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CADTH COMMON DRUG REVIEW

Clinical Review Report

Brodalumab (SILIQ)

(Valeant Canada LP)

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

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Abbreviations

ACE	Arthritis Consumer Experts
AE	adverse event
BDL	brodalumab
BSA	body surface area
CAPP	Canadian Association of Psoriasis Patients
CDA	Canadian Dermatology Association
CDR	CADTH Common Drug Review
CMH	Cochran–Mantel–Haenszel
CPN	Canadian Psoriasis Network
CSPA	Canadian Skin Patient Alliance
CVD	cardiovascular disease
DLQI	Dermatology Life Quality Index
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels (questionnaire)
EQ-VAS	EuroQol 5-Dimensions 3-Levels 20 cm visual analogue scale
HRQoL	health-related quality of life
IL	interleukin
ITC	indirect treatment comparison
ITT	intention-to-treat
IVRS	interactive voice response system
LOCF	last observation carried forward
MCS	mental component summary
MID	minimally important difference
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NRI	nonresponder imputation
PASI	Psoriasis Area and Severity Index
PCS	physical component summary
PGA	Physician's Global Assessment
PP	per-protocol
PsA	psoriatic arthritis
PSI	Psoriasis Symptom Inventory
QoL	quality of life
RA	receptor A

RCT	randomized controlled trial
SAE	serious adverse event
SC	subcutaneous
SF-36	Short Form (36) Health Survey
sPGA	static Physician's Global Assessment
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumour necrosis factor
URTI	upper respiratory tract infection
VAS	visual analogue scale
WDAE	withdrawal due to adverse event
USK	ustekinumab

Drug	Brodalumab (Siliq)
Indication	For the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
Reimbursement Request	As per indication
Dosage Form(s)	210 mg/1.5 mL (single-dose pre-filled syringe)
NOC Date	March 6, 2018
Manufacturer	Valeant Canada LP

Executive Summary

Introduction

Psoriasis is a chronic, inflammatory, immune-mediated skin disorder that follows a waxing-waning pattern.[1] Plaque psoriasis is the most common form of psoriasis and is characterized by silvery scales, redness, erythematous patches, papules, and plaques on the extensor surfaces, trunk, and scalp that are often pruritic.[1-3] Moderate-to-severe plaque psoriasis can be defined by the extent of skin coverage, with involvement of more than 5% to 10% of body surface area (BSA); location, i.e., involvement of the face, palm, groin, or sole; or severity, with a Psoriasis Area and Severity Index (PASI) score of more than 10.[2] The high visibility of the symptoms of plaque psoriasis has a significant impact on patients' physical and psychosocial functioning and well-being as well as overall quality of life.[2,4] In addition, psoriasis patients are at an increased risk of a wide variety of serious comorbidities and inflammatory conditions, including cardiovascular disease (CVD), metabolic syndrome, psoriatic arthritis (PsA), and even early mortality.[1-4]

Brodalumab (BDL) is a human anti–interleukin-17 receptor A (IL-17 RA) monoclonal antibody that selectively targets human IL-17 RA and antagonizes the effects of IL-17A, IL-17F, IL-17A/F, and IL-25, all of which are pro-inflammatory cytokines implicated in the pathogenesis of psoriasis.[5-8] The Health Canada–approved indication of BDL is for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.[9] The recommended dose of BDL is 210 mg, to be given as a subcutaneous (SC) injection at week 0, week 1, and week 2, followed by 210 mg every two weeks thereafter; if an adequate response has not been achieved after 12 weeks to 16 weeks, treatment discontinuation should be considered because continued treatment beyond 16 weeks in patients who have not achieved an adequate response is not likely to result in greater success.[9] The objective of this report was to perform a systematic review of the beneficial and harmful effects of BDL 210 mg every two weeks administered as an SC injection for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Results and Interpretation

Included Studies

Three industry-sponsored, published, multi-centre, phase III, double-blind, parallel-group, randomized controlled trials (RCTs) of adults with moderate-to-severe plaque psoriasis were included in the systematic review: AMAGINE-1 (N = 661),[6,10] AMAGINE-2 (N = 1,831),[7,11] and AMAGINE-3 (N = 1,881).[8,11]

AMAGINE-1 was a placebo-controlled trial that consisted of a 12-week double-blind induction phase in which patients were randomized to one of two doses of BDL (140 mg or 210 mg) or placebo followed by a 40-week withdrawal and retreatment phase during which BDL-treated responders with a static Physician's Global Assessment (sPGA) score of 0 or 1 were re-randomized to either continue their original BDL dose or switch to placebo. BDL-treated nonresponders and those originally randomized to placebo were not re-randomized at week 12 but rather were to receive BDL 210 mg for the remaining 40 weeks. After week 52, patients could enter the long-term open-label extension phase.

AMAGINE-2 and AMAGINE-3 were identically designed, double-dummy, active-controlled trials consisting of a 12-week double-blind induction phase in which patients were randomized to one of two doses of BDL (140 mg or 210 mg every two weeks), ustekinumab (USK) (45 mg if ≤ 100 kg or 90 mg if > 100 kg at day 1 and week 4), or placebo. The induction phase was followed by a 40-week maintenance phase in which all patients originally randomized to either dose of BDL were combined and re-randomized to one of four BDL maintenance doses. Patients originally randomized to USK were to continue USK treatment, and patients originally randomized to placebo were switched to BDL 210 mg. After week 52, patients could enter a long-term open-label phase. This review is restricted to the Health Canada–approved BDL dosage (210 mg every two weeks).

All three trials measured the following co-primary and secondary outcomes at week 12 (unless otherwise specified) in the given sequence to evaluate the superiority of BDL 210 mg every two weeks to placebo: 75% reduction in the PASI 75 score and sPGA success (score of 0 or 1), PASI 100, sPGA score of 0, sPGA success at week 52 (AMAGINE-1 only), and Psoriasis Symptom Inventory (PSI) response (total score ≤ 8, with no item scores > 1). In AMAGINE-2 and -3, the following co-primary and secondary outcomes were assessed at week 12 in the given sequence to evaluate the superiority of BDL 210 mg every two weeks to USK: PASI 100 and PASI 75. The sequential testing scheme was pre-specified to control the type I error rate. Health-related quality of life (HRQoL) measures (including the Dermatology Life Quality Index [DLQI] in all trials, and the EuroQol 5-Dimensions 3-Levels [EQ-5D-3L] and Short Form (36) Health Survey [SF-36] in AMAGINE-1 only) were included as other secondary outcomes, but statistical analyses of them were not controlled for multiplicity.

Efficacy

Brodalumab 210 mg Versus Placebo at Week 12 (AMAGINE-1, AMAGINE-2, AMAGINE-3)

All three trials met their co-primary end points for the comparison of BDL with placebo. Compared with placebo, the percentage of BDL patients achieving PASI 75 was statistically significantly greater for BDL groups in all trials: 83.3% versus 2.7%, 86.3% versus 8.1%, and 85.1% versus 6.0% (adjusted $P < 0.001$, all trials). Further, the percentage of BDL-

treated patients achieving sPGA success was 75.7% versus 1.4%, 78.6% versus 3.9%, and 79.6% versus 4.1% (adjusted *P* < 0.001 in all trials).

Key secondary outcomes supported the findings for the primary outcomes:

- Compared with placebo, the percentage of patients achieving PASI 100 was statistically significantly greater in the BDL groups in all trials: 41.9% versus 0.5%, 44.4% versus 0.6%, and 36.7% versus 0.3% (adjusted *P* < 0.001 in all trials).
- The percentage of patients in the BDL groups who achieved a sPGA score of 0 was statistically significantly greater than in the placebo groups in all three trials: 41.9% versus 0.5%, 44.8% versus 0.6%, and 36.7% versus 0.3% (adjusted *P* value < 0.001 in all trials).
- Compared with placebo, a statistically significantly greater proportion of patients in the BDL group achieved a PSI response at week 12 in all trials: 60.8% versus 4.1%, 67.6% versus 6.8%, and 61.2% versus 6.3% (adjusted *P* < 0.001 in all trials).

DLQI total scores in the BDL group had a [redacted] reduction (improvement) at week 12 from baseline compared with placebo in all three trials. Between-treatment differences at week 12 were [redacted] in AMAGINE-1, AMAGINE-2, and AMAGINE-3, respectively. However, statistical comparisons of between-treatment differences were not controlled for multiplicity.

Brodalumab 210 mg Versus Placebo at Week 52 (AMAGINE-1, Withdrawal and Retreatment Phase)

At week 52 (end of the withdrawal and retreatment phase), [redacted] early BDL 210 mg responders (sPGA or 0 or 1 at week 12) who were re-randomized to continue BDL maintained sPGA success (score of 0 or 1) compared with those re-randomized to placebo, [redacted] Among the BDL 210 responders at week 12 who were then re-randomized to placebo [redacted]

Brodalumab Versus Ustekinumab at Week 12 (AMAGINE-2, AMAGINE-3)

The primary end point for the comparison of BDL 210 mg with USK in AMAGINE-2 and AMAGINE-3 was met; the percentage of patients achieving PASI 100 at week 12 was statistically significantly greater for BDL compared with USK: 44.4% versus 21.7% and 36.7% versus 18.5% respectively (adjusted *P* < 0.001 in both trials).

Compared with USK, the percentage of patients achieving PASI 75 at week 12 was statistically significantly greater in the BDL 210 mg group in AMAGINE-3 (85.1% versus 69.3%; adjusted *P* 0.007), but not in AMAGINE-2 (86.3% versus USK 70.0%; adjusted *P* 0.078).

Indirect Treatment Comparisons

CADTH Common Drug Review (CDR) critically appraised two indirect treatment comparisons (ITCs), one submitted by the manufacturer and one undertaken by Sawyer et al. (funded by Leo Pharma). Trials included in both ITCs exhibited heterogeneity in terms of placebo response, likely due to differences in patient characteristics across trials, which may bias the results of the ITCs. [redacted] Sawyer

et al. adjusted for placebo response; however, it is uncertain whether this approach is adequate to control for differences in patient characteristics that may bias results. [redacted], with Sawyer et al. suggesting that, over short-term induction periods (ranging from 10 weeks to 16 weeks), the relative risk of achieving PASI 50, PASI 75, PASI 90, and PASI 100 responses is statistically greater for BDL than for adalimumab, apremilast, etanercept, USK, infliximab, and secukinumab in patients with moderate-to-severe chronic plaque psoriasis. BDL and ixekizumab appear to result in similar PASI responses after short-term induction treatment, [redacted], while the comparative efficacy of BDL versus guselkumab is less certain, given it was not included in the ITC conducted by Sawyer et al. In addition, the relative efficacy of BDL in comparison with other biologics beyond the short-term induction periods remains unknown. Safety outcomes and HRQoL data were not evaluated in the ITCs.

Harms

Overall, the percentage of patients who experienced treatment-emergent adverse events (TEAEs) during the induction phase were balanced between the treatment groups and ranged from 48% to 60% across the trials. The overall frequency and exposure-adjusted rate of serious adverse events (SAEs) and events leading to study discontinuation were low and were similar across treatment groups in both the induction and maintenance phases within each trial.

Adverse events (AEs) of particular interest were identified for this review, including inflammatory bowel disease (IBD) and suicidal ideation and behaviour, both of which are featured in the Warnings and Precautions section of the Health Canada–approved product monograph. Given the limited data in patients with a history of Crohn's disease, BDL is contraindicated in such patients. The product monograph contains a boxed warning regarding suicidal ideation and behaviour that recommends prescribers weigh the potential risks and benefits in patients with a history of depression or suicidal ideation or behaviour, as well as recommendations for referral of patients with such manifestations. The boxed warning does state that a causal association between treatment with BDL and suicidal ideation and behaviour has not been established. [redacted] risk of suicidal ideation and behaviour. [redacted] physician education, [redacted] enrolment forms [redacted]. The clinical expert consulted for this review indicated that due to this identified risk and the existence of a boxed warning, he expects to monitor patients more frequently than he would with other biologics.

Potential Place in Therapy[1]

Currently, there are eight biologics (including BDL) approved for the treatment of plaque psoriasis. BDL is one of three anti–IL-17 drugs; the other two are monoclonal antibodies (secukinumab and ixekizumab).

The currently available biologics provide good efficacy and a durable response. Less than 10% to 20% of patients fail to respond to one of the biologics or lose efficacy or have a contraindication. BDL is one of eight biologics that may be tried when another drug fails.

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

Biologics are currently used as continuous therapy. When a patient is started on a biologic, the treatment is expected to be continuous and lifelong. Therefore, a major unmet need is a treatment that is remittive or would work well on an intermittent "as needed" basis. So far, neither BDL nor any of the biologics have been demonstrated to fulfill this need.

It does not appear that BDL has any significant advantage over the other drugs. It is simply another choice for patients and physicians.

Conclusions

Based on the results of three phase III RCTs in adults with moderate-to-severe plaque psoriasis, compared with placebo and USK, BDL 210 mg resulted in statistically significant and clinically important improvements in skin clearance and dermatological symptoms over the short-term induction phase, as measured by the PASI and sPGA. Results from [redacted] suggest that over the short-term induction phase, BDL may be more efficacious than a number of other biologics in attaining PASI 75, PASI 90, and PASI 100 responses, but is similar in efficacy to ixekizumab. However, there is some uncertainty in the results of the ITC for short-term efficacy due to between-study heterogeneity that may not have been adequately controlled. Further, longer-term comparative efficacy data from RCTs are lacking.

The size and duration of the included trials were likely insufficient to assess comparative safety, particularly for rare or latent harms. However, the Health Canada–approved product monograph for BDL includes a boxed warning related to the risk of suicidality that may influence prescriber behaviour.

Table 1: Summary of Results

Outcome	Treatment Group Week 12	AMAGINE-1		AMAGINE-2			AMAGINE-3		
		BDL 210	PLB	BDL 210	USK	PLB	BDL 210	USK	PLB
	Week 52	BDL 210	PLB	BDL 210	USK	BDL 210	BDL 210	USK	BDL 210
PASI 75 at Week 12									
n (%)		185 (83.3)	6 (2.7)	528 (86.3)	210 (70.0)	25 (8.1)	531 (85.1)	217 (69.3)	19 (6.0)
***P* value (vs. PLB)**		< 0.001[a]				< 0.001[a]			< 0.001[a]
***P* value (vs. USK)**					0.078			0.007[a]	
PASI 100 at Week 12									
n (%)		93 (41.9)	1 (0.5)	272 (44.4)	65 (21.7)	2 (0.6)	229 (36.7)	58 (18.5)	1 (0.3)
***P* value (vs. PLB)**		< 0.001[a]			< 0.001[a]	< 0.001[a]			< 0.001[a]
***P* value (vs. USK)**					< 0.001[a]			< 0.001[a]	
sPGA Success (Score 0 or 1) at Week 12									
n (%)		168 (75.7)	3 (1.4)	481 (78.6)	183 (61.0)	12 (3.9)	497 (79.6)	179 (57.2)	13 (4.1)
***P* value (vs. PLB)**		< 0.001[a]				< 0.001[a]			< 0.001[a]
***P* value (vs. USK)**					< 0.001			< 0.001	
sPGA Clear (Score 0) at Week 12									
n (%)		93 (41.9)	1 (0.5)	274 (44.8)	65 (21.7)	2 (0.6)	229 (36.7)	58 (18.5)	1 (0.3)
***P* value (vs. PLB)**		< 0.001[a]				< 0.001[a]			< 0.001[a]
***P* value (vs. USK)**					< 0.001			< 0.001	

Outcome	Treatment Group Week 12	AMAGINE-1		AMAGINE-2			AMAGINE-3		
		BDL 210	PLB	BDL 210	USK	PLB	BDL 210	USK	PLB
	Week 52	BDL 210	PLB	BDL 210	USK	BDL 210	BDL 210	USK	BDL 210
PSI Responder (Total Score ≤ 8 With No Item Scores > 1) at Week 12									
n (%)		135 (60.8)	9 (4.1)	414 (67.6)	166 (55.3)	21 (6.8)	382 (61.2)	162 (51.8)	20 (6.3)
***P* value (vs. PLB)**		< 0.001[a]				< 0.001[a]			< 0.001[a]
***P* value (vs. USK)**					ND			ND	
DLQI Improvement ≥ 5 at Week 12									
n (%)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
***P* value (vs. PLB)**		[redacted]				[redacted]			[redacted]
***P* value (vs. USK)**					[redacted]			[redacted]	
sPGA Success (Score 0 or 1) at Week 52									
n (%)		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	
***P* value**		[redacted]		[redacted]			[redacted]		
Study Discontinuations									
Week 12, n (%)		10 (4.5)	12 (5.5)	15 (2.5)	9 (3.0)	9 (2.9)	16 (2.6)	10 (3.2)	14 (4.4)
Week 52, n (%)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs									
Week 12, n (%)		4 (1.8)	3 (1.4)	6 (1.0)	4 (1.3)	8 (2.6)	9 (1.4)	2 (0.6)	3 (1.0)
Week 52, n (r)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs									
Week 12, n (%)		2 (0.9)	3 (1.4)	3 (0.5)	2 (0.7)	0 (0.0)	4 (0.6)	1 (0.3)	0 (0.0)
Week 52, n (%)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Suicidal Ideation, Behaviour, and Attempt (Through Data Cut-Off)									
n (r)		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	

BDL 210 = brodalumab 210 mg; DLQI = Dermatology Life Quality Index; ND = not done; NR = not reported; PASI = Psoriasis Area and Severity Index; PLB = placebo; PSI = Psoriasis Symptom Inventory (total score); SAE = serious adverse event; sPGA = static Physician's Global Assessment; USK = ustekinumab; vs. = versus; WDAE = withdrawal due to adverse event; wk = week.

Notes: *P* values for testing the proportions of patients achieving an outcome were between the BDL and placebo/USK groups and based on the Cochran–Mantel–Haenszel test stratified by total body weight at baseline (≤ 100 kg, > 100 kg), prior biologic use (yes, no), geographic region, and baseline outcome score (or week 12 body weight, week 12 sPGA score, and induction phase treatment only for outcomes measured at week 52) and are nominal without multiplicity adjustment (unless otherwise specified with a superscript [a]). For the AMAGINE-1 trial, *P* values for primary and key secondary outcomes (PASI 100, sPGA 0, sPGA success [week-52], PSI responder) were obtained by applying a sequential testing procedure for multiplicity adjustment so that the statistical significance of a test could be obtained by comparing the adjusted *P* value with a nominal significance level of 0.05. For the AMAGINE-2 and -3 trials, *P* values were based on a testing procedure consisting of a combination of parallel, sequential, and weighted Bonferroni-based recycling testing, which includes all primary and key secondary end point comparisons (PASI 75 and 100, sPGA 0, PSI responder) against placebo and USK, and are to be compared with a significance level of 0.05.

[a] Multiplicity-adjusted *P* values.

