonale antistoffer rettet mod IL-12, - 17 og -23 samt en Janus kinase-hæmmer.

Den nuværende lægemiddelrekommandation for biologisk behandling af PsA [18] er delt op i behandling til flere forskellige patientgrupper, afhængigt af om patienten har samtidig moderat til svær psoriasis, uveitis eller inflammatorisk tarmsygdom. Flere af lægemidlerne er godkendt til både PsA og en eller flere af de nævnte indikationer, hvilket har betydning for, hvilke lægemidler der anvendes til de relevante patientgrupper.

TNF-hæmmeren adalimumab er p.t. førstevalg for behandling af alle patientpopulationerne i Medicinrådets lægemiddelrekommandation [18]. Jf. RADS' baggrundsnotat for biologiske og syntetiske targeterede lægemidler til behandling af PsA udelukker behandlingssvigt ved anvendelse af en TNF-hæmmer ikke muligheden for effekt af en ny TNF-hæmmer eller lægemidler med anden virkningsprofil. Efter svigt af to effektfulde TNF-hæmmere (sekundært svigt) eller ved manglende respons fra start (primært svigt) kan lægemiddel med anden virkningsprofil overvejes [19]. Ixekizumab er p.t. andet valg efter forudgående behandling med TNF-hæmmer [18].

I DANBIO (Dansk Reumatologisk Database) var der ved udgangen af 2019 registreret ca. 2560 patienter i biologisk behandling for PsA, hvoraf ca. 330 patienter startede på biologisk behandling (behandlingsnaive) og ca. 860 patienter skiftede behandling (behandlingserfarne). Tallene dækker over alle PsA-patienter, inklusiv dem der har følgesygdommene uveitis, Crohns sygdom og colitis ulcerosa.

3. Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel, Medicinrådet undersøger (interventionen), af den behandling, Medicinrådet sammenligner med (komparator(er)), og af effektmålene.

De kliniske spørgsmål afspejler populationerne i lægemiddelrekommandationen. Da guselkumab imidlertid ikke er godkendt til behandling af uveitis, Crohns sygdom og colitis ulcerosa, vil Medicinrådets vurdering af guselkumab ikke omhandle patienter med PsA, der har en af disse sygdomme, men alene tage stilling til patienter med og uden samtidig moderat til svær plaque psoriasis. Derudover afspejler de kliniske spørgsmål, at der i dansk klinisk praksis skelnes mellem behandlingsnaive patienter (der ikke tidligere har været behandlet med b/tsDMARDs og skal begynde behandling med en af disse) og behandlingserfarne patienter (der tidligere har været behandlet med b/tsDMARDs og skal skifte til en anden).

3.1 Klinisk spørgsmål 1

Hvilken værdi har guselkumab sammenlignet med adalimumab for behandlingsnaive patienter med PsA uden moderat til svær plaque psoriasis?

Population
Patienter med PsA uden moderat til svær plaque psoriasis, som endnu ikke har modtaget behandling med b/tsDMARDs.

Intervention
Guselkumab subkutan injektion à 100 mg i uge 0 og 4 samt herefter hver 8. uge.

Komparator
Adalimumab subkutan injektion à 40 mg hver 14. dag.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.2 Klinisk spørgsmål 2

Hvilken værdi har guselkumab sammenlignet med ixekizumab for behandlingserfarne patienter med PsA uden moderat til svær plaque psoriasis?

Population
Patienter med PsA uden moderat til svær plaque psoriasis, som tidligere har modtaget behandling med b/tsDMARDs.

Intervention
Guselkumab subkutan injektion à 100 mg i uge 0 og 4 samt herefter hver 8. uge.

Komparator
Ixekizumab subkutan injektion à 160 mg i uge 0 og herefter 80 mg hver 4. uge.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.3 Klinisk spørgsmål 3

Hvilken værdi har guselkumab sammenlignet med adalimumab for behandlingsnaive patienter med PsA og moderat til svær plaque psoriasis?

Population
Patienter med PsA og moderat til svær plaque psoriasis, som endnu ikke har modtaget behandling med b/tsDMARDs.

Intervention
Guselkumab subkutan injektion à 100 mg i uge 0 og 4 samt herefter hver 8. uge.

Komparator
Adalimumab subkutan injektion à 40 mg hver 14. dag.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.4 Klinisk spørgsmål 4

Hvilken værdi har guselkumab sammenlignet med ixekizumab for behandlingserfarne patienter med PsA og moderat til svær plaque psoriasis?

