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CADTH COMMON DRUG REVIEW

Clinical Review Report

Guselkumab (Tremfya)

(Janssen Inc.)

Indication: For the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy

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Abbreviations

AE	adverse event
ADAL	adalimumab
BMI	body mass index
BSA	body surface area
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
DLQI	Dermatology Life Quality Index
f-PGA	Fingernail Physician Global Assessment
GUSE	guselkumab
hf-PGA	Physician Global Assessment of Hands and/or Feet
HRQL	health-related quality of life
IDC	indirect treatment comparison
IGA	Investigator Global Assessment
IL	interleukin
ITT	intention-to-treat
IWRS	Interactive Web Response System
LOCF	last observation carried forward
MCID	minimal clinically important difference
MCS	Mental Component Summary
MID	minimally important difference
NAPSI	Nail Psoriasis Severity Index
NMA	network meta-analysis
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PGA	Physician Global Assessment
PL	placebo
PP	per-protocol
PSSD	Psoriasis Symptoms and Signs Diary
RCT	randomized controlled trial
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SF-36	Medical Outcomes Study Short Form (36) Health Survey
ss-IGA	Scalp-Specific Investigator Global Assessment
TB	tuberculosis
TNF	tumour necrosis factor
URTI	upper respiratory tract infection
WDAE	withdrawal due to adverse event

Drug	Guselkumab (Tremfya)
Indication	For the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Reimbursement request	Treatment of adult patients with moderate-to-severe plaque psoriasis
Dosage form(s)	100 mg/mL pre-filled syringe
NOC date	November 10, 2017
Manufacturer	Janssen Inc.

Executive Summary

Introduction

Psoriasis is a common, immune-mediated, chronic inflammatory skin disease that is associated with significant symptoms (e.g., skin pain, pruritus, and psychosocial effects) with significant negative impact on patients' quality of life.[1,2] Plaque psoriasis is the most common variant and typically manifests as well-demarcated, erythematous plaques with thick silvery scaling on the extensor surfaces, trunk, and scalp.[2,3] Moderate-to-severe plaque psoriasis is defined by the extent of skin coverage, with involvement of more than 10% of body surface area (BSA).[1] Patients with psoriasis are also at increased risk of various serious comorbidities (e.g., stroke, cardiometabolic disease, metabolic syndrome, fatty liver, obesity, mood disorders, and malignancy) and increased mortality.[3] There are approximately one million Canadians living with psoriasis,[4] and of these, 85% to 90% have plaque psoriasis.[3]

It is now known that dysregulation of the immune system plays a key role in the pathogenesis of psoriasis.[1-3] Research has shown that psoriasis is a T cell-mediated disease primarily driven by pathogenic T cells that produce high levels of interleukin (IL)-17 in response to IL-23.[3] This has led to the development of a number of targeted monoclonal antibody therapies against specific cytokines (IL-12, IL-17, IL-23) that are the predominant disease drivers.[2] Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody that binds selectively to the p19 subunit of the IL-23 protein with high specificity and affinity, thus blocking the IL-23 cytokine pathway.[5] Guselkumab (Tremfya) is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[6] The recommended dose of guselkumab is 100 mg to be given as subcutaneous (SC) injection at week 0 and week 4, followed by maintenance dosing every eight weeks thereafter.[5]

Indication under review
For the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Reimbursement criteria requested by sponsor
As per indication

The objective of this review was to perform a systematic review of the beneficial and harmful effects of guselkumab 100 mg administered as a SC injection for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Results and Interpretation

Included Studies

Three manufacturer-sponsored, published, phase III, double-blind, randomized controlled trials (RCTs) were included in the systematic review: VOYAGE 1 (N = 837),[7,8] VOYAGE 2 (N = 992),[9,10] and NAVIGATE (N = 268 randomized patients).[11-13] Both VOYAGE 1 and VOYAGE 2 were multi-centre, placebo and active (adalimumab) controlled, parallel-group trials with randomization stratified by investigational site. The first 24 weeks of treatment were identical in the two trials, which included a 16-week placebo-controlled period, after which placebo-treated patients were switched to guselkumab. In VOYAGE 1, treatment with guselkumab or adalimumab was continued for 48 weeks. In VOYAGE 2, a subset of PASI 90 responders at week 28 were re-randomized to guselkumab (maintenance) or placebo (withdrawal/re-treatment). Both VOYAGE 1 and VOYAGE 2 evaluated the superiority of guselkumab to placebo at week 16 as a primary outcome and the noninferiority and superiority of guselkumab to adalimumab at week 16 as a secondary outcome. The NAVIGATE trial employed an enrichment design such that all patients underwent an open-label ustekinumab run-in period, after which patients with inadequate response to ustekinumab were randomized to either guselkumab or continued ustekinumab in the active treatment period. Patients were stratified by baseline body weight (less than and equal to 100 kg and greater than 100 kg) at study entry. The manufacturer also supplied an indirect treatment comparison (IDC) of guselkumab with currently available drugs used for the treatment of plaque psoriasis that is reviewed and critically appraised in Appendix 7.

All three trials enrolled patients with moderate-to-severe plaque psoriasis, defined as a confirmed diagnosis of chronic plaque psoriasis for at least six months, a Psoriasis Area and Severity Index (PASI) score of greater than and equal to 12, an Investigator Global Assessment (IGA) score of greater than and equal to 3, and BSA involvement of 10% or more, and who were candidates for phototherapy or systemic therapy. The mean duration of psoriasis in enrolled patients was between 15 years to 18 years and 15% to 20% of patients also had a diagnosis of psoriatic arthritis. Biologics had previously been used by 19% to 23% of patients across the trials. The VOYAGE trials also had identical co-primary end points that were based on the proportion of patients who achieved an IGA score of 0 or 1 (cleared or minimal disease) and a PASI 90 response (90% reduction in PASI score from baseline) at week 16 during the induction or placebo-controlled period. The primary end point in the NAVIGATE trial was the number of visits in which patients achieved an IGA score of 0 or 1 and greater than and equal to 2-grade improvement (from week 16) during week 28 to 40. Various secondary end points were also evaluated in the trials that were primarily based on IGA and PASI responses. In all three trials, major secondary end points were tested according to a pre-specified fixed-sequence statistical testing approach to control the type I error rate.

Key limitations of the included trials are the head-to-head comparison of guselkumab with only one active comparator (adalimumab) and not directly with another IL inhibitor (e.g., secukinumab, ixekizumab, or directly with ustekinumab), the size and short duration of the trials which precludes assessment of long-term efficacy and safety or rare or latent adverse

events (AEs), differential withdrawals between treatment groups, compromised randomization due to diminished sample sizes following re-randomization of PASI 90 responders in VOYAGE 2 or in subgroup analyses, and the lack of adjustment for multiplicity for secondary outcomes that were not considered to be major. The NAVIGATE trial should not be considered as a head-to-head comparison of guselkumab and ustekinumab, but more appropriately as a switch study, although the trial is limited by bias in favour of guselkumab due to comparison with ustekinumab in patients who were previously identified as inadequate responders to ustekinumab.

Efficacy

The key efficacy outcomes identified in the review protocol were health-related quality of life (HRQL) and PASI response, whereas other efficacy outcomes were patient and/or IGA (overall and regional disease) and the Nail Psoriasis Severity Index (NAPSI) response. In all three trials, HRQL was assessed by the disease-specific Dermatology Life Quality Index (DLQI) instrument and the generic Medical Outcomes Study Short Form (36) Health Survey (SF-36) in VOYAGE 2 only. In VOYAGE 1 and VOYAGE 2, there was a statistically significant ($P < 0.001$) greater reduction in the DLQI score (i.e., which ranges from 0 to 30, with higher scores indicating a greater effect on quality of life) from baseline to week 16 with guselkumab versus placebo. The mean standard deviation (SD) magnitude of the reduction was –11.2 (7.2) and –11.3 (6.8) with guselkumab compared with –0.6 (6.4) and -2.6 (6.9) with placebo in VOYAGE 1 and VOYAGE 2, respectively *(*$P < 0.001$; adjusted for multiplicity). The reduction in DLQI score from baseline to week 16 with adalimumab (–9.3 [7.8] and –9.7 [6.8]) was also larger than the change from baseline with placebo; however, the testing was not adjusted for multiplicity. The change in DLQI score with guselkumab is considered to be clinically relevant, given that the minimal clinically important difference (MCID) in patients with psoriasis is reported to range from 2.2 to 6.9, as per Appendix 5. Additional comparisons of DLQI scores at different time points or levels of response were made; however, these secondary end points were not tested according to the fixed-sequence statistical testing to control the type I error rate.

In the NAVIGATE trial, the mean (SD) change in overall DLQI score from baseline to week 28 was reported, but not compared statistically, between guselkumab (–11.6 [6.9]) and ustekinumab (–7.3 [6.9)]. As well, other secondary end points based on DLQI were reported but were not adjusted for multiplicity in this trial.

VOYAGE 2 was the only trial to include the SF-36 generic quality of life instrument; however, its analysis was not included in the fixed-sequence statistical testing. Although the change from baseline to week 16 in the physical component summary (PCS) and the mental component summary (MCS) scores (which range between 0 and 100, with higher scores indicating better levels of function and/or health) of the SF-36 compared with placebo was reported, the analysis was not adjusted for multiplicity. The minimally important difference (MID) for the SF-36 PCS and MCS scores is generally considered to be 2 and 3 points, respectively, as per Appendix 5.

A co-primary end point in both VOYAGE 1 and VOYAGE 2 was the proportion of patients achieving a PASI 90 score at week 16, which is considered to be a clinically significant improvement for patients as confirmed by the clinical expert consulted on this review. At week 16, statistically significantly more patients achieved a PASI 90 score with guselkumab (73.3% and 70.0%) compared with placebo (2.9% and 2.4%) in VOYAGE 1 and VOYAGE 2, respectively ($P < 0.001$ for both). The proportion of patients achieving a PASI 90 response with adalimumab was 49.7% and 46.8% in the two trials, respectively. Comparisons of the

proportion of patients achieving a PASI 90 response between guselkumab and adalimumab at weeks 16 and 24 (VOYAGE 1 and VOYAGE 2) and at week 48 (VOYAGE 1 only) was conducted according to the fixed-sequence statistical testing. At week 24, the proportion of patients achieving a PASI 90 response was statistically significantly larger with guselkumab (80.2% and 75.2%) compared with adalimumab (53.0% and 54.8%) in VOYAGE 1 and VOYAGE 2, respectively ($P < 0.001$ for both). In VOYAGE 1, at week 48, statistically significantly more patients treated with guselkumab (76.3%) achieved a PASI 90 response compared with adalimumab (47.9%); $P < 0.001$. Additional analyses of PASI 75 and PASI 100 responses between guselkumab and adalimumab at weeks 24 and 48 (VOYAGE 1 only) were conducted; however, these comparisons were not adjusted for multiplicity.

The other co-primary end point in VOYAGE 1 and VOYAGE 2 was the proportion of patients achieving an IGA score of 0 or 1 (cleared or minimal) at week 16. A statistically significantly higher proportion of patients achieved an IGA score of 0 or 1 at week 16 with guselkumab (85.1% and 84.1%) and adalimumab (65.9% and 67.7%) when compared with placebo (6.9% and 8.5%), in the two trials, respectively ($P < 0.001$ for both). The difference in the proportion of patients treated with guselkumab compared with adalimumab with an IGA score of 0 at week 24 or week 48 (VOYAGE 1 only), IGA score of 0 or 1 at week 24 or week 48 (VOYAGE 1 only) were tested according to the fixed sequence and for all outcomes, guselkumab was statistically significantly superior to adalimumab ($P < 0.001$). The clinical expert consulted on this review agreed that the attainment of an IGA score of 0 or 1 should be considered to be a clinically meaningful improvement from baseline (i.e., as an inclusion criterion in the trials was that at study entry patients were to have an IGA score greater than and equal to 3).

In VOYAGE 1 and VOYAGE 2, noninferiority and superiority testing of the proportion of patients with PASI 90 and PASI 75 responses at week 16 between guselkumab and adalimumab was conducted and tested according to the fixed-sequence statistical testing. For both outcomes, the noninferiority margin was –10% (i.e., if the lower bound of the 95% confidence interval (CI) for the difference between treatments was greater than or equal to –10% for guselkumab - adalimumab), then noninferiority was concluded. In both trials, noninferiority of guselkumab with adalimumab was demonstrated and subsequently, guselkumab was also found to be statistically significantly superior to adalimumab for the proportion of patients achieving a PASI 90 or PASI 75 response at week 16. The noninferiority and superiority of guselkumab and adalimumab for the proportion of patients with IGA score of 0 or 1 at week 16 was also investigated and tested according to the fixed sequence. Based on the same noninferiority margin of –10%, guselkumab was shown to be noninferior to adalimumab, and superior for the proportion of patients achieving an IGA score of 0 or 1 at week 16.

In VOYAGE 2, a secondary end point was the loss of PASI 90 response (in PASI 90 responders at week 28) which was compared between the guselkumab maintenance group and the withdrawal/re-treatment group and was tested according to the fixed sequence. PASI 90 responses appeared to be maintained for a longer duration in patients who were maintained on guselkumab compared with patients who were re-randomized to placebo (withdrawal/re-treatment group). The median time to loss of response in the withdrawal/re-treatment group was 15.2 weeks. [redacted] and at week 48, 35.4% maintained a PASI 90 response. Through week 48, 88.6% of patients in the guselkumab maintenance group maintained a PASI 90 response and [redacted]

[redacted].

In the NAVIGATE trial, a major secondary end point was the number of visits where patients achieved a PASI 90 response from week 28 to week 40 in randomized patients with an inadequate response to ustekinumab (IGA score of 2 or more at week 16). The mean [SD] number of visits was 2.2 (1.7) in patients randomized to guselkumab and 1.1 (1.5) in patients who continued on ustekinumab, which was statistically significant ($P < 0.001$; adjusted for multiplicity).

In the NAVIGATE trial, the primary end point was the number of visits where patients achieved an IGA score of 0 or 1 and at least a 2-grade improvement (from week 16) from week 28 through week 40 in randomized patients with an inadequate response (IGA score of 2 or more) to ustekinumab at week 16. The mean (SD) number of visits was higher (1.5 [1.6]) with guselkumab compared with ustekinumab (0.7 [1.3]) and the difference between groups was statistically significant ($P < 0.001$).

In the three trials, pre-specified subgroup analyses were conducted on the individual components of the co-primary end points (i.e., IGA score of 0 or 1 and PASI 90 response at week 16), including examination of the subpopulations of interest identified in the review protocol (i.e., baseline PASI score, prior biologic use, and body weight). In general, the subgroup results were consistent with the results of the primary analysis, although some inconsistencies were identified in certain subgroups with very small sample sizes and imprecise CIs. A pooled analysis of the VOYAGE 1 and VOYAGE 2 trials in which the efficacy of guselkumab in patient subgroups measured by the achievement of IGA scores of 0 or 1 or IGA scores of 0 across subgroups defined by demographics, baseline disease characteristics, and previous psoriasis treatment found a high degree of consistency in the comparison of guselkumab with placebo at week 16 and adalimumab at week 24 across the subgroups.[14]

Regional psoriasis end points (i.e., Scalp-Specific Investigator Global Assessment [ss-IGA], Fingernail Physician Global Assessment [f-PGA], Physician Global Assessment of Hands and/or Feet [hf-PGA], and NAPSI scores) were only included in VOYAGE 1 and VOYAGE 2, and of these, only the ss-IGA score was included in the fixed-sequence statistical testing. Overall, the results of the regional psoriasis end points corroborated those of the overall disease and primary end points of the VOYAGE trials. The proportion of patients with a ss-IGA score of 0 (absence of disease) or 1 (very mild disease) and at least a 2-grade improvement from baseline at week 16 was statistically significantly greater with guselkumab (83.4% and 80.6%) compared with placebo (14.5% and 10.9%) in VOYAGE 1 and VOYAGE 2, respectively ($P < 0.001$; adjusted for multiplicity). Results of the additional regional psoriasis outcomes all appeared to favour guselkumab over placebo; however, these comparisons were all made without adjustment for multiplicity.

Harms

In general, guselkumab appeared to be well tolerated based on the harms data reported in the three included trials, although the size and duration of the trials were likely insufficient to identify rare or latent AEs. In the VOYAGE trials, AEs occurred in approximately 50% of patients over the 16-week induction period, regardless of treatment group. Similarly, the frequency of AEs was similar between guselkumab and adalimumab up to week 48 (VOYAGE 1) or week 28 (VOYAGE 2). The most frequently reported AEs across all trials and treatment periods with guselkumab were nasopharyngitis, upper respiratory tract

infections (URTIs), and headache. In the NAVIGATE trial, a higher proportion of patients treated with guselkumab (64.4%) as compared with ustekinumab (55.6%) experienced AEs from week 16 to week 60; however, it is difficult to make comparisons because patients in the randomized ustekinumab arm had been receiving the drug from week 0 to 16 in addition to week 16 to 60 which allowed for more time for tolerance to or resolution of AEs, whereas patients in the guselkumab arm initiated guselkumab at week 16. Serious AEs (SAEs) and withdrawal due to AEs (WDAEs) occurred infrequently in all of the three trials regardless of the treatment period or treatment group. Treatment with guselkumab did not appear to be associated with increased mortality as there were only three deaths reported across the three included trials (i.e., one death in VOYAGE 1 and two deaths in NAVIGATE) with no deaths reported in VOYAGE 2. Notable harms identified in the review protocol were infections, injection-site reactions, serious hypersensitivity reactions, major cardiovascular events, and malignancy. The frequency of the notable harms was low across all three trials, generally occurring in less than 1% of patients. The only exception to this was injection-site reactions in the VOYAGE 1 and VOYAGE 2 trials where the proportions of patients with injection-site reactions was more than double in adalimumab-treated patients (7.5% and 6.9%) compared with guselkumab-treated patients (2.4% and 2.6%), which may be attributed to the higher frequency of injections with adalimumab, as necessitated by the dosing regimen.

Potential Place in Therapy[1]

The clinical expert involved in the review noted that all currently available agents (tumour necrosis factor [TNF]-alpha inhibitors, IL-12/23 inhibitor [ustekinumab], and the IL-17A inhibitors) for the treatment of moderate-to-severe plaque psoriasis have specific drawbacks that limit their use in some patient populations. Examples include relatively low efficacy with etanercept, need for intravenous administration with infliximab and its biosimilar, limited efficacy in psoriatic arthritis with ustekinumab, and the possibility of exacerbating inflammatory bowel disease with secukinumab. As well, with currently available agents, in some patients efficacy may drop off over time, requiring dosage intensification and ultimately a switch to another biologic agent. Guselkumab is the first member in a new class of biologic agents for plaque psoriasis – the IL-23 inhibitors. The clinical trial data indicates a rapid onset of action and high efficacy. There is also some data to suggest that it may be effective in patients who have achieved a suboptimal response to adalimumab and ustekinumab. Therefore, guselkumab expands the available treatment options for disease control in plaque psoriasis with a highly efficacious drug option. However, there are no other unique features that clearly differentiate guselkumab from other biologics.

When first introduced in Canada, guselkumab will likely be used principally in patients who have failed to respond to, or have become intolerant to, or have experienced side effects from one or more, previous biologic agents. Over time, if data indicate long-term safety, persistence of efficacy, and utility in treating psoriatic arthritis, guselkumab may become a first-line biologic agent.

[1] This information is based on information provided in draft form by the clinical expert consulted by CADTH Common Drug Review (CDR) reviewers for the purpose of this review.

Conclusions

The results from two double-blind RCTs, VOYAGE 1 and VOYAGE 2, support that treatment with guselkumab is associated with clinically and statistically significant improvements in HRQL as measured by the DLQI. The results from the VOYAGE trials also support that guselkumab is superior to placebo during induction based on attainment of an IGA score of 0 or 1 (cleared or minimal disease) or PASI 90 response at week 16. In addition, guselkumab was demonstrated to be noninferior to, and subsequently superior to, adalimumab at week 16 based on the same outcomes as well as PASI 75 response. In a third double-blind RCT (NAVIGATE), patients with an inadequate response to ustekinumab were randomized to either guselkumab or continued ustekinumab. Patients switched to guselkumab had a statistically significantly higher number of visits in which they achieved an IGA score of 0 or 1 and at least a 2-grade improvement compared with patients who continued ustekinumab; however, interpretation of the results are compromised by the many identified limitations of the trial. In general, the efficacy results with guselkumab were consistent and of similar magnitude across all trials. Guselkumab also appeared to be well tolerated, although the size and duration of the trials were likely insufficient to detect rare or latent AEs. Similar proportions of patients experienced AEs regardless of treatment arm or period and the frequency of SAEs and WDAEs was low. The frequency of notable harms (i.e., infections, injection-site reactions, serious hypersensitivity reactions, major cardiovascular events, and malignancy) was also low in all three trials. [redacted]

Table 1: Summary of Results

	VOYAGE 1			VOYAGE 2			NAVIGATE	
	PL N = 174	GUSE N = 329	ADAL N = 334	PL N = 248	GUSE N = 496	ADAL N = 248	GUSE N = 135	USTE N = 133
Health-Related Quality of Life Outcomes								
DLQI Change From Baseline to Week 16							**DLQI Change From Baseline to Week 28[i]**	
Mean (SD)	–0.6 (6.4)	–11.2 (7.2)	–9.3 (7.8)	–2.6 (6.9)	–11.3 (6.8)	–9.7 (6.8)	[redacted]	[redacted]
***P value* vs. PL[a]**	–	< 0.001	< 0.001	-	< 0.001	< 0.001	NR	
SF-36 Change from Baseline to Week 16[i]								
PCS Mean (SD)	NR	NR	NR	0.941 (6.605)	5.462 (7.800)	3.918 (6.555)	NR	NR
***P value*[a]**	–	–	–	–	< 0.001	< 0.001	–	–
MCS Mean (SD)	NR	NR	NR	0.568 (8.761)	5.659 (9.509)	4.569 (9.356)	NR	NR
***P value*[a]**	–	–	–	–	< 0.001	< 0.001	–	–
Efficacy End Points in VOYAGE 1 and VOYAGE 2 (IGA and PASI Response)								
Proportion of pts achieving an IGA score[b] of 0 or 1 at Week 16								
n (%)	12 (6.9)	280 (85.1)	220 (65.9)	21 (8.5)	417 (84.1)	168 (67.7)	NR	NR
***P value* vs. PL[c]**	–	< 0.001	< 0.001	–	< 0.001	< 0.001	–	–
Proportion of Pts Achieving PASI 90 at Week 16								
n (%)	5 (2.9)	241 (73.3)	166 (49.7)	6 (2.4)	347 (70.0)	116 (46.8)	NR	NR
***P value* vs. PL[c]**	–	< 0.001	< 0.001	–	< 0.001	< 0.001	–	
Noninferiority[d] and Superiority[e] Analyses of GUSE and ADAL at Week 16, n (%)								
IGA score of 0 or 1								
n (%)	–	280 (85.1)	220 (65.9)	–	417 (84.1)	168 (67.7)	NR	NR
Diff. (95% CI) ***P value*[e]**	–	19.3 (12.9; 25.7) < 0.001		–	16.4 (10.0; 23.2) < 0.001		–	–
PASI 90								
n (%)	–	241 (73.3)	166 (49.7)	–	347 (70.0)	116 (46.8)	NR	NR
Diff (95% CI) ***P value*[e]**	–	24.1 (17.0; 31.0) < 0.001		–	23.3 (16.0; 30.4) < 0.001		–	–
Efficacy End Points in NAVIGATE (IGA and PASI Response)								
Number of Visits Where Pts Achieved IGA 0 or 1 and ≥ 2-Grade Improvement[f] from Week 28 to 40								
Mean (SD)	NR						1.5 (1.6)	0.7 (1.3)
***P* value[g]**	NR						< 0.001	
Number of Visits Where Pts Achieved PASI 90 From Week 28 to 40								
Mean (SD)	NR						2.2 (1.7)	1.1 (1.5)
***P* value[g]**	NR						< 0.001	
Harms								
Time	**Weeks 0 to 48**			**Weeks 0 to 28**			**Weeks 16 to 60**	
Deaths, n (%)	–	0 (0)	1 (< 1)	–	0 (0)	0 (0)	1 (< 1)	0 (0)
SAEs, n (%)	–	16 (4.9)	15 (4.5)	–	18 (3.6)	9 (3.6)	9 (6.7)	6 (4.5)

	VOYAGE 1			VOYAGE 2			NAVIGATE	
	PL N = 174	GUSE N = 329	ADAL N = 334	PL N = 248	GUSE N = 496	ADAL N = 248	GUSE N = 135	USTE N = 133
AEs, n (%)	–	243 (73.9)	248 (74.5)	–	288 (58.3)	156 (62.9)	87 (64.4)	74 (55.6)
WDAEs, n (%)	–	9 (2.7)	12 (3.6)	–	11 (2.2)	6 (2.4)	3 (2.2)	2 (1.5)

ADAL = adalimumab; AE = adverse event; ANOVA = analysis of variance; CMH = Cochran-Mantel-Haenszel; CI = confidence interval; DLQI = Dermatology Life Quality Index; GUSE = guselkumab; IGA = Investigator Global Assessment; MCS = Mental Component Summary; NR = not reported; PASI = Psoriasis Area and Severity Index; PCS = Physical Component Summary; PL = placebo; Pts = patients; SAE = serious adverse event; SD = standard deviation; SF-36 = Medical Outcomes Study Short Form (36) Health Survey; USTE = ustekinumab; WDAE = withdrawal due to adverse event.

[a] Based on an ANOVA model stratified by investigator site (pooled) and is the comparison vs. placebo.

[b] An IGA score of 0 = cleared and a score of 1 = minimal.

[c] Based on the Cochran-Mantel-Haenszel (CMH) chi-square test stratified by investigator site (pooled) and is the comparison vs. placebo.

[d] Noninferiority and superiority of guselkumab in comparison with adalimumab was only investigated in VOYAGE 1 and VOYAGE 2. The designated noninferiority margin was –10% (i.e., if the lower bound of the 2-sided 95% CI was greater than –10%, noninferiority was concluded).

[e] Based on 1-sided CMH Z test adjusted for investigator site (pooled).

[f] In the NAVIGATE trial, the primary end point was the number of visits at which patients achieved an IGA response of 0 or 1 and at least a 2-grade improvement (from week 16) from week 28 through week 40, among randomized patients with an inadequate response (IGA ≥ 2) to ustekinumab at week 16.

[g] Based on CMH row mean scores test stratified by baseline weight (≤ 100 kg; > 100 kg) and is the comparison between guselkumab vs. ustekinumab. [h] Based on CMH chi-square test stratified by baseline weight (≤ 100 kg; > 100 kg).

[i] Outcomes that were not tested according to fixed-sequence statistical testing to adjust for multiplicity.