Source: AMAGINE-1 CSR,[6] Papp et al. (2016),[10] AMAGINE-2 CSR,[7] AMAGINE-3 CSR,[8] Lebwohl et al. (2015).[11]

Introduction

Disease Prevalence and Incidence

Psoriasis is a chronic, inflammatory, immune-mediated skin disorder that affects approximately 1 million people in Canada and 125 million worldwide.[12] Plaque psoriasis is the most common form of psoriasis. It is characterized by well-demarcated erythematous plaques with silver flaking scales, redness, and papules that are often symmetrically distributed and pruritic. The disorder follows a relapsing-remitting pattern.[1] The common sites for involvement are scalp, extensor elbows, knees, and back. However, the extent of involvement can vary from limited, localized disease to involvement of the majority of the body surface area (BSA).[3] Moderate-to-severe plaque psoriasis can be defined by: the extent of skin coverage, with involvement of more than 5% to 10% of BSA; location, i.e., involvement of the face, palm, groin or sole; or severity, with Psoriasis Area and Severity Index (PASI) score of more than 10.[2] The high visibility of the symptoms of plaque psoriasis may lead to social isolation, stigmatization, embarrassment, high levels of stress, and difficulty in developing interpersonal relationships, and may compromise success at school or work.[4,13] Therefore, psoriasis has a significant impact on patients' physical and psychosocial functioning and well-being as well as on their overall quality of life (QoL).[2,4] In addition, psoriasis patients are at an increased risk of a wide variety of serious comorbidities and inflammatory conditions, including cardiovascular disease (CVD), metabolic syndrome, PsA, and even early mortality.[1-4]

Standards of Therapy

Treatment decision for psoriasis depends on the stage of the disease. According to Canadian Guidelines for the Management of Plaque Psoriasis by Canadian Dermatology Association (CDA),[4,14] first-line therapies for mild presentation include topical therapies such as corticosteroids, calcipotriol, tazarotene, anthralin, and tars, alone or in combination. Calcipotriol/betamethasone is not recommended for use on facial, flexural, and genital areas.[2,4,14,15] Moderate-to-severe plaque psoriasis is defined on the basis of the BSA or PASI cut-offs described previously; however, the CDA guideline recommends the use of the following definition in clinical and daily practices to diagnose patients with moderate-to-severe plaque psoriasis: "if they cannot achieve, or would not be expected to achieve, adequate control using topical drugs, with adequacy defined by the patient's own perception of the disease and its burdens."[4,15] For some patients with moderate-to-severe disease, short-term improvement and limited long-term disease control may be adequate; however, full clearance is often an achievable and appropriate treatment goal.[2,4,14,15] Moderate-to-severe plaque psoriasis requires the use of systemic therapies, often administered concomitantly with topical drugs. Psoriasis is essentially an immune disorder; therefore, the systemic therapies all work by suppressing components of the immune system. The common oral systemic drugs include acitretin, cyclosporine, and methotrexate; prescription of these drugs is based on careful consideration of their clinical benefits and side effects.[2,4,14,15] Acitretin is often given in combination with other topical drugs for rapid and complete control; however, acitretin is highly teratogenic and strictly contraindicated in pregnancy. Cyclosporine is an immunosuppressant that is highly effective in severe disease, but may induce renal toxicity, hypertension, and hypertriglyceridemia; therefore, it is recommended for intermittent rather than continuous long-term use.[2,4,14,15] Methotrexate is an immunomodulatory and anti-proliferative drug that may be used for long-term

management; however, this is associated with liver and systemic toxicity, and is strictly contraindicated in pregnancy due to teratogenic and abortifacient effects.[2,4,14,15]

Biologics were the next systemic therapies to be developed. Initially, all of these drugs targeted tumour necrosis factor (TNF), a key mediator of inflammation. TNF-alpha inhibitors include adalimumab, etanercept, and infliximab, all of which have been approved for use in plaque psoriasis by Health Canada. However, they may be associated with an elevated risk of certain cancers, demyelinating disorders, and tuberculosis (TB) with long-term use.[2,4,14,15] The newest biological drugs target interleukins (ILs) and include ustekinumab (USK) (targets IL-12 and IL-23), guselkumab (targets IL-23), ixekizumab, and secukinumab (both target IL-17). Additional details regarding these treatment options are in Table 2.

Phototherapy is also used for the treatment of moderate-to-severe psoriasis and involves ultraviolet A (UVA) with psoralen (PUVA) and UVB therapy. In PUVA therapy, psoralen is administered orally or by immersing affected areas in a psoralen solution before UVA exposure (oral versus bath PUVA, respectively). While successful in achieving skin clearance and durable response for at least six months following treatment cessation, PUVA is associated with non-melanoma skin cancer; therefore, it is recommended to be combined with other drugs to reduce UV exposure.[2,4,14,15] Broadband UVB has traditionally been used in the past; it is now often applied using a more effective option, narrowband irradiation, which has been shown to have a more benign safety profile and offer remission for at least six to 12 months. However, it is recommended to be given in combination with topical, systemic, or biologic drugs for more rapid and complete control, potentially reducing exposure to both UV light and other therapeutic drugs.[2,4,14,15]

Drug

Brodalumab (BDL) is a human anti–IL-17 receptor A (IL-17 RA) monoclonal antibody that selectively targets human IL-17 RA and antagonizes the effects of IL-17A, IL-17F, IL-17A/F, and IL-25, all of which are pro-inflammatory cytokines implicated in the pathogenesis of psoriasis.[5-8] The Health Canada–approved indication of BDL is for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.[9] The Health Canada–recommended dose of BDL is 210 mg administered by subcutaneous (SC) injection at week 0, week 1, and week 2 followed by 210 mg every two weeks; if an adequate response has not been achieved after 12 weeks to 16 weeks, treatment discontinuation should be considered because continued treatment beyond 16 weeks in patients who have not achieved an adequate response is not likely to result in greater success.[9]

Table 2: Key Characteristics of Biologic Agents for the Treatment of Psoriasis

Biologic	Mechanism of Action	Health Canada–Approved Indication	Route of Administration	Recommended Dose	Serious Side Effects or Safety Issues
Infliximab	TNF inhibitor	Treatment of adult patients with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, infliximab should be used after phototherapy has been shown to be ineffective or inappropriate. When assessing the severity of psoriasis, the physician should consider the extent of involvement, location of lesions, response to previous treatments, and impact of disease on the patient's quality of life.	IV	5 mg/kg given as an IV infusion followed by additional similar doses at 2 weeks and 6 weeks after the first infusion, then every 8 weeks thereafter. If a patient shows no response at 24 weeks, no additional treatment with infliximab should be given.	Infection Cancer
Adalimumab		Treatment of adult patients with chronic moderate-to-severe plaque 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.	SC	80 mg administered SC, followed by 40 mg SC 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.	Infection Cancer
Etanercept		Treatment of adult patients with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.	SC	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.	Infection Cancer
Ustekinumab	IL-12 and IL-23 inhibitor	Treatment of patients with chronic moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy.	SC	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.	Infection Cancer Serious hypersensitivity reactions Immunization

Biologic	Mechanism of Action	Health Canada–Approved Indication	Route of Administration	Recommended Dose	Serious Side Effects or Safety Issues
				For patients who respond inadequately to administration every 12 weeks, consideration may be given to treating as often as every 8 weeks.	
Guselkumab	IL-23 inhibitor	Treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.	SC	100 mg administered at week 0 and week 4, followed by maintenance administration every 8 weeks thereafter.	Infection
Secukinumab	IL-17A inhibitor	Treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.	SC	300 mg with initial administration at weeks 0, 1, 2 and 3, followed by monthly maintenance administration starting at week 4.	Infection Serious hypersensitivity reactions Vaccination Crohn's disease
Ixekizumab		Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.	SC	160 mg at week 0 followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12; then 80 mg every 4 weeks.	Infection Serious hypersensitivity reactions IBD Vaccination
Brodalumab	IL-17 RA	Treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.	SC	210 mg administered by SC injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.	Infection Suicidal ideation and behaviour

IBD = inflammatory bowel disease; IL = interleukin; IV = intravenous; RA = receptor antibody; SC = subcutaneous; TNF = tumour necrosis factor.
Source: Humira Product Monograph;[16] Siliq Product Monograph;[9] Enbrel Product Monograph;[17] Remicade Product Monograph;[18] Taltz Product Monograph;[19] Tremfya Product Monograph;[20] Cosentyx Product Monograph;[21] Stelara Product Monograph.[22]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of BDL 210 mg subcutaneous injection for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CADTH Common Drug Review (CDR) and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adult (≥ 18 years) patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy Subpopulations: prior biologic use, body weight (e.g., < 100 kg vs. ≥ 100 kg)
Intervention	Brodalumab alone or in combination with other therapies: • 210 mg as a subcutaneous injection at week 0, week 1, and week 2, followed by 210 mg every 2 weeks
Comparators	Monotherapy or combination therapy (including adjunctive topical therapy) with: **Non-biologic systemic drugs:** Acitretin, apremilast, cyclosporine, methotrexate **Biologic drugs targeting TNF-alpha:** Adalimumab, etanercept, infliximab **Biologic drugs targeting interleukins:** Ixekizumab, secukinumab, ustekinumab, guselkumab
Outcomes	**Key efficacy outcomes:** • Health-related quality of life by a validated instrument (e.g., DLQI, SF-36, EQ-5D)[a] • Skin clearance/ psoriasis score (e.g., PASI response, global assessment)[a] • Patient-reported symptoms (e.g., PSI)[a] **Harms outcomes:** Mortality, AEs, SAEs, WDAEs Notable harms including but not limited to: • Infections • Injection-site reactions • Inflammatory bowel disease • Suicidal ideation and behaviour • Serious hypersensitivity reactions • Malignancy
Study Design	Published and unpublished RCTs; phase III and higher

AE = adverse events; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimensions questionnaire; PASI = Psoriasis Area and Severity Index; PSI = Psoriasis Symptom Inventory; RCT = randomized controlled trial; SAE = serious adverse event; SF-36 = Short Form (36) Health Survey; TNF = tumour necrosis factor; vs. = versus; WDAE = withdrawal due to adverse event.

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

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 ALL (1946–) through Ovid; Embase (1974–) through 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 Siliq (BDL).

No methodological filters were applied to limit retrieval to 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 January 19, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on May 16, 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 CADTH *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; Databases; and Internet search.

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 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; differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in Table 13.

Results

Findings From the Literature

A total of three studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Table 13.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

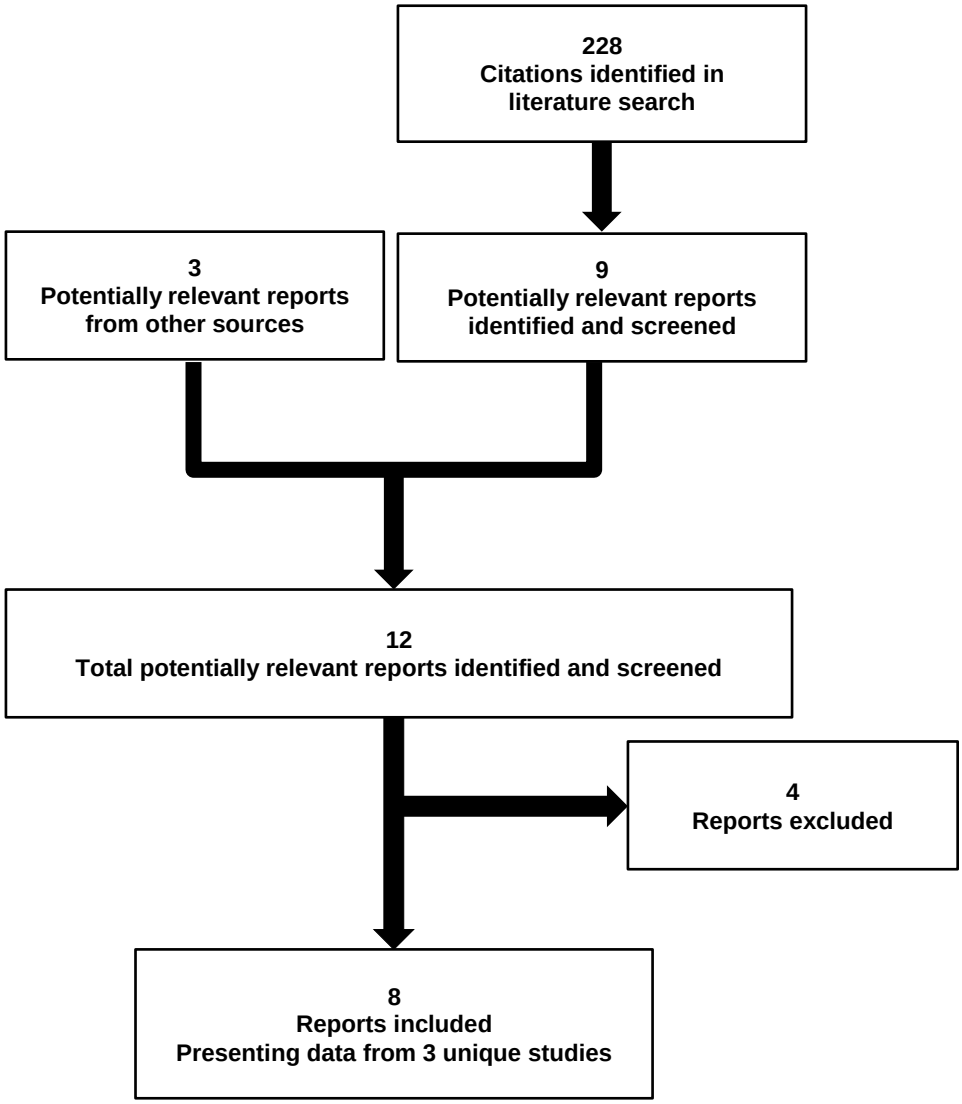


Table 4: Details of Included Studies

		AMAGINE-1	AMAGINE-2	AMAGINE-3
Designs and Populations	**Study Design**	DB, placebo-controlled RCT	DB, placebo- and active-controlled RCT	DB, placebo- and active-controlled RCT
	Locations	73 centres in Europe, Canada, and US	142 centres in Australia, Canada, Europe, and US	142 centres in Australia, Canada, Europe, and US
	Randomized (N)	661	1,831	1,881
	Inclusion Criteria	• Men and non-pregnant women ≥ 18 and ≤ 75 years of age • Stable moderate-to-severe plaque psoriasis (defined as BSA ≥ 10%, PASI ≥ 12, and sPGA ≥ 3 at screening and at baseline) diagnosed at least 6 months prior to study • No known history of active tuberculosis and negative for tuberculosis during screening		
	Exclusion Criteria	• Interfering skin conditions (pustular, erythrodermic, guttate forms of psoriasis, medication-induced psoriasis, and eczema) • Active infection within 28 days or history of serious infection within 8 weeks • History of Crohn's disease, hepatitis B, hepatitis C or HIV • Myocardial infarction or unstable angina pectoris within 12 months; active malignancy or a history of malignancy within 5 years; or any concurrent disease considered to be clinically significant and uncontrolled • Previous history of the following medications (allowed within washout period): super-potent or potent topical therapy, non-biological systemic therapy for psoriasis or live vaccines, biological immune modulator (ever), phototherapy, USK, anti–IL-17 biological therapy		
Drugs	**Intervention**	**Week 0 to 12:** SC BDL 210 mg q.2.w. or 140 mg q.2.w. **Week 12 to 52:** BDL at induction dose	**Week 0 to 12:** SC BDL 210 mg q.2.w. or 140 mg q.2.w. **Week 12 to 52:** BDL 210 mg q.2.w., 140 mg q.2.w., 140 mg q.4.w., or 140 mg q.8.w.	**Week 0 to 12:** SC BDL 210 mg q.2.w. or 140 mg q.2.w. **Week 12 to 52:** BDL 210 mg q.2.w., 140 mg q.2.w., 140 mg q.4.w. or 140 mg q.8.w.
	Comparator(s)	**Week 0 to 12:** PLB **Week 12 to 52:** PLB	**Week 0 to 12:** USK (45 mg if ≤ 100 kg or 90 mg if > 100 kg) PLB **Week 12 to 52:** USK at induction dose	**Week 0 to 12:** USK (45 mg if ≤ 100 kg or 90 mg if > 100 kg) PLB **Week 12 to 52:** USK at induction dose
Duration	**Phase**			
	Screening	Day 0 **to** 30	Day 0 **to** 30	Day 0 **to** 30
	Double-blind	Induction phase: week 0 **to** 12 Withdrawal phase: week 12 **to** 52	Induction phase: week 0 **to** 12 Maintenance phase: week 0 **to** 52	Induction phase: week 0 **to** 12 Maintenance phase: week 12 **to** 52
	Extension	Up to 266 wks	Up to 266 wks	Up to 266 wks
Outcomes	**Primary End Points**	Co-primary: proportion of patients with sPGA success (0 to 1) at wk 12 Proportion of patients with PASI 75 at wk 12	**Within PLB family:** Co-primary: proportion of patients with sPGA success (0 to 1) at wk 12 Proportion of patients with PASI 75 at wk 12 **Within USK family:** Proportion of patients with PASI 100 at wk 12	
	Key Secondary End Points	**Induction phase** Proportion of patients with sPGA 0 at wk 12 Proportion of patients with PASI 100 at wk 12 Proportion of patients with PSI score ≤ 8 and no item > 1 at wk 12	**Induction phase** **Within PLB family:** Proportion of patients with PASI 100 at wk 12 Proportion of patients with sPGA 0 at wk 12 Proportion of patients with PSI score ≤ 8 and no item > 1 at wk 12 **Within USK family:** Proportion of patients with PASI 75 at wk 12	

		AMAGINE-1	AMAGINE-2	AMAGINE-3
		Withdrawal phase Proportion of patients with sPGA success (0 to 1) at wk 52		
	Other Secondary End Points	**Health-related quality of life outcomes (week 12 and 52)** • Proportion of patients with DLQI ≥ 5 points improvement • Proportion of patients with DLQI score 0/1 • Change in EQ-5D-3L index score and VAS from baseline • Change in SF-36 PCS and MCS from baseline **Symptoms-related outcomes** • Proportion of patients with sPGA 0 (wk 52) • Proportion of patients with PSI 0 score (wk 12 and 52)	**Within PLB family: health-related quality of life outcomes (week 12 and 52)** • Proportion of patients with DLQI ≥ 5 points improvement • Proportion of patients with DLQI score 0/1 **Symptoms-related outcomes** • Proportion of patients with sPGA 0 and success (wk 52) • Proportion of patients with PSI 0 score (wk 12 and 52)	
NOTES	**Publications**	Papp et al. (2016)	Lebwohl et al. (2015)	

BDL = brodalumab; BSA = body surface area; DB = double-blind; DLQI = Dermatology Life Quality Index; EMA = European Medicines Agency; EQ-5D = EuroQol 5-Dimensions questionnaire; IL = interleukin; MCS = mental component summary; PASI = Psoriasis Area and Severity Index; PCS = physical component summary; PLB = placebo; PSI = Psoriasis Symptoms Inventory; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.8.w. = every 8 weeks; RCT = randomized controlled trial; SC = subcutaneous; SF-36 = Short Form (36) Health Survey; sPGA = static Physician Global Scale; USK = ustekinumab; VAS = visual analogue scale; wk = week.

Note: Three additional reports were included (FDA Briefing Document,[3] National Institute for Health and Care Excellence Single Technology Appraisal report,[13] EMA Assessment report[23]).

Source: AMAGINE-1 CSR,[6] Papp et al. (2016),[10] AMAGINE-2 CSR,[7] AMAGINE-3 CSR,[8] Lebwohl et al. (2015).[11]

Included Studies

Description of Studies

Three phase III, double-blind, parallel-group, multi-centre randomized controlled trials (RCTs) that evaluated the efficacy and safety of BDL were included in this review: AMAGINE-1 (N = 661)[6], AMAGINE-2 (N = 1,831),[7] and AMAGINE-3 (N = 1,881).[8]

AMAGINE-1 was a placebo-controlled trial that consisted of a 12-week, double-blind induction phase in which patients were randomized to one of two doses of BDL (140 mg or 210 mg) or placebo followed by a 40-week withdrawal and retreatment phase during which BDL-treated responders (based on static Physician's Global Assessment [sPGA]) were re-randomized to either continue their original BDL dose or switch to placebo. BDL-treated nonresponders and those originally randomized to placebo were not re-randomized at week 12, but rather were to receive BDL 210 mg for the remaining 40 weeks. After week 52, patients could enter the long-term open-label extension phase, up to 266 weeks (further described in Appendix 6).