Population
Patienter med PsA og moderat til svær plaque psoriasis, som tidligere har modtaget behandling med b/tsDMARDs.

Intervention
Guselkumab subkutan injektion à 100 mg i uge 0 og 4 samt herefter hver 8. uge.

Komparator
Ixekizumab subkutan injektion à 160 mg i uge 0 og herefter 80 mg hver 4. uge.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.5 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer Medicinrådet for valget af effektmål og MKRF.

Tabel 1. Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Sygdomsaktivitet - ledaffektion	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever respons på ACR50	15 %-point
			Andel patienter uden progression, jf. mTSS	10 %-point
Bivirkninger	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever alvorlige bivirkninger	5 %-point
			Kvalitativ gennemgang af bivirkningsprofil	

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Livskvalitet	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring fra baseline på Short Form 36 (SF-36), det fysiske funktion-subdomæne	7,1 point
			Gennemsnitlig ændring fra baseline på SF-36, det fysiske smerte-subdomæne	4,9 point
			Gennemsnitlig ændring fra baseline på SF-36, den fysiske komponent summary	7,2 point
			Gennemsnitlig ændring fra baseline på SF-36, den mentale komponent summary	3,1 point
Sygdomsaktivitet - hudaffektion	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever respons på PASI90***	10 %-point

*For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.
**Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.
***Kun for klinisk spørgsmål 3 og 4, hvor patienterne har PsA og moderat til svær plaque psoriasis.

3.5.1 Kritiske effektmål

Sygdomsaktivitet – ledaffektion

Medicinrådet finder, at sygdomsaktivitet ift. ledaffektion er et kritisk effektmål, da patienter, der oplever nedsat sygdomsaktivitet, opnår forbedret funktionsniveau, livskvalitet og tilknytning til arbejdsmarkedet [20,21]. Medicinrådet betragter sygdomsaktivitet som et selvstændigt kritisk effektmål og ikke som et surrogat for livskvalitet. Sygdomsaktivitet kan blandt andet måles ved de kompositte værktøjer American College of Rheumatology *(ACR)* og modified Total Sharp Score *(mTSS).*

ACR50

Det primære mål for effekt på sygdomsaktivitet er ACR50. Dette er defineret som en 50 %'s forbedring i både ømme og hævede led samt 50 %'s forbedring inden for mindst tre ud af følgende fem domæner: patientens overordnede vurdering af, hvor meget gigten som helhed påvirker hverdagen (*Visual Assessment Scale* (VAS) global), patientens vurdering af smerte, lægens overordnede vurdering af patientens samlede sygdomsaktivitet (VAS doctor), HAQ-DI score, som måler patientens funktionsniveau, og C-Reaktivt Protein (CRP). Medicinrådet vurderer, at en 50 %'s forbedring er et patientrelevant effektmål og betragtes her som tilstrækkeligt for at definere respons.

Medicinrådet vurderer, at en forskel på 15 %-point i andelen af patienter, der opnår ACR50, er klinisk relevant. Dette er i overensstemmelse med Medicinrådets tidligere vurderinger af lægemidler til PsA [22,23].

mTSS

Medicinrådet ønsker at benytte et radiografisk effektmål, der kan tolkes som udtryk for leddestruktion og dermed sygdomsprogression. Medicinrådet ønsker at benytte en modificeret udgave af *Total Sharp Score* (mTSS), som er udviklet til scoring af patienter med PsA [24].

Medicinrådet vurderer, at en forskel på 10 %-point i andelen af patienter uden progression, dvs. fravær af radiologiske ændringer, jf. mTSS, er klinisk relevant. Dette er i overensstemmelse med Medicinrådets tidligere vurderinger af lægemidler til PsA [22,23].

Bivirkninger

Medicinrådet vægter effektmålet bivirkninger som kritisk for vurderingen af lægemidlets værdi.

Alvorlige bivirkninger

Medicinrådet ønsker data på alvorlige bivirkninger (serious adverse reactions, SAR), da disse særligt frygtes af patienter og klinikere, siden de kan forårsage pauser i behandlingen med risiko for forværring af symptomer og sygdomsprogression. Medicinrådet vurderer, at den mindste klinisk relevante forskel er 5 %-point.