Source: Blauvelt et al. (2017);[7] VOYAGE 1 CSR;[8] Reich et al. (2017);[9] VOYAGE 2 CSR;[10] Langley et al. (2017);[11] NAVIGATE CSRs (40 weeks) and (60 weeks).[12,13]

Introduction

Disease Prevalence and Incidence

Psoriasis is a common, immune-mediated, chronic inflammatory skin disease that is associated with significant symptoms (e.g., skin pain, pruritus, and psychosocial effects) with significant negative impact on patients' quality of life.[1,2] Plaque psoriasis is the most common disease variant and typically manifests as well-demarcated, erythematous plaques with thick silvery scaling on the extensor surfaces, trunk, and scalp.[2,3] Since the plaques can be highly visible, psoriasis may affect patients' self-esteem, resulting in negative impacts on social functioning and work productivity. The severity of plaque psoriasis ranges from mild disease with few localized inflammatory skin lesions, to more severe disease involving widespread plaques.[3] Moderate-to-severe plaque psoriasis is defined by the extent of skin coverage, with involvement of more than 10% of body surface area (BSA).[1] Patients with psoriasis are also at increased risk of various serious comorbidities (e.g., cardiometabolic disease, stroke, metabolic syndrome, fatty liver, obesity, mood disorders, and malignancy) and increased mortality.[3]

Early explanation of the pathogenesis of psoriasis focused primarily on keratinocyte hyperproliferation; however, it is now known that dysregulation of the immune system plays a key role.[1-3] Research has shown that psoriasis is a T cell-mediated disease, primarily driven by pathogenic T cells that produce high levels of interleukin (IL)-17 in response to IL-23.[3] This has led to the development of a number of monoclonal antibody therapies that are targeted against the specific cytokines (IL-12, IL-17, IL-23) that are the predominant drivers of psoriatic disease.[2]

There are approximately one million Canadians living with psoriasis.[4] Of these, approximately 85% to 90% of all cases of psoriasis are plaque psoriasis.[3]

Standards of Therapy

Numerous topical and systemic therapies are available for the treatment of psoriasis. Therapies are typically chosen on the basis of disease severity, relevant comorbidities, patient preference, efficacy, and evaluation of patient response.[1] Mild disease is usually effectively treated with topical agents (e.g., corticosteroids, vitamin D3 analogues, retinoids, anthralin and tars, or combination therapy).[15,16] Patients with moderate-to-severe disease may require phototherapy or systemic therapy, although even patients on systemic therapy will likely continue to need topical agents.[1] Traditional systemic agents include methotrexate, cyclosporine, and acitretin and, although effective, their use is limited by toxicity and drug interactions.[15,16]

Systemic biologic agents represent a significant breakthrough in the treatment of psoriasis. The first biologic agents include adalimumab, etanercept, and infliximab, all of which share a common mechanism of action by targeting tumour necrosis factor (TNF)-alpha, a key mediator of inflammation. While effective, and associated with rapid disease control, these TNF-alpha inhibitors are associated with a number of overlapping safety concerns including serious infections (e.g., sepsis, reactivated tuberculosis [TB], viral infections), autoimmune conditions (e.g., lupus and demyelinating disorders), and malignancies such as lymphoma.[15,16] The newest biological agents target IL; the discovery of the central role for the IL-23/type 17 T cell axis in the development of psoriasis has led to a major paradigm shift in the pathogenic model and development of various monoclonal antibodies that target IL-12/23 (ustekinumab) and IL-17 signaling (secukinumab, ixekizumab) as detailed in Table 2, although their use is associated with serious infections or potential activation of inflammatory bowel disease in the case of IL-17 inhibitors.[2,3,15,16] Due to the association of all currently available systemic biologic products with serious adverse consequences, there remains an unmet need for additional therapeutic options, despite the number of available therapies.[17]

Drug

Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody that binds selectively to the p19 subunit of the IL-23 protein with high specificity and affinity.[5] IL-23 is an upstream regulatory cytokine that affects the differentiation, expansion, and maintenance of T cell subsets and innate lymphoid cell subsets, which represent some sources of effector cytokines, including IL-17A, IL-17F, and IL-22 that drive inflammatory disease.[5] Levels of IL-23 are elevated in the skin of patients with plaque psoriasis and guselkumab exerts its clinical effects in plaque psoriasis through blockade of the IL-23 cytokine pathway. Guselkumab (Tremfya) is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[6] The recommended dose is 100 mg to be given as subcutaneous (SC) injection at week 0 and week 4, followed by maintenance dosing every eight weeks thereafter.[5]

Table 2: Key Characteristics of Biologic Drugs Used for the Treatment of Plaque Psoriasis

	Guselkumab	Infliximab			Adalimumab	Etanercept	
MOA	**IL-23 inhibitor**	**TNF inhibitor**			**IL-12 and IL-23 inhibitor**	**IL-17A inhibitor**	
Health Canada Indication	Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.	Treatment of adult patients with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, should be used after phototherapy has been shown to be ineffective or inappropriate.	Treatment of adult patients with chronic moderate-to-severe psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, adalimumab should be used after phototherapy has been shown to be ineffective or inappropriate.	Treatment of adult patients with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.	Treatment of adult patients with chronic moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy.	Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.	Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
ROA	Subcutaneous	Intravenous	Subcutaneous				
Recommended Dose	100 mg administered subcutaneously at week 0, week 4, and every 8 weeks thereafter.	5 mg/kg given as an intravenous infusion; followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion; then every 8 weeks thereafter. No additional treatment with infliximab should be given if a patient does not show an adequate response at week 14.	80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose. Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period.	50 mg dose given twice weekly (administered 3 or 4 days apart) for 3 months; followed by a reduction to a maintenance dose of 50 mg per week. A maintenance dose of 50 mg given twice weekly has also been shown to be efficacious.	45 mg at week 0 and week 4; then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg. For patients who inadequately respond to dosing every 12 weeks, consideration may be given to treating as often as every 8 weeks.	300 mg with initial dosing at weeks 0, 1, 2, and 3; followed by monthly maintenance dosing starting at week 4.	160 mg at week 0; followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12; followed by 80 mg every 4 weeks.
Serious Side Effects / Safety Issues	Infection	Infection Cancer			Infection Cancer **Serious skin reactions**	Infection Serious hypersensitivity reactions	Infection Injection-site reactions Serious hypersensitivity reactions Major cardiovascular events

IL = interleukin; MOA = mechanism of action; ROA = route of administration; TNF = tumour necrosis factor.
Source: Health Canada Drug Product Database (DPD);[18] Guselkumab Product Monograph.[5]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of guselkumab 100 mg administered as a subcutaneous injection for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adult (≥ 18 yrs) patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Subpopulations: disease severity (by PASI or BSA), prior biologic use, body weight (≤ 100 kg vs. > 100 kg)
Intervention	Guselkumab alone or in combination with other therapies: • 100 mg as a subcutaneous injection at week 0 and week 4, followed by maintenance dosing every 8 weeks thereafter
Comparators	Monotherapy or combination therapy (including adjunctive topical therapy) with: **Non-biologic systemic agents:** Acitretin, apremilast, cyclosporine, methotrexate **Biologic agents targeting TNF-alpha:** Adalimumab, etanercept, infliximab **Biologic agents targeting interleukins:** Ixekizumab, secukinumab, ustekinumab
Outcomes	**Key efficacy outcomes:** • Health-related quality of life by a validated instrument (e.g., DLQI, SF-36)[a] • PASI response[a] **Other efficacy outcomes:** • Patient and/or investigator global assessment (overall and regional disease) • NAPSI response **Harms outcomes:** Mortality, AEs, SAEs, WDAEs Notable harms including but not limited to: • Infections • Injection-site reactions • Serious hypersensitivity reactions • Major cardiovascular events • Malignancy
Study Design	Published and unpublished phase III RCTs

AE = adverse events; BSA = body surface area; DLQI = Dermatology Life Quality Index; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; RCT = randomized controlled trial; SAE = serious adverse events; SF-36 = Medical Outcomes Study Short Form (36) Health Survey; TNF = tumour necrosis factor; WDAE = withdrawal due to adverse events; yrs = years.

[a] Outcomes important to patients, as per the patient input received for this submission.

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The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Tremfya (guselkumab).

No methodological filters were applied to limit retrieval by study type. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on September 20, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on January 17, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, clinical trials, and databases (free). Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Results

Findings From the Literature

A total of three (3) studies were identified from the literature for inclusion in the systematic review (Table 3). The included studies are summarized in Table 4 and described in the Included Studies section. A list of excluded studies is presented in Appendix 3.

Figure 1: Diagram for Inclusion and Exclusion of Studies

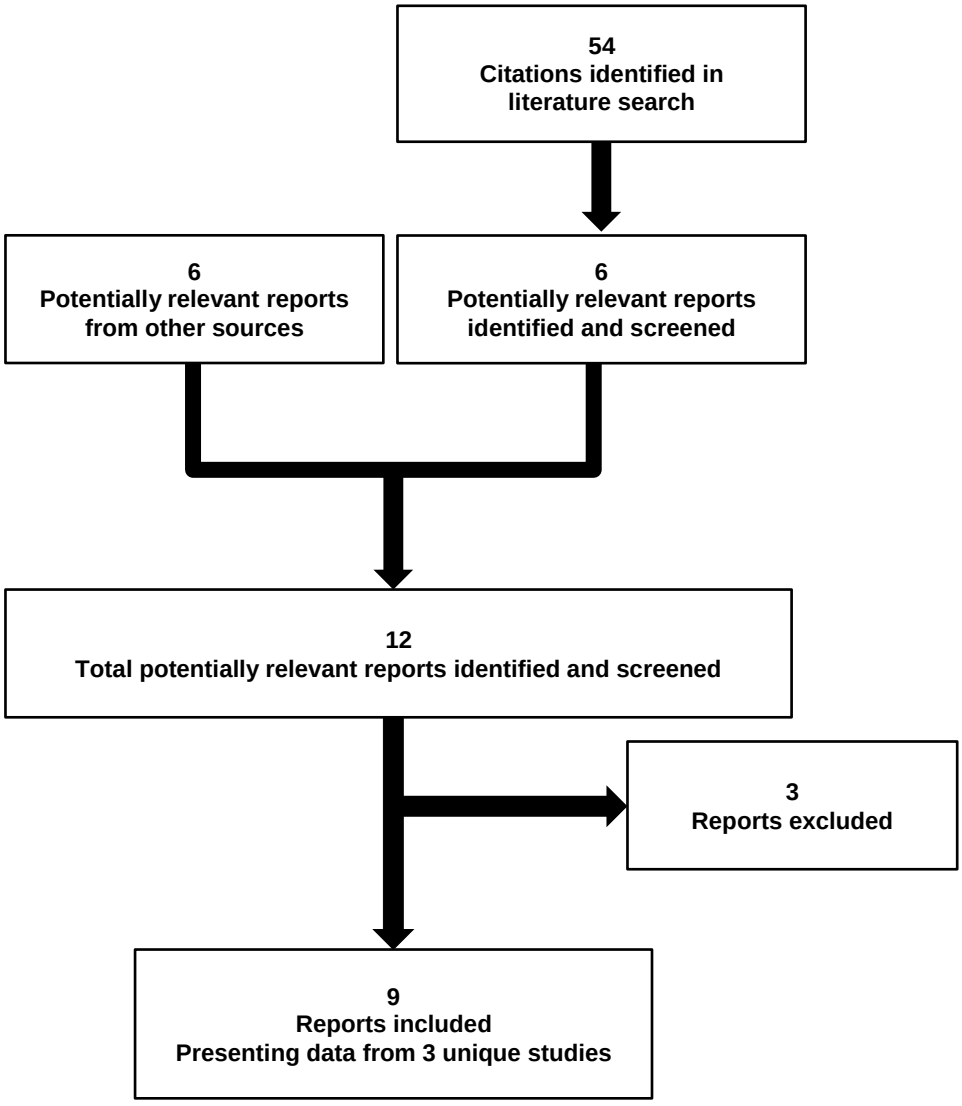


Table 4: Details of Included Studies

		VOYAGE 1	VOYAGE 2	NAVIGATE
Designs and Populations	**Study Design**	Phase III MC, PG, PC & AC, DB RCT		Phase III MC, PG, AC, DB RCT
	Locations	101 sites in 10 countries (Canada, US, Europe, Russia, Australia, South Korea, Taiwan).	115 sites in 9 countries (Canada, US, Europe, Russia, Australia, South Korea)	100 sites in 10 countries (Canada, US, Europe, Russia, Australia, South Korea, UK, Taiwan)
	Randomized (N)	837	992	268
	Inclusion Criteria	Adult (≥ 18 years) pts with moderate-to-severe plaque psoriasis (i.e., IGA score ≥ 3, PASI ≥ 12, BSA ≥ 10%) for at least six months who are candidates for systemic therapy or phototherapy. For NAVIGATE, after 16 weeks of OL ustekinumab, patients had to have an inadequate response (IGA ≥ 2) to be randomized in the active treatment period.		
	Exclusion Criteria	History or current signs of a severe, progressive, or uncontrolled medical condition, current or history of malignancy (except melanoma skin cancer within 5 years), history or symptoms of active TB, received prior guselkumab, adalimumab, or ustekinumab, anti-TNF therapy (within 3 months), other treatment targeting IL-12/23, IL-17, or IL-23 (within 6 months), or any systemic immunosuppressants or phototherapy (within 4 months).		
Drugs	**Intervention**	**Group I:** Guselkumab 100 mg at week 0, 4, and 12, and every 8 weeks by SC injection	**Group I:** Guselkumab 100 mg at week 0, 4, 12, and 20, and every 8 weeks by SC injection	Guselkumab 100 mg at week 16 and 20 and every 8 weeks by SC injection
	Comparator(s)	**Group II:** Placebo at week 0, 4, and 12, and guselkumab 100 mg at week 16 and 20 and every 8 weeks by SC injection **Group III:** Adalimumab 80 mg at week 0 and 40 mg at week 1 and every 2 weeks thereafter by SC injection	**Group II:** Placebo at week 0, 4, and 12, and guselkumab at week 16 and 20 and every 8 weeks by SC injection **Group III:** Adalimumab 80 mg at week 0 and 40 mg at week 1 and every 2 weeks thereafter by SC injection	Ustekinumab (45 mg if ≤ 100 kg and 90 mg if ≥ 100 kg body weight) at week 16 and every 12 weeks thereafter
Duration	**Phase**			
	Induction	DB PC Induction: 16 weeks	DB PC Induction: 16 weeks	OL run-in: 16 weeks
	Maintenance	DB AC Treatment: 48 weeks	DB AC Treatment: 24 weeks RW and RT: 44 weeks	DB treatment: 28 weeks
	Follow-Up	OL treatment: 112 weeks (week 48 through week 160)	OL treatment: 88 weeks (week 76 through week 160)	Follow-up: 16 weeks
Outcomes	**Primary End Point**	Number and proportion of pts at week 16: • achieving IGA score of cleared (0) or minimal (1) • achieving PASI 90 response		Number of visits pts achieved IGA score of 0 or 1 and ≥ 2-grade improvement from week 16 during week 28 to week 40
	Other Relevant End Points	IGA,PASI, ss-IGA, hf-PGA, f-PGA, NAPSI, DLQI, SF-36 (VOYAGE 2 only) and harms outcomes		IGA, PASI, DLQI
Notes	**Publications**	Blauvelt et al. (2017)	Reich et al. (2017)	Langley et al. (2017)

AC = active-controlled; BSA = body surface area; DB = double-blind; DLQI = Dermatology Life Quality Index; f-PGA = Fingernail Physician Global Assessment; hf-PGA = Physician Global Assessment of Hands and/or Feet; IGA = Investigator Global Assessment; IL = interleukin; MC = multi-centre; NAPSI = Nail Psoriasis Severity Index; OL = open-label; PASI = Psoriasis Area and Severity Index; PC = placebo-controlled; PG = parallel group; pts = patients; RCT = randomized controlled trial; RW and RT = randomized withdrawal and re-treatment; SC = subcutaneous; SF-36 = Medical Outcomes Study Short Form (36) Health Survey; ss-IGA = Scalp-Specific Investigator Global Assessment; TB = tuberculosis; TNF = tumour necrosis factor; yrs=years.

Note: Six additional reports were included (Source: VOYAGE 1 CSR;[8] VOYAGE 2 CSR;[10] NAVIGATE CSRs (40 weeks) and (60 weeks),[12,13] CDR submission;[6] FDA Multi-discipline Review[17]).

Source: Blauvelt et al. (2017);[7] VOYAGE 1 CSR;[8] Reich et al. (2017);[9] VOYAGE 2 CSR;[10] Langley et al. (2017);[11] NAVIGATE CSRs (40 weeks) and (60 weeks).[12,13]

Included Studies

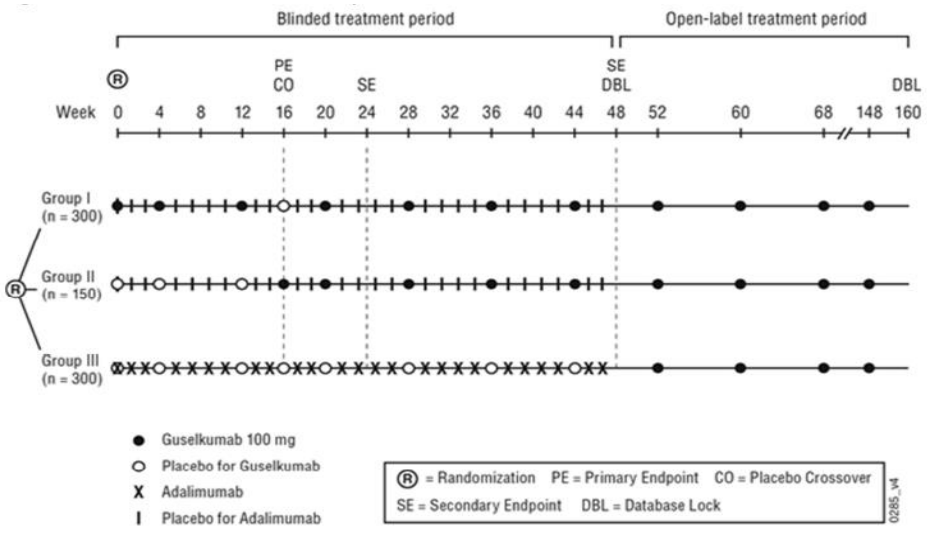
Description of Studies

Three phase III, randomized, double-blind, placebo- and/or active-controlled trials that evaluated the efficacy and safety of guselkumab were included in this review: VOYAGE 1 (N = 837), VOYAGE 2 (N = 992), and NAVIGATE (N = 268 randomized patients). All three trials had similar inclusion and exclusion criteria and enrolled patients with moderate-to-severe plaque psoriasis (Table 4). In the trials, patients underwent central randomization using an interactive web response system (IWRS). Investigators were not provided with the randomization codes and the codes were maintained within the IWRS. To maintain the study blind, each active study drug and corresponding placebo were matched in appearance and packaging.

VOYAGE 1 included three treatment groups in which patients received the following: Group I: guselkumab; Group II: placebo followed by guselkumab; or Group III: adalimumab, as illustrated in Figure 2. The trial consisted of two double-blind treatment periods: a 48-week active-controlled period in which guselkumab was directly compared with adalimumab (weeks 0 to 48), and a 16-week placebo-controlled period (weeks 0 to 16) after which placebo-treated patients crossed over to guselkumab and were maintained as a separate treatment arm through week 48. After completion of the double-blind treatment periods, patients entered an open-label treatment period in which all patients received guselkumab (weeks 48 to 160).

At study entry, patients were randomized using a permuted block method in a 2:1:2 ratio to Group I: guselkumab 100 mg at weeks 0. 4, 12, and every eight weeks through week 44; Group II: placebo at weeks 0, 4, 12, and followed by guselkumab 100 mg at weeks 16, 20, and every eight weeks through week 44; or Group III: adalimumab 80 mg at week 0, 40 mg at week 1, and every two weeks through week 47 (Figure 2). Randomization was stratified by investigator site.

Figure 2: VOYAGE 1 Study Design



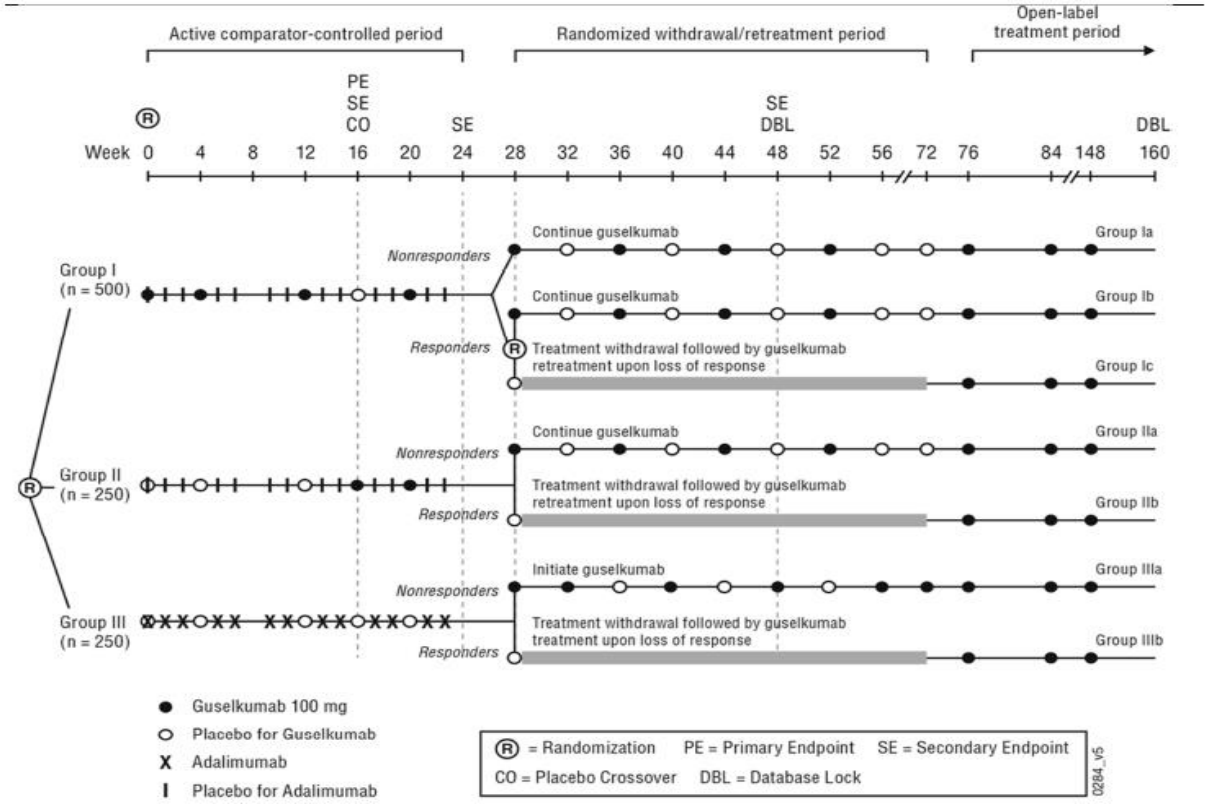
Source: VOYAGE 1 CSR.[8]

VOYAGE 2 also included three treatment groups in which patients received the following: Group I: guselkumab; Group II: placebo followed by guselkumab; or Group III: adalimumab, as illustrated in Figure 3. The trial consisted of a 28-week active-controlled period during which guselkumab was directly compared with adalimumab, and a 16-week placebo-controlled period after which placebo-treated patients crossed over to guselkumab through week 28. Following this, patients who were Psoriasis Area and Severity Index (PASI) 90 responders at week 28 entered a randomized withdrawal and re-treatment period (weeks 28 to 72).

At study entry, patients were randomized 2:1:1 using a permuted block method to Group I: guselkumab 100 mg at weeks 0, 4, 12, and 20; Group II: placebo at weeks 0, 4, 12 and then guselkumab at weeks 16 and 20, or Group III: adalimumab 80 mg at week 0 and 40 mg at week 1 and every two weeks thereafter through week 23. Randomization was stratified by investigator site.

At week 28, patients in Group I who were PASI 90 nonresponders, continued guselkumab 100 mg every eight weeks; while PASI 90 responders were re-randomized in a 1:1 ratio to receive guselkumab 100 mg every eight weeks or placebo through week 76 or until a loss of greater than and equal to 50% of the PASI improvement achieved at week 28, at which point patients were re-treated with guselkumab 100 mg followed by a 100 mg dose four weeks later, then guselkumab 100 mg every eight weeks thereafter. Patients in Group II who were PASI 90 nonresponders at week 28 continued guselkumab 100 mg every eight weeks, while PASI 90 responders received placebo until a loss of greater than and equal to 50% of the PASI improvement achieved at week 28, at which point patients were re-treated with guselkumab 100 mg followed by a 100 mg dose four weeks later, and guselkumab 100 mg every eight weeks thereafter. Patients in Group III who were PASI 90 nonresponders at week 28 initiated guselkumab 100 mg at week 28 followed by a 100 mg dose four weeks later, then guselkumab 100 mg every eight weeks thereafter, while PASI 90 responders received placebo until a loss of greater than and equal to 50% of the improvement in PASI achieved at week 28, at which point patients initiated guselkumab 100 mg followed by a 100 mg dose four weeks later, then guselkumab 100 mg every eight weeks through week 76. The open-label guselkumab treatment period began at week 76 and extended through week 160.

Figure 3: VOYAGE 2 Study Design

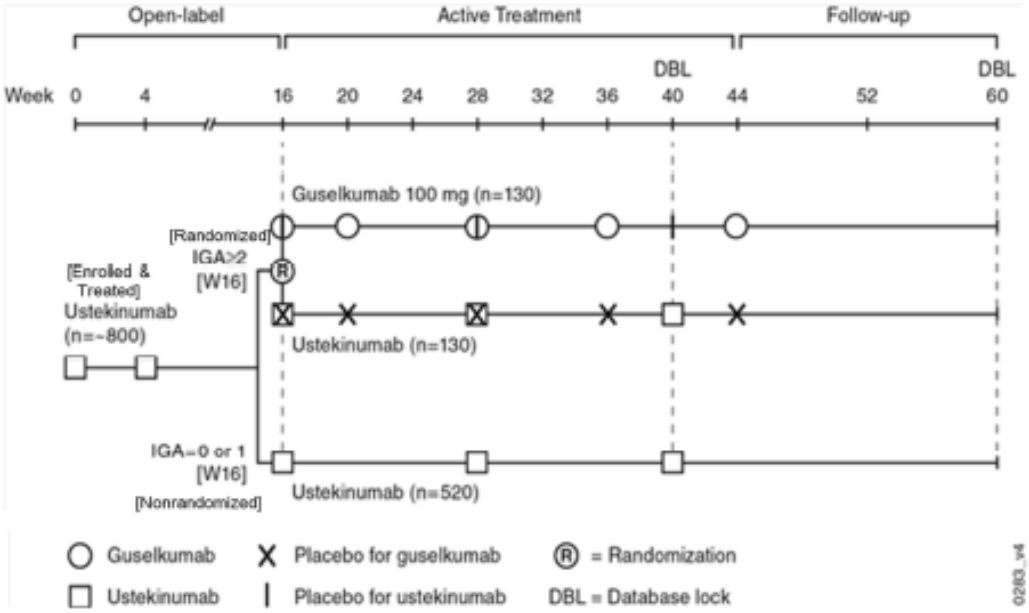


Source: VOYAGE 2 CSR.[10]

In the NAVIGATE trial, all enrolled patients initially received open-label ustekinumab 45 mg or 90 mg (according to the patient's baseline [week 0] body weight) at week 0 and week 4. At week 16 patients were assessed for efficacy according to the IGA, which

determined the subsequent treatment through week 44. Patients with Investigator Global Assessment (IGA) score greater than and equal to 2 at week 16 were randomized 1:1 to either guselkumab 100 mg at weeks 16 and 20 and then every eight weeks thereafter, or to continued ustekinumab every 12 weeks (Figure 4). Randomization was stratified by investigator site and baseline (week 0) body weight (≤ 100 kg; > 100 kg). Patients with an IGA of 0 or 1 continued to receive open-label ustekinumab every 12 weeks through week 44. Starting at week 16, visits for randomized patients were every four weeks through week 44 for guselkumab, whereas visits for patients who continued on open-label ustekinumab were every 12 weeks through week 40. All patients were to have an additional follow-up visit at week 52 for efficacy assessment and a final safety visit at week 60 (see Appendix 6 for the long-term extension data).