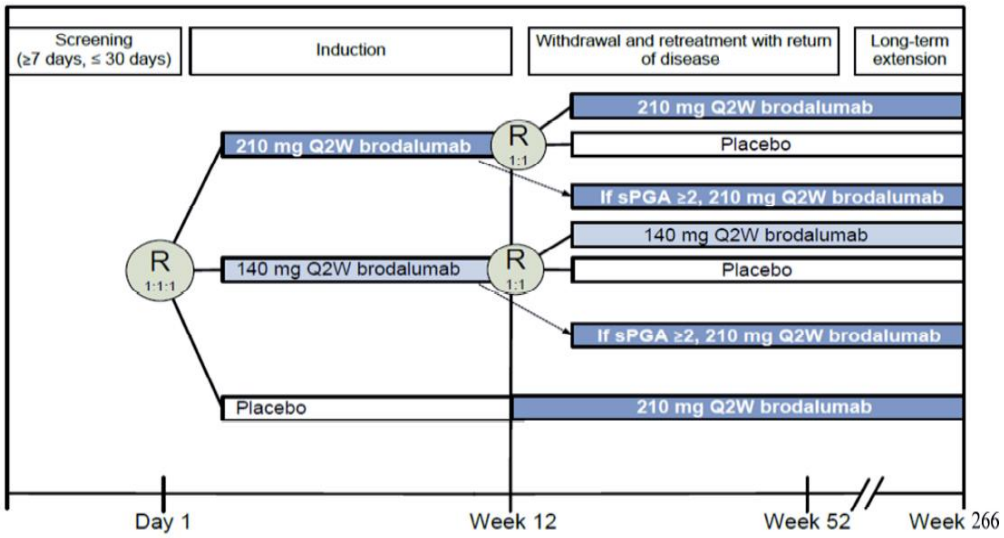
AMAGINE-2 and AMAGINE-3 were identically designed, double-dummy, active-controlled trials consisting of a 12-week double-blind induction phase in which patients were randomized to one of two doses of BDL (140 mg or 210 mg), USK (dose based on baseline

weight), or placebo. The induction phase was followed by a 40-week maintenance phase in which all patients originally randomized to either dose of BDL were combined and re-randomized to one of four BDL maintenance doses. Patients originally randomized to USK were to continue USK treatment, and patients originally randomized to placebo were switched to BDL 210 mg. Subsequent to week 52, patients could enter a long-term open-label phase up to 266 weeks. (Refer to Appendix 6 for details).

Given the approved Health Canada dosage, comparisons of interest for efficacy in AMAGINE-1 include the BDL 210 mg versus placebo groups, both at week 12 and through week 52 for responders to BDL 210 mg re-randomized to placebo or continued treatment. In AMAGINE-2 and AMAGINE-3, comparisons of interest for efficacy include BDL 210 mg versus both placebo and USK at week 12. Given that longer-term comparative efficacy is of interest, we also report data through week 52 for patients originally randomized to BDL 210 mg and subsequently re-randomized to continue on the same dose of BDL (BDL 210/BDL 210) as well as for those patients who were originally randomized to USK. In terms of safety data, we report the harms associated with BDL 210 mg, placebo, and USK from week 0 to week 12. Beyond week 12 (i.e., through week 52), we provide harms as exposure-adjusted rates for USK, as well as for BDL 210 mg exposure only, and "all BDL" exposure (i.e., exposure-adjusted rate for any BDL dose).

Participants in all three trials were randomized centrally (i.e., independent of the study team) at baseline and re-randomized at week 12 through an interactive voice response system (IVRS). The randomization (and re-randomization) was done using a permuted block design and stratified by baseline total body weight (≤ 100 kg; > 100 kg), prior biologic use, and geographic region for the induction phase, and by week-12 total body weight, week-12 response (sPGA = 0, sPGA ≥ 1), and the original randomization treatment group (210 mg every two weeks, 140 mg every two weeks) for the withdrawal/maintenance phase.

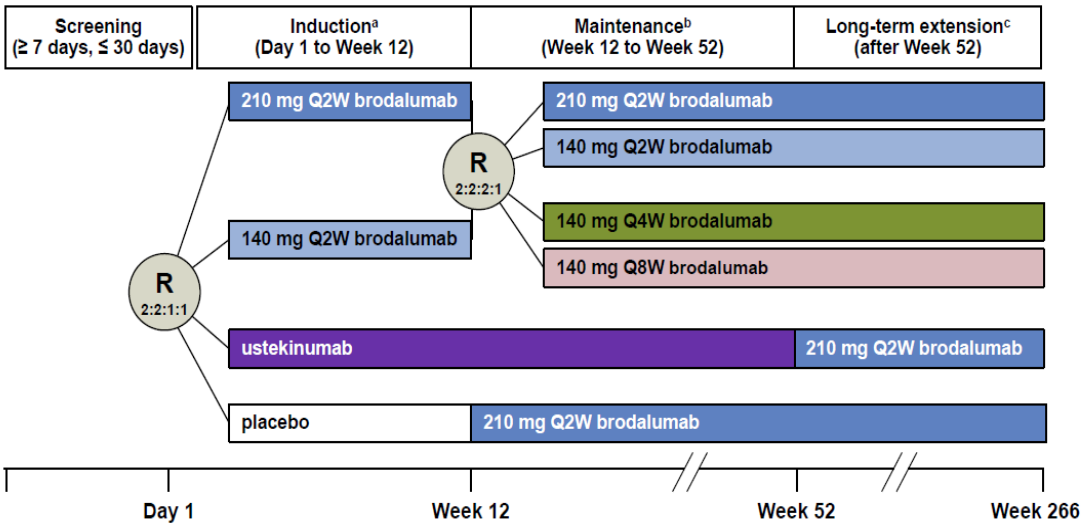
Figure 2: Study Design and Treatment Schema (AMAGINE-1)



q.2.w. = every 2 weeks; R = randomization; sPGA = static Physician Global Scale.

Source: AMAGINE-1 CSR.[6]

Figure 3: Study Design and Treatment Schema (AMAGINE-2 and -3)



q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; R = randomization.

Source: AMAGINE-2 and -3 CSRs.[7,8]

Populations

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria of all three trials were similar and are described in Table 4. Eligible patients were men and non-pregnant women aged ≥ 18 to ≤ 75 years with stable moderate-to-severe plaque psoriasis for at least six months prior to study entry who were eligible for biologic treatment (at the discretion of the site investigator). Patients were required to have a BSA involvement of ≥ 10%, a PASI score ≥ 12, and a sPGA score ≥ 3 at screening and at baseline. Additionally, patients had no known history of active TB and tested negative for TB at screening (or received prophylactic treatment). They must also have completed appropriate washout periods for drugs (details follow).

Patients were excluded if they had any of the following medical conditions: any interfering skin conditions (pustular, erythrodermic, guttate forms of psoriasis, medication-induced psoriasis, and eczema); active infection or history of serious infection; known history of Crohn's disease, hepatitis B, hepatitis C, or HIV; history of myocardial infarction or unstable angina pectoris; previous (unless treated and cured) or active malignancy (including cutaneous basal or squamous cell carcinoma or melanoma, cervical cancer, breast ductal carcinoma); and any clinically significant and uncontrolled concurrent disease.

Patients who administered the following therapy were either excluded or underwent the washout periods specified: topical therapy, either super-potent or potent topical steroids or topical anthralin/dithranol (within 28 days); other formulation or potency of topical therapy (within 14 days); phototherapy; non-biological systemic therapy for psoriasis or live vaccines (within 28 days); USK; anti–IL-17 biological therapy (ever); or other biological immune modulator (within 12 weeks). Of note, patients with prior use of biologics were capped at 50% of the study population in all three trials.

Baseline Characteristics

Details regarding baseline characteristics of study patients are provided in Table 5. Overall, baseline demographic characteristics were similar between the trials as well as among the treatment groups within trials. The majority of the patients were male (~70%) and white (~90%). The mean age and weight of the patients across the trials were approximately 45 years and 90 kg, respectively. Patients in the AMAGINE-1 trial had a slightly longer duration of psoriasis than AMAGINE-2 and -3 (approximately 20 years compared with 18 years, respectively). In addition, AMAGINE-1 had a greater proportion of patients with PsA than AMAGINE-2 and -3 (approximately 27% in AMAGINE-1 versus a range of 16% and 20% across treatment groups in AMAGINE-2 and -3).

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. More than half of the patients (51% to 61%) had a baseline sPGA score of 3 (moderate). Across the trials, the mean PASI score and weekly Psoriasis Symptoms Inventory (PSI) score were approximately 20 and 18, respectively, while BSA involvement was approximately 26%.

There was no notable imbalance in the prior psoriasis therapy history across the treatment groups within each trial. The majority of the patients (~90%) in all trials received at least one therapy for psoriasis prior to enrolling into the study. Approximately three-quarters of the patients across the trials received any topical treatment (steroids or non-steroids; e.g., vitamin D analogues, anthraline, tar compounds, and calcineurin inhibitors). The proportions of patients receiving phototherapy were greater in the AMAGINE-1 and -2 trial compared with AMAGINE-3 (approximately 50% compared with 40%, respectively). A greater proportion of patients had previously received non-biologic systemic therapy in the AMAGINE-1 trial (~70%) compared with AMAGINE-2 (~60%) and -3 (~53%). The proportion of patients having previously received biologic medications for psoriasis was also greater in the AMAGINE-1 trial (~45%) compared with AMAGINE-2 and -3 (ranging between 24% and 28% between treatment arms across trials). Overall, the most common prior non-biologic medications included methotrexate, oral retinoids, and cyclosporine; etanercept, USK, adalimumab, infliximab, and efalizumab constituted the most common prior biologics.

In AMAGINE-2 and -3, baseline demographics and physical and disease characteristics were examined separately for patients who entered the maintenance phase — specifically, those re-randomized to BDL 210 mg at week 12 and those who remained on USK. In both AMAGINE-2 and -3, the proportion of patients with PsA was greater in the BDL 210 mg arm compared with USK (22.6% versus 17.0% and 24.0% versus 20.3%, respectively), Among other notable factors, BDL-treated patients in AMAGINE-2 had a lower mean duration of psoriasis and a smaller proportion with an sPGA score of 4 compared with USK (16.9 versus 19.3 years and 38.7% versus 44.3%, respectively). In contrast, patients in the BDL 210 mg arm in AMAGINE-3 had a greater proportion of patients with an sPGA score of 4 compared with USK (37.4% versus 32.9%). With the exception of these disease characteristics, other demographics, patient, and disease characteristics were largely similar among treatment groups within trials for patients receiving consistent BDL 210 mg and USK administration through week 52 (data not shown).

Table 5: Summary of Baseline Characteristics

Baseline Characteristic	AMAGINE-1		AMAGINE-2			AMAGINE-3		
	BDL 210	PLB	BDL 210	USK	PLB	BDL 210	USK	PLB
N	222	220	612	300	309	624	313	315
Age, yr **Mean (SD)**	46.3 (12.2)	46.9 (13.2)	44.5 (12.7)	45.4 (13.0)	43.7 (12.9)	45.2 (13.3)	44.8 (13.1)	44.2 (12.5)
Male, n (%)	161 (72.5)	161 (73.2)	421 (68.8)	205 (68.3)	219 (70.9)	431 (69.1)	212 (67.7)	208 (66.0)
Race, n (%) **White** **Asian** **Black**	 203 (91.4) 10 (4.5) 3 (1.4)	 202 (91.8) 8 (3.6) 6 (2.7)	 551 (90.0) 19 (3.1) 19 (3.1)	 271 (90.3) 12 (4.0) 7 (2.3)	 273 (88.3) 12 (3.9) 14 (4.5)	 565 (90.5) 20 (3.2) 17 (2.7)	 280 (89.5) 12 (3.8) 13 (4.2)	 294 (93.3) 9 (2.9) 6 (1.9)
Weight, kg **Mean (SD)**	91.37 (23.36)	90.36 (20.12)	91.16 (22.86)	91.30 (23.72)	91.53 (23.43)	90.06 (23.18)	90.16 (21.98)	88.74 (21.93)
Weight group, n (%) **≤ 100 kg** **> 100 kg**	 156 (70.3) 66 (29.7)	 159 (72.3) 61 (27.7)	 428 (69.9) 184 (30.1)	 214 (71.3) 86 (28.7)	 216 (69.9) 93 (30.1)	 458 (73.4) 166 (26.6)	 227 (72.5) 86 (27.5)	 233 (74.0) 82 (26.0)
BMI, kg/m^2 **Mean (SD)**	31.03 (7.70)	30.25 (6.58)	30.53 (7.23)	30.61 (7.07)	30.49 (7.02)	30.29 (7.33)	30.43 (6.82)	29.88 (6.71)
Duration of Ps, yr **Mean (SD)**	20.4 (13.2)	20.7 (12.1)	18.7 (12.1)	19.1 (12.7)	17.6 (12.3)	18.1 (12.4)	18.0 (11.7)	17.9 (11.7)
Presence of PsA, n (%) **Yes**	58 (26.1)	63 (28.6)	114 (18.6)	50 (16.7)	51 (16.5)	127 (20.4)	64 (20.4)	59 (18.7)
BSA, % **Mean (SD)**	25.06 (15.25)	26.90 (17.11)	26.04 (16.26)	27.04 (19.34)	27.88 (16.95)	28.27 (17.66)	28.11 (17.62)	27.67 (17.40)
PASI **Mean (SD)**	19.41 (6.61)	19.72 (7.71)	20.29 (8.28)	19.98 (8.35)	20.36 (8.20)	20.39 (8.25)	20.11 (8.37)	20.11 (8.68)
sPGA – n (%) **0/1/2** **3** **4** **5**	 0 (0.0) 121 (54.5) 87 (39.2) 14 (6.3)	 0 (0.0) 114 (51.8) 91 (41.4) 15 (6.8)	 0 (0.0) 316 (51.6) 254 (41.5) 42 (6.9)	 – 153 (51.0) 132 (44.0) 15 (5.0)	 – 167 (54.0) 120 (38.8) 22 (7.1)	 0 (0.0) 373 (59.8) 226 (36.2) 25 (4.0)	 0 (0.0) 192 (61.3) 103 (32.9) 18 (5.8)	 0 (0.0) 192 (61.0) 113 (35.9) 10 (3.2)
PSI – wkly avg **Mean (SD)**	18.9 (6.7)	19.0 (6.7)	18.6 (6.8)	18.9 (7.0)	18.6 (7.1)	18.7 (7.2)	18.7 (6.8)	19.0 (6.7)
DLQI (0 to 30), **Mean (SD)**	14.2 (7.3)	13.9 (6.8)	14.7 (7.1)	15.1 (7.2)	15.0 (7.1)	14.5 (7.2)	14.6 (7.4)	14.2 (6.6)
Prior treatment, n (%) **Topicals (any)** **Phototherapy** **Non-Biologic Systemic** **Biologics**	173 (77.9) 112 (50.5) 155 (69.8) 105 (47.3)	175 (79.5) 119 (54.1) 164 (74.5) 101 (45.9)	496 (81.0) 318 (52.0) 378 (61.8) 177 (28.9)	258 (86.0) 151 (50.3) 187 (62.3) 84 (28.0)	263 (85.1) 160 (51.8) 182 (58.9) 90 (29.1)	477 (76.4) 252 (40.4) 332 (53.2) 157 (25.2)	239 (76.4) 137 (43.8) 168 (53.7) 75 (24.0)	236 (74.9) 118 (37.5) 162 (51.4) 76 (24.1)
Prior Failure of Biologics (%)	44 (19.8)	41 (18.6)	85 (13.9)	40 (13.3)	40 (12.9)	65 (10.4)	22 (7.0)	24 (7.6)

BDL 210 = brodalumab 210 mg; BMI = body mass index; BSA = body surface area; DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area and Severity Index; PLB = placebo; Ps = psoriasis; PsA = psoriatic arthritis; PSI = Psoriasis Symptom Inventory total score; SD = standard deviation; sPGA = static Physician's Global Assessment; USK = ustekinumab; wkly avg = weekly average; yr = years.

Source: AMAGINE-1 CSR,[6] Papp et al.(2016),[10] AMAGINE-2 CSR,[7] AMAGINE-3 CSR,[8] Lebwohl et al. (2015).[11]

Interventions

All investigational products (BDL, USK, and placebo) were administered using single-use, pre-filled syringes. Injections were administered SC to the abdomen, thigh, gluteal region, or upper arm. Administration of all investigational products was conducted by a qualified staff member before week 24 (AMAGINE-1) or week 28 (AMAGINE-2 and -3), and all subsequent injections were self-administered (self-administration included administration by a trained caregiver).

AMAGINE-1

Induction Phase (Week 0 to Week 12)

- BDL 210 mg, 140 mg, or placebo (randomized in a 1:1:1 ratio) administered at day 1 and weeks 1, 2, 4, 6, 8, and 10.

Withdrawal and Retreatment Phase (Week 12 to Week 52)

- During the withdrawal phase and retreatment phase, patients originally randomized to BDL who achieved sPGA success (clear [0] or almost clear [1]) at week 12 were re-randomized to receive either their induction dose of BDL or placebo (in a 1:1 ratio). The treatments were administered at weeks 12, 13, 14, and every other week thereafter. Notably, patients assigned to receive either dose of BDL received placebo injections at week 13. This report will only focus on patients re-randomized to either BDL 210 mg or placebo.
- Beginning at week 16, any re-randomized patients with a return of disease (sPGA ≥ 3) was eligible for retreatment and received three weekly induction doses of BDL, followed by BDL every two weeks at their induction dose. In addition, retreated patients who had an inadequate response to retreatment (persistent sPGA value of 2 over at least a four-week period or a single sPGA ≥ 3) received rescue therapy consisting of open-label BDL 210 mg every two weeks. Patients receiving rescue therapy for at least 12 weeks were assessed for nonresponse (persistent sPGA values ≥ 3 over at least a four-week period while on continuous treatment for at least 12 weeks) and had to discontinue the study if nonresponsiveness persisted.
- Patients who did not achieve sPGA success (score of 0 or 1) and those who received placebo during the induction phase were not re-randomized but instead received open-label BDL 210 mg every two weeks to week 52 without undergoing retreatment or rescue therapy. Those who were nonresponders (assessed at week 24 using the same criteria described previously) discontinued the study. No efficacy data for patients who were not re-randomized are included in this report.

Subsequent to week 52, patients continued their withdrawal phase, retreatment, or rescue dose, as appropriate, through the open-label long-term extension phase.

AMAGINE-2 and AMAGINE-3

Induction Phase (Week 0 to Week 12)

Patients were randomized (2:2:1:1) respectively to:

- BDL 210 mg at day 1 and weeks 1, 2, 4, 6, 8, and 10
- BDL 140 mg at day 1 and weeks 1, 2, 4, 6, 8, and 10
- USK (45 mg if ≤ 100 kg or 90 mg if > 100 kg at baseline) at day 1 and week 4

- Placebo as double-blind, double-dummy injections.

Maintenance Phase (Week 12 to Week 52)

- Patients originally randomized to receive either dose of BDL were combined and re-randomized (in a 2:2:2:1 ratio) to receive BDL 210 mg every two weeks, 140 mg every two weeks, 140 mg every four weeks, and 140 mg every eight weeks at weeks 12, 13, 14, 16, 17, 18, and every other week thereafter. Notably, patients re-randomized to receive BDL (210 mg or 140 mg) every two weeks received placebo injections during week 13 and week 17. In addition, those who were assigned to receive BDL 140 mg every four weeks and every eight weeks received the active treatment every fourth or eighth week starting from week 12, respectively. During every alternate week, these patients received placebo injections to maintain the blind with the every-two-weeks group.
- Patients originally randomized to receive placebo were not re-randomized, but rather switched to BDL 210 mg every two weeks through the maintenance phase. Patients originally randomized to USK were also not re-randomized and instead continued to receive USK at their induction phase dose starting at week 16 and every 12 weeks thereafter until week 52, after which patients could receive BDL 210 mg every two weeks in the open-label extension phase. Original treatment blinding was maintained until week 52.
- Rescue treatment was provided to patients who, at or after week 16, had an inadequate response (single sPGA of ≥ 3 or persistent sPGA values of 2 over at least a four-week period). The treatment regimen of rescue therapy varied depending on when rescue therapy was needed. At week 16, rescue therapy consisted of BDL 210 mg for all treatment groups, including patients on USK. However, rescue therapy after week 16 consisted of BDL 210 mg for patients in any of the BDL arms, whereas patients on USK continued to receive USK. Patients who were nonresponsive to rescue therapy (persistent sPGA values ≥ 3 over at least a four-week period while on continuous treatment for at least 12 weeks) discontinued the study.