Kvalitativ gennemgang af bivirkningsprofil

Medicinrådet ønsker en kvalitativ gennemgang af guselkumab og komparatorernes bivirkningsprofiler for at vurdere bivirkningernes type, håndterbarhed og reversibilitet. Ansøger bedes derfor levere bivirkningsdata fra lægemidlernes produktresuméer og i den forbindelse forholde sig eksplicit til alvorlige infektioner (som defineret i de kliniske studier), da dette er af særlig betydning for patienterne.

Livskvalitet

Livskvalitet er et patientrelevant effektmål, som udover at give indblik i sygdomsbyrden kan indikere, om bivirkningerne ved lægemidlet påvirker patienternes livskvalitet. Patienter med PsA er ofte mærket af deres sygdom både fysisk og mentalt, og det er derfor af stor betydning, om et nyt lægemiddel kan afhjælpe dette. På baggrund heraf betragter Medicinrådet livskvalitet som et kritisk effektmål.

Medicinrådet ønsker effektmålet opgjort med det generiske instrument SF-36 (Short Form 36). SF-36 er et spørgeskema, som bygger på 36 spørgsmål og måler helbredsrelateret livskvalitet og funktionsevne. Spørgeskemaet er inddelt i 8 helbredsrelaterede domæner (subdomæner): fysisk funktion, fysisk betingede begrænsninger, psykisk betingede begrænsninger, social funktion, fysisk smerte, psykisk helbred, energi og alment helbred. Derudover kan to sammenfattede scores også

opgøres: fysisk komponent summary og mental komponent summary. Scoren måles på en skala fra 0 til 100, hvor høj score repræsenterer bedre livskvalitet.

I kliniske studier bliver livskvalitet ofte opgjort på de individuelle subdomæner eller de to sammenfattede scorer fremfor på en global score for SF-36. Inden for kronisk leddegigt har de to individuelle domæner fysisk funktion og fysisk smerte samt den sammenfattede score for fysiske komponenter vist sig at reflektere klinisk relevant respons [25]. Mindste klinisk relevante forskel er rapporteret som en forskel på hhv. 7,1, 4,9 og 7,2 point fra baseline for hhv. det fysiske funktion-subdomæne, fysiske smerte-subdomæne og den fysiske komponent summary [25]. Derudover ønsker Medicinrådet at se på data fra den sammenfattede score for mentale komponenter, hvor der inden for kronisk leddegigt er blevet rapporteret en mindste klinisk relevant forskel på 3,1 point [26]. Medicinrådet finder, at disse mindste klinisk relevante forskelle rapporteret for kronisk leddegigt også kan anvendes inden for PsA.

3.5.2 Vigtige effektmål

Sygdomsaktivitet – hudaffektion
Medicinrådet vurderer, at det er af betydning, at patienter med PsA og moderat til svær plaque psoriasis opnår nedsat sygdomsaktivitet i forhold til hudaffektion, da patienterne er særligt plaget deraf. I den forbindelse ønsker Medicinrådet data på det kompositte værktøj *Psoriasis Area Severity Index (PASI)* på de populationer, hvor dette er relevant (klinisk spørgsmål 3 og 4). Medicinrådet betragter effektmålet som vigtigt og ikke kritisk, da det primært er patienternes ledaffektioner, der ønskes behandlet.

PASI kombinerer størrelsen på det areal af huden, som er ramt, med alvorligheden heraf på en score fra 0 til 72, hvor 72 udtrykker maksimal sygdom. PASI90 afspejler andelen af patienter, som opnår en 90 %'s reduktion i PASI-score. Medicinrådet vurderer, at en forskel på 10 %-point i andelen af patienter, der opnår PASI90, er klinisk relevant. Dette er i overensstemmelse med Medicinrådets behandlingsvejledning vedr. lægemidler til moderat til svær plaque psoriasis [27].

Hvis der ikke foreligger data på PASI90, kan ansøger indsende data på PASI75. Her vurderer Medicinrådet, at den mindste klinisk relevante forskel er 15 %-point, hvilket ligeledes er i overensstemmelse med Medicinrådets behandlingsvejledning vedr. lægemidler til moderat til svær plaque psoriasis [27].