Figure 4: NAVIGATE Study Design



Key: IGA=Investigator's Global Assessment; W=week.

Source: NAVIGATE CSRs (40 weeks) and (60 weeks).[12,13]

Populations

Inclusion and Exclusion Criteria

All three included trials had similar inclusion criteria. Eligible adult patients (≥ 18 years) had moderate-to-severe plaque psoriasis for at least six months and were candidates for systemic therapy or phototherapy. Patients were required to have an IGA score greater than and equal to 3, PASI score greater than and equal to 12 and BSA involvement greater than and equal to 10% at baseline.

Key exclusion criteria included a history of, or a current severe, progressive, or uncontrolled medical condition or malignancy, except for non-melanoma skin cancer within five years. Patients were ineligible if they had a history or symptoms of active TB, or if they tested positive for hepatitis B, or for antibodies to hepatitis C. In VOYAGE 1 and VOYAGE 2, patients could not have received prior treatment with guselkumab or adalimumab, whereas in NAVIGATE patients could not have received prior treatment with guselkumab or ustekinumab. In all three included trials, patients were ineligible if they received anti-TNF-alpha therapy within three months, other treatments targeting IL-12/23, IL-17, or IL-23 within six months, or any systemic immunosuppressants (e.g., methotrexate), or phototherapy within four weeks of the first dose of study drug.

Baseline Characteristics

Details regarding baseline characteristics of study patients are provided in Tables 5 and 6. Baseline demographic characteristics were generally similar among the treatment groups in the three included trials. The majority of patients were white (74% to 83%) and male (66% to 74%). The mean age of included patients was between 42 years and 44 years of age, mean weight ranged from 87 kg to 91 kg, and mean body mass index (BMI) from 29 kg/m^2 to 31 kg/m^2. In comparison with the VOYAGE trials, patients in the NAVIGATE trial were obese (mean BMI greater than 30 kg/m^2) and had more (greater than 30%) mean BSA involvement. The mean duration of psoriasis was between 15 years to 18 years and appeared to be balanced between groups in the VOYAGE trials, but possibly imbalanced in the NAVIGATE trial (i.e., 18.2 years in the guselkumab group and 15.6 years in the ustekinumab group). Overall, 15% to 20% of patients in the trials had psoriatic arthritis.

Baseline patient disease characteristics were consistent with a population with moderate-to-severe plaque psoriasis and were generally comparable between treatment groups across the three trials. The majority of patients (72% to 78%) had a baseline IGA score of 3 (moderate), a mean PASI score between 20 to 22, and BSA involvement of 25% to 31%. Baseline regional psoriasis measurements were reported for VOYAGE 1 and VOYAGE 2 only, and results were similar to those for the overall disease. The majority of patients had baseline scores of 3 (moderate) for Scalp-Specific Investigator Global Assessment (ss-IGA) (57% to 63%), Fingernail Physician Global Assessment (f-PGA) (41% to 46%), and Physician Global Assessment of Hands and/or Feet (hf-PGA) (42% to 52%). The mean Nail Psoriasis Severity Index (NAPSI) score ranged from 4.5 to 5, and baseline mean Dermatology Life Quality Index (DLQI) scores ranged from 13 to 15.

Almost all patients had used prior topical therapy (88% to 96%), and the majority of patients had used conventional systemic therapy (52% to 66%). In addition, 49% to 59% of patients had prior phototherapy. Biologics had previously been used by 19% to 23% of patients across the trials. In VOYAGE 1 and VOYAGE 2, the category of 'biologics' included etanercept, infliximab, alefacept, efalizumab, ustekinumab, briakinumab, secukinumab, ixekizumab, or brodalumab. In the NAVIGATE trial, the category of 'biologics' only included anti-TNF-alpha agents (e.g., etanercept, infliximab, and adalimumab). In addition, the distribution of patients with body weight greater than 100 kg and less than and equal to 100 kg was similar in the guselkumab and ustekinumab groups (i.e., approximately 27% to 28%, and 72% to 73%, respectively). The primary reason for discontinuation of prior biologics was a contraindication, an inadequate response, intolerance to treatment, or 'other'.

Interventions

In all three trials patients self-administered study drug or matched placebo by subcutaneous injection using pre-filled syringes supplied at each study visit. At week 0, patients underwent training and self-administered the study drug at the study site and then all subsequent administrations were self-administered by the patient at home. No specific information on the type of training received by patients was provided, other than the Clinical Study Reports (CSRs) for the trials stating that, after receiving appropriate training at week 0, patients then self-administered study drug at home. At each study visit patients received two blinded types of pre-filled syringes.

In VOYAGE 1, patients received the following study drugs:

Week 0 through week 48 (placebo- and active-comparator controlled periods):

- **Group I:** Guselkumab 100 mg at weeks 0, 4, 12, and every eight weeks thereafter through week 44 plus matching placebo for guselkumab at week 16, plus matching placebo for adalimumab at week 0, week 1, and every two weeks thereafter through week 47.
- **Group II:** Matching placebo for guselkumab at weeks 0, 4, 12, plus matching placebo for adalimumab at week 0, week 1, and every two weeks thereafter through week 15 to maintain the blind. At week 16, placebo-treated patients were crossed over to receive guselkumab 100 mg at weeks 16 and 20 and every eight weeks thereafter through week 44, plus matching placebo for adalimumab at weeks 17, and every two weeks thereafter through week 47.
- **Group III:** Adalimumab 80 mg at week 0, then 40 mg at week 1, and every two weeks thereafter through week 47, plus matching placebo for guselkumab at weeks 0, 4, 12, 16, and 20, and every eight weeks thereafter through week 44.

Week 48 through week 160 (open-label treatment period):

- All patients were to receive guselkumab 100 mg every eight weeks starting at week 48 and continuing through week 160.

In VOYAGE 2, patients received the following study drugs:

Week 0 through week 24 (placebo- and active-comparator controlled periods):

- Group I: Guselkumab 100 mg at weeks 0, 4, 12, and 20, plus matching placebo for guselkumab at week 16, plus matching placebo for adalimumab at week 0, week 1, and every two weeks thereafter through week 23.
- Group II: Matching placebo for guselkumab at weeks 0, 4, 12, plus matching placebo for adalimumab at week 0, week 1, and every two weeks thereafter through week 15 to maintain the blind. At week 16, placebo-treated patients were crossed over to receive guselkumab 100 mg at weeks 16 and 20, plus matching placebo for adalimumab at weeks 17, 19, 21, and 23.
- Group III: adalimumab 80 mg at week 0, followed by 40 mg at week 1, and every two weeks thereafter, through week 23, plus matching placebo for guselkumab at weeks 0, 4, 12, 16, and 20.

There were no injections of study drug for any treatment groups between weeks 23 to 28.

Week 28 up to week 72 (randomized withdrawal and re-treatment period):

- Patients originally randomized to guselkumab (Group I):
    - Group Ia (PASI 90 nonresponders at week 28) received guselkumab 100 mg at weeks 28 and 36 and every eight weeks thereafter, plus matching placebo for guselkumab at weeks 32 and 40, and every eight weeks thereafter until week 72.

- Group Ib (PASI responder at week 28 re-randomized to guselkumab) received guselkumab 100 mg at weeks 28 and 36 and every eight weeks thereafter, plus matching placebo for guselkumab at weeks 32 and 40, and every eight weeks thereafter until week 72.
- Group Ic (PASI responder at week 28 re-randomized to withdrawal) received matching placebo for guselkumab at week 28 and every four weeks thereafter, until loss of greater than and equal to 50% of their week 28 PASI response prior to week 72, or if the patient reached week 72 before losing greater than and equal to 50% of their week 28 PASI response. If patients lost greater than and equal to 50% of their week 28 PASI response, they re-initiated guselkumab 100 mg at that visit, then received a dose four weeks later, and then every eight weeks thereafter, plus matching placebo administrations as needed to maintain the blind to week 72.

- Patients originally randomized to placebo (Group II)
  - Group IIa (PASI 90 nonresponders at week 28) received guselkumab 100 mg at weeks 28 and 36, and every eight weeks thereafter, plus matching placebo for guselkumab at weeks 32 ad 40, and every eight weeks thereafter until week 72.
  - Group IIb (PASI 90 responders at week 28) received matching placebo for guselkumab at week 28, and every four weeks thereafter, until loss of greater than and equal to 50% of their week 28 PASI response prior to week 72, or if the patient reached week 72 before losing greater than and equal to 50% of their week 28 PASI response. If patients lost greater than and equal to 50% of their week 28 PASI response, they re-initiated guselkumab 100 mg at that visit, then received a dose four weeks later, and then every eight weeks thereafter, plus matching placebo administrations as needed to maintain the blind to week 72.

Week 76 through week 160 (open-label treatment period):

- All patients received guselkumab 100 mg every eight weeks starting at week 76 and continuing through week 148.

In NAVIGATE, patients received the following study drugs:

- All patients received open-label ustekinumab at weeks 0 and 4, according to their weight at baseline (week 0), as described below:
  - Patients weighing less than and equal to 100 kg (220 lbs): ustekinumab 45 mg
  - Patients weighing greater than 100 kg (220 lbs): ustekinumab 90 mg

At week 16, patients were assessed for efficacy according to the IGA as follows:

- **Patients with an IGA score greater than and equal to 2** (mild to severe disease; patients with an inadequate response to ustekinumab) were randomized in a 1:1 ratio to one of two treatment arms:

        - Guselkumab 100 mg at weeks 16 and 20, then every eight weeks thereafter through week 44, plus matching placebo for ustekinumab at weeks 16, 28, and 40.
        - Continue ustekinumab every 12 weeks according to baseline weight through to week 40, plus matching placebo for guselkumab at weeks 16, 20, 28, 36, and 44.
    - **Patients with an IGA score of 0 or 1** (cleared or minimal disease) continued to receive open-label ustekinumab (according to their baseline weight at weeks 16, 28, and 40).

Concomitant medications permitted during the trials were moisturizers, corticosteroids for conditions other than psoriasis, and concomitant medication for latent TB (if appropriate treatment for latent TB was initiated prior to, or simultaneously with, the first administration of study drug). In general, concomitant medication use was very low (i.e., ranging from less than 1% to 8% of patients).

Table 5: Summary of Demographic and Baseline Characteristics

Baseline Characteristic	VOYAGE 1			VOYAGE 2			NAVIGATE[a]	
	Placebo	Guselkumab	Adalimumab	Placebo	Guselkumab	Adalimumab	Guselkumab	Ustekinumab
n	174	329	334	248	496	248	135	133
Age, y **Mean (SD)**	44.9 (12.9)	43.9 (12.7)	42.9 (12.6)	43.3 (12.4)	43.7 (12.2)	43.2 (11.9)	44.2 (13.4)	43.0 (13.7)
Male, n (%)	119 (68.4)	240 (72.9)	249 (74.6)	173 (69.8)	349 (70.4)	170 (68.5)	95 (70.4)	88 (66.2)
Race, n (%) **White** **Asian** **Black**	 145 (83.3) 23 (13.2) 3 (1.7)	 262 (79.6) 51 (15.5) 6 (1.8)	 277 (82.9) 47 (14.1) 8 (2.4)	 206 (83.1) 27 (10.9) 8 (3.2)	 408 (82.3) 72 (14.5) 6 (1.2)	 200 (80.6) 37 (14.9) 5 (2.0)	 109 (80.7) 22 (16.3) 3 (2.2)	 99 (74.4) 27 (20.3) 3 (2.3)
BMI, kg/m^2 **Mean (SD)**	28.9 (6.9)	29.7 (6.2)	29.8 (6.5)	29.6 (6.6)	29.6 (6.5)	29.6 (6.6)	30.3 (7.2)	31.0 (8.6)
Duration of Ps, y **Mean (SD)**	17.6 (12.4)	17.9 (12.3)	17.0 (11.3)	17.9 (11.9)	17.9 (12.0)	17.6 (11.7)	18.2 (12.7)	15.6 (10.9)
BSA, % **Mean (SD)**	25.8 (15.9)	28.3 (17.1)	28.6 (16.7)	28.0 (16.5)	28.5 (16.4)	29.1 (16.7)	31.5 (19.8)	30.5 (17.9)
Weight, kg **Mean (SD)**	88.0 (24.4)	89.5 (20.1)	90.5 (21.8)	88.6 (20.0)	89.2 (20.8)	87.6 (21.0)	90.3 (22.2)[b]	91.3 (25.8)[b]
IGA (0-4) **Mild (2)** **Moderate (3)** **Severe (4)**	 0 131 (75.3) 43 (24.7)	 0 252 (76.6) 77 (23.4)	 3 (0.9) 241 (72.2) 90 (26.9)	 0 (0) 191 (77.0) 57 (23.0)	 1 (0.2) 380 (76.6) 115 (23.2)	 0 (0) 195 (78.6) 53 (21.4)	 0 (0) 103 (76.3) 32 (23.7)	 0 (0) 100 (75.2) 33 (24.8)
PASI (0-72) **Mean (SD)**	20.4 (8.7)	22.1 (9.5)	22.4 (9.0)	21.5 (8.0)	21.9 (8.8)	21.7 (9.0)	22.6 (9.3)	22.8 (9.4)
PsA, n (%)	30 (17.2)	64 (19.5)	62 (18.6)	46 (18.5)	89 (17.9)	44 (17.7)	28 (20.7)	21 (15.8)
Prior txt, n (%) **Topicals** **Phototherapy** **Con. Systemic** **Biologics**	 154 (88.5) 86 (49.4) 92 (52.9) 34 (19.5)	 299 (90.9) 188 (57.3) 210 (63.8) 71 (21.6)	 309 (92.8) 180 (53.9) 215 (64.4) 70 (21.0)	 233 (94.0) 137 (55.2) 149 (60.1) 54 (21.8)	 477 (96.2) 293 (59.1) 331 (66.7) 101 (20.4)	 237 (96.0) 135 (54.7) 159 (64.1) 49 (19.8)	 128 (94.8) 70 (51.9) 80 (59.3) 32 (23.7)[c]	 126 (94.7) 74 (55.6) 73 (54.9) 26 (19.5)[c]
DLQI (030), n **Mean (SD)**	170 13.3 (7.1)	322 14.0 (7.5)	328 14.4 (7.3)	248 15.1 (7.2)	495 14.7 (6.9)	247 15.0 (6.9)	133 15.5 (7.9)	132 14.4 (6.7)

Baseline Characteristic	VOYAGE 1			VOYAGE 2			NAVIGATE[a]	
	Placebo	Guselkumab	Adalimumab	Placebo	Guselkumab	Adalimumab	Guselkumab	Ustekinumab
PSSD (0100), n	129	249	274	198	411	201	133	132
Symptom score Mean (SD)	48.3 (23.8)	54.4 (24.6)	53.9 (25.8)	58.6 (23.6)	54.2 (26.1)	53.8 (26.1)	55.7 (25.5)	52.9 (25.6)
Sign score Mean (SD)	53.6 (20.3)	56.9 (21.3)	58.5 (21.7)	60.9 (20.2)	56.3 (22.5)	56.8 (21.5)	64.9 (20.3)	63.7 (20.8)

BMI = body mass index; BSA = body surface area; Con. = conventional; DLQI = Dermatology Life Quality Index; IGA = Investigator Global Assessment; PASI = Psoriasis Area and Severity Index; Ps = psoriasis; PsA = psoriatic arthritis; PSSD = Psoriasis Symptoms and Signs Diary; pts = patients; SD = standard deviation; txt = treatment; y = years.

[a] For the NAVIGATE trial, results are presented only for pts randomized at week 16.

[b] The proportion of pts with body weight > 100 kg was n = 37 (27.4%) in the guselkumab group, and n = 37 (27.8%) in the ustekinumab group. The proportion of pts with body weight ≤ 100 kg was n = 98 (72.6%) and n = 96 (72.2%), respectively.

[c] Includes only anti-TNF agents (etanercept, infliximab, and adalimumab). The proportion of pts who had a contraindication, an inadequate response, or were intolerant to ≥ 1 therapy was n = 18 (56.3%) in the guselkumab group and n = 16 (61.5%) in the ustekinumab group.

Source: Blauvelt et al. (2017);[7] VOYAGE 1 CSR;[8] Reich et al. (2017);[9] VOYAGE 2 CSR;[10] Langley et al. (2017);[11] NAVIGATE CSRs (40 weeks) and (60 weeks).[12,13]

Table 6: Summary of Baseline Regional Psoriasis Characteristics

Baseline Characteristic	VOYAGE 1			VOYAGE 2			NAVIGATE	
	Placebo	Guselkumab	Adalimumab	Placebo	Guselkumab	Adalimumab	Guselkumab	Ustekinumab
n	174	329	334	248	496	248	135	133
ss-IGA (0-4), n (%) **Very mild (1)** **Mild (2)** **Moderate (3)** **Severe (4)**	150 (86.2) 5 (3.3) 31 (20.7) 89 (59.3) 25 (16.7)	291 (88.4) 14 (4.8) 49 (16.8) 171 (58.8) 57 (19.6)	295 (88.3) 9 (3.1) 54 (18.3) 175(59.3) 57 (19.3)	212 (85.5) 10 (4.7) 33 (15.6) 133 (62.7) 36 (17.0)	423 (85.3) 15 (3.5) 80 (18.9) 267 (63.1) 61 (14.4)	205 (82.7) 11 (5.4) 43 (21.0) 118 (57.6) 33 (16.1)	NR	NR
f-PGA (0-4), n (%) **Minimal (1)** **Mild (2)** **Moderate (3)** **Severe (4)**	99 (56.9) 11 (11.1) 33 (33.3) 42 (42.4) 13 (13.1)	198 (60.2) 24 (12.1) 62 (31.3) 83 (41.9) 29 (14.6)	194(58.1) 21 (10.8) 66 (34.0) 90 (46.4) 17 (8.8)	139 (56.0) 16 (11.5) 40 (28.8) 65 (46.8) 18 (12.9)	280 (56.5) 34 (12.1) 92 (32.9) 122 (43.6) 32 (11.4)	139 (56.0) 15 (10.8) 51 (36.7) 59 (42.4) 14 (10.1)	NR	NR
NAPSI (0-8), n (%) **Mean (SD)**	99 (56.9) 4.7 (1.9)	194 (59.0) 4.9 (2.0)	191 (57.2) 4.6 (2.0)	140 (56.5) 5.0 (2.0)	280 (56.5) 4.8 (2.0)	140 (56.5) 4.5 (1.9)	NR	NR
hf-PGA (0-4), n (%) **Almost clear (1)** **Mild (2)** **Moderate (3)** **Severe (4)**	44 (25.3) 1 (2.3) 15 (34.1) 21 (47.7) 7 (15.9)	100 (30.4) 10 (10.0) 34 (34.0) 42 (42.0) 14 (14.0)	101 (30.2) 6 (5.9) 37 (36.6) 45 (44.6) 13 (12.9)	67 (27.0) 4 (6.0) 23 (34.3) 35 (52.2) 5 (7.5)	127 (25.6) 13 (10.2) 43 (33.9) 58 (45.7) 13 (10.2)	62 (25.0) 6 (9.7) 17 (27.4) 32 (51.6) 7 (11.3)	NR	NR

f-PGA = Fingernail Physician Global Assessment; hf-PGA = Physician Global Assessment of Hands and/or Feet; NAPSI = Nail Psoriasis Severity Index; NR = not reported; SD = standard deviation; ss-IGA = Scalp-Specific Investigator Global Assessment.
Source: Blauvelt et al. (2017);[7] VOYAGE 1 CSR;[8] Reich et al. (2017);[9] VOYAGE 2 CSR.[10]

Outcomes

Investigator-reported outcomes (e.g., IGA, PASI, ss-IGA, NAPSI, f-PGA, and hf-PGA) were performed on-site by trained personnel. Patient-reported outcomes (e.g., DLQI, SF-36) were completed by patients at the site and were captured electronically in a tablet device at the appropriate visits. All visit-specific patient-reported outcomes were conducted before any tests, procedures, or other consultations for that visit to prevent influencing patients. The outcomes were defined as follows, with additional details available on the validity of the outcomes in Appendix 5.

Dermatology Life Quality Index (DLQI): The DLQI is a dermatology-specific quality of life instrument designed to assess the impact of the disease on a patient's quality of life. It is a 10-item patient-reported outcome questionnaire that, in addition to evaluating overall quality of life, can be used to assess six different aspects that may affect quality of life: symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment. The DLQI produces a numeric score that can range from 0 to 30 (or a percentage of 30); the higher the score, the more quality of life is impaired. For example, a score of 0 to 1 indicates no effect on quality of life, and a score of 21 to 30 indicates an extremely large effect on quality of life. The minimal clinically important difference (MCID) is reported to range from 2.2 to 6.9, as detailed in Appendix 5.

Medical Outcomes Study Short Form (36) Health Survey (SF-36): The SF-36 is a general health status instrument that consists of eight multi-item scales or domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. A physical component summary (PCS) score and mental component summary (MCS) score can be derived from aggregating the eight domains according to a scoring algorithm. The PCS and MCS scores range from 0 to 100 with higher scores indicating better health status. The proposed minimally important differences (MIDs) associated with the summary scores are 2 points (PCS) and 3 points (MCS).[19] The concepts measured by the SF-36 are not specific to age, disease, or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments.

Investigator Global Assessment (IGA): The IGA documents the investigator's assessment of the patient's psoriasis at a given time point. Overall lesions are graded for induration, erythema, and scaling. The patient's psoriasis is assessed as: cleared (0), minimal (1), mild (2), moderate (3), or severe (4). No MCID has been established for psoriasis for the IGA at this time.

Psoriasis Area and Severity Index (PASI): The PASI is a system used for assessing and grading the severity of psoriatic lesions and response to therapy. In the PASI system, the body is divided into four regions: the head, trunk, upper extremities, and lower extremities. Each of these areas is assessed separately for the percentage of the area involved, which translates to a numeric score that ranges from 0 (no involvement) to 6 (90% to 100% involvement), and for erythema, induration, and scaling, which are each rated on a scale of 0 to 4. The PASI produces a numeric score that ranges from 0 (no psoriasis) to 72. The PASI response (i.e., PASI 75, PASI 90, or PASI 100) reflects the per cent reduction (75%, 90%, or 100%) in the PASI score from baseline. The PASI is a widely used instrument in clinical trials of psoriasis therapies. A 75% reduction in the PASI score (PASI 75) is the current benchmark for most clinical trials in psoriasis and the criterion for efficacy of new

psoriasis treatments approved by the US FDA.[20] According to the clinical expert consulted on this review, a PASI 90 or PASI 100 score is clinically relevant.

Scalp-Specific Investigator Global Assessment (ss-IGA): The ss-IGA instrument is used to evaluate the disease severity of scalp psoriasis. The lesions are assessed in terms of the clinical signs of redness, thickness, and scaliness, which are scored as: absence of disease (0), very mild disease (1), mild disease (2), moderate disease (3), and severe disease (4). It does not appear that a MCID has been established for the ss-IGA score.

Nail Psoriasis Area and Severity Index (NAPSI): The NAPSI is an index used for assessing and grading the severity of nail psoriasis. Each nail is divided into quadrants and is graded for a nail matrix score (pitting, leukonychia, red spots in the lunula, and nail plate crumbling) ranging from 0 to 4, and a nail bed score (onycholysis, splinter hemorrhages, oil drop discoloration, and nail bed hyperkeratosis) ranging from 0 to 4. The sum of the two scores results in each nail having a score of 0 to 8, for a total of 0 to 80 for the fingernails, and 0 to 160, if the toenails are also included in the analysis. A higher score indicates worse nail involvement and potentially worse disease; however, it is not clear if the index has been validated such that worse nail involvement predicts worse overall disease. No MCID has been identified for the NAPSI.

Fingernail Physician Global Assessment (f-PGA): The f-PGA is used to evaluate the current status of a subject's fingernail psoriasis on a scale of 0 to 4, similar to the IGA (clear [0], minimal [1], mild [2], moderate [3], or severe [4]).

Physician Global Assessment of Hands and/or Feet (hf-PGA): The severity of hand and foot psoriasis has been assessed in various clinical studies using an hf-PGA instrument. The plaques are scored on a 5-point scale as: clear (0), almost clear (1), mild (2), moderate (3), or severe (4).

The safety and tolerability of study treatments was monitored by collecting information on adverse events (AEs), serious AEs (SAEs), and withdrawal due to AEs (WDAEs). In addition, information on injection-site reactions, allergic reactions, clinical laboratory tests, physical examinations, vital signs, electrocardiograms, concomitant medication review, and early detection of active TB were monitored.

Statistical Analysis

Sample Size

In VOYAGE 1 and VOYAGE 2, assumptions for sample size and power calculations were based on results for IGA scores and PASI 90 responses from a previous phase II guselkumab trial (CNTO1959PSO2001).[21] In VOYAGE 1, based on these assumptions, it was determined that a total of 750 patients randomized in a 2:1:2 ratio to guselkumab, placebo, and adalimumab as per the study design, would result in (all at a significance level of 0.05):

- greater than 99% power to detect a treatment effect for both co-primary end points in the proportion of patients achieving an IGA score of cleared (0) or minimal (1) [redacted].

- [redacted].
- [redacted].
- [redacted].

In VOYAGE 2, based on these assumptions, a total of 1,000 patients randomized in a 2:1:1 ratio to guselkumab (n = 500), placebo (n = 250), and adalimumab (n = 250) at week 0 would result in (all at a significance level of 0.05):

- greater than 99% power to detect a treatment effect for both co-primary end points in the proportion of patients achieving an IGA score of cleared (0) or minimal (1) [redacted].
- [redacted].
- [redacted].
- [redacted].

[redacted]

Primary and Secondary Efficacy Analyses

All statistical testing in the three included trials was performed 2-sided at the 0.05 level of significance.