Following the 52-week double-blind phase, patients who entered the long-term extension phase continued their BDL dose as per the maintenance or rescue phase. Patients who were receiving USK during maintenance were switched to BDL 210 mg every two weeks at week 52 (with an additional dose at week 53). Patients who qualified for rescue after week 52 received BDL 210 mg every two weeks.

Patients were prescribed any concomitant medications or treatments that were deemed necessary to provide adequate supportive care, including low- to mid-strength topical therapy (except calcineurin inhibitors and vitamin D analogues, but only until week 64); oral, parenteral, intramuscular, intra-articular corticosteroids (only after week 64 and for non–psoriasis-related conditions; exceptions included otic, nasal, ophthalmic, or inhaled corticosteroids before week 64); and live vaccines (only after week 55).

The following treatments were prohibited throughout the duration of the studies: phototherapy (UVA or UVB), methotrexate, mycophenolate mofetil, cyclophosphamide, cyclosporine, calcineurin inhibitors, azathioprine, thioguanine, oral retinoids, hydroxyurea, fumarates, and other biologics for psoriasis treatment (including but not limited to etanercept, alefacept, anakinra, adalimumab, infliximab, and IL-12 or IL-23 inhibitors [other than USK], and any other systemic therapy).

Outcomes

The following symptoms-related efficacy end points were measured in all three trials and assessed throughout the double-blind phase:

- sPGA success (sPGA score of 0 indicating clear or 1 indicating almost clear)
- PASI scores of 75, 90, or 100 (i.e., a 75% or 100% improvement in the score)
- PSI response (total score ≤ 8, with no item scores > 1)

Static Physician's Global Assessment

The sPGA is a single estimate of a physician's impression of a patient's psoriasis.[24] This is an ordinal scale where psoriatic lesions are graded for induration, erythema, and scaling based on a scale of 0 to 5, where higher scores indicate a more severe condition.[25,26] The sum of the three scales are added and divided by three to obtain a final sPGA, interpreted as:

- 0 = Cleared, except for residual discoloration
- 1 = Minimal
- 2 = Mild
- 3 = Moderate
- 4 = Marked
- 5 = Severe

No minimally important difference (MID) for patients with plaque psoriasis was identified.

Psoriasis Area and Severity Index

PASI is a widely used instrument in psoriasis trials and clinical practices that grades the severity of psoriatic lesions and the patient's response to treatment. It combines the extent of BSA involvement in four anatomical regions (head, trunk, arms, and legs) and the severity of desquamation, erythema, and plaque induration or infiltration (thickness) in each region. Patients are given a numeric score ranging from 0 to 72, where higher scores indicate worsened symptoms.[24] In general, a PASI score of > 5 to 10 is considered moderate disease and a score of more than 10 is considered severe. A 75% reduction in the PASI score (PASI 75) is the current benchmark for most clinical trials in psoriasis and is the criterion for efficacy of new psoriasis treatments approved by the FDA.[27] However, newer biologics have been shown to be capable of achieving PASI 90 to PASI 100.[27,28]

Psoriasis Symptoms Inventory

PSI is a psoriasis-specific, patient-reported outcome used to assess the severity of psoriasis-related symptoms. PSI involves eight items — including itch, redness, scaling, burning, stinging, cracking, flaking, and pain — that are measured using a 5-point Likert-type scale ranging from 0 (not at all severe) to 4 (very severe). Individual scores are summed to create a total score ranging from 0 to 32, with higher scores indicating a more severe condition.[28-30] No reported MID was found for this outcome.

The following health-related quality of life (HRQoL) end points were measured in the trials, assessed throughout the double-blind phase:

- Dermatology Life Quality Index (DLQI)
- EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) questionnaire (index score and visual analogue scale [VAS])

- Short Form (36) Health Survey (SF-36), physical component summary (PCS) and mental component summary (MCS)

Dermatology Life Quality Index

The DLQI is a widely used dermatology-specific questionnaire to assess the impact of disease on a patient's QoL. It consists of a 10-item, patient-reported questionnaire assessing six different domains that may affect QoL: symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment.[31] The DLQI produces a numeric score that can range from 0 to 30; the higher the score, the greater the impairment in QoL.[32,33] DLQI scores are interpreted in the following way, with estimates of MID ranging from 2.2 to 6.9:[32-36]

- 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

EuroQol 5-Dimensions 3-Levels Questionnaire

The EQ-5D-3L is a generic, preference-based measure of HRQoL that has been applied to a wide range of health conditions and treatments, including psoriasis. It consists of two parts: a descriptive system and a VAS.[37,38] The descriptive system consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose one level that reflects their own health state for each of the five dimensions.[37,38] A scoring function is used to assign a value (EQ-5D-3L index score) to self-reported health states, with estimates of MID for the EQ-5D-3L index score ranging from 0.09 to 0.22.[32,37,38] The second part of the EQ-5D-3L is a 20 cm VAS that has end points labelled 0 and 100, representing the "worst imaginable health state" and "best imaginable health state," respectively.[37,38] Respondents are asked to rate their own health on the EQ-VAS that best represents their health on that day, with reported MID ranging from 3.82 to 10.34 in psoriasis patients.[32,37,38]

Short Form (36) Health Survey

The SF-36 is a generic measure of HRQoL that has been used extensively in clinical trials in many disease areas. It is composed of 36 items covering eight domains: physical functioning, role physical, role emotional, bodily pain, vitality, social functioning, mental health, and general health. The eight domains are aggregated to create the PCS and MCS, with scores ranging from 0 to 100; higher scores indicate better health status. The MIDs for the PCS and MCS in psoriasis have been reported to range between 2.57 to 3.91 and 3.89 to 6.05, respectively.[32,39-41]

Safety

A number of safety end points were measured throughout the duration of each study and involved adverse events (AEs), serious adverse events (SAEs), serious infectious events, laboratory assessments, vital signs, electrocardiograms, and anti-BDL antibody formation. In addition, several AEs of interest were recorded, including injection-site reactions, neutropenia, hypersensitivity reactions, suicidal ideation and behaviour, and malignancies.

An AE was defined as any untoward medical occurrence in a patient regardless of a causal relationship between the treatment and the AE outcome. This included worsening of pre-existing medical conditions (i.e., an increase in severity, frequency, duration), or was associated with a significantly worse outcome. Incidences of SAEs were also recorded and involved any one of the following criteria: was fatal or life-threatening, required in-patient hospitalization (overnight) or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity or a congenital anomaly or birth defect, and any other medically important serious event.

Statistical Analysis

Analyses of Primary and Key Secondary Efficacy End Points

For AMAGINE-1 in the induction phase, sPGA success and PASI 75 at week 12 (co-primary end points) were compared between the BDL 210 mg every two weeks and placebo treatment arms using Cochran–Mantel–Haenszel (CMH) tests adjusting for baseline total body weight (≤ 100 kg, > 100 kg), prior biologic use (yes, no), and geographic region. For sPGA success, the baseline sPGA was also included as a covariate in the model, while the baseline PASI group (≤ median, > median) was included in the model for PASI 75. For the secondary end points, all continuous variables were analyzed with analysis of covariance (ANCOVA), adjusting for the same baseline and stratification factors as the CMH tests. The analyses for the withdrawal and retreatment phase (week 12 to week 52) were adjusted for the same covariates as the analyses for the induction phase. Dichotomous secondary end points were analyzed in the same manner as the dichotomous primary end points in the induction phase; however, the analyses of the withdrawal and retreatment phase (week 12 to week 52) were adjusted for week 12 sPGA (0/1) and week 12 body weight.

For AMAGINE-2 and AMAGINE-3, the statistical methods were similar to AMAGINE-1 for the induction phase. However, the primary end point was defined differently for the active comparison between BDL 210 mg versus USK, as outlined in Table 7. In the maintenance phases of AMAGINE-2 and AMAGINE-3, no statistical comparisons were made between BDL 210 mg and USK.

Sensitivity Analyses

For all categorical and continuous variables, a set of additional and sensitivity analyses were conducted using logistic regression and stratified Wilcoxon rank sum test, respectively, adjusting for the same covariates. The stratified Wilcoxon rank sum test was conducted in case the (continuous) data did not have a normal distribution; however, data from these analyses were not presented in this report.

Subgroup Analyses

Subgroup analyses were also conducted to assess the response to treatment within a number of different subgroups. This review includes subgroup analyses by prior biologic use, prior failure to biologics, and total body weight. These subgroups were specified a priori.

Adjustment for Multiplicity

In AMAGINE-1, a sequential testing procedure for the primary and key secondary efficacy analyses was implemented to maintain the two-sided, family-wise, type-1 error rate at 5%. With sequential testing procedure, each prior comparison must have a significant difference before another comparison can be tested for significance. The adjusted *P* values for the primary and key secondary outcomes were tested to maintain an overall alpha level of 0.05 in the order listed in Table 6. The *P* values for the analyses of all other outcomes, including withdrawal phase outcomes, were nominal (without adjusting for multiple comparisons).

In AMAGINE-2 and -3, a combination of parallel, sequential, and Bonferroni-based recycling testing procedure was followed to maintain the two-sided, family-wise, type-1 error rate at 5% for the primary and key secondary efficacy analyses. Within the placebo and USK families, the primary outcomes were tested first, and if found to statistically significant, the key secondary outcomes were tested subsequently, in the order listed in Table 7. In the parallel, sequential, and Bonferroni-based recycling combination testing approach, the primary and key secondary efficacy outcomes were initially tested in the placebo family at alpha = 0.01 and in the USK family at alpha = 0.04, both two-sided. If and only if these outcomes were found to be statistically significant at the given alpha level within the respective placebo and USK family, the null hypotheses were again tested subsequently with a fraction of the overall alpha in the other family. For example, if and only if all primary and key secondary outcomes within the placebo family were statistically significant at 1%, then the outcomes for the USK family were tested at 5%. Similarly, if and only if all primary and key secondary outcomes within the USK family were statistically significant at 4%, then the outcomes for the placebo family were tested at 5%. The *P* values for all other analyses of outcomes were nominal without adjusting for multiplicity.

Table 6: Sequential Testing Procedure for AMAGINE-1

	AMAGINE-1 (Placebo Family)	
Co-Primary End Points	PASI 75 at week 12 (BDL 210 mg vs. placebo)	sPGA success at week 12 (BDL 210 mg vs. placebo)
	PASI 75 at week 12 (BDL 140 mg vs. placebo)	sPGA success at week 12 (BDL 140 mg vs. placebo)
Key Secondary End Points	PASI 100 at week 12 (BDL 210 mg vs. placebo)	
	sPGA 0 at week 12 (BDL 210 mg vs. placebo)	
	sPGA success at week 52 (BDL 210 mg vs. placebo)	
	PASI 100 at week 12 (BDL 140 mg vs. placebo)	
	sPGA 0 at week 12 (BDL 140 mg vs. placebo)	
	sPGA success at week 52 (BDL 140 mg vs. placebo)	
	PSI responder definition at week 12 (BDL 210 mg vs. placebo)	
	PSI responder definition at week 12 (BDL 140 mg vs. placebo)	

BDL = brodalumab; PASI 75 = 75% or greater improvement from baseline in Psoriasis Area and Severity Index score; PASI 100 = 100% improvement from baseline in Psoriasis Area and Severity Index score; PSI = Psoriasis Severity Index; sPGA = Static Physician's Global Assessment; vs. = versus.
Note: A PSI responder is a patient with a PSI total score ≤ 8, with no item score > 1; sPGA success means clear (0) or almost clear (1).
Source: AMAGINE-1 CSR.[6]

Table 7: Sequential Testing Procedure for AMAGINE-2 and -3

	AMAGINE-2 and -3 (Placebo Family)		AMAGINE-2 and -3 (USK Family)
Co-Primary End Points	PASI 75 at week 12 (BDL 210 mg vs. placebo)	sPGA success at week 12 (BDL 210 mg vs. placebo)	PASI 100 at week 12 (BDL 210 mg vs. USK)
	PASI 75 at week 12 (BDL 140 mg vs. placebo)	sPGA success at week 12 (BDL 140 mg vs. placebo)	PASI 100 at week 12 (BDL [140 mg for patients ≤ 100 kg and 210 mg for patients > 100 kg] vs. USK)
Key Secondary End Points	PASI 100 at week 12 (BDL 210 mg vs. placebo)		PASI 100 at week 12 (BDL 140 mg vs. USK)
	sPGA 0 at week 12 (BDL 210 mg vs. placebo)		PASI 75 at week 12 (BDL 210 mg vs. USK)
	PASI 100 at week 12 (BDL 140 mg vs. placebo)		PASI 75 at week 12 (BDL [140 mg for patients ≤ 100 kg and 210 mg for patients > 100 kg] vs. USK)
	sPGA 0 at week 12 (BDL 140 mg vs. placebo)		
	PSI responder definition at week 12 (BDL 210 mg vs. placebo)		
	PSI responder definition at week 12 (BDL 140 mg vs. placebo)		

BDL = brodalumab; PASI 75 = 75% or greater improvement from baseline in Psoriasis Area and Severity Index score; PASI 100 = 100% improvement from baseline in Psoriasis Area and Severity Index score; sPGA = Static Physician's Global Assessment; USK = ustekinumab; vs. = versus.
Note: A PSI responder is a patient with a PSI total score ≤ 8, with no item score > 1; sPGA success means clear (0) or almost clear (1).
Source: AMAGINE-2 CSR,[7] AMAGINE-3 CSR.[8]

Safety End Points

Safety data during the induction phase were summarized for all randomized patients as the percentage of patients experiencing the AE. Through week 52 (withdrawal/maintenance phases), exposure-adjusted event rates were provided for all planned treatment groups (based on randomization, re-randomization, retreatment and/or rescue, constant BDL dosage, combination of different BDL dosage, mixed dosage, and USK group). The patient incidence and exposure-adjusted event rates of AEs were tabulated by system organ class and preferred term.

Imputation for Missing Data

The methods for imputing missing data were similar across the trials and varied by trial phase, type of variable (categorical or continuous), and whether the analysis was for the primary or secondary efficacy outcome. For analyses of all primary and secondary efficacy outcomes through week 12 (induction phase), the primary methods of imputing missing categorical and continuous data were nonresponder imputation (NRI) and multiple imputation, respectively. Further sensitivity analyses for imputing missing data through week 12 were done using the last observation carried forward (LOCF) and as-observed method for all outcomes.

Following week 12, patients' re-randomization status determined the method of imputing missing data. Non–re-randomized patients, i.e., patients in all three trials receiving placebo during the induction phase who were switched to BDL 210 mg at week 12, were analyzed as observed, without any imputation. Among the remaining re-randomized patients, i.e., those who were eligible to undergo a second randomization, missing values for categorical, ordinal, and continuous end points were imputed by NRI, worst-case, and LOCF (multiple imputation in the case of AMAGINE-2 and -3), respectively. Further sensitivity analyses were conducted using the as-observed method for all week 52 end points across the trials or LOCF (in the case of AMAGINE-2 and -3).

In AMAGINE-1, for testing the key withdrawal phase efficacy outcome (sPGA success at week 52), patients who had a return of disease (sPGA ≥ 3) with or without rescue treatment through week 52 were imputed as nonresponders (defined as NRI after inadequate response) at return of disease. For all other week 52 outcomes among patients who received BDL 210 mg every two weeks consistently, no imputations were done, regardless of retreatment or rescue therapy, as no change in treatment occurred (i.e., their observed data were used). However, further sensitivity analyses using NRI imputation (categorical) or LOCF (continuous) at return of disease were performed on this group. Among patients randomized to placebo at week 12, all other week 52 outcomes were imputed using NRI imputation (categorical) or LOCF (continuous) after treatment change at return of disease, since patients received BDL 210 mg every two weeks as retreatment or rescue therapy.

Following week 52, all data were analyzed as observed, without any imputation.

Sample Size

Among the included trials, AMAGINE-1 had one set of comparisons (BDL versus placebo) whereas AMAGINE-2 and -3 had two (BDL versus USK and BDL versus placebo) during the induction phase. Within each, all efficacy end points were compared separately among the different treatment arms constituted by BDL 210 mg every two weeks, BDL 140 mg every two weeks, USK, and placebo. The following response rates were assumed in the three trials for the power calculations to achieve success on all co-primary and secondary end points at week 12, based on results from a previous phase II trial:[42]

PASI 75

- 82.5% for the BDL 210 mg every two weeks group (AMAGINE-1, -2, -3)
- 10% for the placebo group (AMAGINE-1, -2, -3)
- 72.5% for the USK group (AMAGINE-2 and -3)

sPGA success (0/1)

- 77% for the BDL 210 mg every two weeks group (AMAGINE-1, -2, -3)
- 10% for the placebo group (AMAGINE-1, 2, 3)

PASI 100

- 62% for the BDL 210 mg every two weeks group (AMAGINE-2 and -3)
- 10% for the placebo group (AMAGINE-2 and -3)
- 16% for the USK group (AMAGINE-2 and -3)

PSI response

- 85% for the BDL 210 mg every two weeks group (AMAGINE-2 and -3)
- 10% for the placebo group (AMAGINE-2 and -3)

For AMAGINE-1, the total sample size was calculated using a CMH model stratified by total body weight group (with a two-sided alpha = 0.05) with 600 patients randomized in a 1:1:1 ratio to BDL 210 mg every two weeks, BDL 140 mg every two weeks, or placebo. With 200 patients per treatment arm, this study had > 90% power to test the superiority of each BDL dosage regimen to placebo for sPGA (0/1) and PASI 75 at week 12.

For AMAGINE-2 and -3, the total sample size was calculated using a logistic regression model adjusted by total body weight group (with a two-sided alpha = 0.01 for the placebo family and 0.04 for the USK family) with 1,800 patients randomized in a 2:2:1:1 ratio to BDL 210 mg every two weeks, BDL 140 mg every two weeks, USK, or placebo. With 600

patients in each of the BDL groups and 300 patients in the USK and placebo group, these two studies had > 90% power to test the superiority of each BDL dosage regimen to placebo and USK for co-primary and key secondary end points at week 12.

For the withdrawal/maintenance phases, 77% and 85% of the patients originally randomized to receive BDL 210 mg every two weeks in the AMAGINE-1 and AMAGINE-2 and -3 trials, respectively, were assumed to undergo re-randomization at week 12. In addition, the sPGA success rate for the BDL 210 mg every two weeks group at week 52 was assumed to be 65% and 70% in AMAGINE-1 and AMAGINE-2 and -3, respectively. Based on these assumptions,[42] the power to detect a difference between the proportion of responders at week 52 in all three trials was computed to be ≥ 90% for the BDL 210 every two weeks group, regardless of comparators, at an alpha = 0.05 two-sided level.

Analysis Populations

Intention-to-Treat Population

The protocol-specified primary analysis population was the full analysis set (FAS), defined as all randomized patients at their initial randomization — essentially, an intention-to-treat (ITT) population. Patients' data were analyzed according to the treatment to which they were assigned regardless of compliance with the treatment or the study protocol. Analysis for all primary efficacy outcomes during the induction phase (up to week 12) was done using this analysis set.