4. Litteratursøgning

Medicinrådets vurdering af lægemidlets værdi vil i udgangspunktet være baseret på data fra fuldtekstartikler publiceret i videnskabelige, fagfællebedømte (peer-reviewed) tidsskrifter og data fra Det Europæiske Lægemiddelagenturs (EMAs) European Public Assessment Reports (EPAR). Herudover kan data fra Food and Drug Administration (FDA) og internationalt anerkendte HTA-agenturer (fx NICE, EUnetHTA, FINOSE og IQWiG) indgå i vurderingen. Hvis disse data er tilstrækkelige til at kunne vurdere lægemidlet, vil Medicinrådet som hovedregel ikke anvende andre data[1]. Data skal derudover stemme overens med protokollens beskrivelser. Hvis ansøger har kendskab til upublicerede data, der kan belyse eventuelle angivne mangler, kan de indgå/indsendes, jf. Medicinrådets kriteriepapir.

Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der ikke findes studier, hvor guselkumab er sammenlignet direkte med hverken adalimumab eller ixekizumab. Derfor skal ansøger søge efter studier til en indirekte sammenligning.

Søgestrengene fremgår af bilag 1. Derudover skal ansøger konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator(er).

Ansøger skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler, der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Kriterier for litteratursøgning
Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, fx i form af et skærmklip eller en downloadet søgestrategi. Eventuelle ændringer/tilføjelser til søgestrategien skal fremgå af dokumentationen.

Kriterier for udvælgelse af litteratur
Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med det/de i protokollen definerede kliniske spørgsmål samt kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Den ansøgende virksomhed skal ved screening af artikler først ekskludere på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram som beskrevet i PRISMA-Statement.

[1] For yderligere detaljer se Medicinrådets kriteriepapir om anvendelse af upublicerede data

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal virksomheden anvende et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen skal vurderes.

5. Den endelige ansøgning

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO (population, intervention, komparator og effektmål) mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (fx intention-to-treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jf. appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).

- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jf. appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'-modeller og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier, og vurdér, hvorvidt resultaterne er sammenlignelige.

Særlige forhold i denne protokol

- Andre studiedesign end randomiserede kontrollerede forsøg (RCT) ekskluderes.
- Fase I- og IIa-studier, studier med andre populationer end de valgte og studier, som ikke rapporterer mindst et af de kritiske eller vigtige effektmål, ekskluderes.

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

Sundhedsøkonomiske analyser
En sundhedsøkonomisk ansøgning består af en sammenhængende, dynamisk sundhedsøkonomisk model og et teknisk dokument, hvor modellen og de antagelser, der er bygget ind i modellen, beskrives, og hvor ansøgers sundhedsøkonomiske analyse fremgår. Ved dynamisk forstås, at en variabel kun skal ændres ét sted for at være gennemgående for hele modellen. Anvend eventuelt Medicinrådets metodevejledning og tjekliste til sundhedsøkonomiske modeller til at teste modellens dynamik, og at modellen overholder formelle krav.

En sundhedsøkonomisk analyse er ikke et resultat, men en bred analyse af modellens dynamik, hvilke parametre der har indflydelse på resultaterne, samt hvorfor og hvordan disse parametre indgår. Derfor skal det tekniske dokument som minimum indeholde følgende:

- Beskriv den valgte modelstruktur grundigt.
- Beskriv, hvis der er anvendt en indirekte analyse, hvordan den vil blive håndteret i den sundhedsøkonomiske analyse.
- Begrund og beskriv samtlige antagelser i modellen, og lad specifikke analysevalg fremgå tydeligt.
- Beskriv alle de inkluderede studier, argumentér for deres relevans, og beskriv, hvor og hvordan data anvendes i modellen.
- Begrund både de inkluderede og ekskluderede omkostninger.
- Beskriv, hvad der driver modellen, fx behandlingslængde eller lægemiddelomkostninger.
- Ekstrapoleret data skal beskrives.
- Udfør følsomhedsanalyser, som belyser, hvilke parametre i modellen der har størst indflydelse på resultatet.
- Argumentér for eventuelle afvigelser fra protokollen og den kliniske ansøgning.
- Budgetkonsekvensanalysen skal være dynamisk med omkostningsanalysen, uden diskontering og patientomkostninger.

6. Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessment, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad man kan have tiltro til den evidens, Medicinrådet baserer vurderingen af lægemidlets værdi på.

7. Andre overvejelser

Medicinrådet er opmærksom på, at der for nogle af populationerne i de kliniske spørgsmål kan være problemer med at fremskaffe data. I disse tilfælde vil Medicinrådet forholde sig til, om det er muligt at ekstrapolere fra de populationer, hvor der er data.

8. Relation til behandlingsvejledning

Medicinrådet vil i forbindelse med vurderingen af guselkumab tage stilling til, hvor lægemidlet foreløbigt kan placeres i RADS' *Behandlingsvejledning for biologisk behandling af Psoriasis Artritis (PsA)*.