In VOYAGE 1 and VOYAGE 2, the co-primary end points and binary major secondary end points were analyzed using a Cochran-Mantel-Haenszel (CMH) chi-square test stratified by investigator site (pooled). The studies were considered positive if the guselkumab groups were significantly different from the placebo groups for both co-primary end points which were tested separately. If one of the comparisons was not significant at the 2-sided alpha level of 0.05, the co-primary end points were considered not significant.

In both VOYAGE 1 and VOYAGE 2, continuous response parameters were compared using an analysis of variance (ANOVA) model with investigator site as a covariate. In VOYAGE 2, the log-rank test stratified by site was used for the time to loss of PASI 90 response.

In NAVIGATE, the primary and major secondary end points in the randomized treatment groups were compared using the CMH test stratified by body weight at baseline (≤ 100 kg; > 100 kg).

Fixed-Sequence Testing Approach

To control the overall type I error rate in the VOYAGE trials, the co-primary and major secondary analyses were tested according to a fixed-sequence or statistical gatekeeping approach. The first major secondary end point was tested only if the co-primary end points were both significant at the 0.05 level and the subsequent end point(s) were tested only if the preceding end point was positive as detailed in Table 7.

Table 7: Summary of Fixed-Sequence Testing of Co-Primary and Major Secondary End Points in the VOYAGE Trials

End Points		Guselkumab vs. Placebo	Guselkumab vs. Adalimumab	Maintenance vs. Withdrawal	Study Visit No.
Co-Primary End Points					
1	Proportion of pts with IGA 0/1 and PASI 90	Yes	-	-	Week 16 (V1 & V2)
Major Secondary End Points					
2	Proportion of pts with IGA 0	–	Yes	–	Week 24 (V1 & V2)
3	Proportion of pts with IGA 0/1	–	Yes	–	Week 24 (V1 & V2)
4	Proportion of pts with PASI 90	–	Yes	–	Week 24 (V1 & V2)
5	Proportion of pts with IGA 0	–	Yes	–	Week 48 (V1 only)
6	Proportion of pts with IGA 0/1	–	Yes	–	Week 48 (V1 only)
7	Proportion of pts with PASI 90	–	Yes	–	Week 48 (V1 only)
8	Time to loss of PASI 90	–	–	Yes	Week 28 to 48 (V2)
9	Change in DLQI from baseline	Yes	–	–	Week 16 (V1 & V2)
10	Proportion of pts with IGA 0/1[a]	–	Yes	–	Week 16 (V1 & V2)
11	Proportion of pts with PASI 90[a]	–	Yes	–	Week 16 (V1 & V2)
12	Proportion of pts with PASI 75[a]	–	Yes	–	Week 16 (V1 & V2)
13	Proportion of pts with ss-IGA 0/1[b]	Yes	–	–	Week 16 (V1 & V2)

DLQI = Dermatology Life Quality Index; IGA = Investigator Global Assessment; PASI = Psoriasis Area and Severity Index; pts = patients; ss-IGA = Scalp-Specific Investigator Global Assessment; V1 = VOYAGE 1; V2 = VOYAGE 2.

[a] Tested for noninferiority and superiority of the guselkumab group compared with the adalimumab group.

[b] Included only a subset of randomized patients with scalp psoriasis with ss-IGA ≥ 2 at baseline and ≥ 2-grade improvement.

Source: Blauvelt et al. (2017);[7] Reich et al. (2017).[9]

In the NAVIGATE trial, the primary analysis was performed first and then the major secondary analyses were tested in a fixed sequence in the following order: 1) number of visits at which patients achieved a PASI 90 response from week 28 to week 40; 2) number of visits at which patients achieved an IGA score of 0 (cleared) from week 28 to week 40; and 3) proportion of patients who achieved an IGA score of 0 or 1 and at least a 2-grade improvement (from week 16) at week 28. The first major secondary outcome was tested only if the primary outcome was positive, and subsequent outcomes were tested only if the preceding major secondary outcome was positive.

Noninferiority and Superiority Testing

In VOYAGE 1 and VOYAGE 2 noninferiority and superiority testing of the end points of IGA score of 0 or 1, PASI 90 and PASI 75 response between guselkumab and adalimumab was conducted in the randomized analysis intention-to-treat (ITT) populations and in the per-protocol populations. To test the noninferiority of guselkumab to adalimumab, a one-sided (alpha = 0.025) CMH z test adjusted by investigator site (pooled) was used. The 95% confidence interval (CI) for the treatment difference between guselkumab and adalimumab treatment groups was determined. The designated noninferiority margin was –10% (i.e., the lower bound of the 2-sided 95% CI for the difference in proportions between guselkumab minus adalimumab at week 16 would have to exceed –10% to conclude noninferiority).

[redacted]

If noninferiority was demonstrated, then the superiority of guselkumab to adalimumab could be investigated.

Imputation for Missing Data

In all three trials, patients who discontinued treatment due to lack of efficacy, an AE of psoriasis worsening, or who initiated a prohibited psoriasis treatment, were considered to be treatment failures or nonresponders (binary end points) or had baseline values carried over (continuous end points). The primary imputation method in all the trials for the handling of missing data was the nonresponder imputation approach for binary end points and the last observation carried forward (LOCF) method for continuous variables.

In addition to the primary analyses, per-protocol analyses, sensitivity analyses, and subgroup analyses were also performed. Other descriptive statistics such as mean, median, and range were provided for baseline demographic and disease characteristic variables.

Subgroup Analyses

Various subgroups were pre-defined in the three included trials, including the subgroups of interest identified in the review protocol (i.e., baseline PASI score, prior biologic use, and baseline body weight). In the NAVIGATE trial, randomization was stratified by baseline body weight (≤ 100kg; > 100 kg). The co-primary end points (VOYAGE 1 and VOYAGE 2) or primary end point (NAVIGATE) were analyzed by subgroups such that the difference in means and corresponding 95% CI under the assumptions of normal distribution were calculated and presented in forest plots.

Analysis Populations

All patients who were randomized were included in the efficacy analyses in all three included trials.

Intention-to-Treat Population

The protocol-specified primary analysis population was the randomized analysis set, defined as all randomized patients, which may be considered to be analogous to an ITT population. All randomized patients were included in the primary analyses and selected secondary analyses of the included trials, regardless of whether or not the patients received the assigned treatment. Data from all randomized patients were analyzed according to their assigned treatment group.

Per-Protocol Population

The per-protocol population excluded patients with major protocol violations that could have potentially affected efficacy assessments.

Safety Population

The safety population included all patients who received greater than and equal to one administration of study drug.

For regional psoriasis end points (e.g., ss-IGA, NAPSI, f-PGA, hf-PGA) in VOYAGE 1 and VOYAGE 2, the analysis populations only included patients who had baseline measurements and/or who met baseline disease criteria.

Patient Disposition

Details of the patient disposition during the various periods of the three included trials are provided in Tables 8 and 9. In VOYAGE 1 and VOYAGE 2, during the first 16 week placebo-controlled periods, the rates of discontinuations were low (i.e., 4.0% and 6.0% in the placebo groups, compared with 2.1% and 3.6% [guselkumab] or 3.0% and 4.4% [adalimumab]) with greater than and equal to 94% of patients crossing over to guselkumab or continuing active treatment (Table 8). During the maintenance dosing period, in VOYAGE 1, almost twice the proportion of adalimumab-treated patients (15.6%) discontinued at week 48 compared with patients who received continuous guselkumab (8.5%). The main reasons for withdrawal in the adalimumab group were lack of efficacy and patient withdrawal. In VOYAGE 2, at week 28 patients underwent randomized withdrawal and re-treatment (Table 9). Overall, rates of discontinuation after re-randomization were low across treatment arms (1.3% to 5.3%) with no apparent pattern of discontinuation.

In NAVIGATE, more randomized patients in the continued ustekinumab group (15.0%) discontinued treatment compared with those switched to guselkumab group (6.7%) (Table 8). The main reason for discontinuation in the ustekinumab group was lack of efficacy.

Table 8: Patient Disposition

	VOYAGE 1			VOYAGE 2			NAVIGATE	
	PL	GUSE	ADAL	PL	GUSE	ADAL	GUSE	USTE
Screened, N	1,036			1,279			872/871[a]	
Randomized – overall, N	837			992			NA	
Randomized – per group, N	174	329	334	248	496	248	135[a]	133[a]
Completed to week 16, n (%)	167 (96.0)	322 (97.9)	324 (97.0)	233 (94.0)	478 (96.4)	237 (95.6)	853[a]	
Discontinued at week 16 for VOYAGE 1 and VOYAGE 2 and from week 16 to week 44 for NAVIGATE, n (%)	7 (4.0)	7 (2.1)	10 (3.0)	15 (6.0)	18 (3.6)	11 (4.4)	9 (6.7)	20 (15.0)
Most Frequent Reason for Discontinuation – Induction (Week 0 to 16 for VOYAGE 1 and VOYAGE 2 and Week 16 to 44 for NAVIGATE), n (%)								
AE	2 (1.1)	4 (1.2)	2 (< 1)	2 (< 1)	9 (1.8)	4 (1.6)	3 (2.2)	2 (1.5)
Lack of efficacy	2 (1.1)	0 (0)	1 (< 1)	4 (1.6)	0 (0)	2 (< 1)	3 (2.2)	10 (7.5)
Patient withdrawal	2 (1.1)	0 (0)	4 (1.2)	7 (2.8)	1 (< 1)	0 (0)	2 (1.5)	5 (3.8)
Lost to follow-up	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	3 (< 1)	2 (< 1)	0 (0)	1 (< 1)
Protocol violation	0 (0)	0 (0)	1 (< 1)	1 (< 1)	3 (< 1)	1 (< 1)	0 (0)	0 (0)
Txt noncompliance	0 (0)	2 (< 1)	1 (< 1)	0 (0)	1 (< 1)	2 (< 1)	1(< 1)	0 (0)
Other	0 (0)	0 (0)	0 (0)	0 (0)	1 (< 1)	0 (0)	0 (0)	2 (1.5)
Crossed over or continued txt at week 16, n (%)	165[b] (94.8)	322 (97.9)	324 (97.0)	233 (94.0)	478 (96.4)	237 (95.6)	NA	NA
Discontinued at week 48 (VOYAGE 1) and week 28 (VOYAGE 2), n (%)	3 (1.7)	21 (6.4)	42 (12.6)	6 (2.4)	8 (1.6)	9 (3.6)	NA	NA
Most Frequent Reason for Discontinuation – Maintenance (Week 16 to 48 for VOYAGE 1 and Week 16 to 24 for VOYAGE 2), n (%)[c]								
AE	1 (< 1)	6 (1.8)	9 (2.7)	0 (0)	3 (< 1)	2 (< 1)	NA	NA
Lack of efficacy	0 (0)	3 (< 1)	11 (3.3)	0 (0)	0 (0)	2 (< 1)		
Patient withdrawal	1 (< 1)	4 (1.2)	10 (3.0)	3 (1.2)	3 (< 1)	2 (< 1)		
Lost to follow-up	1 (< 1)	2 (< 1)	5 (1.5)	1 (< 1)	2 (< 1)	2 (< 1)		
Protocol violation	0 (0)	1 (< 1)	0 (0)	1 (< 1)	0 (0)	1 (< 1)		
Txt noncompliance	0 (0)	3 (< 1)	3 (< 1)	0 (0)	0 (0)	0 (0)		
Other	0 (0)	2 (< 1)	4 (1.2)	1 (< 1)	0 (0)	0 (0)		
Continued through week 48 for VOYAGE 1 and VOYAGE 2, and week 44 for NAVIGATE, n (%)[d]	162 (93.1)	301 (91.5)	282 (84.4)	219 (88.3)	457 (92.1)	220 (88.7)	126 (93.3)	113 (85.0))

	VOYAGE 1			VOYAGE 2			NAVIGATE	
	PL	GUSE	ADAL	PL	GUSE	ADAL	GUSE	USTE
ITT, N	174	329	334	248	496	248	135	133
Safety, N	174	329	333	248	496	248	135	133

ADAL = adalimumab; AE = adverse event; GUSE = guselkumab; IGA = Investigator Global Assessment; ITT = intention-to-treat; NA = not applicable; PL = placebo; txt = treatment.

[a] A total of 872 patients were enrolled of which 871 were treated with open-label ustekinumab for 16 weeks. Of these, 18 patients discontinued, 585 had IGA 0/1 at week 16 and continued open-label ustekinumab and 268 had IGA ≥ 2 at week 16 and were randomized to guselkumab (n = 135) or ustekinumab (n = 133).

[b] Two patients did not cross over from placebo to guselkumab.

[c] The placebo column represents patients originally randomized to placebo and reassigned to guselkumab for the maintenance phase in VOYAGE 1 and 2.

[d] See Table 9 for details on patient disposition following randomized withdrawal or re-treatment.

Source: Blauvelt et al. (2017);[7] VOYAGE 1 CSR;[8] Reich et al. (2017);[9] VOYAGE 2 CSR;[10] Langley et al. (2017);[11] NAVIGATE CSRs (40 weeks) and (60 weeks).[12,13]

Table 9: VOYAGE 2 – Patient Disposition Following Randomized Withdrawal and Re-Treatment

	VOYAGE 2						
Crossover or Continued	**Placebo → Guselkumab**		**Continued Guselkumab**			**Continued Adalimumab**	
Entered at Week 28, n	227		470			228	
Randomized Withdrawal or Re-Treatment Group	**Responder PL Withdrawal n = 147**	**Nonresponder Continue Guselkumab n = 80**	**Responder n = 375**		**Nonresponder Continue Guselkumab n = 95**	**Responder PL Withdrawal n = 116**	**Nonresponder Initiate Guselkumab n = 112**
			Randomized to PL n = 182	**Randomized to Continue Guselkumab n = 193**			
Discontinued, n (%)	7 (4.8)	1 (1.3)	4 (2.2)	4 (2.1)	5 (5.3)	5 (4.3)	3 (2.7)
Most Frequent Reason for Discontinuation, n (%)							
AE	3 (2.0)	0 (0)	1 (< 1)	0 (0)	1 (< 1)	2 (1.7)	1 (< 1)
Lack of efficacy	0 (0)	0 (0)	1 (< 1)	0 (0)	1 (< 1)	1 (< 1)	1 (< 1)
Patient withdrawal	0 (0)	1 (1.3)	0 (0)	2 (1.0)	0 (0)	0 (0)	1 (< 1)
Lost to follow-up	2 (1.4)	0 (0)	1 (< 1)	1 (< 1)	3 (3.2)	2 (1.7)	0 (0)
Protocol violation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Txt noncompliance	1 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	1 (< 1)	0 (0)	1 (< 1)	1 (< 1)	0 (0)	0 (0)	0 (0)
Continued Through Week 48, n (%)	140 (95.2)	79 (98.7)	178 (97.8)	189 (97.9)	90 (94.7)	111 (95.7)	109 (97.3)

AE = adverse event; PL = placebo; txt = treatment.

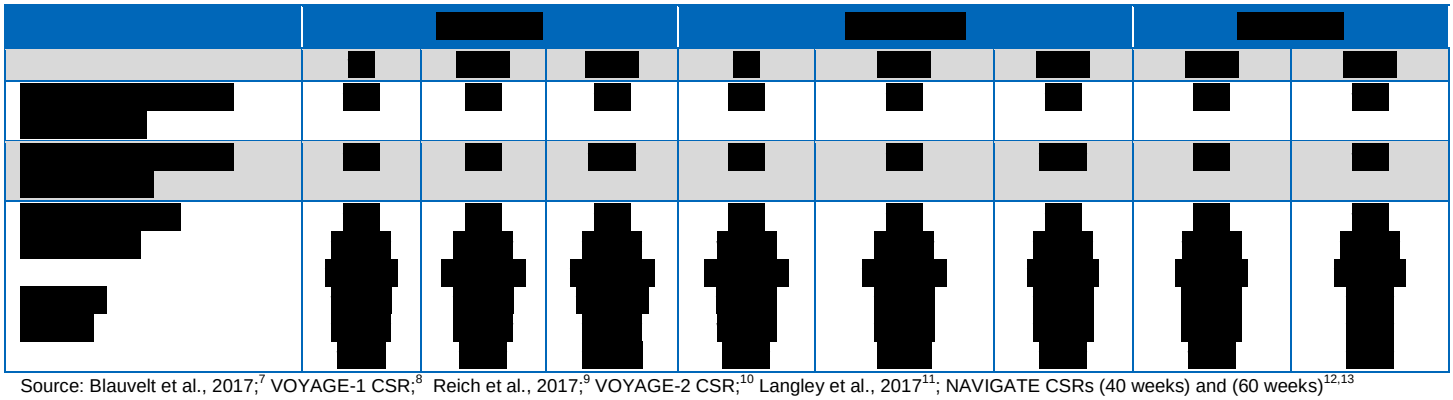
Source: Reich et al. (2017);[9] VOYAGE 2 CSR.[10]

Exposure to Study Treatments

[redacted]

[redacted]

Table 10: Extent of Exposure to Study Treatment



Source: Blauvelt et al., 2017;[7] VOYAGE-1 CSR;[8] Reich et al., 2017;[9] VOYAGE-2 CSR;[10] Langley et al., 2017[11]; NAVIGATE CSRs (40 weeks) and (60 weeks)[12,13]

[redacted]

Critical Appraisal

Internal Validity

Study Design and Methodology

All three trials used an appropriate centralized method for randomization (i.e., IWRS) and stratified patients at study entry by investigator site (VOYAGE 1 and VOYAGE 2) or by baseline body weight (≤ 100 kg or > 100 kg) in the NAVIGATE trial. The design of the initial 24 weeks of the VOYAGE 1 and VOYAGE 2 trials was identical and the results of each trial corroborated the results of the other. It should be noted that the initial randomization was only maintained for 16 weeks in the trials. Therefore, comparisons of outcomes after week 16 following crossover of placebo-treated patients to guselkumab or in patients allocated to treated based on PASI 90 response after week 28 (VOYAGE 2) may have been affected by the lack of preservation of the original randomization.

In VOYAGE 2, patients who were PASI 90 responders at week 28 were re-randomized to either continued guselkumab or to placebo (withdrawal/re-treatment) in order to assess on-going maintenance therapy compared with intermittent therapy. Re-treatment with guselkumab was initiated upon loss of a pre-specified magnitude of response (i.e., greater

than and equal to 50% of PASI response at week 28). Although the results from the re-randomized period may provide useful clinical information on the time frame for loss of PASI 90 response, it must be noted that the treatment groups represent diminished sample sizes which may be compromised due to failure to preserve the initial randomization. Patients who were nonresponders for PASI 90 at week 28 were also not part of the randomization. The manufacturer only compared results between treatment groups in the population of re-randomized PASI-90 responders at week 28; however, as stated earlier, the strength of randomization may have been compromised. If randomization was compromised, the benefit of controlling for the effect of unknown confounders is lost. Furthermore, no information was provided regarding the balance of patient characteristics between the re-randomized treatment groups so it is not possible to ascertain if any patient characteristics could have affected response to treatment and if the characteristics were balanced in this period of the study.[28]

The study design of the NAVIGATE trial included an open-label ustekinumab run-in phase after which patients with an inadequate response to ustekimumab (IGA score greater than and equal to 2) at week 16 were randomized in a double-blind manner to either guselkumab or continued ustekinumab. Although this type of enrichment design and selected patient population may inform clinical practice (i.e., with regard to successive use of guselkumab after inadequate response to ustekinumab), this trial should be considered as a switch trial in a selected population and not a direct head-to-head comparison of guselkumab and ustekinumab. Furthermore, the switch of ustekinumab nonresponders to guselkumab compared with the continued treatment of ustekinumab nonresponders with a drug that they have previously demonstrated an inadequate response to, biases results in favour of guselkumab. It must also be noted that patients were switched without a washout period, which further limits the validity of the findings from the randomized treatment period in this trial.

Overall, blinding, as maintained by use of matched placebos and allocation concealment, appears to be appropriate as investigators were not provided with the randomization codes which were maintained within the IWRS. [redacted]. The run-in phase of the NAVIGATE trial was conducted under open-label conditions which may have introduced selection bias as inadequate response to ustekinumab was based on the IGA score at week 16.

There was no obvious indication of unblinding in the trials; however, in the VOYAGE trials the magnitude of the treatment response with guselkumab compared with placebo might have indicated which patients were randomized to guselkumab during the induction period. Similarly, in the NAVIGATE trial, ustekinumab nonresponders who experienced a response after being randomized (as compared with nonresponders who continued on the drug they were not responding to) may have alerted to patients who were switched to guselkumab. As a result, it is possible that patients or physicians may have inferred to which treatment group a patient was randomized in the trials. It did not appear that there were any imbalances in AEs or SAEs that could have led to unblinding.

Discontinuation rates were generally low in the VOYAGE trials (approximately 5%) during the 16-week induction periods which comprised the primary analysis period. At week 48 in the VOYAGE 1 trial, almost twice the proportion of adalimumab-treated patients (15.6%) discontinued treatment compared with patients who received continuous guselkumab (8.5%), which could have compromised the randomization. In the NAVIGATE trial, more randomized patients in the continued ustekinumab group (15.0%) discontinued treatment compared with those switched to guselkumab group (6.7%), which also may have affected the strength of the randomization.

Patient Characteristics

Baseline demographic and disease characteristics appeared to be balanced between treatment groups in the individual trials. Patients in the NAVIGATE trial may have been slightly more obese than in the VOYAGE trials; however, patients were stratified by baseline body weight at study entry and dosing for ustekinumab was done according to body weight. The stratification of randomization by body weight in the NAVIGATE trial maintains the randomization for this subgroup; however, this may not be the case with other subgroups in which the initial randomization is compromised due to diminished sample sizes or inadequate power.

Statistical Analysis

The included trials appeared to have sufficient power to test the significance of the primary outcomes. In addition, all three trials utilized a pre-specified fixed sequence or statistical gatekeeping approach to control the type I error rate for multiple comparisons of the treatment groups on major secondary end points, which was appropriate. Nonetheless, there was no control for multiplicity in the testing of other secondary end points not considered to be major end points or in the comparison of subgroups.

In VOYAGE 1 and VOYAGE 2, the testing of noninferiority and subsequently, the superiority of guselkumab and adalimumab was included in the fixed-sequence statistical testing methodology, which was appropriate. The manufacturer also provided reasonable justification for the choice of the noninferiority margin as detailed in the Statistical Analysis section of the report. Noninferiority was evaluated in both the randomized analysis (ITT) and per-protocol populations, and the results corroborated each other. Furthermore, the results of the noninferiority analyses are mitigated by the results of the superiority analyses.

The methods used for handling missing values (i.e., nonresponder imputation and LOCF) are commonly used techniques in clinical trials, but have limitations, especially in the case of differential withdrawals between groups. In the case of the LOCF method, it is possible that patients could have worsened had they stayed on treatment. Of note, the statistical reviewer for the US FDA review of guselkumab conducted an additional sensitivity analysis of the data from the VOYAGE trials under the worst case scenario (i.e., missing data for guselkumab was imputed as nonresponders and missing data for placebo was imputed as responders).[17] In this extreme case, guselkumab remained statistically superior to placebo (P values < 0.001) for both co-primary end points in both VOYAGE trials.[17]

External Validity

Patient Selection

The inclusion and exclusion criteria were identical across the three trials and according to the clinical expert consulted on this review reflect a patient population with moderate-to-

severe plaque psoriasis that is consistent with what would be seen in Canadian clinical practice. [redacted]. Therefore, the results are considered to be generalizable to similarly afflicted Canadian patients. The studies excluded patients with non-plaque forms of psoriasis (e.g., erythrodermic, guttate, or pustular) or with drug-induced psoriasis (e.g., a new onset or exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium). Thus, the results would not be generalizable to these groups; however, guselkumab is not indicated for use in these other forms of psoriasis. In addition, patients who had ever received guselkumab, adalimumab, or ustekinumab were also excluded from the respective trials, so the results may not be generalizable to heavily pre-treated and refractory patients. In the NAVIGATE trial, the enrichment design and selected patient population (i.e., based on inadequate response to ustekinumab) precludes the generalizability of results to patients not fitting the selection criteria.

Comparators and Duration of Trials

The choice of active comparators (i.e., adalimumab in the VOYAGE trials and ustekinumab in the NAVIGATE trial) was appropriate as these are regularly used in Canadian clinical practice for the treatment of plaque psoriasis, although according to the clinical expert, this may vary regionally. Adalimumab does possess a different mechanism of action (TNF-alpha antagonist) whereas ustekinumab (IL-12/23 inhibition) possesses a similar mechanism of action as guselkumab. Nonetheless, the only head-to-head comparison between guselkumab and another biologic is with adalimumab in the VOYAGE trials. A direct head-to-head comparison with some of the newer biologics, especially those that specifically target IL (e.g., ustekinumab, secukinumab, ixekizumab) would have provided relevant clinical information as to relative efficacy and safety of the respective drugs. The manufacturer did submit an indirect treatment comparison (IDC) comparing guselkumab with various comparators used in the treatment of plaque psoriasis to address this knowledge gap, which is reviewed and critically appraised in Appendix 7.

Outcome Measures

The primary and secondary outcome measures and definitions in the VOYAGE trials (i.e., IGA score, PASI response, DLQI, SF-36) are well accepted measures to evaluate treatment response in clinical trials of therapeutic interventions for psoriasis and are considered valid and reliable, as detailed in Appendix 5. As corroborated by the clinical expert consulted for this review, the outcomes measured in the trials are clinically relevant measures of treatment effect. The clinical expert acknowledged that while measurement of PASI 90 is clinically meaningful, the incremental relevance above PASI 75 to patients is unknown and of uncertain clinically significant value. Nonetheless, as stated in the patient input received for this review, patients' hopes and expectations about new therapies are that they will provide 100% effectiveness and eliminate all of their symptoms. In addition, the MCID for certain outcomes (e.g., IGA or NAPSI), or the MID (e.g., SF-36) in plaque psoriasis, are unknown.

A responder analysis undertaken in VOYAGE 1 and VOYAGE 2 was the proportion of patients with a change in DLQI score of greater than and equal to 5 points. As the MCID for the DLQI is reported to range from 2.2 to 6.9, the value of 5 points (used to define a responder) does not exceed the upper threshold for a clinically important difference. While an improvement of 5 points in DLQI score does fall within the reported range of MCID for the DLQI in psoriasis, it remains possible that patients may not find this change to be clinically

meaningful. Furthermore, this outcome was not included in the fixed-sequence statistical testing, so the results were not adjusted for multiplicity.

In VOYAGE 2; the SF-36 was not included in the fixed-sequence statistical testing to control for type I error; therefore the comparison of differences in the PCS and MCS scores was not adjusted for multiplicity. The choice of primary end point in the NAVIGATE trial (i.e., number of visits at which patients achieved an IGA score of 0 or 1 and greater than and equal to a 2-grade improvement [from week 16] during weeks 28 to 40) does not reflect a clinical response. Nonetheless, the results are supported by one major secondary end point that is a direct measure of clinical response (i.e., the proportion of patients who achieved an IGA score of 0 or 1 and at least a 2-grade improvement [from week 16] at week 28), which was statistically significant (P = 0.001). Lastly, the NAVIGATE trial did not report any regional psoriasis outcomes (e.g., ss-IGA, f-PGA, NAPSI, or hf-PGA).