Efficacy Analysis Set/Population (Maintenance/Withdrawal Phase)

Patients who completed the induction phase and subsequently entered the maintenance phase (withdrawal phase for AMAGINE-1) at week 12 composed the efficacy analysis set. Further categorization depended on patients' re-randomization status. Patients originally randomized to receive placebo or USK (AMAGINE-2 and -3 only) did not qualify for re-randomization; instead, they received BDL 210 mg every two weeks or continued with USK, respectively, and were classified as the efficacy evaluable subset with non-re-randomized patients. The efficacy evaluable subset with re-randomized patients comprised individuals who underwent re-randomization at week 12 to receive the same or different dosage of BDL. All secondary efficacy end points through week 52 were analyzed by re-randomized treatment group (re-randomized patients only), as well as by a combination of the initial randomized treatment and planned treatment during the maintenance phase (both re-randomized and non-re-randomized patients).

Patients who qualified for rescue therapy due to a return of disease (AMAGINE-1) or inadequate response (AMAGINE-2 and -3) through week 52 were analyzed separately using a subset of the efficacy analysis set, which was further categorized into rescue therapy among all patients and among only re-randomized patients.

Safety Population

The safety analysis set consisted of all randomized patients who received at least one dose of the investigational product. Safety end points for patients were analyzed according to the treatment group, as randomized.

Per-Protocol Set

An analysis of efficacy outcomes using the per-protocol (PP) set was conducted only in the AMAGINE-2 and -3 trials. The PP set comprised of patients who did not significantly deviate from the protocol and included all randomized patients who completed their initial

12-week induction phase (week 12 PP set) and all non-rescued patients as well as those qualified for rescue treatment through the 52-week maintenance phase (week 12 to 52 or week 52 PP set).

Patient Disposition

Patient disposition throughout the trials is provided in Table 8 and Table 9. BDL treatment arms that did not employ the Health Canada–recommended dose (210 mg) are not included in the tables. The proportions of patients who discontinued the study before the end of the induction phase at week 12 ranged between 3% and 5% overall. Discontinuation rates during the initial 12-week period, as well as reasons for discontinuation, were generally balanced between treatment arms within each included trial and ranged from approximately 2% to 5%. Through weeks 12 to 52, re-randomized and non–re-randomized patients differed in the treatment they received across the trials. Therefore, they are discussed separately.

In the AMAGINE-1 trial, the non–re-randomized patients included those who were originally randomized to BDL but had an inadequate response (sPGA ≥ 2) during the induction phase and those originally randomized to placebo; they all received BDL 210 mg every two weeks during weeks 12 to 52. The re-randomized patients received either BDL at their induction dose or matching placebo. Among the patients who underwent re-randomization at week 12, of those re-randomized to BDL 210 mg every two weeks, [redacted] discontinued before week 52, [redacted] required retreatment, and [redacted] completed the withdrawal and retreatment phase as randomized. Of those re-randomized to placebo at week 12, [redacted] discontinued before week 52, [redacted] required retreatment, and [redacted] completed as randomized.

In the AMAGINE-2 and -3 trials, patients who were not re-randomized at week 12 included those who continued to receive USK or switched to BDL 210 mg every two weeks from placebo. Among USK patients entering the maintenance phase in both trials, approximately [redacted] discontinued, [redacted] received rescue therapy, and [redacted] completed on USK. Among the placebo patients switched to BDL 210 mg every two weeks at week 12 in both trials, approximately [redacted] discontinued, and [redacted] completed BDL 210 mg every two weeks. Among patients who were re-randomized to continue BDL 210 mg every two weeks, the percentage of patients who discontinued from the study, entered rescue, or completed as re-randomized was [redacted] respectively in AMAGINE-2, and [redacted] respectively in AMAGINE-3.

The reasons for discontinuation were generally balanced between the treatment arms throughout the duration of all trials and mostly included AEs, noncompliance with protocol or treatment, need for alternative treatment, loss to follow-up, and withdrawal of consent.

Table 8: Patient Disposition (AMAGINE-1)

	AMAGINE-1	
	BDL 210	**PLB**
Screened, N	805	
Induction phase – week 1 to week 12		
Randomized – overall, N	N = 661	
Randomized – per group, N	222	220
Completed – per group, n (%)	212 (95.5)	209 (95.0)
Discontinued – per group, n (%)	10 (4.5)	12 (5.5)
Reasons for discontinuation – induction phase (week 1 to week 12), n (%)		
AE **Alternative treatment needed** **Consent withdrawal** **Lost to follow-up** **Protocol violation** **Administrative decision** **Ineligibility determined**	2 (0.9) 0 (0.0) 4 (1.8) 1 (0.5) 2 (0.9) 1 (0.5) 0 (0.0)	3 (1.4) 1 (0.5) 3 (1.4) 1 (0.5) 2 (0.9) 0 (0.0) 2 (0.9)
Withdrawal and retreatment phase – week 12 to week 52		
Treatment groups in non–re-randomized pts – Withdrawal and retreatment phase (wk 12 to 52)[a]	BDL 210/ BDL 210	PLB/BDL 210
Non–re-randomized – per group, N	45	207
Completed – per group, n (%)[b]	31 (68.9)	187 (89.9)
Discontinued – per group, n (%)	14 (31.1)	20 (9.6)
Reasons for discontinuation among non-re-randomized pts – withdrawal (week 12 to week 52), n (%)[a]		
AE **Alternative treatment needed** **Consent withdrawal** **Lost to follow-up** **Administrative decision** **Ineligibility determined** **Death** **Other**	[redacted]	[redacted]
Treatment groups in re-randomized pts – withdrawal and retreatment phase (week 12 to 52)[c]	BDL 210	PLB
Re-randomized – per group, N	[redacted]	[redacted]
Completed – per group, n (%)[d]	[redacted]	[redacted]
Entered retreatment phase – per group, n (%)	[redacted]	[redacted]
Discontinued – per group, n (%)	[redacted]	[redacted]
Reasons for discontinuation among re-randomized pts – withdrawal phase (week 12 to week 52), n (%)[c]		
AE **Consent withdrawal** **Lost to follow-up** **Administrative decision** **Death**	[redacted]	[redacted]

	AMAGINE-1	
Continued study after wk 52, total, n (%)	[redacted]	
ITT/FAS, N	222	220
Safety, N	[redacted]	[redacted]

AE = adverse event; BDL 210 = brodalumab 210 mg; FAS = full analysis set; ITT = intention-to-treat; PLB = placebo; pts = patients.
[a] Subset of the efficacy evaluable subset in the withdrawal phase who were originally randomized to placebo in the induction phase or who did not qualify for re-randomization and had the planned week 12 assessment.
[b] Completing was defined as completing sPGA assessment at or after study day 351. Five patients were counted as completing and discontinuing study during induction phase by discontinuing study at their week 12 visit.
[c] Subset of the efficacy evaluable subset who were re-randomized at week 12.
[d] Completing was defined as completing sPGA assessment or other assessments on or after study day 351 without entering retreatment phase.
Source: AMAGINE-1 CSR,[6] Papp et al. (2016).[10]

Table 9: Patient Disposition (AMAGINE-2 and -3)

	AMAGINE-2			AMAGINE-3		
	BDL 210	**USK**	**PLB**	**BDL 210**	**USK**	**PLB**
Screened, N	2,329			2,446		
Induction phase – week 1 to week 12						
Randomized – overall, N	1,831			1,881		
Randomized – per group, N	612	300	309	624	313	315
Completed – per group, n (%)	597 (97.5)	291 (97.0)	300 (97.1)	608 (97.4)	303 (96.8)	301 (95.6)
Discontinued – per group, n (%)	15 (2.5)	9 (3.0)	9 (2.9)	16 (2.6)	10 (3.2)	14 (4.4)
Reasons for discontinuation – induction phase (week 1 to week 12), n (%)						
AE	3 (0.5)	2 (0.7)	0 (0.0)	4 (0.6)	1 (0.3)	0 (0.0)
Alternative treatment needed	1 (0.2)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	1 (0.3)
Consent withdrawal	2 (0.3)	3 (1.0)	5 (1.6)	5 (0.8)	3 (1.0)	7 (2.2)
Lost to follow-up	3 (0.5)	2 (0.7)	1 (0.3)	5 (0.8)	3 (1.0)	1 (0.3)
Protocol violation	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)	1 (0.3)	1 (0.3)
Treatment noncompliance	3 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Administrative decision	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)
Death	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ineligibility determined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.6)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Maintenance phase – week 12 to week 52						
Treatment groups in non–re-randomized pts – maintenance phase (week 12 to week 52)[a]		USK/ USK	PLB/BDL 210		USK/ USK	PLB/BDL 210
Non–re-randomized – per group, N		[redacted]	[redacted]		[redacted]	[redacted]
Completed – per group, n (%)[b]		[redacted]	[redacted]		[redacted]	[redacted]
Discontinued – per group, n (%)		[redacted]	[redacted]		[redacted]	[redacted]
Reasons for discontinuation among non–re-randomized pts – maintenance phase (week 12 to week 52), n (%)[a]						
AE **Alternative treatment needed** **Consent withdrawal** **Lost to follow-up** **Treatment noncompliance** **Administrative decision** **Ineligibility determined** **Death** **Pregnancy**		[redacted]	[redacted]		[redacted]	[redacted]

	AMAGINE-2			AMAGINE-3		
	BDL 210	USK	PLB	BDL 210	USK	PLB
Other		[redacted]	[redacted]		[redacted]	[redacted]
Treatment groups in re-randomized pts – maintenance phase (week 12 to week 52)[c]	BDL 210 /BDL 210			BDL 210 /BDL 210		
Re-randomized – per group, N	[redacted]			[redacted]		
Completed, n (%)[b]	[redacted]			[redacted]		
Discontinued, n (%)	[redacted]			[redacted]		
Reasons for discontinuation among re-randomized pts – maintenance (week 12 to week 52), n (%)[c]						
AE **Consent withdrawal** **Treatment noncompliance** **Administrative decision** **Pregnancy** **Other**	[redacted]			[redacted]		
Continued study after week 52, Total n (%)		[redacted]			[redacted]	
Entered rescue phase through wk 52, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ITT/FAS, N	612	300	309	624	313	315
Safety, N	612	300	309	622	313	313

AE = adverse events; BDL 210 = brodalumab 210 mg; FAS = full analysis set; ITT = intention-to-treat; PLB = placebo; pts = patients; USK = ustekinumab.
[a] Subset of the efficacy evaluable subset in the maintenance phase who were originally randomized to placebo or ustekinumab in the induction phase or who did not qualify for re-randomization and had the planned week 12 assessment.
[b] Completing was defined as having a study assessment on or after study day 351 without entering rescue phase.
[c] Subset of the efficacy evaluable subset who were re-randomized at week 12.
Source: AMAGINE-2 CSR,[7] AMAGINE-3 CSR,[8] Lebwohl et al. (2015).[11]

Critical Appraisal

Internal Validity

Study Design, Intervention, and Comparator

All three trials used an appropriate centralized method for randomization (i.e., IVRS) independent of the study team. The centralized IVRS method of randomization helped conceal treatment allocation in all trials, and the initial randomization resulted in the lack of any notable imbalance in measured baseline characteristics between the treatment groups within each trial. In AMAGINE-2 and AMAGINE-3, between patients initially randomized to BDL 210 mg who were re-randomized at week 12 to continue BDL 210 mg versus the non–re-randomized patients who were to continue USK, the measured baseline characteristics were generally well-balanced within each trial; however, a notable imbalance in PsA, mean duration of psoriasis, and an sPGA score of 3 and 4 were found in some instances. Blinding of patients' randomization status was performed for all involved parties: patients and their care providers, investigators, and outcome assessors, up to week 52 or study termination, whichever came first. Both placebo and USK were supplied, stored, and presented in containers identical to those used for BDL during the blinded portion of the study. In order to maintain the blinding during treatment, administration of double-dummy placebos was employed. Rescue treatment was also blinded throughout the double-blind phase of the studies.

In all three trials, the two groups created during the induction and withdrawal/maintenance phase varied in their treatment such that not all patients within the same trial received the same dose throughout the 52-week double-blind phase. This CDR review only focused on patients receiving constant BDL 210 mg every two weeks, USK, or placebo through week 52. However, the availability of rescue therapy at any stage after week 16 complicated the effects of each treatment regimen between week 12 and 52. In addition, conducting two rounds of randomization at week 0 and at week 12 meant the initial randomization was only maintained until the induction phase.

In AMAGINE-2 and -3, the relevant treatment groups post week 12 included the re-randomized BDL 210 mg arm and the non-re-randomized USK arm. The comparison between the re-randomized BDL 210 mg every two weeks and non-re-randomized USK arm during the maintenance phase in AMAGINE-2 and -3 may be adversely affected by any imbalances in the measured and unmeasured covariates that were originally randomized to be balanced between these groups. Further, there were no statistical comparisons conducted between these two groups for any outcomes during the maintenance phase. Finally, there were fewer patients in each treatment arm during the withdrawal/maintenance phase after conducting a second round of randomization at week 12. It is unclear if, and to what extent, a smaller sample size in each comparator arm within the trials affected the statistical power. These factors should be taken into consideration when interpreting the results beyond week 12.

Disposition of Patients

The proportion of patients who discontinued the study prior to the end of the induction phase was generally low in all three trials (≤ 5%) and relatively balanced between treatment groups.

Statistical Analysis

Each of the included studies had sufficient power to demonstrate statistical significance for testing of the primary and secondary outcomes at week 12. Other than the primary and key secondary efficacy outcomes, none of the other symptoms-related outcomes at week 12 and week 52 were part of the sequential testing procedure (except sPGA success at week 52 only in AMAGINE-1); therefore, they were not controlled for multiple comparisons. None of the HRQoL outcomes at either phase of any trial were adjusted for multiplicity. Additionally, none of the outcomes were compared statistically between the BDL 210 mg every two weeks and USK arms during the maintenance phase in AMAGINE-2 and -3.

All analyses for primary and secondary outcomes were conducted using data from the PP populations to corroborate the primary findings, and the results were consistent with those from the ITT population (data not shown). Additionally, a number of sensitivity analyses were performed to assess the effect of imputing missing data for all efficacy variables, including a combination of LOCF, as observed (i.e., without any imputation), and treatment effect with and without treatment change (among nonresponders only, i.e., those who underwent retreatment or rescue therapy).

Outcome Measures

The outcome measures and definitions used in all three trials, including the sPGA, PASI, and PSI response, have evidence of validity in psoriasis, and are considered appropriate to evaluate treatment response in psoriasis clinical trials. Patient-reported outcome measures, i.e., DLQI, EQ-5D-3L, and SF-36, are also frequently used to capture different aspects of patients' lives that are affected and are considered valid and reliable. An appraisal of BDL led by the National Institute for Health and Care Excellence (NICE) indicated that PASI may underestimate disease severity in people with darker skin, as redness may be less evident.[13] However, the majority of the patients in the three included trials were white; therefore, this is likely not an issue in the AMAGINE trials.

External Validity

Patient Selection

Inclusion and exclusion criteria in all three trials appeared relevant and reasonable given that, according to the clinical expert consulted for this review, baseline characteristics were consistent with those of real-life patients seen in clinical practice. As well, the higher percentage of patients with prior experience with biologics in AMAGINE-1 did not seem to be a significant issue, and likely did not affect the interpretation of the findings. Notably, patients who had prior experience with IL-17 inhibitors and USK were excluded from the studies. In addition, various groups of patients with comorbid conditions were excluded, including current or history of malignant diseases; significant CVDs, serious infections, active or latent TB, HIV, hepatitis B, hepatitis C, and Crohn's disease. Therefore, the findings from these trials are not generalizable to these patients. Of note, none of the trials excluded patients with a history of suicidal thoughts. Patients with forms of psoriasis other than plaque psoriasis (pustular, erythrodermic, guttate) were excluded from the trials; however, BDL is not indicated for those types of psoriasis, according to the product monograph.

In AMAGINE-1, following the induction phase, the relevant treatment groups in AMAGINE-1 included a selective, enriched population that responded to treatment before week 12. An FDA report on the guidance to industries for the approval of biologic products discussed the effect of enrichment in clinical trials.[43] Based on the guidance report, the selection of responders to BDL during the induction phase for the subsequent re-randomization in the withdrawal phase is a form of predictive enrichment strategy. With this approach, patients chosen are more likely than the unselected general population to respond to the treatment. This leads to an increased likelihood of detecting a treatment difference with a relatively small sample size, and an enhanced benefit-risk relationship whereby the treatment effects of a drug are magnified (in both absolute and relative terms) among responders while avoiding exposure and potential toxicity compared with nonresponders.

Treatment Regimen, Administration, and Length of Follow-up

The clinical efficacy and safety profile of various BDL regimens were investigated across the trials among patients with psoriasis; however, only BDL 210 mg every two weeks was relevant for this review, since this is the only Health Canada–approved dose.[9,23] The use of USK as a comparator, in addition to placebo, offered active treatment comparisons. Even though USK acts on a different target (IL-23) than BDL (IL-17 RA), USK is considered an appropriate comparator since it is a relatively new biologic for moderate-to-severe psoriasis,

and the dosage used in the trials was consistent with the dosage approved by Health Canada.

Patients in all three trials received their treatment from study personnel in-office during the induction phase, which may not reflect real-world use. Therefore, the results during the induction phase might not be generalizable to patient self-administration, as compliance with treatment may vary with self-administration.

After week 24 in AMAGINE-1 and week 28 in AMAGINE-2 and AMAGINE-3, patients were not required to undergo in-office administration. Instead, they were able to self-administer treatment (or do so with the help of a trained caregiver). Thus, it is unclear if the results obtained in the early part of the study, during which treatments were administered by qualified staff members in an in-office setting, reflect the results that would be obtained with self-administration.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported (Table 3). These include results up to week 12 (induction phase) for all three trials. Due to a number of design and statistical issues, there is little comparative efficacy data beyond week 12 that are relevant to the current review. These include the assessment of outcomes in an enriched population (AMAGINE-1), the availability of retreatment or rescue therapy beginning in week 16 (all trials), and the lack of statistical comparisons between relevant treatment arms with adjustment for multiplicity (all trials) or at all (AMAGINE-2 and -3) during the withdrawal/maintenance phase. In addition, the re-randomization of BDL-treated patients at week 12 in AMAGINE-2 and AMAGINE-3 risks imbalance in patient characteristics between the two patient groups (i.e., USK and constant BDL 210 mg). An assessment of baseline characteristics between these treatment groups did identify some imbalances in measured characteristics (see Baseline Characteristics). Results through week 52 are provided in Appendix 4; however, their interpretation is uncertain.

Health-Related Quality of Life Outcomes

Dermatology Life Quality Index

DLQI total score (ranging from 0 [no effect on a patient's life] to 30 [extremely large effect on a patient's life]) was the common HRQoL outcome measured in all three trials; baseline scores ranged from approximately 14 to 15 across trial arms (Table 10). Compared with placebo, the BDL 210 mg group had [redacted] in AMAGINE-1, AMAGINE-2, and AMAGINE-3 respectively. Statistical comparisons of between-treatment differences were not controlled for multiplicity. [redacted] however, no statistical comparisons between USK and placebo or between USK and BDL 210 were conducted.

Compared with placebo, the percentage of patients achieving a DLQI reduction (improvement) of ≥ 5 points from baseline was [redacted] Statistical comparisons of between-treatment differences were not controlled for multiplicity. In AMAGINE-2 and AMAGINE-3, the percentage of patients achieving a ≥ 5-point

improvement in DLQI score in the USK group was [redacted] However, no statistical testing was conducted for USK groups.

Further, in all three trials, compared with placebo, the percentage of patients achieving a DLQI score of 0 or 1 at week 12 was [redacted] statistical comparisons of between-treatment differences not controlled for multiplicity. The percentage of patients achieving a DLQI score of 0 or 1 at week 12 in the USK groups was [redacted] in both AMAGINE-2 and AMAGINE-3 ([redacted]); no statistical testing of between-group differences was conducted.