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende gigtsygdomme

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Ulrik Tarp *Ledende overlæge*	Lægevidenskabelige Selskaber og Dansk Reumatologisk Selskab
Medlemmer	**Udpeget af**
Salome Kristensen *Overlæge*	Region Nordjylland
Lars Erik Bartels *Afdelingslæge*	Region Midtjylland
Hanne M. Lindegaard *Overlæge, klinisk lektor*	Region Syddanmark
Thomas Adelsten *Uddannelsesansvarlig overlæge*	Region Sjælland
Annemarie Lyng Svensson *Overlæge*	Region Hovedstaden
Per Damkier *Professor, overlæge*	Dansk Selskab for Klinisk Farmakologi
Thomas Loof Hedegård *Farmaceut*	Dansk Selskab for Sygehusapotekledelse
Dorte Vendelbo Jensen *Overlæge, sekretariatsleder*	DANBIO
Udpegning i gang	Dansk Reumatologisk Selskab
Connie Ziegler *Patient/patientrepræsentant*	Danske Patienter
Lene Mandrup Thomsen *Patient/patientrepræsentant*	Danske Patienter

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Medicinrådet
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medicinraadet@medicinraadet.dk

11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	25. januar 2021	Godkendt af Medicinrådet

12. Bilag 1: Søgestrenge

Søgestrenge for identifikation af relevant litteratur i PubMed.
https://www.ncbi.nlm.nih.gov/pubmed/advanced

#	Søgetermer	Kommentar
1	"Arthritis, Psoriatic"[mh]	Søgetermer for populationen
2	PsA[tiab] OR (psoria*[tiab] AND (arthriti*[tiab] OR arthropath*[tiab] OR polyarthriti*[tiab] OR poly-arthriti*[tiab] OR oligoarthr*[tiab] OR oligo-arthr*[tiab] OR rheumato*[tiab]))	
3	#1 OR #2	
4	guselkumab[nm]	Søgetermer for intervention og komparatorer
5	guselkumab[tiab] OR CNTO-1959[tiab] OR tremfya*[tiab]	
6	adalimumab[mh]	
7	adalimumab[tiab] OR humira*[tiab] OR D2E7[tiab] OR amjevita*[tiab] OR cyltezo*[tiab]	
8	ixekizumab[nm]	
9	ixekizumab[tiab] OR taltz*[tiab] OR LY-2439821[tiab] OR LY2439821[tiab]	
10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	
11	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh])	Filter til identifikation af RCT'er
12	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Guideline[pt] OR Review[pt] OR case report[ti]	Søgetermer for ikke relevante publikationstyper (der ekskluderes)
13	animal*[ti] OR murine[ti] OR mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti] OR rodent[ti]	
14	#12 OR #13	
15	#3 AND #10 AND #11 NOT #14	Endelig søgning

Feltkoder: mh = MeSH Term nm = Supplementary Concept/Substance tiab = title/abstract, inkl. forfatterkeywords pt = publication type

Søgestrenge for identifikation af relevant litteratur i CENTRAL (Cochrane Library).
https://www.cochranelibrary.com/advanced-search/search-manager

#	Søgetermer	Kommentar
1	[mh "Arthritis, Psoriatic"]	Søgetermer for populationen
2	(psoria* near (arthriti* or arthropath* or polyarthriti* or poly-arthriti* or oligoarthr* or oligo-arthr* or rheumato*)):ti,ab,kw	
3	(PsA):ti,ab	
4	#1 or #2 or #3	

5	(guselkumab or CNTO-1959 or tremfya*):ti,ab,kw	Søgetermer for intervention og komparatorer
6	(adalimumab or humira* or D2E7 OR amjevita* OR cyltezo*):ti,ab,kw	
7	(ixekizumab or taltz* or LY-2439821 or LY2439821):ti,ab,kw	
8	#5 or #6 or #7	
9	#4 and #8	
10	("conference abstract" or review):pt	Søgetermer for ikke relevante publikationstyper (der ekskluderes)
11	(clinicaltrials.gov or trialsearch):so	
12	NCT*:au	
13	#10 or #11 or #12	
14	#9 not #13	
15	#14 not pubmed:an	Endelig søgning

Feltkoder: ti: title ab: abstract kw: keywords, her kontrollerede/indekserede termer fra databaserne Medline og/eller Embase. pt = publication type