Length of Follow-Up

The initial 16-week placebo-controlled period in the VOYAGE trials for the primary outcomes appeared to be sufficient to assess efficacy during induction compared with placebo. The duration of the maintenance period; however, may not have been adequate. For example, the comparison with adalimumab in VOYAGE 2 was limited (i.e., only 24 weeks) although comparative data are available from VOYAGE 1 for up to 48 weeks. Nonetheless, overall the size and duration of the trials were likely insufficient for assessing rare AEs or those with a long latency. The primary end point in the NAVIGATE trial was also assessed over a relatively short (24 weeks) time period (i.e., week 28 to week 40) which did not include a washout period. The long-term use of guselkumab from the open-label extension of the NAVIGATE trial for up to 52 weeks (efficacy) and 60 weeks (safety) is reported in Appendix 6. Results from the extension phases of the VOYAGE trials are preliminary at this point in time.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below. See Appendix 4: Detailed Outcome Data for detailed efficacy data.

Health-Related Quality of Life

Health-related quality of life (HRQL) and functional outcomes were assessed in both VOYAGE 1 and VOYAGE 2 as the change in DLQI score from baseline to week 16. In both VOYAGE 1 and VOYAGE 2, there was a statistically significant greater reduction in the DLQI score from baseline with guselkumab when compared with placebo as detailed in Table 11. The mean (SD) magnitude of the reduction was -11.2 (7.2) and –11.3 (6.8) with guselkumab compared with –0.6 (6.4) and –2.6 (6.9) with placebo in VOYAGE 1 and VOYAGE 2, respectively. The reduction in DLQI score from baseline with adalimumab (–9.3 [7.8] and –9.7 [6.8]) was also statistically significantly greater compared with placebo; however, the testing of this outcome was not adjusted for multiplicity. The change in DLQI score for guselkumab from baseline at week 16 is considered to be clinically significant, given that change exceeds the MCID for the DLQI score which is reported to range from 2.2 to 6.9, as detailed in Appendix 5.

The change from baseline in DLQI score to week 24 and week 28 (VOYAGE 2 only) or week 48 (VOYAGE 1 only) was also reported, but not statistically compared (Table 20). The magnitude of the reductions in DLQI score appeared to be maintained over time in patients

who remained on continuous guselkumab or adalimumab at week 28 (VOYAGE 2) and week 48 (VOYAGE 1).

Additional analyses such as the proportion of patients with DLQI score of 0 or 1 (i.e., implying minimal or no effect on patient quality of life) at week 24 and week 28 (VOYAGE 2) and week 48 (VOYAGE 1) were conducted comparing guselkumab and adalimumab (Table 20). For all comparisons, consistently a larger proportion of patients achieved a DLQI score of 0 or 1 with guselkumab compared with adalimumab. Although the differences were compared statistically and were significant in VOYAGE 1, the results were not tested in the fixed sequence to control for multiplicity.

[redacted]

[redacted]

VOYAGE 2 was the only trial to include the SF-36 generic quality of life instrument. The change from baseline to week 16 in the PCS and MCS scores was statistically significantly higher with both guselkumab and adalimumab as compared with placebo; however, the SF-36 instrument was not included in the statistical gatekeeping procedure and the analysis was not adjusted for multiplicity (Table 11). Additional analyses included the change from baseline to week 24 in SF-36 scores and proportion of patients with an improvement of five or more points from baseline at week 16 (Table 22). The change from baseline to week 24 for both the PCS and MCS scores with guselkumab appeared to be larger than the change in patients who received continuous adalimumab and patients who were initially randomized to placebo, but switched to guselkumab at week 16; however, the results were not statistically compared. [redacted], but the analysis was not tested in the fixed sequence to control for multiplicity.

Psoriasis Area and Severity Index (PASI)

A co-primary end point in both VOYAGE 1 and VOYAGE 2 was the proportion of patients achieving a PASI 90 score at week 16, which is considered to be a clinically significant improvement for patients as confirmed by the clinical expert consulted on this review. At week 16, statistically significantly more patients achieved a PASI 90 score with guselkumab (73.3% and 70.0%) compared with placebo (2.9% and 2.4%) in VOYAGE 1 and VOYAGE 2, respectively (Table 11). The proportion of patients achieving a PASI 90 score with adalimumab was 49.7% and 46.8% in the two trials, respectively, which were both

statistically significantly greater than placebo. As detailed in the Statistical Analysis section, the comparison of the proportion of patients achieving a PASI 90 response between guselkumab and adalimumab at weeks 16 and 24 (VOYAGE 1 and VOYAGE 2) and at week 48 (VOYAGE 1 only) was permitted by the statistical gatekeeping procedure. At week 24, the proportion of patients achieving a PASI 90 response was statistically significantly larger with guselkumab (80.2% and 75.2%) compared with adalimumab (53.0% and 54.8%) in VOYAGE 1 and VOYAGE 2, respectively (Table 17). In VOYAGE 1, at week 48, statistically significantly more patients treated with guselkumab (76.3%) achieved a PASI 90 response compared with adalimumab (47.9%) (Table 17).

Additional analyses of PASI 75 and PASI 100 responses between guselkumab and adalimumab at weeks 24 and 48 (VOYAGE 1 only) were conducted; however, these comparisons were not included in the fixed-sequence testing, and thus were not adjusted for multiplicity (Table 17). In all comparisons of the proportion of patients achieving PASI 75 or PASI 100 at week 24, guselkumab was shown to be statistically significantly superior to adalimumab in both VOYAGE 1 and VOYAGE 2. Similarly in VOYAGE 1, the proportion of patients achieving PASI 75 or PASI 100 at week 48 was statistically significantly greater with guselkumab compared with adalimumab (Table 17).

In VOYAGE 1 and VOYAGE 2, noninferiority and superiority testing of the proportion of patients with PASI 90 and PASI 75 responses at week 16 between guselkumab and adalimumab was conducted in the per-protocol populations and in the randomized analysis (ITT) populations, which corroborated each other. The noninferiority testing was included in the statistical gatekeeping procedure. For both outcomes, the noninferiority margin was –10% (i.e., if the lower bound of the 95% CI for the difference between treatments was greater than or equal to –10%) for guselkumab minus adalimumab, then noninferiority was concluded. In both trials, noninferiority of guselkumab with adalimumab was demonstrated (Table 11). As noninferiority was demonstrated, the treatments were tested for superiority and in both VOYAGE 1 and VOYAGE 2, guselkumab was found to be statistically significantly superior to adalimumab for the proportion of patients achieving a PASI 90 or PASI 75 response at week 16.

In VOYAGE 2, the time to loss of PASI 90 response from week 28 to week 40 between the maintenance group and the withdrawal/re-treatment group was included in the statistical gatekeeping procedure. As detailed in Table 18, loss of PASI 90 responses appeared to be maintained for a longer duration of time in patients who were PASI 90 responders at week 28 and who were maintained on guselkumab (maintenance group) as compared with responders who were re-randomized to placebo (withdrawal group). The median time to loss of response in responders who were in the withdrawal group was 15.2 weeks (Table 18). [redacted] (Table 17). Of note, through week 48, 88.6% of patients in the maintenance group sustained a PASI 90 response. In [redacted] (Table 18). In addition, the proportion of adalimumab nonresponders who initiated guselkumab at week 28 (n = 112) who achieved PASI 90 and PASI 100 responses from baseline at week 48 were 66.1% and 28.6%, respectively after the switch from adalimumab to guselkumab.

In the NAVIGATE trial, a secondary end point was the number of visits where patients achieved a PASI 90 response from week 28 to week 40, in randomized patients with an

inadequate response to ustekinumab (IGA score greater than and equal to 2 at week 16) (Table 11). The mean (SD) number of visits was higher (2.2 [1.7]) in patients randomized to guselkumab compared with patients who continued on ustekinumab (1.1 [1.5]) and the difference was statistically significant ($P < 0.001$; adjusted for multiplicity). Additional analyses included the number of visits at which patients achieved PASI 100 or PASI 75 and the average per cent improvement from baseline in PASI response; however, although guselkumab was statistically superior to ustekinumab in all three instances, the testing of these outcomes was not adjusted for multiplicity (Table 19).

Pre-specified subgroup analyses were conducted on the individual components of the co-primary end points in the VOYAGE trials and the primary end point in the NAVIGATE trial. Results for the subpopulations of interest identified in the protocol for this review (i.e., baseline PASI response, prior use of biologics, and body weight) are presented in Tables 24 to 26. In VOYAGE 1 and VOYAGE 2, results at week 16 and week 24 for the proportion of patients achieving a PASI 90 response were consistent with the results of the primary analysis, as 95% CI for all of the differences between groups for each subgroup comparison excluded zero, indicating that a greater proportion of patients treated with guselkumab achieved each of the co-primary outcomes compared with placebo. However, none of these subgroup comparisons, nor their 95% CIs, were adjusted for multiplicity. [redacted]. As noted previously, interpretation of these results is difficult and compromised by the small sample sizes and imprecise CIs in these subgroups.

Other Efficacy Outcomes

Investigator Global Assessment

The other co-primary end point in VOYAGE 1 and VOYAGE 2 was the proportion of patients who achieved an IGA score of 0 or 1 (cleared or minimal) at week 16. A statistically significantly higher proportion of patients achieved an IGA score of 0 or 1 at week 16 with guselkumab (85.1% and 84.1%) and adalimumab (65.9% and 67.7%) when compared with placebo (6.9% and 8.5%), in VOYAGE 1 and VOYAGE 2, respectively (Table 11). As detailed in the Statistical Analysis section, the difference in the proportion of patients treated with guselkumab compared with adalimumab with an IGA score of 0 at week 24 or week 48 (VOYAGE 1 only) and IGA score of 0 or 1 at week 24 or week 48 (VOYAGE 1 only) was tested in a fixed sequence to control for multiplicity. For all the preceding outcomes, guselkumab was statistically significantly superior to adalimumab as detailed in Table 15.

In VOYAGE 1 and VOYAGE 2, noninferiority and superiority testing of the proportion of patients with IGA score of 0 or 1 at week 16 between guselkumab and adalimumab was conducted in the per-protocol and randomized analysis (ITT) populations, which corroborated each other, and was included in the statistical gatekeeping procedure. Based on the same noninferiority margin of –10% used for the PASI 90 and PASI 75 responses, guselkumab was shown to be noninferior to adalimumab for the proportion of patients with IGA score of 0 or 1 at week 16 (Table 11). As noninferiority was demonstrated, the treatments were subsequently tested for superiority and in both VOYAGE 1 and VOYAGE 2,

the proportion of patients who achieved an IGA score of 0 or 1 at week 16 was statistically significantly greater with guselkumab than with adalimumab.

In the NAVIGATE trial, the primary end point was the number of visits where patients achieved an IGA score of 0 or 1 and at least a 2-grade improvement (from week 16) during week 28 through week 40 in randomized patients with an inadequate response (IGA score of 2 or more) to ustekinumab at week 16 (Table 11). The mean (SD) number of visits was higher (1.5 [1.6]) with guselkumab compared with ustekinumab (0.7 [1.3]) and the difference between groups was statistically significant. The median number of visits where patients achieved an IGA score of 0 or 1 and at least a 2-grade improvement was 1.0 (guselkumab) and 0.0 (ustekinumab); both with a range of 0 to four visits.

As with the PASI 90 response, pre-specified subgroup analyses were conducted on the IGA component of the co-primary or primary outcomes, as appropriate, in the three included trials. In VOYAGE 1 and VOYAGE 2, results at week 16 and week 24 for the proportion of patients achieving an IGA score of 0 or 1 were also consistent with the results of the primary analysis, as the 95% CI excluded 0 (Tables 24 to 26). [redacted]. As noted previously, interpretation of these results is difficult and compromised by the small sample sizes in these subgroups.

Regional Psoriasis

Regional psoriasis end points (i.e., ss-IGA, f-PGA, NAPSI, and hf-PGA scores) were only included in VOYAGE 1 and VOYAGE 2 and of these, only the ss-IGA score was included in the fixed testing sequence that controlled for multiplicity.

The proportion of patients with a ss-IGA score of 0 (absence of disease) or 1 (very mild disease) and at least a 2-grade improvement from baseline at week 16 was statistically significantly greater with guselkumab (83.4% and 80.6%) compared with placebo (14.5% and 10.9%) in VOYAGE 1 and VOYAGE 2, respectively, both $P < 0.001$ (Table 23). The proportion of patients achieving this outcome was also statistically significantly ($P < 0.001$) greater with adalimumab (70.3% and 67.0%) in VOYAGE 1 and VOYAGE 2, respectively; however, the comparison of adalimumab with placebo was not adjusted for multiplicity. No statistical comparisons were made between guselkumab and adalimumab. At week 24, ss-IGA responses appeared to be maintained in the continuous guselkumab and adalimumab groups; [redacted](Table 23). No statistical comparisons were made at week 24 or week 48.

In patients with a f-PGA score of 2 or more at baseline, the proportion who achieved a f-PGA score of 0 or 1 at week 16 was also higher with guselkumab (39.1% and 52.0%) and adalimumab (50.9% and 59.7%) compared with placebo (15.9% and 14.6%) although the testing was not adjusted for multiplicity (Table 23). At week 24, the proportions were guselkumab (56.3% and 62.6%), adalimumab (62.4% and 66.9%), [redacted]. At

week 48 (VOYAGE 1 only), the proportions of patients achieving this outcome were [redacted], 74.7%, and 61,8%, respectively, and no statistical comparisons were made.

In patients with a baseline NAPSI score greater than 0, the mean per cent improvement from baseline at week 16 in NAPSI score was greater in patients who received guselkumab (34.37% and 39.61%) or adalimumab (37.95% and 46.92%) compared with placebo (–0.93% and 1.82%) in VOYAGE 1 and VOYAGE 2, respectively (Table 23). Statistical testing of the change in NAPSI score was not adjusted for multiplicity. The per cent improvement in NAPSI score progressively increased in all treatment groups at week 24 and week 48 (VOYAGE 1 only). No statistical comparisons were made at week 24 or week 48.

In patients with a hf-PGA score of 2 or more at baseline, the proportion of patients achieving a hf-PGA score of 0 (clear) or 1 (almost clear) at week 16 was greater in patients who received guselkumab (73.3% and 77.2%) or adalimumab (55.8% and 71.4%) compared with placebo (14.0% and 14.3%) in VOYAGE 1 and VOYAGE 2, respectively (Table 23). Statistical testing of this outcome was not adjusted for multiplicity. Similar to the other regional scores, the proportion of patients achieving a hf-PGA score of 0 or 1 progressively increased in all groups that reported this outcome at week 24 and week 48 (VOYAGE 1 only).

Table 11: Key Efficacy Outcomes

	VOYAGE 1			VOYAGE 2			NAVIGATE	
	PL N = 174	**GUSE N = 329**	**ADAL N = 334**	**PL N = 248**	**GUSE N = 496**	**ADAL N = 248**	**GUSE N = 135**	**USTE N = 133**
Health-Related Quality of Life Outcomes								
DLQI Change From Baseline to Week 16							**DLQI Change From Baseline to Week 28[i]**	
n	170	322	328	248	495	247	133	132
Mean (SD)	–0.6 (6.4)	–11.2 (7.2)	–9.3 (7.8)	–2.6 (6.9)	–11.3 (6.8)	–9.7 (6.8)	[redacted]	[redacted]
***P value* vs. PL[a]**	–	< 0.001	< 0.001	–	< 0.001	< 0.001	[redacted]	
SF-36 Change From Baseline to Week 16[l]								
n	NR	NR	NR	248	494	246	NR	NR
PCS Mean (SD)	NR	NR	NR	0.941 (6.605)	5.462 (7.800)	3.918 (6.555)	NR	NR
***P value*[a]**				–	[redacted]	[redacted]		
MCS Mean (SD)	NR	NR	NR	0.568 (8.761)	5.659 (9.509)	4.569 (9.356)	NR	NR
***P value*[a]**				–	[redacted]	[redacted]		
Efficacy End Points in VOYAGE 1 and VOYAGE 2 (IGA and PASI Response)								
Proportion of Pts Achieving an IGA Score[b] of 0 or 1 at Week 16								
n (%)	12 (6.9)	280 (85.1)	220 (65.9)	21 (8.5)	417 (84.1)	168 (67.7)	NR	NR
***P value* vs. PL[c]**	–	< 0.001	< 0.001	–	< 0.001	< 0.001		
Proportion of Pts Achieving PASI 90 at Week 16								
n (%)	5 (2.9)	241 (73.3)	166 (49.7)	6 (2.4)	347 (70.0)	116 (46.8)	NR	NR
***P value* vs. PL[c]**	–	< 0.001	< 0.001	–	< 0.001	< 0.001		
Noninferiority[d] and Superiority[e] Analyses of GUSE and ADAL at Week 16, n (%)								
IGA Score of 0 or 1								
n (%)	–	280 (85.1)	220 (65.9)	–	417 (84.1)	168 (67.7)	NR	NR
Diff. (95% CI)	–	19.3 (12.9; 25.7)		–	16.4 (10.0; 23.2)			

	VOYAGE 1			VOYAGE 2			NAVIGATE	
	PL N = 174	GUSE N = 329	ADAL N = 334	PL N = 248	GUSE N = 496	ADAL N = 248	GUSE N = 135	USTE N = 133
P value[e]		< 0.001			< 0.001			
PASI 90								
n (%)	–	241 (73.3)	166 (49.7)	–	347 (70.0)	116 (46.8)	NR	NR
Diff (95% CI) ***P value***[e]		24.1 (17.0; 31.0) < 0.001		–	23.3 (16.0; 30.4) < 0.001			
PASI 75								
n (%)	10 (5.7)	300 (91.2)	244 (73.1)	20 (8.1)	428 (86.3)	170 (68.5)	NR	NR
***P* value**[c]	–	< 0.001	< 0.001	–	< 0.001	< 0.001		
Diff. (95% CI) ***P* value**[e]	–	18.0 (12.4; 23.8) < 0.001		–	17.7 (11.4; 24.4) < 0.001			
PASI 100								
n (%)	1 (0.6)	123 (37.4)	57 (17.1)	2 (0.8)	169 (34.1)	51 (20.6)	NR	NR
***P* value**[c]	–	< 0.001	< 0.001	–	[redacted]	[redacted]		
Efficacy End Points in NAVIGATE (IGA and PASI Response)								
Number of Visits Where Pts Achieved IGA 0 or 1 and ≥ 2-Grade Improvement[f] From Week 28 to 40								
Mean (SD)	NR						1.5 (1.6)	0.7 (1.3)
***P* value**[g]	NR						< 0.001	
Proportion of Pts With IGA 0 or 1 and ≥ 2-Grade Improvement[f] at Week 28								
n (%)	NR						42 (31.1)	19 (14.3)
***P* value**[h]	NR						0.001	
No. of Visits Where Pts Achieved PASI 90 From Week 28-40								
Mean (SD)	NR						2.2 (1.7)	1.1 (1.5)
***P* value**[g]	NR						< 0.001	
Proportion of pts With PASI 90 at Week 28[i]								
n (%)	NR						65 (48.1)	30 (22.6)
***P* value**[h]	NR						< 0.001	

ADAL = adalimumab; CI = confidence interval; Diff. = difference; DLQI = Dermatology Life Quality Index; GUSE = guselkumab; IGA = Investigator Global Assessment; MCS = mental component summary; NR = not reported; PASI = Psoriasis Area and Severity Index; PCS = physical component summary; PL = placebo; SD = standard deviation; SF-36 = Medical Outcomes Study Short Form (36) Health Survey; USTE = ustekinumab.

[a] Based on an ANOVA model stratified by investigator site (pooled) and is the comparison vs. placebo.

[b] An IGA score of 0 = cleared and a score of 1 = minimal.

[c] Based on the CMH chi-square test stratified by investigator site (pooled) and is the comparison vs. placebo.

[d] Noninferiority and superiority of guselkumab in comparison with adalimumab was only investigated in VOYAGE 1. The designated noninferiority margin was 10% (i.e., if the lower bound of the 2-sided 95% CI was > 10% noninferiority was concluded).

[e] Based on 1-sided mental health Mantel-Haenszel (MH) Z test adjusted for investigator site (pooled).

[f] In the NAVIGATE trial, the primary end point was the number of visits at which patients achieved an IGA response of 0 or 1 and at least a 2-grade improvement (from week 16) from week 28 through week 40 among randomized patients with an inadequate response (IGA ≥ 2) to ustekinumab at week 16.

[g] Based on CMH row mean scores test stratified by baseline weight (≤ 100 kg; > 100 kg) and is the comparison between guselkumab vs. ustekinumab.

[h] Based on CMH chi-square test stratified by baseline weight (≤ 100 kg; > 100 kg).

[i] Outcomes that were not tested according to fixed-sequence statistical testing to adjust for multiplicity.

Source: Blauvelt et al. (2017);[7] VOYAGE 1 CSR;[8] Reich et al. (2017);[9] VOYAGE 2 CSR;[10] Langley et al. (2017);[11] NAVIGATE CSRs (40 weeks) and (60 weeks).[12,13]

Harms

Only those harms identified in the review protocol are reported below (see Protocol). See Tables 12 to 14 for detailed harms data.

Adverse Events

In VOYAGE 1, during week 0 to week 16 (induction or placebo-controlled period), AEs occurred in a similar proportion of patients in all treatment groups: guselkumab (51.7%), adalimumab (51.1%) and placebo (49.4%)
(Table 12). During weeks 0 to 48 (active-controlled period), the proportion of patients with AEs was also similar between guselkumab (73.9%) and adalimumab (74.5%). In patients who were initially randomized to placebo and switched to guselkumab after week 16, 64.8% experienced AEs. The most frequently reported AEs across all treatment periods were nasopharyngitis, upper respiratory infection (URTIs), and headache as per Table 12.

In VOYAGE 2, AEs occurred in similar proportions of patients between treatment arms in each treatment period (Table 13). From week 0 to week 16 (placebo-controlled period), 47.6% (guselkumab), 48.4% (adalimumab) and 44.8% (placebo) patients experienced AEs. From week 0 to week 28 (active-controlled period), AEs occurred in 58.3% of guselkumab-treated patients and 62.9% of adalimumab-treated patients. In patients switched from placebo to guselkumab, 33.5% of patients reported AEs from week 16 to 28. During the randomized maintenance versus withdrawal/re-treatment period (week 28 to week 40), 51.6% of patients in the guselkumab maintenance group and 44.5% of patients re-randomized to placebo withdrawal reported AEs. Similar to VOYAGE 1, the most frequently reported AEs were nasopharyngitis, headache, and URTIs.

In the NAVIGATE trial, from week 0 to week 16, 29.2% of patients in the open-label ustekinumab run-in period and 41.4% of patients in the open-label ustekinumab continuation period reported AEs (Table 14). From week 16 to week 60, 64.4% of patients randomized to guselkumab and 55.6% of patients randomized to ustekinumab experienced AEs. As with VOYAGE trials, the most frequently reported AEs were nasopharyngitis and URTIs.

Serious Adverse Events

SAEs occurred infrequently regardless of the treatment period and treatment group in all three included trials. Across the various treatment periods in VOYAGE 1, the proportion of patients with SAEs ranged from 2.4% to 4.9% with guselkumab, 1.8% to 4.5% with adalimumab, and 1.7% with placebo (week 0 to 16 only) (Table 12). In placebo-treated patients switched to guselkumab after week 16, SAEs were reported by 3.0% of patients. The most frequent SAEs occurring in more than two patients were renal disorders and injury/poisoning.

In VOYAGE 2, regardless of treatment periods, the frequency of SAEs ranged from 1.6% to 3.6% with guselkumab, 2.4% to 3.6% with adalimumab, and 1.2% with placebo (week 0 to 16 only) (Table 13). In placebo-treated patients switched to guselkumab after week 16, SAEs were reported in 1.7% of patients. During the randomized maintenance versus withdrawal/re-treatment period (week 28 to week 40), 1.0% of patients in the guselkumab maintenance group and 1.6% of patients in the withdrawal group reported SAEs. The most frequent SAEs occurring in more than two patients were cardiac disorders, infections, and injury/poisoning.

In the NAVIGATE trial, SAEs were infrequent during the open-label ustekinumab periods (1.3% and 3.4%) (Table 14). From week 16 to week 60, the frequency of SAEs was 6.7% in patients randomized to guselkumab, and 4.5% in patients randomized to continued ustekinumab. No particular SAE occurred in more than two patients.

Withdrawal Due to Adverse Events

In all three included trials, withdrawal due to adverse events (WDAEs) were very infrequent and did not exceed 3.0% in any treatment group with the exception of patients treated with adalimumab during the active-controlled period (week 0 to week 48) of VOYAGE 1. In this treatment group, WDAEs occurred in 3.6% of patients, primarily due to skin and subcutaneous tissue disorders (Table 12).

Mortality

There were no deaths reported in VOYAGE 2 (Table 13). In VOYAGE 1, one death occurred in a patient treated with the two initial doses of adalimumab (i.e., 80 mg at week 0 and 40 mg at week 1) due to a staphylococcal pneumonia following a prolonged hospitalization for ischemic hepatitis (Table 12). In the NAVIGATE trial, two deaths were reported (Table 14). One death was reported in the open-label ustekinumab continuation period and one death in a patient treated with guselkumab during the randomized treatment period. The deaths were due to pancreatic carcinoma and squamous cell carcinoma, respectively.

Notable Harms

Notable harms identified in the protocol for this review included infections, injection-site reactions, serious hypersensitivity reactions, major cardiovascular events, and malignancy. As detailed in Tables 12 to 14, the frequency of these notable harms was low across all three trials, generally occurring in less than 1% of patients. The only exception to this was injection-site reactions in the VOYAGE 1 and VOYAGE 2 trials, where the proportion of patients with injection-site reactions was 2.4% and 2.6% in guselkumab-treated patients and 7.5% and 6.9% in adalimumab-treated patients during week 0 to week 16, respectively.