In AMAGINE-1, at 52 weeks, the proportion of patients with a DLQI reduction (improvement) of ≥ 5 points from baseline and who achieved a DLQI score of 0 or 1 was [redacted] respectively (Table 14).

EuroQol 5-Dimensions 3-Levels Questionnaire

The EQ-5D-3L was administered at baseline and at week 12 only in the AMAGINE-1 trial. Improvements in both index scores and VAS scores were [redacted], respectively. Statistical comparisons of between-treatment differences were not controlled for multiplicity.

Short Form (36) Health Survey Version 2

The SF-36 version 2 (range: 0 to 100, with higher scores indicating better levels of function and/or better health) PCS and MCS were measured only in the AMAGINE-1 trial at week 12 and 52. For both the PCS and MCS, the increase (improvement) from baseline to week 12 was [redacted] (Table 10). Statistical comparisons of between-treatment differences were not controlled for multiplicity

Symptom-Related Outcomes

Results from the efficacy end point analyses are given in Table 11 (week 12 results), Table 15 (week 52 results), and Table 23 (long-term open-label results).

Psoriasis Area and Severity Index

Week 0 to Week 12

PASI 75 at week 12 was considered a co-primary efficacy outcome for all trials within the placebo family and a key secondary outcome within the USK family in AMAGINE-2 and -3. PASI 100 at week 12 was the primary efficacy outcome within the USK family in AMAGINE-2 and -3, whereas this was a key secondary efficacy outcome within the placebo family in all trials. Compared with placebo, the percentage of patients achieving PASI 75 was statistically significantly greater in the BDL 210 mg groups in all trials; 83.3% versus 2.7%, 86.3% versus 8.1%, and 85.1% versus 6.0% (adjusted $P < 0.001$, all trials). Compared with USK, the percentage of patients achieving PASI 75 was statistically significantly greater in the BDL 210 mg group in AMAGINE 3 (85.1% versus 69.3%), (adjusted $P = 0.007$). In AMAGINE-2, the percentage of patients achieving PASI 75 was not statistically significantly different between BDL 210 mg (86.3%) and USK (70.0%) (adjusted $P = 0.078$).

Compared with placebo, the percentage of patients achieving PASI 100 was statistically significantly greater in the BDL 210 mg groups in all trials: 41.9% versus 0.5%, 44.4% versus 0.6%, and 36.7% versus 0.3% (adjusted *P* < 0.001 in all trials). In addition, the percentage achieving PASI 100 was statistically significantly greater in the BDL 210 mg groups compared with USK in both AMAGINE-2 and AMAGINE-3: 44.4% versus 21.7% and 36.7% versus 18.5%, respectively (adjusted *P* value < 0.001 in both trials). The percentage of patients achieving PASI 90 was consistently higher in the BDL 210 mg groups compared with placebo and USK; however, statistical analyses of between-treatment differences for PASI 90 were not controlled for multiplicity.

Subgroups of Interest

Across all three trials at week 12, the percentage of patients receiving BDL 210 mg who achieved PASI 75 and PASI 100 did not appear to differ between patients who had or had not reported prior biologic use or failure for psoriasis except in AMAGINE-2, in which the percentage of BDL-treated patients achieving PASI 100 was lower for patients reporting prior biologic use and prior biologic failure compared with those who did not report such use or failure (see Table 17). Among patients receiving USK in AMAGINE-2 and -3, those with prior use or failure of biologics for psoriasis reported a noticeably lower percentage of PASI 75 and PASI 100 response compared with those who did not (Table 17). [redacted] (Table 19). [redacted] (Table 19).

Week 12 to Week 52

[redacted]

Sensitivity Analyses

Sensitivity analyses using the different methods to impute missing data (described in statistical analyses) as well as analyses of all PASI-related outcomes using PP population did not change the results in any of the trials.

Static Physician's Global Assessment

Week 0 to Week 12

In all three trials within the placebo family, sPGA success (0 [clear] to 1 [almost clear]) at week 12 was a co-primary efficacy outcome; an sPGA score of 0 (clear) at week 12 was a key secondary efficacy outcome. Additionally, sPGA success at week 52 was a key secondary efficacy outcome in AMAGINE-1 but not in AMAGINE-2 and -3. Within the USK family, none of the sPGA-related outcomes were considered a primary or key secondary outcome. Compared with placebo, the proportions of patients achieving sPGA success at week 12 were statistically significantly greater among the BDL 210 mg group: 75.7% versus 1.4%, 78.6% versus 3.9%, and 79.6% versus 4.1% in AMAGINE-1, AMAGINE-2, and AMAGINE-3, respectively (adjusted *P* < 0.001 in all trials). Likewise, a statistically significantly greater proportion of patients in the BDL-treated group achieved an sPGA score of 0 compared with placebo in all three trials: 41.9% versus 0.5%, 44.8% versus 0.6%, and 36.7% versus 0.3% (adjusted *P* < 0.001 in all trials). The percentage of patients achieving success in both sPGA outcomes at week 12 was higher in the BDL group

compared with the USK groups in AMAGINE-2 and -3; however, no statistical comparisons were done to test the between-group differences. The results are given in Table 11.

Week 12 to Week 52

[redacted]

Subgroups of Interest

A consistent response pattern was not shown for the sPGA-related outcomes between the included subgroups across the trials. In AMAGINE-1, the proportions of BDL-treated patients who achieved sPGA success and clearance at week 12 were somewhat similar among patients who had experience with prior use or failure of biologics compared with those who did not. However, in AMAGINE-2 and -3, a noticeably lower percentage of BDL-treated patients reported sPGA success and clearance at week 12 if they had prior exposure or failure of biologics compared with those who did not (see Table 17). [redacted] (Table 19). Subgroup data for the sPGA outcomes for the USK groups in AMAGINE-2 and -3 were not reported.

Sensitivity Analyses

Sensitivity analyses using the different methods to impute missing data (described in statistical analyses) as well as analyses of all sPGA-related outcomes using PP population did not change the results in any of the trials.

Psoriasis Symptom Inventory

Week 0 to Week 12

PSI response was assessed in each trial as the proportion of patients who achieved PSI response (total score ≤ 8, with no item scores > 1) and a PSI score of 0. PSI response rate at week 12 was part of the sequential testing procedure within the placebo family in all trials. Compared with placebo, a statistically significantly greater proportion of patients in the BDL 210 mg arm achieved PSI response in all trials: 60.8% versus 4.1%, 67.6% versus 6.8%, and 61.2% versus 6.3% (adjusted $P < 0.001$ in all trials). A greater proportion of the BDL-treated patients also achieved a PSI score of 0 compared with placebo across the trials; however, the results were not adjusted for multiplicity. A somewhat lower proportion of patients in the USK group achieved both PSI response and a score of 0 compared with the BDL group in AMAGINE-2 and -3; however, no statistical comparisons were done to test the between-treatment difference.

Week 12 to Week 52

[redacted]; Table 15.

Subgroups of Interest

Across the trials, PSI response at week 12 was largely similar among patients on BDL regardless of prior use or failure of biologics (Table 17). However, [redacted] (Table 19).

Sensitivity Analyses

Sensitivity analyses using the different methods to impute missing data (described in statistical analyses) as well as analyses of all PSI-related outcomes using PP population did not change the results in any of the trials.

Table 10: Key Efficacy Outcomes (Quality of Life–Related Outcomes) Through Week 12

	AMAGINE-1		AMAGINE-2			AMAGINE-3		
	BDL 210 N = 222	PLB N = 220	BDL 210 N = 612	USK N = 300	PLB N = 309	BDL 210 N = 624	USK N = 313	PLB N = 315
DLQI Total Score (MI)								
Baseline, N	[redacted]							
Baseline, mean (SD)								
Wk 12, N								
Wk 12, mean (SE)								
Treatment difference, LS mean (SE) vs. PLB								
95% CI								
P value vs. PLB[a]								
DLQI Improvement ≥ 5 (Nonresponder Imputation)								
N								
n (%)								
P value vs. PLB[b]								
DLQI 0/1 (NRI)								
N								
n (%)								
P value vs. PLB[b]								
EQ-5D-3L (MI)								
Baseline, N								
Baseline, mean (SD)								
Wk 12, N								
Wk 12, mean (SE)								
Treatment difference, LS mean (SE)								
95% CI								

	AMAGINE-1		AMAGINE-2			AMAGINE-3		
	BDL 210 N = 222	PLB N = 220	BDL 210 N = 612	USK N = 300	PLB N = 309	BDL 210 N = 624	USK N = 313	PLB N = 315
P value[a]								
EQ-5D VAS (MI)								
Baseline, N								
Baseline, mean (SD)								
Wk 12, N								
Wk 12, mean (SE)								
Treatment difference, LS mean (SE)								
95% CI								
P value[a]								
SF-36 PCS (MI)								
Baseline, N								
Baseline, mean (SD)								
Wk 12, N								
Wk 12, mean (SE)								
Treatment difference, LS mean (SE)								
95% CI								
P value[a]								
SF-36 MCS (MI)								
Baseline, N								
Baseline, mean (SD)								
Wk 12, N								
Wk 12, mean (SE)								
Treatment difference, LS mean (SE)								
95% CI								
P value[a]								

BDL 210 = brodalumab 210 mg; CI = confidence interval; DLQI = Dermatology Life Quality Index; EQ-5D-3L = EuroQol 5 Dimensions 3-Levels questionnaire; LS = least squares; MCS = mental component summary; MI = multiple imputation; ND = not done; NR = not reported; NRI = nonresponder imputation; PCS = physical component summary; PLB = placebo; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; USK = ustekinumab; VAS = visual analogue scale; vs. = versus; wk = week.

Note: Nonresponder imputation (NRI) was used to impute missing dichotomous data; missing continuous data were imputed with multiple imputation. All efficacy end points up to week 12 were evaluated using the full analysis set.

[a] The *P* value for testing outcome change from baseline between BDL and placebo/USK was based on an ANCOVA model adjusted for baseline body weight (≤ 100 kg, > 100 kg), prior biologic use (yes, no), geographic region, and baseline outcome score, and is nominal without multiplicity adjustment.

[b] The *P* values for testing the proportion of patients achieving an outcome were between the BDL and placebo/USK and based on the Cochran–Mantel–Haenszel test stratified by total body weight at study baseline (≤ 100 kg, > 100 kg), prior biologic use (yes, no), geographic region, and baseline outcome score, and are nominal without multiplicity adjustment.

Source: AMAGINE-1 CSR,[6] Papp et al. (2016),[10] AMAGINE-2 CSR,[7] AMAGINE-3 CSR,[8] Lebwohl et al. (2015).[11]

Table 11: Key Efficacy Outcomes (Symptom-Related Outcomes) Through Week 12

	AMAGINE-1		AMAGINE-2			AMAGINE-3		
	BDL 210 N = 222	PLB N = 220	BDL 210 N = 612	USK N = 300	PLB N = 309	BDL 210 N = 624	USK N = 313	PLB N = 315
Absolute PASI Score (MI)								
Baseline, N	[redacted]							
Baseline, mean (SD)	[redacted]							
Wk 12, N	[redacted]							
Wk 12, mean (SE)	[redacted]							
Treatment difference, LS mean (SE) vs. PLB	[redacted]							
95% CI	[redacted]							
P value vs. PLB [a]	[redacted]							
PASI 75 (Nonresponder Imputation)								
N	222	220	612	300	309	624	313	315
n (%)	185 (83.3)	6 (2.7)	528 (86.3)	210 (70.0)	25 (8.1)	531 (85.1)	217 (69.3)	19 (6.0)
P value vs. PLB [b]	< 0.001		< 0.001	–	–	< 0.001	–	–
P value vs. USK [b]	NA		0.078[c]	–	–	0.007[c]	–	–
PASI 90 (Nonresponder Imputation)								
N	222	220	612	300	309	624	313	315
n (%)	156 (70.3)	2 (0.9)	430 (70.3)	141 (47.0)	10 (3.2)	429 (68.8)	149 (47.6)	5 (1.6)
P value vs. PLB [b]	< 0.001		< 0.001	–	–	< 0.001	–	–
P value vs. USK [b]	NA		< 0.001	–	–	< 0.001	–	–
PASI 100 (Nonresponder Imputation)								
N	222	220	612	300	309	624	313	315
n (%)	93 (41.9)	1 (0.5)	272 (44.4)	65 (21.7)	2 (0.6)	229 (36.7)	58 (18.5)	1 (0.3)
P value vs. PLB [b]	< 0.001		< 0.001[c]	NR	–	< 0.001[c]	–	–
P value vs. USK [b]	NA		< 0.001	–	–	< 0.001	–	–
sPGA Success [0 (Clear) to 1 (Almost Clear)] (Nonresponder Imputation)								
N	222	220	612	300	309	624	313	315
n (%)	168 (75.7)	3 (1.4)	481 (78.6)	183 (61.0)	12 (3.9)	497 (79.6)	179 (57.2)	13 (4.1)
P value vs. PLB [b]	< 0.001[c]		< 0.001 [c]	–	–	< 0.001 [c]	–	–
P value vs. USK [b]	NA		< 0.001	–	–	< 0.001	–	–
sPGA Clear 0 (Nonresponder Imputation)								
N	222	220	612	300	309	624	313	315

	AMAGINE-1		AMAGINE-2			AMAGINE-3		
	BDL 210 N = 222	PLB N = 220	BDL 210 N = 612	USK N = 300	PLB N = 309	BDL 210 N = 624	USK N = 313	PLB N = 315
n (%)	93 (41.9)	1 (0.5)	274 (44.8)	65 (21.7)	2 (0.6)	229 (36.7)	58 (18.5)	1 (0.3)
P value vs. PLB [b]	< 0.001 [c]		< 0.001 [c]	–	–	< 0.001 [c]	–	–
P value vs. USK [b]	NA		< 0.001	–	–	< 0.001	–	–
PSI Total Score (LOCF)								
Baseline, N	209	211	577	283	289	582	295	290
Baseline, mean (SE)	18.9 (0.5)	19.0 (0.5)	18.6 (0.3)	18.9 (0.4)	18.6 (0.4)	18.7 (0.3)	18.7 (0.4)	19.0 (0.4)
Wk 12, N	220	220	605	298	306	608	308	307
Wk 12, mean (SE)	4.7 (0.4)	19.1 (0.6)	3.9 (0.2)	5.6 (0.3)	17.7 (0.5)	4.6 (0.2)	6.6 (0.4)	16.8 (0.5)
Treatment difference, LS mean (SE) vs. PLB	–14.3 (0.7)		–13.9 (0.5)	ND	–	–	ND	–
95% CI	–15.6 to –12.9		–14.8 to –13.0	–	–	–	–	–
P value vs. PLB [a]	< 0.001		< 0.001	–	–	–	–	–
PSI Responder (Total Score ≤ 8, With No Item Scores > 1) (Nonresponder Imputation)								
N	222	220	612	300	309	624	313	315
n (%)	135 (60.8)	9(4.1)	414 (67.6)	166 (55.3)	21 (6.8)	382 (61.2)	162 (51.8)	20 (6.3)
P value vs. PLB [b]	< 0.001		< 0.001	–		< 0.001	–	
PSI Score 0 (Nonresponder Imputation)								
N	222	220	612	300	309	624	313	315
n (%)	48 (21.6)	1 (0.5)	156 (25.5)	38 (12.7)	1 (0.3)	124 (19.9)	44 (14.1)	1 (0.3)
P value vs. PLB [b]	< 0.001		< 0.001	–		< 0.001	–	

BDL 210 = brodalumab 210 mg; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; ND = not done; MI = multiple imputation; NR = not reported; PASI = Psoriasis Area and Severity Index; PLB = placebo; PSI = Psoriasis Symptom Inventory (total score); SD = standard deviation; SE = standard error; sPGA = static Physician's Global Assessment; USK = ustekinumab; vs. = versus; wk = week.

Note: If MI data for missing continuous data were unavailable, LOCF data were used. All efficacy end points up to week 12 were evaluated using the full analysis set.

[a] The *P* value for testing outcome change from baseline between BDL and PLB/USK was based on an ANCOVA model adjusted for baseline body weight (≤ 100 kg, > 100 kg), prior biologic use (yes, no), geographic region, and baseline outcome score, and is nominal without multiplicity adjustment.

[b] The *P* values for testing the proportion of patients achieving an outcome were between BDL and PLB/USK and based on the Cochran–Mantel–Haenszel test stratified by total body weight at study baseline (≤ 100 kg, > 100 kg), prior biologic use (yes, no), geographic region, and baseline outcome score, and are nominal without multiplicity adjustment.

[c] Adjusted *P* values are based on a testing procedure consisting of a sequential testing procedure (AMAGINE-1) or a combination of parallel, sequential, and weighted Bonferroni-based recycling testing (AMAGINE-2 and -3), which includes all primary and key secondary end point comparisons against placebo and USK and are to be compared with a significance level of 0.05.

Source: AMAGINE-1 CSR,[6] Papp et al. (2016),[10] AMAGINE-2 CSR,[7] AMAGINE-3 CSR,[8] Lebwohl et al. (2015).[11]

Harms

Only those harms identified in the review protocol are reported (Table 3). Similar to efficacy outcomes, data on AEs during the induction phase are presented here for all patients across the trials randomized to receive BDL 210 mg every two weeks, placebo, and USK (Table 12). Data through week 52 are only presented for re-randomized or non–re-randomized patients across the trials who received BDL 210 mg, any dose of BDL (all BDL), and USK (Table 16). Data on AEs were presented as frequency during the induction phase and as exposure-adjusted event rate (per 100 patient-years) during the withdrawal/maintenance phase. See Appendix 6 for long-term harms data.

Adverse Events

Overall, the percentage of patients who experienced a treatment-emergent adverse event (TEAE) during the induction phase ranged from 48% to 60% between treatment groups across the trials. The most commonly reported TEAEs (≥ 5% in any treatment group) across the trials included nasopharyngitis, upper respiratory tract infection (URTI), headache, and arthralgia. A list of TEAEs at week 12 with a reported patient incidence rate of ≥ 2% in any treatment group within a trial is given in Table 12. For the majority of the patients in AMAGINE-1, these TEAEs were reported by investigators as mild (grade 1), whereas this information was not available for AMAGINE-2 and -3.

Through week 52, exposure-adjusted event rates ranged from 368 to 413 events per 100 patient-years between treatment groups across the trials (Table 16). Similar to the results for the induction phase, the most commonly reported TEAEs (exposure-adjusted event rate, i.e., r, ≥ 5 in all groups) across the trials were nasopharyngitis, URTI, headache, and arthralgia. Other TEAEs commonly found among the BDL group across the trials (exposure-adjusted event rate: ≥ 5 in any treatment arm) included urinary tract infection, sinusitis, pruritus, hypertension, back pain, nausea, fatigue, bronchitis, diarrhea, and cough (in no particular order).

Serious Adverse Events

The overall frequency of SAEs across the trials during the induction phase was low: < 3% for any relevant treatment group. The proportions of patients experiencing SAEs were generally similar between patients receiving BDL and placebo in all trials, as well as between patients receiving BDL and USK in AMAGINE-2 and -3. Table 12 lists the SAEs by system organ class, since the SAE frequencies for individual diseases were reported inconsistently across the trials due to infrequent incidence. The most commonly reported SAEs (incidence ≥ 2) among patients receiving BDL during the induction phase include cellulitis (AMAGINE-1); appendicitis and acute pancreatitis (AMAGINE-2); and gastroenteritis (AMAGINE-3).

Through week 52, the overall exposure-adjusted event rate of SAEs for patients exposed to BDL (either 210 mg or all BDL) was < 10 events per 100 patient-years across all trials. Additionally, the rates were generally similar across the treatment groups in all trials. Table 16 lists the SAEs as system organ class, since the exposure-adjusted event rates for individual diseases were reported inconsistently across the trials due to infrequent incidence.

Withdrawals Due to Adverse Events

Overall, the rate of withdrawals due to adverse events (WDAEs) was low in all trials: ≤ 1% during the induction phase and fewer than four events per 100 patient-years through week 52. WDAEs did not vary substantially between the treatment arms; however, patients receiving BDL consistently had more WDAEs compared with those receiving placebo or USK.

Mortality

A total of four, seven, and five deaths were reported through the end of the data cut-off period in AMAGINE-1, -2, and -3, respectively. None of the deaths in the AMAGINE-1 trial were adjudicated as treatment-related by the site investigator. In AMAGINE-2, four patients who received BDL 210 mg every two weeks died, reasons include sudden death, cerebral infarction, completed suicide, and traumatic lung injury. Two patients in the USK arm died, one of pancreatic cancer and the other classified as sudden death. Other than pancreatic carcinoma, none of the causes of death were adjudicated as treatment-related by the site investigator. In AMAGINE-3, two out of the five deaths occurred within the exposure period, with reasons including cardiac arrest, accidental death, hematophagic histiocytosis syndrome, and cardiopulmonary failure. Only the hematophagic histiocytosis syndrome–related death was adjudicated as treatment-related. The incidence of mortality through week 12 and through week 52 for the relevant treatment groups may be seen in Table 12 and Table 16 respectively.

Notable Harms

Several harms outcomes of particular interest were identified in the study protocol.

During the induction phase, [redacted] The incidence of this outcome during the induction phase was not reported for AMAGINE-2. Across all trials, there were a few cases of neutropenia and injection-site reactions in the BDL group (< 2%), but [redacted]

Through week 52, infections remained the most common form of TEAE, with exposure-adjusted event rates (per 100 patient-years) ranging from 112 events to 127 events across the BDL 210 mg groups in all trials, compared with 123 events and 103 events for USK groups in AMAGINE-2 and -3. Injection-site reactions occurred at a rate ranging between one and seven events per 100 patient-years across the trials; the rates were generally similar between the treatment groups in all trials. The rates of IBD and neutropenia were low among the BDL-treated patients (exposure-adjusted event rate: < 1 event per 100 patient-years) [redacted]

[redacted] In AMAGINE-2, a total of 13 suicide-related events (suicidal attempt, ideation, or behaviour) were recorded in nine patients receiving BDL at the end of the data cut-off period (exposure-adjusted event rate: 0.6 events per 100 patient-years). Additionally, one patient in this group committed suicide after the exposure end date. Another reported incidence of suicide attempt was found in a patient receiving USK. In AMAGINE-3, two

suicide attempts were recorded in two patients at the end of the data cut-off period (exposure-adjusted event rate: 0.1 event per 100 patient-years): one each in the BDL group (0.3 per 100 patient-years) and the USK group (0.4 per 100 patient-years). Neither event resulted in a completed suicide. In addition, suicidal ideation was also reported in one patient in the BDL group and one patient in the USK group.

A few instances of malignancies and neoplasms were reported through week 12. During the induction phase of AMAGINE-2, one patient in the BDL 140 mg arm experienced pancreatic carcinoma. Another patient in the USK group developed prostate cancer. In AMAGINE-3, one patient in the BDL 210 arm experienced bladder cancer. Another patient in the 140 mg arm reported basal cell carcinoma. No cases of malignancies were reported in the AMAGINE-1 trial.

[redacted]

Table 12: Treatment-Emergent Adverse Events Through Week 12

	AMAGINE-1		AMAGINE-2			AMAGINE-3		
AEs	**BDL 210 N = 222**	**PLB N = 220**	**BDL 210 N = 612**	**USK N = 300**	**PLB N = 309**	**BDL 210 N = 622**	**USK N = 313**	**PLB N = 313**
TEAEs								
Subjects with > 1 AEs, n (%)	131 (59.0)	112 (50.9)	354 (57.8)	177 (59.0)	165 (53.4)	353 (56.8)	168 (53.7)	152 (48.6)
Common AEs (n ≥ 2%)								
Nasopharyngitis	21 (9.5)	22 (10.0)	45 (7.4)	18 (6.0)	14 (4.5)	31 (5.0)	16 (5.1)	22 (7.0)
URTI	18 (8.1)	14 (6.4)	33 (5.4)	20 (6.7)	23 (7.4)	33 (5.3)	16 (5.1)	17 (5.4)
Headache	11 (5.0)	7 (3.2)	31 (5.1)	12 (4.0)	9 (2.9)	21 (3.4)	11 (3.5)	14 (4.5)
Arthralgia	[redacted]	[redacted]	28 (4.6)	9 (3.0)	12 (3.9)	36 (5.8)	6 (1.9)	10 (3.2)
Pruritus	[redacted]	[redacted]	–	–	–	–	–	–

	AMAGINE-1		AMAGINE-2			AMAGINE-3		
AEs	**BDL 210 N = 222**	**PLB N = 220**	**BDL 210 N = 612**	**USK N = 300**	**PLB N = 309**	**BDL 210 N = 622**	**USK N = 313**	**PLB N = 313**
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
SAEs								
SAEs, n (%)	4 (1.8)	3 (1.4)	6 (1.0)	4 (1.3)	8 (2.6)	9 (1.4)	2 (0.6)	3 (1.0)
Infections and infestations			2 (0.3)	0 (0.0)	1 (0.3)	4 (0.6)	2 (0.6)	1 (0.3)
Skin and subcutaneous tissue disorders			0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)
Musculoskeletal and connective tissue disorders			0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders			0 (0.0)	1 (0.3)	1 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)
Nervous system disorder			2 (0.3)	0 (0.0)	1 (0.3)	2 (0.3)	0 (0.0)	0 (0.0)
Gastrointestinal disorders			1 (0.2)	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)
Hepatobiliary disorders			0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders			0 (0.0)	0 (0.0)	1 (0.3)	–	–	–
Cardiac disorders			0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders			–	–	–	1 (0.2)	0 (0.0)	1 (0.3)
Fatal Events								
n (%)	0 (%)	0 (%)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study Discontinuation								
WDAEs, n (%)	2 (0.9)	3 (1.4)	3 (0.5)	2 (0.7)	0 (0.0)	4 (0.6)	1 (0.3)	0 (0.0)
Notable Harms								
[redacted]								
[redacted]			9 (1.5)	2 (0.7)	3 (1.0)	9 (1.4)	10 (3.2)	6 (1.9)
[redacted]								
Suicidal ideation, behaviour, attempt			1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
[redacted]								
Neutropenia	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.7)	0 (0.0)	7 (1.1)	1 (0.3)	0 (0.0)
[redacted]			0 (0.0)	1 (0.3)	0 (0.0)			

	AMAGINE-1		AMAGINE-2			AMAGINE-3		
AEs	BDL 210 N = 222	PLB N = 220	BDL 210 N = 612	USK N = 300	PLB N = 309	BDL 210 N = 622	USK N = 313	PLB N = 313
[redacted]								

AE = adverse event; BDL 210 = brodalumab 210 mg; PLB = placebo; SAE = severe adverse event; TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection; USK = ustekinumab; WDAE = withdrawal due to adverse event.
Note: "–" indicates either an incidence of 0 or AEs that were not reported/listed.
Source: AMAGINE-1 CSR,[6] Papp et al. (2016),[10] AMAGINE-2 CSR,[7] AMAGINE-3 CSR,[8] Lebwohl et al. (2015).[11]

Discussion

Summary of Available Evidence

Three phase III, double-blind RCTs were included in this review. One was placebo-controlled (AMAGINE-1), while two had an active comparator, USK (AMGINE-2 and -3). An initial 12-week induction phase was conducted in an identical manner across all trials using a set of primary and key secondary outcomes measured at week 12 to evaluate the superiority of BDL over placebo (all trials) and over USK (AMAGINE-2 and -3). A 12-week to 52-week phase followed, during which AMAGINE-1 assessed the effect of withdrawal and retreatment of BDL. AMAGINE-2 and -3 assessed the continued efficacy of BDL and USK treatment.

All three trials presented data through week 52 (limited long-term data beyond week 52 are available); however, much of the data from week 12 to week 52 did not provide useful comparative information for this review. In AMAGINE-1, only those patients who responded to treatment during the induction phase were re-randomized; therefore, BDL 210 mg efficacy is likely to be overestimated beyond week 12. For AMAGINE-2 and -3, the comparative efficacy of continued BDL and USK treatment is of interest. However, the re-randomization of BDL-treated patients at week 12 in AMAGINE-2 and AMAGINE-3 risks imbalance in patient characteristics between the USK and constant BDL 210 mg treatment groups. In addition, the availability of rescue therapy with BDL 210 mg or USK after week 16 further complicates the interpretation of the data through week 52. Finally, the comparison between BDL and USK at week 52 was not done through formal statistical tests; results were instead presented descriptively.

A number of symptoms-related end points were assessed at week 12, including PASI 75 and PASI 100, sPGA success and clear, PSI response and PSI 0 score. HRQoL outcomes were also assessed at week 12, and involved the DLQI, EQ-5D-3L, and SF-36 version 2 (AMAGINE-1 only). However, none of the HRQoL outcomes were controlled for multiple comparisons.

This systematic review identified published trials comparing BDL (anti–IL-17 RA) and USK (anti–IL-12 and anti–IL-23) only. No published RCTs with direct comparisons of BDL and other biologics for the treatment of plaque psoriasis were identified; i.e., comparisons to TNF inhibitors (infliximab, adalimumab, or etanercept), IL-17 inhibitors (secukinumab, ixekizumab), or IL-23 inhibitors (guselkumab). Thus, we conducted a separate literature search to identify published indirect treatment comparisons (ITCs) between BDL and other biologics, described in Appendix 7.

In summary, the included trials generally appear to have been performed with methodological rigour with low risk of bias during the 12-week induction phase, including preservation of blinding and randomization, concealment of treatment allocation, use of validated instruments to measure outcomes, an appropriate statistical analysis plan, and a trial population that reflected patient characteristics and treatments typical of the Canadian context. However, the reviewed trials did include a number of exclusion criteria that limit the generalizability of the results, including patients with significant CVD, a history of Crohn's disease, and prior use of IL-17 inhibitors, and patients who self-administer or have a caregiver administer the medication. Finally, given the limitations of the withdrawal and retreatment phase (in AMAGINE-1) and the maintenance phase (in AMAGINE-2 and -3), as described previously, the most relevant results for the CDR review are limited to the 12-week induction phase. The lack of longer-term comparative efficacy data is a limitation of the available evidence, as is the lack of direct head-to-head comparisons with biologic treatments other than USK.

Interpretation of Results

Efficacy

Results from AMAGINE-1, -2, and -3 demonstrated that BDL was superior to placebo for the primary and secondary outcomes at week 12: achievement of an sPGA score of 0 or 1, PASI 75 and PASI 100, and PSI response in patients with moderate-to-severe plaque psoriasis. BDL was also shown to be superior to USK in achieving a PASI 100 score at week 12 in both AMAGINE-2 and -3, and a PASI 75 score at week 12 (only in AMAGINE-3). These results were robust to a number of sensitivity analyses to account for missing data imputation and analyses in the PP population. Improvement in symptoms and skin clearance as measured by the PASI and sPGA are important goals of therapy based on CDA clinical practice guidelines, which indicate that the PASI and sPGA are commonly used in clinical practice in Canada.[2,44] Further, the observed differences in the co-primary and secondary outcomes represent a clinically meaningful improvement for psoriasis patients, according to the clinical expert consulted by CDR. Assessment of other symptoms-related outcomes at week 12 (e.g., PASI 90, PSI score of 0) were supportive of the findings for the previously mentioned efficacy outcomes and suggest a beneficial effect of BDL over placebo, but they were not adjusted for multiplicity.

In the AMAGINE-1 trial, data through week 52 suggest that patients who were BDL 210 mg responders at week 12 continue to have good response to treatment, based on sPGA success at week 52; however, as noted, week 52 results may overstate the effect of BDL due to the focus on the enriched population of responders.

Analysis of primary outcomes by subgroup showed a somewhat similar or lower response rate among BDL-treated patients with prior biologic use or failure of biologics across trials at week 12; however, USK-treated patients with prior biologic use or failure also reported a lower frequency of PASI 75 response compared with those without prior biologic use or failure in AMAGINE-2 and -3. Additionally, BDL-treated patients with body weight > 100 kg consistently showed a lower response rate for all primary outcomes. USK-treated patients with body weight > 100 kg also reported a lower frequency of PASI 75 response compared with those with body weight ≤ 100 kg, despite patients with body weight > 100 kg having received the higher dose (90 mg versus 45 mg).

According to patient group input, the most significant physical symptoms of psoriasis include scales, flaking, itching, joint pain, cracking and bleeding, and pain. The input also suggests that lesions affect psychological well-being. The PSI assesses a number of the specific symptoms mentioned by patients, including the aforementioned scales, flaking, and itching. As noted previously, the PSI responder results from all three studies supported the superiority of BDL compared with placebo for addressing psoriasis symptoms. Results from the disease-specific DLQI instrument in all trials — and the ED-5D-3L and SF-36 PCS and MCS in AMAGINE-1 only — suggest that improvements in the symptoms of plaque psoriasis (demonstrated by PASI, sPGA, and PSI) result in improvements in HRQoL for BDL-treated patients compared with placebo at week 12. However, statistical comparisons for these outcomes were not adjusted for multiplicity. No statistical comparisons for HRQoL measures were made between BDL and USK.

As described previously, a number of biologics are currently available on the market to treat moderate-to-severe psoriasis, including anti-TNF drugs (adalimumab, etanercept, and infliximab), IL-12 or -23 inhibitor (USK), and the IL-17A inhibitors, secukinumab and ixekizumab. The AMAGINE trials include as a comparator only one of many options for plaque psoriasis: USK. To address the lack of direct comparative evidence from other drug treatments for psoriasis, CDR reviewed and critically appraised the manufacturer's submitted ITC in addition to one other identified published ITC of relevance. Trials included in [redacted] exhibited heterogeneity in terms of placebo response, likely due to differences in patient characteristics across trials, which may bias the results of the ITC. [redacted], the additional published ITC adjusted for placebo response; however, it is uncertain whether such adjustment, which may be the current preferred approach, is adequate to control for differences in patient characteristics that may bias results. Thus, beyond USK (for which direct comparative short-term efficacy data are available), there remains uncertainty regarding the short-term efficacy of BDL compared with other biologics. In addition, the long-term efficacy of BDL in comparison with other biologics remains unknown.

A number of treatment guidelines indicate that biologics are to be used only when standard systemic therapies have failed, are contraindicated, or are not tolerated.[4,14,15] According to the clinical expert, BDL is likely to be used as another alternative to existing biologics. The clinical expert also emphasized the need for a treatment stopping rule after a certain period instead of lifelong treatment. There is no evidence from the manufacturer-submitted product monograph for such a stopping rule. The trials do not provide any relevant data related to the time to relapse after treatment withdrawal or discontinuation. The withdrawal phase of the AMAGINE-1 trial re-randomized BDL responders to receive placebo through week 52; however, [redacted] This suggests (albeit in a small sample) that the [redacted]; with no information on how long patients need to be treated before withdrawal will not necessitate retreatment.

Harms

Overall, the proportion of patients with an AE during the induction phase in the BDL 210 mg every two weeks group was comparable to the USK group and higher than the placebo group across the trials. This pattern continued through the withdrawal/maintenance and long-term phase, where the rate of exposure-adjusted AEs among patients receiving any dose of BDL and those in the 210 mg every two weeks group was comparable to those in

the USK group. The most common AEs in both phases of all three trials were nasopharyngitis, URTI, headache, and arthralgia. This indicates that the AE profile of BDL remained similar with longer exposure. Additionally, the frequency and rate of these AEs through the induction and withdrawal/maintenance phase were not notably different in the BDL 210 mg every two weeks group compared with the placebo or USK groups.

The overall frequency and exposure-adjusted rate of SAEs and events leading to discontinuation of the study was low, and was similar across treatment groups in both the induction and maintenance phases within each trial. The most common SAEs among BDL-exposed patients during the induction phase in AMAGINE-1, AMAGINE-2, and AMAGINE-3 were cellulitis, appendicitis and acute pancreatitis, and gastroenteritis, respectively. During the induction and withdrawal/maintenance phase, the frequency and exposure-adjusted event rate of SAEs in the BDL group were < 2% and ≤ 10 events per 100 patient-years, respectively, across all trials. The number of patients who discontinued the study due to AEs was low in the BDL group throughout the double-blind period across the trials, with the frequency and exposure-adjusted rate never exceeding 1% and four events per 100 patient-years, respectively. A total of four, seven, and five deaths were registered throughout the duration of AMAGINE-1, AMAGINE-2, and AMAGINE-3, respectively. Only one of these cases was adjudicated as BDL-related.

A number of AEs of particular interest were identified for this review, including inflammatory bowel disease and suicidal ideation and behaviour, both of which are featured in the Warnings and Precautions section of the Health Canada–approved product monograph. Given the limited data in patients with a history of Crohn's disease, BDL is contraindicated in such patients.[9] Further, the Health Canada–approved product monograph[9] contains a boxed warning stating that, while a causal association between BDL and suicidal ideation and behaviour has not been established, prescribers should weigh the potential risk and benefit in patients with a history of depression and/or suicidal ideation or behaviour, as well as providing recommendations for referral of patients with such manifestations. The product monograph further states that, because of the observed suicidal ideation and behaviour in patients treated with BDL, if an adequate response to BDL has not been achieved within 12 weeks to 16 weeks, the prescriber and patient should consider discontinuing therapy.[9]

[redacted]risk of suicidal ideation and behaviour[redacted] physician education, [redacted] enrolment forms [redacted]. The clinical expert consulted for this review indicated that due to this identified risk and the existence of a boxed warning, he expects to monitor patients more frequently than he would with other biologics.

Potential Place in Therapy

Currently, there are eight biologics (including BDL) approved for the treatment of plaque psoriasis. BDL is one of three anti–IL-17 drugs; the other two are monoclonal antibodies (secukinumab and ixekizumab).

The currently available biologics provide good efficacy and a durable response. Less than 10% to 20% of patients fail to respond to one of the biologics, experience a loss of efficacy, or have a contraindication. BDL is one of eight biologics that may be tried when another drug fails.

Biologics are currently used as continuous therapy. When a patient is started on a biologic, the treatment is expected to be continuous and lifelong. Therefore, there is a major unmet need for a treatment that is remittive or would work well on an intermittent “as needed” basis. So far, neither BDL nor any of the biologics have been demonstrated to fulfill this need.

It does not appear that BDL has any significant advantage over the other drugs. It is simply another choice for patients and physicians.

Conclusions

Based on the results of three phase III RCTs in adults with moderate-to-severe plaque psoriasis, compared with placebo and USK, BDL 210 mg resulted in statistically significant and clinically important improvements in skin clearance and dermatological symptoms over the short-term induction phase, as measured by the PASI and sPGA. Results from [redacted] suggest that, over the short-term induction phase, BDL may be more efficacious than a number of other biologics in attaining PASI 75, PASI 90, and PASI 100 responses, and may be similar in efficacy to ixekizumab. However, there is some uncertainty in the results of the ITC for short-term efficacy due to between-study heterogeneity that may not have been adequately controlled. Further, longer-term comparative efficacy data from RCTs is lacking.

The size and duration of the included trials were likely insufficient to assess comparative safety, particularly for rare or latent harms. However, the Health Canada–approved product monograph for BDL includes a boxed warning related to the risk of suicidality, which may influence prescriber behaviour.

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 review.

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 dedicated to advocating, educating, and supporting Canadians living with skin diseases, conditions, and traumas. CAPP and CPN are national, not-for-profit organizations that advocate for and provide information to 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 (the manufacturer of the drug under review). 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, Novartis, and Pfizer Canada.