Table 12: Harms: VOYAGE 1 Trial

	Week 0 to 16			Week 0 to 48		Week 16 to 48
	Placebo-controlled period			Active-comparator controlled period		Placebo → Guselkumab
	Placebo	Guselkumab	Adalimumab	Guselkumab	Adalimumab	
n	174	329	333	329	333	165
Duration of Follow-Up						
Mean, wks	15.88	16.27	16.14	46.47	45.56	31.88
Mortality	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)[a]	0 (0)
SAEs, n (%)	3 (1.7)	8 (2.4)	6 (1.8)	16 (4.9)	15 (4.5)	5 (3.0)
Most Frequently Reported SAEs, n (%)						
Cardiac disorders **Infections** **Injury, poisoning** **Hepatobiliary** **GI disorders** **Renal disorders**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs, n (%)	86 (49.4)	170 (51.7)	170 (51.1)	243 (73.9)	248 (74.5)	107 (64.8)
Most Frequently Reported AEs, n (%)						
Nasopharyngitis	17 (9.8)	30 (9.1)	35 (10.5)	83 (25.2)	74 (22.2)	34 (20.6)
URTI	9 (5.2)	25 (7.6)	16 (4.8)	47 (14.3)	42 (12.6)	17 (10.3)
Injection-site erythema	1 (0.6)	6 (1.8)	15 (4.5)	8 (2.4)	22 (6.6)	3 (1.8)
Headache	7 (4.0)	12 (3.6)	13 (3.9)	18 (5.5)	25 (7.5)	1 (0.6)
Arthralgia	3 (1.7)	11 (3.3)	9 (2.7)	18 (5.5)	16 (4.8)	2 (1.2)
Pruritus	10 (5.7)	5 (1.5)	7 (2.1)	8 (2.4)	12 (3.6)	0 (0)
Back pain	2 (1.1)	6 (1.8)	4 (1.2)	12 (3.6)	17 (5.1)	1 (0.6)
WDAEs, n (%)	2 (1.1)	4 (1.2)	3 (0.9)	9 (2.7)	12 (3.6)	1 (0.6)
Most Frequently Reported WDAEs, n (%)						
Skin and SC tissue disorders **General and admin site disorders** **Neoplasms** **Nervous system disorders**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Notable Harms, n (%)						
Serious infections	0 (0)	0 (0)	2 (0.6)	2 (0.6)	3 (0.9)	1 (0.6)
Injection-site reactions[b]	NR	8 (2.4)	25 (7.5)	2.2%[c]	9.0%[c]	NR
Serious hypersensitivity reactions[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MACE	0 (0)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0 (0)

	Week 0 to 16			Week 0 to 48		Week 16 to 48
	Placebo-controlled period			Active-comparator controlled period		Placebo → Guselkumab
	Placebo	Guselkumab	Adalimumab	Guselkumab	Adalimumab	
NMSC	0 (0)	1 (0.3)	0 (0)	2 (0.6)	1 (0.3)	0 (0)
Malignancies	0 (0)	0 (0)	0 (0)	2 (0.6)	0 (0)	0 (0)

AE = adverse event; GI = gastrointestinal; MACE = major adverse cardiovascular event; NMSC = non-melanoma skin cancer; NR = not reported; PL = placebo; SAE = serious adverse event; SC = subcutaneous; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event; wks = weeks.

[a] One death occurred due to staphylococcal pneumonia following a prolonged hospitalization that was initially due to ischemic hepatitis. The patient received 2 doses of adalimumab (80 mg at week 0 and 40 mg at week 1).

[b] Injection-site reactions were not reported for the individual study periods included in the table. Rather, the proportion of patients with injection-site reactions was reported through week 48 as follows: guselkumab placebo injections (n = 8 [1.0%]), guselkumab injections (n = 11 [2.2%]), adalimumab placebo injections (n = 20 [4.0%]), and adalimumab injections (n = 30 [9.0%]).

[c] Values were not reported in in the clinical study report. Percentages were provided by the manufacturer following review of a draft report.

[d] [redacted]

Source: Blauvelt et al. (2017);[7]; VOYAGE 1 CSR.[8]

Table 13: Harms – VOYAGE 2 Trial

	Week 0 to 16			Week 0 to 28		Week 16 to 28	Week 28 to 48	
	Placebo-controlled period			Active-comparator controlled period		Placebo → GUSE	Randomized withdrawal and re-treatment period	
	PL	GUSE	ADAL	GUSE	ADAL		Maintenance	Withdrawal
n	248	494	248	494	248	233	192	182
Duration of Follow-Up								
Mean, wks	15.89	16.14	16.07	27.70	27.45	11.95	20.20	20.0
Mortality	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAEs, n (%)	3 (1.2)	8 (1.6)	6 (2.4)	18 (3.6)	9 (3.6)	4 (1.7)	2 (1.0)	3 (1.6)
Most Frequently Reported SAEs, n (%)								
Cardiac disorders **GI disorders** **Infections** **Injury, poisoning** **Musculoskeletal**	[redacted]							
AEs, n (%)	111 (44.8)	235 (47.6)	120 (48.4)	288 (58.3)	156 (62.9)	78 (33.5)	99 (51.6)	81 (44.5)
Most Frequently Reported AEs, n (%)								
Nasopharyngitis **Headache** **URTI**	16 (6.5) 7 (2.8) 10 (4.0)	35 (7.1) 25 (5.1) 16 (3.2)	20 (8.1) 5 (2.0) 4 (1.6)	51 (10.3) 29 (5.9) 25 (5.1)	34 (13.7) 9 (3.6) 10 (4.0)	12 (5.2) 5 (2.1) 5 (2.1)	22 (11.5) 3 (1.6) 9 (4.7)	23 (12.6) 2 (1.1) 10 (5.5)
WDAEs, n (%)	2 (0.8)	7 (1.4)	4 (1.6)	11 (2.2)	6 (2.4)	1 (0.4)	0 (0)	0 (0)
Most Frequently Reported WDAE, n (%)								
Infections **Neoplasms**	[redacted]							
Notable Harms, n (%)								
Serious infections	1 (0.4)	1 (0.2)	2 (0.8)	3 (0.6)	3 (1.2)	1 (0.4)	1 (0.5)	0 (0)

	Week 0 to 16			Week 0 to 28		Week 16 to 28	Week 28 to 48	
	Placebo-controlled period			Active-comparator controlled period		Placebo → GUSE	Randomized withdrawal and re-treatment period	
	PL	GUSE	ADAL	GUSE	ADAL		Maintenance	Withdrawal
Injection-site reactions[a]	NR	13 (2.6)	17 (6.9)	NR	NR	NR	NR	NR
Serious hypersensitivity reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MACE	0 (0)	0 (0)	1 (0.4)	1 (0.2)	1 (0.4)	0 (0)	0 (0)	0 (0)
NMSC	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)	1 (0.4)	0 (0)	0 (0)
Malignancies	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)

ADAL = adalimumab; AE = adverse event; GI = gastrointestinal; GUSE = guselkumab; MACE = major adverse cardiovascular event; NMSC = non-melanoma skin cancer; NR = not reported; PL = placebo; SAE = serious adverse event; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event; wks = weeks.
[a] Injection-site reactions were not reported for the individual study periods included in the table. Rather, the proportion of patients with injection-site reactions was reported through week 48 as follows: guselkumab placebo injections (n = 9 [0.9%]), guselkumab injections (n = 25 [2.9%]), adalimumab placebo injections (n = 28 [3.8%]), and adalimumab injections (n = 21 [8.5%]).
Source: Reich et al. (2017);[9] VOYAGE 2 CSR.[10]

Table 14: Harms – NAVIGATE Trial

	Weeks 0 to 16		Weeks 16 to 60	
	Non-Randomized Patients		Randomized patients	
	OL Ustekinumab Run-In	OL Ustekinumab Continuation	Guselkumab	Ustekinumab
n	871	585	135	133
Mortality, n (%)	0 (0)	1 (< 1)	1 (< 1)	0 (0)
SAEs, n (%)	11 (1.3)	20 (3.4)	9 (6.7)	6 (4.5)
Most Frequently Reported SAEs, n (%)				
Cardiac disorders **Neoplasms** **Pregnancy and related conditions** **Metabolism disorders**	[redacted]	[redacted]	[redacted]	[redacted]
AEs, n (%)	254 (29.2)	242 (41.4)	87 (64.4)	74 (55.6)
Most Frequently Reported AEs, n (%)				
Nasopharyngitis **URTI**	47 (5.4) 33 (3.8)	33 (5.6) 27 (4.6)	23 (17.0) 15 (11.1)	23 (17.3) 11 (8.3)
WDAEs, n (%)	2 (0.2)	7 (1.2)	3 (2.2)	2 (1.5)
Most Frequently Reported WDAEs, n (%)[a]				
Notable Harms, n (%)				
Serious infections	2 (0.2)	5 (0.9)	1 (0.7)	0 (0)
Injection-site reactions	NR	NR	6 (4.4)	0 (0)
Serious hypersensitivity reactions	0 (0)	0 (0)	0 (0)	0 (0)
MACE	0 (0)	1 (0.2)	2 (1.5)	1 (0.8)
NMSC	2 (0.2)	2 (0.1)	0 (0)	0 (0)
Malignancies	2 (0.2)	4 (0.7)	2 (1.5)	0 (0)

AE = adverse event; MACE = major adverse cardiovascular event; NMSC = non-melanoma skin cancer; NR = not reported; OL = open-label; SAE = serious adverse event; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event; wks = weeks.
[a] All WDAEs were due to singular events and did not occur in greater than n = 1 patient each.
Source: Langley et al. (2017);[11] NAVIGATE CSRs (40 weeks) and (60 weeks).[12,13]

Discussion

Summary of Available Evidence

Three manufacturer-sponsored, published, phase III, double-blind RCTs were included in the systematic review: VOYAGE 1 (N = 837)[7,8], VOYAGE 2 (N = 992)[9,10], and NAVIGATE (N = 268 randomized patients).[11-13] Both VOYAGE 1 and VOYAGE 2 were multi-centre, placebo and active (adalimumab) controlled, parallel-group trials with randomization stratified by investigational site. The first 24 weeks of treatment were identical in the two VOYAGE trials, following which in VOYAGE 2, a randomized guselkumab maintenance or withdrawal/re-treatment period was undertaken after week 28. In contrast, in VOYAGE 1, treatment with guselkumab or adalimumab continued for 48 weeks. Both VOYAGE 1 and VOYAGE 2 evaluated the superiority of guselkumab to placebo as a primary outcome and the noninferiority and superiority of guselkumab to adalimumab as a secondary outcome. The NAVIGATE trial included an enrichment design which comprised an open-label ustekinumab run-in, following which patients with inadequate response to ustekinumab were randomized to either guselkumab or continued ustekinumab. Although this study design may prove useful for informing clinical practice with regard to successive therapy in patients with inadequate response to ustekinumab, it should not be considered to be a head-to-head comparator trial, but more appropriately as a switch study. The switching of ustekinumab nonresponders to guselkumab compared with the continued treatment of ustekinumab nonresponders with a drug that they have previously not responded to, potentially biases results toward the group of nonresponders who were switched to another active treatment (guselkumab). No trials were identified in which guselkumab was directly compared with another IL inhibitor (e.g., ustekinumab, secukinumab, ixekizumab) although the manufacturer did supply an IDC of guselkumab with currently available biologics to address this gap that is reviewed and critically appraised in Appendix 7.

All three trials enrolled patients with moderate-to-severe plaque psoriasis, defined as a confirmed diagnosis of chronic plaque psoriasis for at least six months, IGA score greater than and equal to 3, a PASI score greater than and equal to 12, and BSA involvement of 10% or more and who were candidates for phototherapy or systemic therapy. The mean duration of psoriasis in enrolled patients was between 15 years to 18 years and 15% to 20% of patients also had a diagnosis of psoriatic arthritis. Almost all patients had used prior topical therapy, the majority had used conventional systemic therapy (52% to 66%) and approximately half of the patients had prior phototherapy. Biologics had previously been used by 19 to 23% of patients across the trials. According to the clinical expert consulted on this review, the baseline characteristics were consistent with Canadian patients with moderate-to-severe plaque psoriasis. The VOYAGE trials had co-primary end points that were based on the proportion of patients who achieved an IGA score of 0 or 1 and a PASI 90 response at week 16. The primary end point in the NAVIGATE trial was the number of visits in which patients achieved an IGA score of 0 or 1 and greater than and equal to 2-grade improvement (from week 16) during week 28 to 40. All three trials included various secondary end points that were primarily based on IGA and PASI 90 responses. Major secondary end points were tested according to a pre-specified statistical gatekeeping procedure to control for multiplicity; however, testing of other secondary end points was not. Health-related quality of life was evaluated in all three trials using the DLQI and the SF-36 in VOYAGE 2 only. In VOYAGE 1 and VOYAGE 2 patients randomized to guselkumab received 100 mg at week 0, week 4, and every eight weeks thereafter and patients randomized to adalimumab received 80 mg at week 0, then 40 mg at week 1 and every two

weeks thereafter, in keeping with the Health Canada-approved dosing regimen.[18] In NAVIGATE, patients received open-label ustekinumab (i.e., ≤ 100 kg: 45 mg and > 100 kg: 90 kg) at weeks 0 and 4 and if randomized to continued ustekinumab received a dose at week 16 and every 12 weeks thereafter.

The design and methodology of the VOYAGE 1 and VOYAGE 2 trials are associated with various limitations, as described previously. In consideration of this, the most robust results from these two trials are likely limited to the first 16-week placebo-controlled induction period which comprised the primary efficacy analyses in both trials. The NAVIGATE trial was also associated with various limitations, especially due to the selection population of patients with inadequate response to ustekinumab for the randomized period of the trial and comparison of patients switched to guselkumab with nonresponder patients who continued to receive ustekinumab. Key limitations are the head-to-head comparison of guselkumab with only one active comparator (adalimumab), the size and short duration of the trials which precludes assessment of longer-term efficacy and safety including rare or latent AEs, the differential withdrawal rates between adalimumab and guselkumab treatment groups, and the re-randomization of PASI 90 responders in VOYAGE 2 to maintenance or withdrawal/re-treatment, which may have compromised the initial randomization.

Interpretation of Results

Efficacy

A key efficacy outcome identified in the review protocol for the systematic review, that was also identified as being important to patients based on the patient input received, was HRQL measured by a validated instrument. In all three included trials, HRQL was measured using the disease-specific DLQI instrument, which evaluates various aspects of a patient's daily life that may be affected by psoriasis symptoms, including scales and flaking, itching, joint pain and self-esteem, as detailed in Appendix 5. The comparison of change in DLQI score from baseline to week 16 between guselkumab and placebo was a secondary end point in the VOYAGE 1 and VOYAGE 2 trials and was included in the fixed-sequence statistical testing procedure to control for multiplicity. In both trials, there was a statistically significant greater reduction in the DLQI score from baseline with guselkumab when compared with placebo at week 16. The magnitude of the reduction exceeded the MCID which is generally considered to range from 2.2 to 6.9, as detailed in Appendix 7. The reduction in DLQI score from baseline with adalimumab was also greater than placebo; however, the testing of this outcome was not included in the fixed-sequence testing so was not adjusted for multiplicity. The change from baseline in DLQI score at different time periods, the proportion of patients with DLQI score of 0 or 1 (indicating no effect on a patients' quality of life), and the proportion of patients with a DLQI score of five or more all favoured guselkumab over placebo; however, these comparisons were not tested in the fixed-sequence testing and therefore not adjusted for multiplicity. In the NAVIGATE trial, the change in DLQI score from baseline to week 28 was reported for both guselkumab and ustekinumab, but was not compared statistically between the treatments.

The SF-36 generic quality of life instrument was only measured in VOYAGE 2. Although the change from baseline to week 16 in the PCS and MCS scores of the SF-36 were reported as statistically significantly higher with both guselkumab and adalimumab compared with placebo, the SF-36 instrument was not included in the fixed-sequence statistical testing and adjusted for multiplicity. Additional analyses included the change from baseline to week 24 in SF-36 scores and proportion of patients with an improvement of five or more (thus

exceeding the MCID) from baseline at week 16. The results also favoured guselkumab over placebo; however, the analyses were not adjusted for multiplicity.

The second key efficacy outcome for the systematic review was PASI response and the achievement of a PASI 90 response comprised a co-primary end point in the VOYAGE trials and different variants of PASI response were included as secondary outcomes in all three trials. Across both trials, guselkumab was associated with statistically significant attainment of PASI 90 response compared with placebo at week 16. In the VOYAGE trials, since statistical significance of the co-primary end points was demonstrated, statistical testing of secondary end points which included comparisons between guselkumab and adalimumab could be conducted according to the pre-specified fixed-sequence statistical testing. Of these, perhaps the most important was the testing of the noninferiority of guselkumab with adalimumab based on both PASI 90 and PASI 75 responses. The pre-specified noninferiority margin was –10% (i.e., if the lower bound of the 95% CI for the difference between treatments was greater than or equal to –10%) for guselkumab minus adalimumab, then noninferiority was concluded. For both PASI 90 and PASI 75, guselkumab was shown to be noninferior, and subsequently, superior to adalimumab at week 16.

In the VOYAGE 2 trial, the time to loss of PASI 90 response from week 28 to week 40 was assessed between the continued guselkumab (maintenance) group and the placebo (withdrawal/re-treatment) group in patients who were PASI 90 responders at week 28 and who were re-randomized to these two groups. This analysis was included in the fixed-sequence statistical testing to control for multiplicity. PASI 90 responses appeared to be maintained for a longer duration of time in patients who received continued guselkumab (maintenance group) when compared with those re-randomized to placebo (withdrawal/re-treatment group). The median time to loss of PASI 90 response in the withdrawal/re-treatment group was 15.2 months. In VOYAGE 2, loss of response was only followed based on PASI 90; however, if a lower threshold of response (e.g., PASI 75) was used, more patients would have been considered as responders and re-randomized in the trial and potentially the median time to loss of PASI 75 response could have been longer.[28] According to the clinical expert, a PASI 75 response is considered to be a good response in clinical practice. Nonetheless, given the uncertainty regarding the strength of randomization due to the diminished samples sizes following re-randomization, these results warrant further exploration and confirmation in a controlled clinical trial.

A key limitation of the included trials is that guselkumab was only compared with one active comparator (adalimumab) in a direct head-to-head manner in the VOYAGE trials. Ideally, guselkumab should have been compared with an IL-17 inhibitor (e.g., secukinumab or ixekizumab) as these agents have the highest short-term efficacy for psoriasis of the approved therapies so far, and it is important to understand how guselkumab compares to these agents.[28] To address this gap, the manufacturer conducted an IDC that has been reviewed and critically appraised in Appendix 7. In order to inform this evidence gap, the CDR review team also conducted a literature search for additional IDCs; however, none were identified in the literature. [redacted]

[redacted]

The other co-primary end point in VOYAGE 1 and VOYAGE 2 was the proportion of patients achieving an IGA score of 0 or 1 (cleared or minimal) at week 16. Guselkumab was also shown to be statistically superior to placebo for this outcome and the statistical gatekeeping approach included the comparison of guselkumab and adalimumab on this and other IGA outcomes (e.g., proportion of patients with IGA score of 0 or IGA score of 0 or 1 at other time points). For all the preceding outcomes, guselkumab was shown to be statistically significantly superior to adalimumab. The fixed-sequence testing also permitted the noninferiority and superiority testing of guselkumab and adalimumab on the proportion of patients with IGA score of 0 or 1 at week 16. Based on the same noninferiority margin of –10% used for the PASI 90 and PASI 75 responses, guselkumab was shown to be noninferior to adalimumab and statistically superior to adalimumab in both VOYAGE trials. In the NAVIGATE trial, the primary end point was the number of visits where patients achieved an IGA score of 0 or 1 and at least a 2-grade improvement (from week 16) during week 28 through week 40 in randomized patients with an inadequate response (IGA score of 2 or more) to ustekinumab. Guselkumab was shown to be superior to ustekinumab for this outcome based on statistically significantly more visits during which patients treated with guselkumab achieved this outcome. The clinical expert consulted on this review agreed that the attainment of an IGA score of 0 or 1 should be considered to be a clinically meaningful improvement from baseline (i.e., as an inclusion criterion in the trials was that at study entry patients were to have an IGA score ≥ 3).

In VOYAGE 1 and VOYAGE 2, pre-specified subgroup analyses were conducted on the individual components of the co-primary end points, including examination of the subpopulations of interest identified in the review protocol (i.e., baseline PASI response, prior biologic use, and body weight). In general, the results for the proportion of patients achieving a PASI 90 response or IGA score of 0 or 1 in the subpopulations were consistent with the results of the primary analyses, as the 95% CI for the difference between subgroups excluded 0, indicating that a greater proportion of patients treated with guselkumab achieved the co-primary outcomes compared with placebo. The only inconsistencies observed were in smaller subgroups of prior biologic use (e.g., prior use of anti-TNF agents or IL-12/23 inhibitors); however, due to the small sample sizes of these subgroups and imprecise CIs, caution should be exercised in any interpretation of the results. A pooled analysis of the VOYAGE 1 and VOYAGE 2 trials in which the efficacy of guselkumab in patient subgroups measured by the achievement of IGA scores of 0 or 1 or IGA scores of 0 across subgroups defined by demographics, baseline disease characteristics, and previous psoriasis treatment, found a high degree of consistency in the comparison of guselkumab with placebo at week 16 and adalimumab at week 24 across the subgroups.[14] [redacted].

Regional psoriasis end points (i.e., ss-IGA, f-PGA, NAPSI, and hf-PGA scores) were only included in VOYAGE 1 and VOYAGE 2, and of these, only the ss-IGA score was included in the fixed testing sequence that controlled for multiplicity. Overall, the results of the regional psoriasis end points corroborated those of the overall disease and primary end points of the VOYAGE trials. The proportion of patients with a ss-IGA score of 0 (absence of disease) or 1 (very mild disease) was statistically significantly higher with guselkumab compared with

placebo in both trials. No statistical comparisons were made between guselkumab and adalimumab. The results of the additional regional psoriasis outcomes favoured guselkumab over placebo; however, these comparisons were all made without adjustment for multiplicity.

Overall, the efficacy of guselkumab in patients with moderate-to-severe plaque psoriasis is supported by the results demonstrated in the VOYAGE trials. This appears to be reiterated by the conclusions of the US FDA review of guselkumab, in which the FDA reviewer stated that there were no major statistical issues affecting the overall (efficacy) conclusions, the treatment effects were large and consistent across trials and end points, the amount of missing data were relatively small, and there were no substantial differences in efficacy among subgroups.[17] The clinical expert consulted on this review also reiterated the efficacy of guselkumab in describing its potential place in therapy.

Harms

In general guselkumab appeared to be well tolerated based on the harms data reported in the three included trials, although the size and duration of the trials were likely insufficient to identify rare or latent AEs. In the VOYAGE trials, AEs occurred in similar proportions of patients in all treatment groups (including placebo). The most frequently reported AEs across all trials and treatment periods with guselkumab were nasopharyngitis, URTIs, and headache. In the NAVIGATE trial, a higher proportion of patients treated with guselkumab as compared with ustekinumab experienced AEs; however, it is difficult to make comparisons because patients in the randomized ustekinumab arm had been receiving the drug from week 0 to 16 in addition to week 16 to 60 which allowed for more time for resolution of AEs, whereas patients in the guselkumab arm initiated guselkumab at week 16. Serious adverse events and similarly, WDAEs occurred infrequently in all the three trials regardless of the treatment period or treatment group. Treatment with guselkumab does not appear to be associated with increased mortality as there were only three deaths reported across the three included trials (i.e., one death in VOYAGE 1 and two deaths in NAVIGATE) with no deaths reported in VOYAGE 2. Notable harms identified in the review protocol were infections, injection-site reactions, serious hypersensitivity reactions, major cardiovascular events, and malignancy. The frequency of the notable harms was low across all three trials, generally occurring in <1% of patients. The only exception to this was injection-site reactions in the VOYAGE 1 and VOYAGE 2 trials where the proportions of patients with injection-site reactions was more than double in adalimumab-treated patients (7.5% and 6.9%) compared with guselkumab-treated patients (2.4% and 2.6%), which may be attributed to the higher frequency of injections with adalimumab, as necessitated by the dosing recommendations.

[redacted]

Potential Place in Therapy[2]

Biologic agents currently available for the treatment of plaque psoriasis in Canada have, over the past eleven years since the first agent was approved, significantly improved treatment outcomes for patients with moderate and severe disease (e.g., patients achieve and maintain a 75% or greater improvement in PASI score). Prior to approval of these agents, the outlook was poor for patients who failed to respond to, or were intolerant of, the older systemic agents including methotrexate, acitretin, and cyclosporine.

The clinical expert involved in the review noted that all currently available agents (TNF-alpha inhibitors, IL-12/23 inhibitor [ustekinumab], and the IL-17A inhibitors) for the treatment of moderate-to-severe plaque psoriasis have specific drawbacks that limit their use in some patient populations. Examples include relatively low efficacy with etanercept, need for intravenous administration with infliximab and its biosimilar, limited efficacy in psoriatic arthritis with ustekinumab and the possibility of exacerbating inflammatory bowel disease with secukinumab. As well, with currently available agents, efficacy may drop off over time in some patients, requiring dosage intensification and ultimately a switch to another biologic agent. Guselkumab is the first member in a new class of biologic agents for plaque psoriasis – the IL-23 inhibitors. The clinical trial data for guselkumab indicates a rapid onset of action and high efficacy. There are also some data to suggest that guselkumab may be effective in patients who have achieved a suboptimal response to adalimumab and ustekinumab. Therefore, guselkumab expands the available treatment options for disease control in plaque psoriasis with a highly efficacious drug option. However, there are no other unique features that clearly differentiate guselkumab from other biologics.

When first introduced in Canada, guselkumab will likely be used principally in patients who have failed to respond to, have become intolerant to, or have experienced side effects from one or more previous biologic agents. Over time, if data indicate long-term safety, persistence of efficacy, and utility in treating psoriatic arthritis, guselkumab may become a first-line biologic agent.

Other Considerations

The manufacturer of guselkumab also manufactures ustekinumab. Ustekinumab's patent in Canada expires in August, 2021(Canadian Intellectual Property Office).[29]

Conclusions

The results from two double-blind RCTs (VOYAGE 1 and VOYAGE 2) support that treatment with guselkumab is associated with clinically and statistically significant improvements in HRQL as measured by the DLQI. The results from the VOYAGE trials also support that guselkumab is superior to placebo during induction based on attainment of an IGA score of 0 or 1 (cleared or minimal disease) or PASI 90 response at week 16. In addition, guselkumab was demonstrated to be noninferior to, and subsequently superior to, adalimumab at week 16, based on the same outcomes as well as PASI 75 response. In a third double-blind RCT (NAVIGATE), patients with an inadequate response to ustekinumab were randomized to either guselkumab or continued ustekinumab. Patients switched to guselkumab had a statistically significantly higher number of visits in which they achieved an

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

IGA score of 0 or 1 and at least a 2-grade improvement, compared with patients who continued ustekinumab; however, interpretation of the results is compromised by the many identified limitations of the trial. In general, the efficacy results with guselkumab were consistent and of similar magnitude across all trials. Guselkumab also appeared to be well tolerated, although the size and duration of the trials were likely insufficient to detect rare or latent AEs. Similar proportions of patients experienced AEs regardless of treatment arm or period and the frequency of SAEs and WDAEs was low. The frequency of notable harms (i.e., infections, injection-site reactions, serious hypersensitivity reactions, major cardiovascular events, and malignancy) was also low in all three trials. [redacted]

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Groups Supplying Input

Two separate patient group submissions were provided regarding this submission.

The Canadian Skin Patient Alliance (CSPA), working with the Canadian Association of Psoriasis Patients (CAPP) as well as the Canadian Psoriasis Network (CPN), submitted input for this review. The CSPA is a non-profit organization serving patients with dermatological conditions, and focuses on advocacy, education, and support for more than 20 allied or affiliated disease-specific organizations. CAPP and the CPN are national, not-for-profit organizations advocating and providing information for patients with psoriasis. In the past two years, the CSPA has received funding from AbbVie Canada, Celgene, Janssen Canada, LEO Pharma, Novartis, Pfizer Canada, and Valeant Canada. In the past two years, CAPP has received funding from AbbVie Canada, Celgene, Eli Lilly, Janssen Canada, and Novartis. In the past two years, CPN has received funding from Amgen, AbbVie Canada, Celgene, Eli Lilly, Janssen Canada, LEO Pharma, Novartis, and Pfizer Canada.

Arthritis Consumer Experts (ACE) is a national organization that aims to provide science-based information, education, and support to all persons suffering from, caring for, or treating patients with arthritis. Over the past 12 months, ACE have received grants-in-aid or research funding from: Amgen Canada, Arthritis Research Canada, AstraZeneca Canada, Canadian Biosimilars Forum, Canadian Institutes of Health Research, Celgene, Eli Lily Canada, Hoffman-La Roche Canada Ltd., Merck Canada, Novartis, Pfizer Canada, Sandoz Canada, Sanofi Canada, St. Paul's Hospital (Vancouver), UCB Canada, and the University of British Columbia. ACE also receives unsolicited donations from its community members (people with arthritis) across Canada.

No conflicts of interest were declared by any of the groups regarding this submission.

2. Condition-Related Information

Information for this submission was obtained using a survey (hosted on Survey Monkey) developed by all three patient groups (CSPA, CAPP, CPN) that was live from June 15 to September 15, 2017. The survey was distributed using various platforms including social media, two different newsletters, and personal contacts. Of 43 respondents, information was used from 34 respondents, of which four were involved in guselkumab clinical trials. ACE obtained their information by a call for input on August 11, 2017, and through one-to-one interactions with patients, caregivers, and health care providers from 2014 to 2017.

Patients with psoriasis experience scales and plaques that can occur anywhere on their bodies. The most significant physical symptoms of psoriasis that patients report include scales, flaking, itching, skin cracking and bleeding, pain, and joint pain. Psoriasis psychologically affects patients, with most experiencing embarrassment, shame, self-confidence issues, anxiety, and depression. Due to the lesions, many patients tend to isolate themselves from social interaction or refrain from participating in different activities such as dancing, swimming, and sports that would expose the affected parts on the skin. Most patients try to hide their lesions, with some wearing particular clothing (e.g., pants rather than skirts, no bathing suits) or wearing their hair in a certain manner for coverage. Sleep can be negatively affected, both due to the physical symptoms and psychological symptoms.

Other related conditions that patients feel are related to their psoriasis include psoriatic arthritis, diabetes, weight gain, and heart disease.

Since lesions often affect the scalp and other more prominent or intimate areas on the body, patients experience isolation and intimacy issues due to the embarrassment of the unsightly lesions. This was evident in the statement of one patient, *"My confidence to be intimate with my wife of 22 years went downhill. Even though she was/is very supporting and understanding, I just could not get over the way this awful condition made my skin look."* The joint pain, lesion pain, and pain from itching lesions can also limit activities such as employment, socialization, and sports. Patients have stated that employment has terminated due to the unsightliness of the lesions. This was evident by one patient stating, *"One day at work I heard a little kid say what's wrong with her hands Daddy? The father said I don't know, let's get away from her. The next day I was let go under the probationary period condition of hire, where they do not have to give a reason for cancelling the job offer. It was a retail supervisory position and they wouldn't take the risk of losing business because you can't hide your hands, no matter what business you're in."* There is also the concern that a number of patients will go on to develop psoriatic arthritis, as this occurs in approximately 30% of patients with psoriasis. The fear can be at the forefront of the patient's mind.

Caregivers of patients with psoriasis often experience increases in the amount of care and household cleaning such as vacuuming, bedding changes, and laundry, along with helping patients who are in pain with simple household chores. In addition, some patients require help to apply creams, go to phototherapy appointments, or travel to infusion clinics (i.e., should the patient be on infusion biologics). Caregivers often find themselves negatively affected psychologically and dysfunctional as the whole family tends to absorb the shame, depression, and isolation associated with the disease. Caregivers' schedules are affected. As one patient stated, *"It was very emotional for my wife to see me go through this. The social aspect of our lives was gone. Unable to go on a vacation or having friends over has pushed my wife into a depression state."*

3. Current Therapy-Related Information

Most respondents to the survey had used topical treatments, with only a small number having used cyclosporine, Humira, Remicade, or Enbrel (with methotrexate). Major issues with treatments include the long wait times associated with seeing a dermatologist, costs of treatments, and barriers to accessing specific treatments.

Respondents made note of the frustration associated with the use of topical treatments due to the lack of efficacy and adverse effects. Many patients ceased using their topical treatments due to ineffectiveness. Some fear was associated with the use of some of the systemic treatments, as patients were concerned with the effects on their immune system. Another patient was worried about the possibility of fighting off cancer, should they acquire cancer from their Humira treatment. In addition, methotrexate was observed to cause GI upset and mucous membrane irritation on occasion.

4. Expectations About the Drug Being Reviewed

Patients with psoriasis would welcome any treatment allowing them to live a normal life with fewer adverse events. Patient expectations are: to halt worrying about the unsightly plaques and scales which would allow them the freedom to go out without being judged, not having their life interrupted by frequent visits for phototherapy, or travelling long distances, or the time required to access infusion clinics. Most patients with psoriasis hope that the next available treatment will provide 100% effectiveness and eliminate all of their symptoms. Patients believe that it is better to have more options and that having more options could mean better access to medication.

For those patients with guselkumab experience (n = 4), it appeared that most found it beneficial with regard to its effectiveness and in treatment adherence. One patient stated, "*I had to put sticky cream and ointment on 85% of my body twice a day for the past six years or so which didn't help much compared to taking one self-injected dose once per month with tremendous positive results.*" No patients provided any comments regarding side effects.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE Epub ahead of print, In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 20, 2017
Alerts:	Bi-weekly search updates until January 17, 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
ppez	Ovid database code; E-pub ahead of print, MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(1350289-85-8 or 089658A12D).rn,nm.
2	(guselkumab* or tremfya* or CNTO 1959 or CNTO1959).ti,ab,kf,ot,hw,rn,nm.
3	or/1-2
4	3 use ppez
5	*guselkumab/
6	(guselkumab* or tremfya* or CNTO 1959 or CNTO1959).ti,ab,kw.
7	or/5-6
8	7 use oemezd
9	8 not conference abstract.pt.
10	4 or 9
11	remove duplicates from 10

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	September 2017
Keywords:	Tremfya (guselkumab), plaque psoriasis
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials
- Databases (free)
- Internet Search.

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
Gordon et al. 2017[30]	Inappropriate intervention and study type (phase II)
Sofen et al. 2014[21]	Inappropriate intervention
Zhuang et al. 2016[31]	Inappropriate intervention and study type (phase I)

Appendix 4: Detailed Outcome Data

Table 15: VOYAGE 1 and VOYAGE 2 – IGA Responses at Weeks 24 and 48

	VOYAGE 1		VOYAGE 2	
	Guselkumab N = 329	**Adalimumab N = 334**	**Guselkumab N = 496**	**Adalimumab N = 248**
Proportion of pts achieving an IGA score[a] of 0 at week 24				
n (%)	173 (52.6)	98 (29.3)	257 (51.8)	78 (31.5)
***P* value[b]**	< 0.001		< 0.001	
Proportion of pts achieving an IGA score[a] of 0 or 1 at week 24				
n (%)	277 (84.2)	206 (61.7)	414 (83.5)	161 (64.9)
***P* value[b]**	< 0.001		< 0.001	
Proportion of pts achieving an IGA score[a] of 0 at week 48				
n (%)	166 (50.5)	86 (25.7)	NA	NA
***P* value[b]**	< 0.001			
Proportion of pts achieving an IGA score[a] of 0 or 1 at week 48				
n (%)	265 (80.5)	185 (55.4)	NA	NA
***P* value[b]**	< 0.001			

IGA = Investigator Global Assessment; NA = not applicable; pts = patients.
Note: In VOYAGE 2 patients were re-randomized at or after week 28 to withdrawal or re-treatment.
[a] An IGA score of 0 = cleared and a score of 1 = minimal.
[b] Based on the CMH chi-square test stratified by investigator site (pooled) and is the comparison of guselkumab vs. adalimumab.
Source: Blauvelt et al. (2017);[7] VOYAGE 1 CSR;[8] Reich et al. (2017);[9] VOYAGE 2 CSR.[10]

Table 16: NAVIGATE: IGA Responses Between Week 28 and 40

	NAVIGATE	
	Guselkumab N = 135	**Ustekinumab N = 133**
Number of visits pts achieved an IGA response of 0		
n	135	133
Mean (SD)	0.9 (1.34)	0.4 (1.06)
***P* value[a]**	< 0.001	

IGA = Investigator Global Assessment; pts = patients; SD = standard deviation.
[a] Based on CMH row mean score test stratified by baseline weight (≤ 100 kg; > 100 kg).
Source: NAVIGATE CSR (40 weeks).[12]

Table 17: VOYAGE 1 and VOYAGE 2 – PASI Responses at Weeks 24 and 48

	VOYAGE 1		VOYAGE 2	
	Guselkumab N = 329	**Adalimumab N = 334**	**Guselkumab N = 496**	**Adalimumab N = 248**
Proportion of pts achieving PASI 75[a] at week 24				
n (%)	300 (91.2)	241 (72.2)	442 (89.1)	176 (71.0)
***P* value[b]**	< 0.001		< 0.001	
Proportion of pts achieving PASI 90[a] at week 24				
n (%)	264 (80.2)	177 (53.0)	373 (75.2)	136 (54.8)
***P* value[b]**	< 0.001		< 0.001	
PASI 100 Proportion of pts achieving PASI 100[a] at week 24				
n (%)	146 (44.4)	83 (24.9)	219 (44.2)	66 (26.6)
***P* value[b]**	< 0.001		< 0.001	
Proportion of pts achieving PASI 75[a] at week 48				
n (%)	289 (87.8)	209 (62.6)	NA	NA
***P* value[b]**	< 0.001			
Proportion of pts achieving PASI 90[a] at week 48				
n (%)	251 (76.3)	160 (47.9)	NA	NA
***P* value[b]**	< 0.001			
Proportion of pts achieving PASI 100[a] at week 48				
n (%)	156 (47.4)	78 (23.4)	NA	NA
***P* value[b]**	< 0.001			

NA = not applicable; PASI = Psoriasis Area and Severity Index; pts = patients.
Note: In VOYAGE 2 patients were re-randomized at or after week 28 to withdrawal or re-treatment.
[a] PASI 75/900100 is a 75%/90%/100% or greater improvement from baseline in the PASI score.
[b] Based on the CMH chi-square test stratified by investigator site (pooled) and is the comparison of guselkumab vs. adalimumab.
Source: Blauvelt et al. (2017);[7] VOYAGE 1 CSR;[8] Reich et al. (2017);[9] VOYAGE 2 CSR.[10]

Table 18: VOYAGE 2 – Maintenance of PASI 90 Response from Week 28 to 48

	VOYAGE 2			
	Placebo[a]	Guselkumab[b]	Combined Placebo → Guselkumab[c]	Adalimumab[d]
Pts withdrawn from study drug at week 28				
n	147	182	329	116
Patients with ≥ 1 non-missing PASI % improvement value after week 28				
n	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance of PASI 90 response rate, % (95% CI)[e]				
Week 32	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]
Week 44	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]
Duration of PASI 90 response from week 28 through 48				
Number of weeks patients maintained initial PASI response[e]				
90% of pts	[redacted]	[redacted]	[redacted]	[redacted]
75% of pts	[redacted]	[redacted]	[redacted]	[redacted]
50% of pts	[redacted]	15.2	[redacted]	[redacted]
25% of pts	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; NA = not applicable; PASI = Psoriasis Area and Severity Index; pts = patients.
Note: In VOYAGE 2 patients were re-randomized at or after week 28 to withdrawal or re-treatment.
[a] Patients randomized to placebo at week 0, crossed over to guselkumab at or after week 16, and were PASI 90 responders at week 28.
[b] Patients randomized to guselkumab at week 0, who were PASI 90 responders at week 28, and were re-randomized to the withdrawal group (placebo) at week 28.
[c] Combined patients are patients randomized to placebo or to guselkumab at week 0, and who were PASI 90 responders at week 28.
[d] Patients randomized to adalimumab at week 0 who were PASI 90 responders at week 28.
[e] Based on life-table estimates using all data collected.
Source: Reich et al. (2017);[9] VOYAGE 2 CSR.[10]

Table 19: NAVIGATE – PASI Responses Between Week 28 and 40

[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: NAVIGATE CSR (40 weeks)[12]

[redacted]

[redacted]

Table 20: VOYAGE 1 and VOYAGE 2 – DLQI Responses at Weeks 16, 24, and 48

	VOYAGE 1			VOYAGE 2		
	PL[a] N = 174	GUSE N = 329	ADAL N = 334	PL[a] N = 248	GUSE N = 496	ADAL N = 248
Change from baseline in DLQI score at week 16						
n	170	322	328	248	495	247
Mean (SD)	–0.6 (6.4)	–11.2 (7.2)	–9.3 (7.8)	–2.6 (6.9)	–11.3 (6.8)	–9.7 (6.8)
***P* value[b]**	–	< 0.001	< 0.001	–	< 0.001	< 0.001
Change from baseline in DLQI score at week 24						
n	[redacted]	322	328	[redacted]	495	247
Mean (SD)	[redacted]	–11.6 (7.6)	–9.5 (7.9)	[redacted]	–11.9 (7.0)	–9.9 (7.4)
Change from baseline in DLQI score at week 48 (VOYAGE 1) or week 28 (VOYAGE 2)						
n	[redacted]	322	328	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	–11.8 (7.9)	–9.2 (8.3)	[redacted]	[redacted]	[redacted]
Proportion of pts with DLQI score[c] of 0 or 1 at week 16						
n	168	320	319	246	491	246
n (%)	7 (4.2)	180 (56.3)	123 (38.6)	8 (3.3)	254 (51.7)	96 (39.0)
***P* value[d]**	–	< 0.001	< 0.001	[redacted]	[redacted]	[redacted]
Proportion of pts with DLQI score of 0 or 1 at week 24						
N	–	320	319	231	491	246
n (%)	–	195 (60.9)	126 (39.5)	[redacted]	283 (57.6)	101 (41.1)
***P* value[e]**	–	< 0.001		[redacted]	[redacted]	[redacted]
Proportion of pts with DLQI score of 0 or 1 at week 48 (VOYAGE 1) or week 28 (VOYAGE 2)						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
***P* value[e]**	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Proportion of pts with a reduction of ≥ 5 from baseline in DLQI score at week 16						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
***P* value[d]**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ADAL = adalimumab; DLQI = Dermatology Life Quality Index; GUSE = guselkumab; NR = not reported; PL = placebo; SD = standard deviation.
Note: Analyses are in patients with a baseline DLQI score > 1. In VOYAGE 2 patients were re-randomized at or after week 28 to withdrawal or re-treatment.
[a] Patients randomized to placebo crossed over to guselkumab after week 16.
[b] Based on ANOVA model stratified by investigator site (pooled) and is the comparison vs. placebo.
[c] The DLQI score that ranges from 0 to 30 with a higher score indicating more severe disease. A score of 0 or 1 is considered to be no effect. The estimated MCID for the DLQI in patients with psoriasis is 3.2; however, estimates of the smallest difference a patient would regard as beneficial have ranged from 2.2 to 6.9.
[d] Based on the CMH chi-square test stratified by investigator site (pooled) and is the comparison with placebo.
[e] Based on the CMH chi-square test stratified by investigator site (pooled) and is the comparison of guselkumab vs. adalimumab.
Source: Blauvelt et al. (2017);[7] VOYAGE 1 CSR;[8] Reich et al. (2017);[9] VOYAGE 2 CSR.[10]

Table 21: NAVIGATE – DLQI Responses Between Week 28 and 40

[redacted]		
	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: NAVIGATE CSR (40 weeks)[12]

[redacted]

Table 22: VOYAGE 2 – SF-36 Response at Week 16 and 24

	VOYAGE 2		
	PL N = 248	**GUSE N = 496**	**ADAL N = 248**
Change from baseline in SF-36 score[a] at week 24			
PCS score			
Mean (SD)	[redacted]	5.602 (8.078)	3.649 (7.249)
MCS score			
Mean (SD)	[redacted]	5.961 (10.196)	4.160 (10.294)
Proportion of pts with an improvement of ≥ 5 from baseline in SF-36 score at week 16			
PCS score			
n (%)	[redacted]	[redacted]	[redacted]
***P* value[b]**	[redacted]	[redacted]	[redacted]
MCS score			
n (%)	[redacted]	[redacted]	[redacted]
***P* value[b]**	[redacted]	[redacted]	[redacted]

ADAL = adalimumab; GUSE = guselkumab; MCS = Mental Component Summary; PASI = Psoriasis Area and Severity Index; PCS = Physical Component Summary; PL = placebo; pts = patients; SD = standard deviation; SF-36 = Medical Outcomes Short Form (36) Health Survey.

[a] The SF-36 produces an aggregate of two component summaries: the physical component and mental component summaries with scores ranging from 0 to 100. Higher scores indicate better health status. MCIDs of 2 points (PCS score) and 3 points (MCS score) has been reported.

[b] Based on CMH chi-square test stratified by investigator site (pooled) and is the comparison with placebo.

Source: Reich et al. (2017);[9] VOYAGE 2 CSR.[10]

Table 23: VOYAGE 1 and VOYAGE 2 – Regional Psoriasis End Points at Weeks 16, 24, and 48

	VOYAGE 1			VOYAGE 2		
	PL N = 174	GUSE N = 329	ADAL N = 334	PL N = 248	GUSE N = 496	ADAL N = 248
ss-IGA score						
Proportion of pts achieving ss-IGA score[a] of 0 or 1 and ≥ 2-grade improvement from baseline						
n[b]	145	277	286	202	408	194
Week 16						
n (%)	21 (14.5)	231 (83.4)	201 (70.3)	22 (10.9)	329 (80.6)	130 (67.0)
***P* value[c]**	–	< 0.001	< 0.001	–	< 0.001	< 0.001
Week 24						
n (%)	[redacted]	234 (84.5)	198 (69.2)	[redacted]	348 (85.3)	131 (67.5)
Week 48						
n (%)	[redacted]	217 (78.3)	173 (60.5)	NA	NA	NA
f-PGA score						
Proportion of pts achieving f-PGA score of 0 or 1						
N[d]	88	174	173	123	246	124
Week 16						
n (%)	14 (15.9)	68 (39.1)	88 (50.9)	18 (14.6)	128 (52.0)	74 (59.7)
***P* value[c]**	–	< 0.001	< 0.001	–	< 0.001	< 0.001
Week 24						
n (%)	32 (37.2)	98 (56.3)	108 (62.4)	[redacted]	154 (62.6)	83 (66.9)
Week 48						
n (%)	[redacted]	130 (74.7)	107 (61.8)	NA	NA	NA
NAPSI score						
Per cent improvement in NAPSI score from baseline						
n[e]	99	194	191	140	280	140
Week 16						
Mean (SD)	–0.93 (57.89)	34.37 (42.45)	37.95 (53.87)	1.82 (53.83)	39.61 (45.65)	46.92 (48.09)
***P value*[f]**	–	< 0.001	< 0.001	–	< 0.001	< 0.001
Week 24						
Mean (SD)	[redacted]	49.78 (44.16)	49.42 (60.04)	[redacted]	54.98 (46.80)	53.69 (49.46)
Week 48						
Mean (SD)	[redacted]	68.14 (42.99)	61.37 (49.20)	NA	NA	NA
hf-PGA score						
Proportion of pts achieving a hf-PGA score[g] of 0 or 1 and ≥ 2-grade improvement from baseline						
n[h]	43	90	95	63	114	56
Week 16						
Mean (SD)	6 (14.0)	66 (73.3)	53 (55.8)	9 (14.3)	88 (77.2)	40 (71.4)
***P* value[c]**		< 0.001	< 0.001	-	< 0.001	< 0.001

	VOYAGE 1			VOYAGE 2		
	PL N = 174	GUSE N = 329	ADAL N = 334	PL N = 248	GUSE N = 496	ADAL N = 248
Week 24						
Mean (SD)	NR	71 (78.9)	54 (56.8)	[redacted]	93 (81.6)	37 (66.1)
Week 48						
Mean (SD)	NR	68 (75.6)	59 (62.1)	NA	NA	NA

ADAL = adalimumab; f-PGA = Physician Global Assessment of Fingernails; GUSE = guselkumab; hf-PGA = Physician Global Assessment of Hands and/or Feet; NA = not applicable; NAPSI = Nail Psoriasis Severity Index; NR = not reported; PL = placebo; SD = standard deviation; ss-IGA = Scalp-Specific Investigator Global Assessment.
[a] An ss-IGA score of 0 = absence of disease and a score of 1 = very mild disease.
[b] Patient randomized at week 0 with an ss-IGA score ≥ 2 at baseline.
[c] Based on the CMH chi-square test stratified by investigator site (pooled) and is the comparison vs. placebo.
[d] Patients randomized at week 0 with an f-PGA score ≥ 2 at baseline.
[e] Patients randomized at week 0 with baseline NAPSI score > 0.
[f] Based on non-parametric ANOVA with investigator site (pooled) as covariate and the comparison is vs. placebo.
[g] A hf-PGS score of 0 = clear and a score of 1 = almost clear.
[h] Patients randomized at week 0 with hf-PGA score ≥ 2 at baseline.
Source: Blauvelt et al. (2017);[7] VOYAGE 1 CSR;[8] Reich et al. (2017);[9] VOYAGE 2 CSR.[10]

Table 24: VOYAGE 1 – Results of Subgroup Analyses at Week 16 or 24

VOYAGE 1						
Guselkumab vs. Placebo at Week 16						
Baseline	**Placebo**		**Guselkumab**		**Difference**	**95% CI**
	n	**%**	**n**	**%**		
IGA score of 0 or 1 at week 16						
Body weight						
≤ 90 kg	111	9.0	189	87.3	78.293	[redacted]
> 90 kg	63	3.2	140	82.1	78.968	
Disease severity						
PASI ≤ 20	[redacted]					
PASI > 20						
Biologics						
Never Used	[redacted]					
Ever Used						
Anti-TNF[a]						
Never Used	[redacted]					
Ever Used						
IL-12/23 inhib.[b]						
Never Used	[redacted]					
Ever Used						
PASI 90 response at week 16						
Body weight						
≤ 90 kg	111	3.6	189	76.7	73.116	[redacted]
> 90 kg	63	1.6	140	68.6	66.984	
Disease severity						
PASI ≤ 20	[redacted]					
PASI > 20						
Biologics						
Never Used	[redacted]					
Ever Used						
Anti-TNF[a]						
Never Used	[redacted]					

VOYAGE 1						
Ever Used	[redacted]					
IL-12/23 inhib.[b] **Never Used** **Ever Used**	[redacted]					
Guselkumab vs. Adalimumab at Week 24						
Baseline	**Adalimumab**		**Guselkumab**		**Difference**	**95% CI**
	n	**%**	**n**	**%**		
IGA score of 0 or 1 at week 24						
Body weight **≤ 90 kg** **> 90 kg**	191 142	72.3 47.9	189 140	84.7 83.6	12.405 35.684	[redacted]
Disease severity **PASI ≤ 20** **PASI > 20**	167 167	57.5 65.9	186 143	85.5 82.5	27.999 16.649	[redacted]
Biologics **Never Used** **Ever Used**	264 70	63.6 54.3	258 71	84.9 81.7	21.247 27.404	[redacted]
Anti-TNF[a] **Never Used** **Ever Used**	[redacted]					
IL-12/23 inhib.[b] **Never Used** **Ever Used**	[redacted]					
PASI 90 response at week 24						
Body weight **≤ 90 kg** **> 90 kg**	[redacted]					
Disease severity **PASI ≤ 20** **PASI > 20**	[redacted]					
Biologics **Never Used** **Ever Used**	[redacted]					
Anti-TNF[a] **Never Used** **Ever Used**	[redacted]					
IL-12/23 inhib.[b] **Never Used** **Ever Used**	[redacted]					

CI = confidence interval; IGA = Investigator Global Assessment; IL = interleukin; inhib. = inhibitor; PASI = Psoriasis Area and Severity Index; TNF = tumour necrosis factor.
[a] Anti-TNF agents include etanercept and infliximab.
[b] IL-12/23 inhibitors include ustekinumab and briakinumab.
Source: VOYAGE 1 CSR.[8]

Table 25: VOYAGE 2 – Results of Subgroup Analyses at Week 16 or 24

VOYAGE 2						
Guselkumab vs. Placebo at Week 16						
Baseline	**Placebo**		**Guselkumab**		**Difference**	**95% CI**
	n	**%**	**n**	**%**		
IGA score of 0 or 1 at Week 16						
Body weight						
≤ 90 kg	141	12.8	277	88.4	75.682	[redacted]
> 90 kg	107	2.8	219	78.5	75.735	
Disease severity						
PASI ≤ 20	[redacted]					
PASI > 20						
Biologics						
Never Used	[redacted]					
Ever Used						
Anti-TNF[a]						
Never Used	[redacted]					
Ever Used						
IL-12/23 inhib.[b]						
Never Used	[redacted]					
Ever Used						
PASI 90 response at week 16						
Body weight						
≤ 90 kg	141	4.3	277	76.5	72.279	[redacted]
> 90 kg	107	0.0	219	61.6	61.644	
Disease severity						
PASI ≤ 20	[redacted]					
PASI > 20						
Biologics						
Never Used	[redacted]					
Ever Used						
Anti-TNF[a]						
Never Used	[redacted]					
Ever Used						
IL-12/23 inhib.[b]						
Never Used	[redacted]					
Ever Used						
Guselkumab vs. Adalimumab at Week 24						
Baseline	**Adalimumab**		**Guselkumab**		**Difference**	**95% CI**
	n	**%**	**n**	**%**		
IGA score of 0 or 1 at Week 24						
Body weight						
≤ 90 kg	153	72.5	277	87.7	15.177	[redacted]
> 90 kg	94	53.2	219	78.1	24.891	
Disease severity						
PASI ≤ 20	138	63.0	276	84.4	21.377	[redacted]
PASI > 20	110	67.3	220	82.3	15.000	
Biologics						
Never Used	199	69.8	395	84.6	14.708	[redacted]
Ever Used	49	44.9	101	79.2	34.310	
Anti-TNF[a]						
Never Used	[redacted]					

VOYAGE 2						
Ever Used	[redacted]					
IL-12/23 inhib.[b] **Never Used** **Ever Used**	[redacted]					
PASI 90 response at week 24						
Body weight **≤ 90 kg** **> 90 kg**	[redacted]					
Disease severity **PASI ≤ 20** **PASI > 20**	[redacted]					
Biologics **Never Used** **Ever Used**	[redacted]					
Anti-TNF[a] **Never Used** **Ever Used**	[redacted]					
IL-12/23 inhib.[b] **Never Used** **Ever Used**	[redacted]					

CI = confidence interval; IGA = Investigator Global Assessment; IL = interleukin; inhib. = inhibitor; PASI = Psoriasis Area and Severity Index; TNF = tumour necrosis factor.
[a] Anti-TNF agents include etanercept and infliximab.
[b] IL-12/23 inhibitors include ustekinumab and briakinumab.
Source: VOYAGE 2 CSR.[10]

Table 26: NAVIGATE – Results of Subgroup Analyses Between Week 28 Through 48

[redacted]

CI = confidence interval; IL = interleukin; PASI = Psoriasis Area and Severity Index; pts = patients; SD = standard deviation; TNF = tumour necrosis factor.
[a] Biologics includes etanercept, infliximab, efalizumab, alefacept, brodalumab, ixekizumab, secukinumab, briakinumab, and adalimumab.
[b] Anti-TNF agents include etanercept, infliximab, and adalimumab.
Source: NAVIGATE CSR (40 weeks).[12]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Dermatology Life Quality Index (DLQI)
- Investigator Global Assessment (IGA)
- Medical Outcomes Study Short Form (36) Health Survey (SF-36)
- Nail Psoriasis Severity Index (NAPSI)
- Physician Global Assessment (PGA)
- Psoriasis Area and Severity Index (PASI).

Findings

Table 27: Instruments Used in the VOYAGE 1, VOYAGE 2, and NAVIGATE Trials

Instrument	Type	Evidence of Validity	MCID	References
DLQI	DLQI is a 10-item, dermatology-specific quality of life questionnaire.	YES	Range 2.2 to 6.9	Basra et al. 2008;[32] Finlay et al. 1994;[33] Shikiar et al. 2006[34]
IGA	The static IGA scale is based on a point-in-time assessment, as opposed to the dynamic IGA scale which is based on a recollection of the baseline disease severity.	YES	None	Langley et al. 2015[35]
NAPSI	The NAPSI was intended to both quantify the severity of psoriatic nail disease and assess the efficacy of drug therapy by looking at the nail involvement.	No	None	Rich et al. 2003[36]
PASI	Single estimate of a patient's disease severity at a given time based on induration, erythema, and scaling.	YES	None	Ashcroft et al. 1999;[37] Carlin et al. 2004;[20] Feldman et al. 2004;[38] Gourraud et al. 2012[39]
PGA	The PGA is used to determine a single estimate of the patient's overall severity of disease at a given point in time. Psoriatic lesions are graded for induration, erythema, and scaling based on scales of 0 to 4 that are then averaged over all lesions.	YES	Unknown	Weisman et al. 2003[40]
SF-36	The SF-36 consists of eight health domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) for which domain scores can be calculated. It also provides two component summary scores: PCS and MCS. Scores range from 0 to100, with higher scores	Only responsive-ness in psoriasis	2 points in the SF-36 PCS and 3 points in the SF-36 MCS	Frendl and Ware 2014;[41] Maruish 2011;[19] Mease et al. 2006[42]

Instrument	Type	Evidence of Validity	MCID	References
	indicating better health.			

DLQI = Dermatology Life Quality Index; IGA = Investigator Global Assessment; MCID = minimal clinically important difference; MCS = Mental Component Summary; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PCS = Physical Component Summary; PGA = Physician Global Assessment; SF-36 = Medical Outcomes Study Short Form (36) Health Survey.

Dermatology Life Quality Index (DLQI)

The DLQI is a widely used dermatology-specific quality of life instrument. It is a 10-item questionnaire that assesses six different aspects that may affect quality of life.[33,34] These aspects are: symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment.[33,34] The maximum score per aspect is either 3 (with a single question) or 6 (with two questions), and the scores for each can be expressed as a percentage of either 3 or 6. Each of the 10 questions is scored from 0 (not at all) to 3 (very much), and the overall DLQI is calculated by summing the score of each question resulting in a numeric score between 0 and 30 (or a percentage of 30).[33,34] The higher the score, the more quality of life is impaired. The meaning of the DLQI scores on a patient's life is as follows:[32]

- 0 to 1 = no effect;
- 2 to 5 = small effect ;
- 6 to 10 = moderate effect;
- 11 to 20 = very large effect;
- 21 to 30 = extremely large effect.

The DLQI has shown good test-retest reliability (correlation between overall DLQI scores was 0.99, $P < 0.0001$, and of individual question scores was 0.95 to 0.98, $P < 0.001$),[33] internal consistency reliability (with Cronbach's alpha coefficients ranging from 0.75 to 0.92 when assessed in 12 international studies),[32] construct validity (as 37 separate studies have mentioned a significant correlation of the DLQI with either generic or dermatology-specific and disease-specific measures),[32] and responsiveness (the DLQI being able to detect changes before and after treatment in patients with psoriasis in 17 different studies).[32]

Estimates of the minimally important difference (MID: the smallest difference a patient would regard as beneficial) have ranged from 2.2 to 6.9.[32,34] It should be noted that some of the anchors that were used in order to obtain the DLQI MID were not patient-based (i.e., Basra et al.[32] derived estimates from PASI and PGA anchors, as well as a distribution-based approach).

Limitations associated with the DLQI are as follows:

- Concerns have been identified regarding unidimensionality and the behaviour of items of the DLQI in different psoriatic patient populations with respect to their cross-cultural equivalence and age and gender; however, these concerns were only identified in two citations out of the 12 international studies identified.[32]
- The patient's emotional aspects may be underrepresented and this may be one reason for unexpectedly low DLQI scores in patients with more emotionally disabling diseases such as vitiligo. To overcome this, it is suggested that the DLQI be combined with more emotionally-oriented measures such as the mental health

component of the SF-36 scales or Hospital Anxiety and Depression Scale (HADS).[32]

- The non-availability of benchmarks for the MCID of DLQI scores in general dermatological conditions, although there have been some attempts to determine these differences for specific conditions such as psoriasis.[32]
- DLQI may lack sensitivity in detecting change from mild to severe psoriasis.[43]

Investigator Global Assessment (IGA)

The static IGA scale is based on a point-in-time assessment, as opposed to the dynamic IGA scale, which is based on a recollection of the baseline disease severity.[35] The Physician Global Assessment (PGA) denotes scales used by clinicians, whereas the IGA is used by investigators in clinical trials.[35]

The following outlines the possible scores on the IGA modified (mod) 2011 scale:[35]

- 0 = clear (e.g., no signs of psoriasis, some post-inflammatory hyperpigmentation may be present);
- 1 = almost clear (e.g., no thickening, normal or pink coloration);
- 2 = mild (e.g., mild thickening, pink to light red coloration);
- 3 = moderate (e.g., moderate thickening, dull to bright red);
- 4 = severe (e.g., severe thickening, bright to deep red).

A recent review of the IGA scale reported the following advantages: it is relatively simple and easy to use; shows good correlation with PASI; it has high clinical construct validity (i.e., correlation with other severity measures); and has high test-retest reliability; there is good usage of the entire range of the scale; and there is moderate agreement among multiple assessors.[35] Limitations of the scale include: its inability to measure the extent of psoriasis; it may not be able to discriminate small changes in severity; there is no consideration for non-skin symptoms; and multiple versions of the scale limit study or trial comparisons.[35] In addition, no MCID has been established for psoriasis at this time.

Medical Outcomes Study Short Form (36) Health Survey (SF-36)

The SF-36 is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[19] The SF-36 consists of eight health domains: physical functioning (PF); role physical (RP); bodily pain (BP); general health (GH); vitality (VT); social functioning (SF); role emotional (RE); and mental health (MH).[19] For each of the eight domains, a subscale score can be calculated. The SF-36 also provides two component summaries: the physical component summary (PCS) and the mental component summary (MCS), derived from aggregating the eight domains according to a scoring algorithm. The PCS, MCS, and eight dimensions are each measured on a scale of 0 to 100, which are t scores (mean of 50 and standard deviation of 10) that have been standardized to the US general population. Thus, a score of 50 on any scale would be at the average or norm of the general US population and a score 10 points lower (i.e., 40) would be one standard deviation below the norm. On any of the scales, an increase in score indicates improvement in health status.[19]

Validity and reliability of the SF-36 in patients with psoriasis is lacking; however, in one systematic review by Frendl and Ware[41] that examined SF-36 concordance and its MCID across many different indications in studies that looked at drug therapy effectiveness, the SF-36 was observed to be responsive (when compared with primary clinical measures) in patients with psoriasis. In addition, of the ten psoriasis studies identified, net PCS or MCS improvement of at least 3 points was observed in 70% of these studies.

Based on anchor data, the SF-36 User's Manual also proposed the following minimal mean group differences, in terms of t score points, for SF-36 version 2 (v2) individual dimension scores: PF = 3; RP = 3; BP = 3; GH = 2; VT = 2; SF = 3; RE = 4; and MH = 3. It should be noted that these minimally important difference (MID) values were determined as appropriate for groups with mean t score ranges of 30 to 40. For higher t score ranges, MID values may be higher.[19] MID values do not represent patient-derived scores. The MIDs for the SF-36v2 are based on clinical and other non-patient-reported anchors.

Nail Psoriasis Severity Index (NAPSI)

The NAPSI was intended to both quantify the severity of psoriatic nail disease and assess the efficacy of drug therapy by looking at the nail involvement.[36] It was developed in part because the PASI does not incorporate anything that focuses on the severity of nail disease and the involvement of nail disease can predict higher disease severity and lower quality of life.[44] The main purpose of the NAPSI is to determine the degree of involvement of the psoriatic nail unit;[45] however, it was noted in the Augustin and Ogilvie[44] systematic overview of outcomes (which assessed nail involvement in patients with psoriasis) that these outcomes are not frequently performed. A larger value indicates more nail involvement and hence, potentially worse disease.[46]

In order to obtain NAPSI scores, the nail is divided into four quadrants with each quadrant being assessed for nail matrix disease (described as pitting, lunular red spots, crumbling, and leukonychia) and nail bed disease (described as onycholysis, splinter hemorrhages, subungual hyperkeratosis, and salmon-patch dyschromia).[36,45,46] Each nail is given a score of 0 to 8 for a total score of 0 to 80 for the fingernails and 0 to 160 if the toenails are also included in the analysis.

Inter-observer reliability of the NAPSI was assessed in one study in which three dermatologists assessed all fingernails and toenails of 25 consecutive patients with psoriatic nail involvement in a dermatology outpatient clinic.[45]The nail quadrants were assessed for nail matrix disease and nail bed disease with a total score between 0 and 160 (as all 20 nails were scored). The authors computed the intraclass correlation coefficient (ICC) total NAPSI as 0.781, indicating that there was moderate to good inter-observer agreement in the total score. The ICC for the nail bed score was 0.869, which was considerably better than the nail matrix ICC at 0.584 (which does not meet the acceptable threshold of 0.70, and thus is inadequate). The authors speculated that the main difference between the two scores may be due to the difficulty in obtaining accurate evaluations of the smaller nail surfaces of the toes.[45] Limitations associated with the study were the small sample size and the lack of longitudinal observation that would incorporate repeated measures after treatment with various therapies.[45] NAPSI inter-rater correlation was also assessed in another study whose authors examined 45 patients who visited another outpatient dermatology clinic.[47]Two investigators independently assessed the nails using the NAPSI on the same day and under the same conditions. A strong Pearson's correlation (r) of 0.768, $P < 0.001$ was obtained for the inter-rater correlation; however, while a strong correlation between the two

dermatologists existed when fingernails were scored (*r* of 0.690, *P* < 0.001) there was weak correlation between when examining the toenails (*r* of 0.183, *P* > 0.05).[47]

While the NAPSI has been used in several studies on psoriasis as an outcome measure,[48-50] it has not yet been formally validated and it has shown significant inter-observer variability,[45] especially when examining affected toenails of patients with psoriasis.[45,47] In addition, there is no MCID associated with this instrument when assessing patients with psoriasis.

Psoriasis Area and Severity Index (PASI)

The PASI is a widely used instrument in psoriasis trials that assesses and grades the severity of psoriatic lesions and the patient's response to treatment. It produces a numeric score ranging from 0 to 72. In general, a PASI score of 5 to 10 is considered moderate disease, and a score over 10 is considered severe. A 75% reduction in the PASI score (PASI 75) is the current benchmark for most clinical trials in psoriasis and the criterion for efficacy of new psoriasis treatments approved by the FDA.[20]

In calculating the PASI, severity is determined by dividing the body into four regions: head (h), upper extremities (u), trunk (t) and lower extremities (l), that account for 10%, 20%, 30%, and 40% of the total body surface area (BSA), respectively.[38] Each of these areas is assessed separately for erythema, induration, and scaling, which is rated on a scale of 0 (none) to 4 (very severe). Extent of psoriatic involvement is graded as follows:

- 0 = no involvement;
- 1 = 1% to 9%;
- 2 = 10% to 29%;
- 3 = 30% to 49%;
- 4 = 50% to 69%;
- 5 = 70% to 89%;
- 6 = 90% to 100%.

The following formula is used to calculate the PASI score:

PASI = 0.1 (Eh + Ih + Sh) Ah + 0.2 (Eu + Iu + Su) Au + 0.3 (Et +It + St) At + 0.4 (El +Il +Sl) Al[38]

Where E = erythema, I = induration, S = scaling, A = area, h = head score, u = upper extremities, t = trunk score, and l = lower extremities score. PASI 75 is a dichotomous scale (Yes/No; patient achieved greater than and equal to 75% improvement from baseline PASI score).

A number of limitations of the PASI have been identified and include the following:

- The PASI has been criticized as not correlating the clinical extent of the disease with quality of life and the psychological stress caused by psoriasis. The patient's measure of quality of life is often worse than the physician-rated clinical severity.[51]

- There are significant inter-rater reliability issues regarding the measurement of BSA.[37,38] There has been some work regarding the development of imaging and analysis systems to objectively measure BSA.[52]
- PASI scores can vary substantially between experienced and inexperienced physicians, raising concerns for inter-rater reliability.[53]
- Improvements in PASI score are not linearly related to severity or improvements in psoriasis.[20,38] The extent of psoriatic involvement is measured using a scale of 1 to 6 and the areas corresponding to each score are nonlinear.
- Some severe disease (clinically) may be scored low. For example, scores as low as 3 (on palms and soles) may represent psoriasis that disables a patient from work and other life activities.
- Most patients fall into a narrow band of scores, thereby decreasing the usefulness of the full range of scores (i.e., scores above 40 are rare).[37] Validity of this scale may be overrated, in part because of the skew toward lower scores.[39]
- There is little research on the reliability of the assessments for erythema, desquamation, and induration, together with overall PASI scores.[37]
- Criterion validity is restricted by the lack of a 'gold standard' measure of psoriatic severity.[54]
- The PASI lacks sensitivity as erythema, desquamation, and induration are scored with equal weight within each of the four body regions. Thus, a reduction in scaling with a concomitant increase in skin erythema could be recorded with the same PASI score.
- Improvement of the histological phenotype of psoriasis can be underestimated by the per cent improvement in PASI (e.g., reduction of T cells, loss of keratin 16 (K16) expression and reduction in epidermal thickness).[20]
- Little work has been done to determine the clinical relevance of derived PASI scores.[37]

Physician Global Assessment (PGA)

The PGA is used to determine a single estimate of the patient's overall severity of disease at a given point in time. Various PGAs have been used in psoriasis with different descriptions and scores.[53] Psoriatic lesions are graded for induration, erythema, and scaling based on scales of 0 to 4 that are then averaged over all lesions.[55] The following table highlights the scoring for induration, erythema, and scaling:

Table 28: Scoring System for PGA

Score	Induration	Erythema	Scaling
0	No evidence	No evidence of erythema although hyperpigmentation may be present	No evidence of scaling
1	Minimal	Faint erythema	Minimal: occasional fine scale
2	Mild or slight	Light red coloration	Fine scale dominates
3	Elevated	Red coloration	Moderate: coarse scale predominates
4	Marked	Dark to deep red coloration	Marked: thick, non-tenacious scale dominates

PGA = Physician Global Assessment.
Source: Caperelli [55]

The sum of the three scales are added and then divided by three (I + E + S/3) to obtain a final PGA score as follows:

- 0 = cleared, except for residual discoloration;
- 1 = minimal – majority of lesions have individual scores for I + E + S/3 that average 1;
- 2 = mild – majority of lesions have individual scores that average 2;
- 3 = moderate – majority of lesions have individual scores that average 3;
- 4 = severe – majority of lesions have individual scores that average 4.

The PGA is more subjective than PASI in that there is no attempt to quantify the individual elements of plaque morphology or BSA involvement.[38,40] There have also been fewer studies using PGA than PASI. This outcome is considered reliable using test-retest data and internal consistency.[40] However inter-rater reliability is poor, due to variability, especially in untrained observers.[40] Many studies now employ only the final value of clear or almost clear as treatment success. Although it would seem that the PGA may be less likely to be open to interpretation, different studies have used different definitions of clear or almost clear, making comparisons between treatments difficult.[40] Construct and content validity are considered strong within a study, but comparison with other studies as well as relationship to other methods are problematic due to the variability in data collection, analysis, and reporting method.[40] No MCID has been identified in patients with psoriasis.

Conclusion

The DLQI is a dermatology-specific quality of life measure that has been validated for use in the psoriasis patient population, with an estimated MCID in the range of 2.2 to 6.9.[32] While the IGA is validated, reliable, and easy to use, it cannot measure the extent of psoriasis, may not be able to discriminate small changes in severity, and has no MCID.[35] Validity and reliability of the SF-36 in patients with psoriasis is lacking; however, in one systematic review by Frendl and Ware[41] that observed SF-36 concordance and its MCID across many different indications in studies that looked at drug therapy effectiveness, the SF-36 was observed to be responsive (when compared to primary clinical measures) in patients with psoriasis. The MID is 2 points in the SF-36 PCS and 3 points in the SF-36 MCS; however, no MID has been identified for patients with moderate-to-severe psoriasis . While the NAPSI has gained wide acceptance and has been used in several studies on psoriasis as an outcome measure,[48-50] it has not yet been formally validated and it has shown significant inter-observer variability,[45] especially when examining affected toenails of patients with

psoriasis.[45,47] In addition, there is no MCID associated with this instrument when assessing patients with psoriasis. The PGA is more subjective than PASI in that there is no attempt to quantify the individual elements of plaque morphology or BSA involvement.[38,40] The PASI is a widely used instrument in psoriasis trials that assesses and grades the severity of psoriatic lesions and the patient's response to treatment, however there is no known MCID associated with it. There have also been fewer studies using PGA than PASI. This outcome is considered reliable using test-retest data and internal consistency.[40] However inter-rater reliability is poor, due to variability, especially in untrained observers.[40]

Appendix 6: Summary of Other Studies

Objective

To summarize the efficacy and safety results of the NAVIGATE follow-up phase (up to week 60).[13] The following summary is based on unpublished data from the clinical study report CSR CNTO1959PSO3003 week 60.

Trial Description

Figure 4 of this review summarizes the study design plan for the NAVIGATE trial. Patients randomized to guselkumab or ustekinumab at week 16 remained in their double-blinded treatment groups following the active treatment phase (ended with database lock at week 40 and final drug administration at week 44) into the follow-up phase. Patients in each group had their final efficacy assessments at week 52 and safety assessments at week 60.

Results

Patient Disposition

[redacted]

Table 29: Disposition of Patients from Week 16 Through Week 60

	NAVIGATE	
	Guselkumab	**Ustekinumab**
Randomized patients, N	135	133
Completed study participation[a], n (%)	[redacted]	[redacted]
Terminated study participation, n (%)	[redacted]	[redacted]
Completed safety follow-up, n (%)	[redacted]	[redacted]
Did not complete safety follow-up, n (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]
Other	[redacted]	[redacted]

[a] Patients who completed study agent administration through week 44 and safety follow-up through week 60.
Source: CSR (CNTO1959PSO3003) (Week 60).[13]

Efficacy Results in the Randomized Patients

[redacted]

Table 30: Efficacy Results at Week 52 of Randomized Patients

	NAVIGATE	
	Guselkumab N = 135	**Ustekinumab N = 133**
Primary Efficacy End Point:		
IGA score of cleared (0) or minimal (1) and at least a 2-grade improvement (from week 16) at week 52		
IGA of cleared (0)	36 (26.7)	11 (8.3)
IGA of 0 or 1 and at least 2-grade improvement from week 16, n (%)	49 (36.3)	23 (17.3)
P value[a]	< 0.001	
Other Efficacy End Points:		
PASI responses (from week 16) at week 52		
PASI 90 response, n (%)	69 (51.1)	32 (24.1)
P value[a]	< 0.001	
PASI 100 response, n (%)	[redacted]	[redacted]
PASI 75 response, n (%)	[redacted]	[redacted]
DLQI scores of 0 or 1 at week 52 among patients with DLQI > 1 at week 16		
DLQI score > 1 at week 16, N	103	105
DLQI of 0 or 1 at week 52, n (%)	40 (38.8)	20 (19.0)
P value[a]	0.002	

DLQI = Dermatology Life Quality Index; IGA = Investigator Global Assessment; PASI = Psoriasis Area and Severity Index.
[a] *P value* is based on CMH chi-square test stratified by baseline weight (≤ 100kg; > 100kg).
Source: CSR (CNTO1959PSO3003) (week 60).[13]

Safety Results in Randomized Patients

More patients randomized to the guselkumab group compared with the ustekinumab group had one or more adverse events (AEs) (64.4% and 55.6%, respectively) from week 16 through week 60, with the most commonly reported AEs being nasopharyngitis and upper respiratory tract infections (Table 31). Serious adverse events (SAEs) occurred in 6.7% and 4.5% of patients treated with guselkumab and ustekinumab, respectively. In addition, 2.2% and 1.5% of patients withdrew due to AEs, respectively. There were no real differences between the rates of notable harms events between the two treatment-randomized groups.

Table 31: Harms From Week 16 Through Week 60 in the Randomized Patients

	NAVIGATE	
	Guselkumab N = 135	**Ustekinumab N = 133**
Average Duration of Follow-Up (Weeks)	[redacted]	[redacted]
Average Exposure (Number of Administrations)	[redacted]	[redacted]
Patients with ≥ 1 AE, n (%)	87 (64.4)	74 (55.6)
AEs (Occurring at a Frequency ≥ 5% MedDRA System-Organ Class Level; ≥ 3% Individual AE Level), n (%)		
Infections and infestations	55 (40.7)	48 (36.1)
Nasopharyngitis	23 (17.0)	23 (17.3)
URTI	15 (11.1)	11 (8.3)
Sinusitis	[redacted]	[redacted]
UTI	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Psoriatic arthropathy	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Injection-site erythema	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Injury, poisoning, and procedural complications	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Patients with ≥ 1 SAE, n (%)	9 (6.7)	6 (4.5)
Cardiac disorders	[redacted]	[redacted]
Neoplasms malignant	2 (1.5)	0 (0)
Infections and infestations	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Deaths	[redacted]	[redacted]
WDAEs	3 (2.2)	2 (1.5)
Notable Harms		
Serious infections	1 (0.7)[a]	0 (0)
Injection-site reactions	[redacted]	[redacted]
Serious hypersensitivity reactions	[redacted]	[redacted]
MACE	2 (1.5)	1 (0.8)
NMSC	0 (0)	0 (0)
Malignancies	2 (1.5)	0 (0)

AE = adverse event; MACE = major adverse cardiovascular event; MedDRA = Medical Dictionary for Regulatory Activities; NMSC = non-melanoma skin cancer; SAE = serious adverse event; URTI = upper respiratory tract infection; UTI = urinary tract infection; WDAE = withdrawal due to adverse event.

[a] Bacterial arthritis.

Source: CSR (CNTO1959PSO3003) (eek 60).[13]

Critical Appraisal

The main limitations of these results are similar to those described for the active phase of NAVIGATE, primarily the lack of a true active control group and the differential withdrawal of patients between treatment groups.

Summary

These results suggest that patients who have not met treatment targets (based on Investigator Global Assessment [IGA]) with ustekinumab may be switched to guselkumab and be able to receive benefit, while not incurring apparently different AEs. However, based on the design of the study, it is not possible to assess whether these patients would have achieved similar or better results switching to another biologic treatment for plaque psoriasis, such as a tumour necrosis factor (TNF)-alpha antagonist or another interleukin (IL) inhibitor. These results do not provide any evidence to answer the question, “what is the comparative benefit of guselkumab versus other treatments for plaque psoriasis among patients not responding to ustekinumab?”

Appendix 7: Summary of Indirect Comparisons

Introduction and Background

[redacted]

Methods

[redacted]

Description of IDCs Identified

[redacted]

[redacted]

Review and Appraisal of the Manufacturer-Submitted IDC

[redacted]

Objectives and Rationale for the Manufacturer-Submitted IDC

[redacted]

[redacted]

Methods for the Manufacturer-Submitted IDC

Study Eligibility and Selection Process

[redacted]

[redacted]

[redacted]

Data Extraction

[redacted]

[redacted]

Table 32: [redacted]

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Source: Manufacturer's Submitted IDC.[56]

Comparators

Outcomes

Quality Assessment of Included Studies

[redacted]

Evidence Networks

Figures 5 to 13 contained confidential information and were removed at the request of the manufacturer.

Figure 5: [redacted]

Figure 6: [redacted]

Figure 7: [redacted]

Figure 8: [redacted]

Figure 9: [redacted]

Figure 10: [redacted]

Figure 11: [redacted]

Figure 12: [redacted]

Figure 13: [redacted]

[redacted]

[redacted]

Table 33: [redacted]

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[redacted]	[redacted]											

Source: Manufacturer supplied indirect comparison.[56]

[redacted]

Results

[redacted]

PASI 90 Response

[redacted]

[redacted]

[redacted]

PASI 100 Response

[redacted]

PASI 75 Response

[redacted]

[redacted]

DLQI Response

[redacted]

PGA/IGA Response

[redacted]

AE, SAEs, WDAEs

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Simultaneous Multi-PASI Outcome Network Meta-Analysis Results

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MAIC Results

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Table 34: [redacted]

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Source: Manufacturer supplied indirect comparison.[56]

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Source: Manufacturer supplied indirect comparison.[56]

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Table 36: [redacted]

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Source: Manufacturer supplied indirect comparison.[56]

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Table 37: [redacted]

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Source: Manufacturer supplied indirect comparison.[56]

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Table 38: [redacted]

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Source: Manufacturer supplied indirect comparison.[56]

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Table 39: [redacted]

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Source: Manufacturer supplied indirect comparison.[56]

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Table 40: [redacted]

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Source: Manufacturer supplied indirect comparison.[56]

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Table 41: [redacted]

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Source: Manufacturer supplied indirect comparison.[56]

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Table 42: [redacted]

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Source: Manufacturer supplied indirect comparison.[56]

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Critical Appraisal

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[57-60]) [redacted]

Discussion

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Conclusion

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