Arthritis Consumer Experts (ACE) is a national patient-led 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 has 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 available for response from June 15 to November 30, 2017. The survey was distributed using various platforms, including social media, two different newsletters, and personal contacts. There were 60 respondents; information was used from 45 respondents, eight of whom were involved in brodalumab (BDL) clinical trials. ACE obtained its information through a call for input on December 13, 2017 and through one-to-one interviews with patients, caregivers, and health care providers. Data were gathered in December 2017 and January 2018. In addition, information that had been submitted by patients for a previous submission regarding plaque psoriasis on September 18, 2017 was used.

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, cracking, bleeding, pain, and joint pain. Psoriasis affects patients psychologically as well, 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 activities such as dancing, swimming, or sports that would expose the affected 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 due to both the physical and psychological symptoms. Other conditions that patients feel are related 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 can experience isolation and intimacy issues due to embarrassment caused by 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 and 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 stated that they have lost jobs due to the unsightliness of their lesions. For example, one patient said: “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.”

A number of patients will go on to develop PsA, as this occurs in approximately 30% of patients with psoriasis. The fear of this can be at the forefront of patients’ minds.

Caregivers of patients with psoriasis often experience increases in the amount of care and household cleaning such as vacuuming, bedding changes, and laundry, and sometimes need to help 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 (if the patient is taking infusion biologics). Caregivers often find themselves negatively affected psychologically; an entire family can become dysfunctional as it tends to absorb the shame, depression, and isolation associated with the disease. Caregivers’ schedules are also 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 they reported with these treatments included costs, long wait times to see a dermatologist, and other barriers to accessing specific treatments.

Respondents noted the frustration associated with the use of topical treatments due to the need for frequent application, lack of efficacy, and adverse effects (including loss of hair, loss of libido, and mood swings). 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 systems. One patient was worried about the possibility of cancer, as she is currently on Humira. One patient said the combination of Enbrel and methotrexate improved their psoriatic arthritis; however, methotrexate was associated with gastrointestinal upset and mucous membrane irritation on occasion. (This was managed with folic acid treatment.)

4. Expectations About the Drug Being Reviewed

Patients with psoriasis would welcome any treatment that might allow them to live a normal life with fewer adverse events. They would like to stop worrying about the unsightly plaques and scales and have the freedom to go out without being judged. They would appreciate not having their lives interrupted by frequent visits for phototherapy, or travelling long distances, or the time required to access infusion clinics. Patients want new treatments that can control or stop the symptoms (itchiness, scaling, pain, and flaking) of plaque psoriasis. Most patients with psoriasis hope that the next available treatment will provide 100% effectiveness and eliminate all of their symptoms with limited side effects. Patients believe that it is better to have more options and that having more options could mean better access to medication.

For patients surveyed who had BDL experience (n = 8), it appeared that most had found it beneficial. One stated, “This is the only study drug that has ever worked for me. I am totally clear.” Another patient said, “This drug is a miracle. It helped clear everything, the redness, scales and all.” Another patient said, “I loved it! In one day, I went from 95% covered to 95% clear.” There were no side effects reported except by one patient, who stated that she suffered from headaches the day after receiving the injection. Another patient stated that he only experienced side effects after he stopped BDL treatment. He said, “I experienced mild cripple-ness and pain almost immediately. I am waiting for the medical plan to cover it so that I can start on BDL again.”

Appendix 2: Literature Search Strategy

OVERVIEW

Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE ALL 1946 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	January 19, 2018
Alerts:	Bi-weekly search updates until May 16, 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were used 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
medall	Ovid database code; MEDLINE ALL 1946 to present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY

1	(1174395-19-7 or 6ZA31Y954Z).rn,nm.
2	(brodalumab* or siliq or kyntheum* or lumicef* or amg827 or amg 827 or BLA 761032 OR KHK4827).ti,ab,kf,ot,hw,rn,nm.
3	or/1-2
4	3 use medal
5	*brodalumab/
6	(brodalumab* or siliq or kyntheum* or lumicef* or amg827 or amg 827 or BLA 761032 OR KHK4827).ti,ab,kw.
7	or/5-6
8	7 use oemezd
9	conference abstract.pt.
10	8 not 9
11	4 or 10
12	remove duplicates from 11

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.
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.

Grey Literature

Dates for Search:	January 2018
Keywords:	Siliq (brodalumab), 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
- Databases (free)
- Internet Search.

Appendix 3: Excluded Studies

Table 13: List of Excluded Studies

Reference	Reason for Exclusion
Sawyer et al. (2018)	NMA
Sbidian et al. (2017)	NMA
Papp et al. (2014)	Phase II open-label extension study
Osamu et al. (2014)	Phase I trial

NMA = network meta-analysis.

Appendix 4: Detailed Outcome Data

Table 14: Key Efficacy Outcomes (Quality of Life–Related Outcomes) Through Week 52

	AMAGINE-1		AMAGINE-2		AMAGINE-3	
N	BDL 210/ BDL 210	PLB	BDL 210 /BDL 210	USK/ USK	BDL 210 /BDL 210	USK/ USK
Withdrawal/Maintenance Phase						
DLQI Total Score[a] (LOCF)						
Wk 12, N						
Wk 12, mean (SE)						
Wk 52, N						
Wk 52, mean (SE)						
Treatment difference, LS mean (SE)						
95% CI						
P value[b]						
DLQI Improvement ≥ 5[c] (NRI)						
Wk 52, N						
n (%)						
P value[d]						
DLQI 0/1[c] (NRI)						
Wk 52, N						
n (%)						
P value[d]						
SF-36 PCS[a] (As Observed)						
Wk 12, N						
Wk 12, Mean (SE)						
Wk 52, N						
Wk 52, mean (SE)						
SF-36 MCS[a] (As Observed)						
Wk 12, N						
Wk 12, mean (SE)						
Wk 52, N						
Wk 52, mean (SE)						

BDL 210 = brodalumab 210 mg; CI = confidence interval; DLQI = Dermatology Life Quality Index; LOCF = last observation carried forward; MCS = mental component summary; ND = not done; NR = not reported; NRI = nonresponder imputation; PCS = physical component summary; PLB = placebo; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; USK = ustekinumab; wk = week.

[a] In AMAGINE-1, results were reported as LOCF, while in AMAGINE-2 and AMAGINE-3, results were reported as "as observed."

[b] The *P* value comparing the BDL and withdrawal (PLB) groups is based on an ANCOVA model total body weight at week 12 (≤ 100 kg, > 100 kg) and week 12 sPGA (0, ≥ 1), and is nominal without multiplicity adjustment.

[c] In AMAGINE-1, results were reported as "nonresponder imputation," while in AMAGINE-2 and AMAGINE-3, results were reported as "as observed."

[d] The *P* value comparing the BDL and withdrawal (PLB) groups is based on the Cochran–Mantel–Haenszel test stratified by week 12 total body weight (≤ 100 kg, > 100 kg) and week 12 sPGA (0, ≥ 1) and induction phase treatment, and is nominal without multiplicity adjustment.

Source: AMAGINE-1 CSR,[6] Papp et al. (2016),[10] AMAGINE-2 CSR,[7] AMAGINE-3 CSR,[8] Lebwohl et al. (2015).[11]

Table 15: Key Efficacy Outcomes (Symptom-Related Outcomes) Through Week 52

	AMAGINE-1		AMAGINE-2		AMAGINE-3	
	BDL 210/ BDL 210 [redacted]	PLB [redacted]	BDL 210/ BDL 210 [redacted]	USK/USK [redacted]	BDL 210/ BDL 210 [redacted]	USK/USK [redacted]
Maintenance/Withdrawal phase (Re-randomized)						
Absolute PASI Score (LOCF)						
Wk 12, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 12, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 52, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 52, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference, LS mean (SE)	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
P value[a]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
PASI 75 (Nonresponder Imputation)						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
PASI 90 (Nonresponder Imputation)						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
PASI 100 (Nonresponder Imputation)						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
sPGA Success [0 (Clear) to 1 (Almost Clear)] (Nonresponder Imputation)						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
sPGA Clear 0 (Nonresponder Imputation)						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
PSI Total Score[c] (LOCF)						
Wk 12, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 12, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 52, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 52,	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	AMAGINE-1		AMAGINE-2		AMAGINE-3	
	BDL 210/ BDL 210 [redacted]	PLB [redacted]	BDL 210/ BDL 210 [redacted]	USK/USK [redacted]	BDL 210/ BDL 210 [redacted]	USK/USK [redacted]
mean (SE)						
Treatment difference, LS mean (SE)	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
P value[a]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
PSI Responder (Total Score ≤ 8, With No Item Scores > 1)[c] (Nonresponder Imputation)						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
PSI Score 0[c] (Nonresponder Imputation)						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]

ANCOVA = analysis of covariance; BDL 210 = brodalumab 210 mg; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; ND = not done; NR = not reported; PASI = Psoriasis Area and Severity Index; PLB = placebo; PSI = Psoriasis Symptom Inventory (total score); SE = standard error; sPGA = static Physician's Global Assessment; USK = ustekinumab; wk = week.

[a] The *P* value comparing the BDL and withdrawal (PLB) groups is based on an ANCOVA model total body weight at week 12 (≤ 100 kg, > 100 kg) and week 12 sPGA (0, ≥ 1), and is nominal without multiplicity adjustment.

[b] The *P* value comparing the BDL and withdrawal (PLB) groups is based on the Cochran–Mantel–Haenszel test stratified by week 12 total body weight (≤ 100 kg, > 100 kg) and week 12 sPGA (0, ≥ 1) and induction phase treatment, and is nominal without multiplicity adjustment.

[c] In AMAGINE-1, results were reported as LOCF, while in AMAGINE-2 and AMAGINE-3, results were reported as "as observed."

Source: AMAGINE-1 CSR,[6] Papp et al. (2016),[10] AMAGINE-2 CSR,[7] AMAGINE-3 CSR,[8] Lebwohl et al. (2015).[11]

Table 16: Exposure-Adjusted Rates of Adverse Events Through Week 52

	AMAGINE-1		AMAGINE-2			AMAGINE-3		
AEs	**Constant BDL 210 N = 345**	**All BDL N = 648**	**Constant BDL 210 N = 486**	**All BDL N = 1,567**	**USK N = 300**	**Constant BDL 210 N = 489**	**All BDL N = 1,613**	**USK N = 313**
Patient-yrs[a]	271.8	517.3	379.7	1,366.8	246.1	383.5	1,410.8	248.6
All TEAEs, n[b] (r[c])	1,034 (380.4)	1,908 (368.8)	1,531 (403.2)	5,593 (409.2)	1,017 (413.3)	1,522 (396.8)	5,474 (388.0)	935 (376.1)
Common AEs, r[c] ≥ 5 (Any Treatment Arm)								
[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]	[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]	[redacted]	[redacted]	[redacted]	[redacted]

	AMAGINE-1		AMAGINE-2			AMAGINE-3		
AEs	**Constant BDL 210 N = 345**	**All BDL N = 648**	**Constant BDL 210 N = 486**	**All BDL N = 1,567**	**USK N = 300**	**Constant BDL 210 N = 489**	**All BDL N = 1,613**	**USK N = 313**
[redacted]								
SAEs								
All TEAEs, n[b] (r[c])	27 (9.9)	49 (9.5)	38 (10.0)	114 (8.3)	32 (13.0)	31 (8.1)	111 (7.9)	10 (4.0)
r[c] > 1 (Any Group)								
Infections and infestations	[redacted]		4 (1.1)	13 (1.0)	2 (0.8)	7 (1.8)	18 (1.3)	3 (1.2)
Gastrointestinal disorders	[redacted]		4 (1.1)	10 (0.7)	1 (0.4)	3 (0.8)	8 (0.6)	0 (0.0)
Nervous system disorders			6 (1.6)	11 (0.8)	0 (0.0)	2 (0.5)	6 (0.4)	0 (0.0)
Cardiac disorders	[redacted]		5 (1.3)	17 (1.2)	3 (1.2)	3 (0.8)	12 (0.9)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders			1 (0.3)	5 (0.4)	3 (1.2)	2 (0.5)	7 (0.5)	1 (0.4)
General disorders and administration site conditions			1 (0.3)	3 (0.2)	3 (1.2)	2 (0.5)	3 (0.2)	0 (0.0)
Psychiatric disorders			–	–	–	1 (0.3)	3 (0.2)	3 (1.2)
Study Discontinuation								
WDAE, n[b] (r[c])	9 (3.3)	14 (2.7)	14 (3.7)	35 (2.6)	3 (1.2)	12 (3.1)	23 (1.6)	4 (1.6)
Death								
	1 (0.4)	4 (0.8)	1 (0.3)	1 (0.1)	1 (0.4)	0 (0.0)	1 (0.1)	0 (0.0)
Fatal Events								
n[b] (r[c])	3 (1.1)	4 (0.8)	1 (0.3)	1 (0.1)	2 (0.8)	0 (0.0)	2 (0.1)	0 (0.0)
Notable Harms								
Infection and infestation	[redacted]		482 (126.9)	1,631 (119.3)	302 (122.7)	432 (112.6)	1,450 (102.8)	283 (113.8)
Injection-site reaction	[redacted]		24 (6.3)	61 (4.5)	9 (3.7)	22 (5.7)	81 (5.7)	18 (7.2)
IBD(S)	[redacted]		1 (0.3)	3 (0.2)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Suicidal attempt/ ideation/behaviour			3 (0.8) + 1 (0.3)	3 (0.2) + 2 (0.1)	1 (0.4)+0 (0.0)	0 (0.0)+1 (0.3)	0 (0.0)+1 (0.1)	0 (0.0)+1 (0.4)
[redacted]								

AEs	AMAGINE-1		AMAGINE-2			AMAGINE-3		
	Constant BDL 210 N = 345	All BDL N = 648	Constant BDL 210 N = 486	All BDL N = 1,567	USK N = 300	Constant BDL 210 N = 489	All BDL N = 1,613	USK N = 313
[redacted]								
Neutropenia	1 (0.4)	2 (0.4)	1 (0.3)	3 (0.2)	2 (0.8)	1 (0.3)	21 (1.5)	2 (0.8)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; BDL 210 = brodalumab 210 mg every 2 weeks; IBD(S) = inflammatory bowel disease (syndrome); PLB = placebo; SAE = severe adverse event; TEAE = treatment-emergent adverse event; USK = ustekinumab; wk = week.
Note: n = Number of adverse events. r = Exposure-adjusted event rate per 100 patient- years (n/Patient-yr*100). Constant BDL 210 = same dose through week 52 after first BDL dose. All BDL = re-randomized to receive any BDL dose during the withdrawal/maintenance phase. "–" indicates either an incidence of 0 or AE were not reported/listed. Exposure and AEs reported during periods of placebo exposure are excluded. AEs and exposure in patients randomized to placebo at day 1 is summarized after their first dose of 210 mg q.2.w. at or after week 12. AEs and exposure in USK patients who were rescued at week 16 are summarized as USK until the first dose of rescue BDL, then summarized as "210 mg q.2.w. After USK" in the original clinical study report; however, they are not relevant. Therefore, they are not included here. Multiple occurrences of the same event for a patient is counted as multiple events.
[a] Subject-yr = Total subject-years of exposure through week 52.
Source: AMAGINE-1 CSR,[6] Papp et al. 2016,[10] AMAGINE-2 CSR,[7] AMAGINE-3 CSR,[8] Lebwohl et al. 2015.[11]

Table 17: Subgroup Analysis by Prior Biologic Therapy (Week 12)

Subgroup	AMAGINE-1		AMAGINE-2			AMAGINE-3		
	BDL 210 N = 222	PLB N = 220	BDL 210 N = 612	USK N = 300	PLB N = 309	BDL 210 N = 624	USK N = 313	PLB N = 315
PASI 75 (Nonresponder Imputation)								
Prior Biologic Psoriasis Therapy								
Yes, N1	105	101	177	84	90	157	75	76
n (%)	92 (87.6)	0 (0.0)	147 (83.1)	52 (61.9)	4 (4.4)	126 (80.3)	47 (62.7)	3 (3.9)
P value	< 0.001			< 0.001	< 0.001		0.005	< 0.001
No, N1	117	119	435	216	219	467	238	239
n (%)	93 (79.5)	6 (5.0)	381 (87.6)	158 (73.1)	21 (9.6)	405 (86.7)	170 (71.4)	16 (6.7)
P value	< 0.001			< 0.001	< 0.001		< 0.001	< 0.001
Failure of Prior Biologic Psoriasis Therapies								
Yes, N1	44	41	85	40	40	65	22	24
n (%)	37 (84.1)	0 (0.0)	70 (82.4)	21 (52.5)	2 (5.0)	52 (80.0)	13 (59.1)	2 (8.3)
P value	< 0.001			0.003	< 0.001		0.16	< 0.001
No, N1	178	179	527	260	269	559	291	291
n (%)	148 (83.1)	6 (3.4)	458 (86.9)	189 (72.7)	23 (8.6)	479 (85.7)	204 (70.1)	17 (5.8)
P value	< 0.001			< 0.001	< 0.001		< 0.001	< 0.001
PASI 100 (Nonresponder Imputation)								
Prior Biologic Psoriasis Therapy								
Yes, N1	105	101	177	84	90	157	75	76
n (%)	45 (42.9)	0 (0.0)	67 (37.9)	13 (15.5)	0 (0.0)	65 (41.4)	14 (18.7)	0 (0.0)
P value		< 0.001		< 0.001	< 0.001		0.002	< 0.001
No, N1	117	119	435	216	219	467	238	239
n (%)	48 (41.0)	1 (0.8)	205 (47.1)	52 (24.1)	2 (0.9)	164 (35.1)	44 (18.5)	1 (0.4)

	AMAGINE-1		AMAGINE-2			AMAGINE-3		
Subgroup	**BDL 210 N = 222**	**PLB N = 220**	**BDL 210 N = 612**	**USK N = 300**	**PLB N = 309**	**BDL 210 N = 624**	**USK N = 313**	**PLB N = 315**
P value		< 0.001		< 0.001	< 0.001		< 0.001	< 0.001
Failure of Prior Biologic Psoriasis Therapies								
Yes, N1	44	41	85	40	40	65	22	24
n (%)	20 (45.5)	0 (0.0)	26 (30.6)	5 (12.5)	0 (0.0)	22 (33.8)	2 (9.1)	0 (0.0)
P value		< 0.001		0.025	0.002		0.095	0.012
No, N1	178	179	527	260	269	559	291	291
n (%)	73 (41.0)	1 (0.6)	246 (46.7)	60 (23.1)	2 (0.7)	207 (37.0)	56 (19.2)	1 (0.3)
P value		< 0.001		< 0.001	< 0.001		< 0.001	< 0.001
sPGA Success (Nonresponder Imputation)								
Prior Biologic Psoriasis Therapy								
Yes, N1	105	101	177	NR	90	157	NR	76
n (%)	85 (81.0)	0 (0.0)	133 (75.1)	NR	1 (1.1)	114 (72.6)	NR	3 (3.9)
P value		< 0.001		NR	< 0.001		NR	< 0.001
No, N1	117	119	435	NR	219	467	NR	239
n (%)	83 (70.9)	3 (2.5)	348 (80.0)	NR	11 (5.0)	383 (82.0)	NR	10 (4.2)
P value		< 0.001		NR	< 0.001		NR	< 0.001
Failure of Prior Biologic Psoriasis Therapies								
Yes, N1	44	41	85	NR	40	65	NR	24
n (%)	34 (77.3)	0 (0.0)	64 (75.3)	NR	0 (0.0)	46 (70.8)	NR	2 (8.3)
P value		< 0.001		NR	< 0.001		NR	< 0.001
No, N1	178	179	527	NR	269	559	NR	291
n (%)	134 (75.3)	3 (1.7)	417 (79.1)	NR	12 (4.5)	451 (80.7)	NR	11 (3.8)
P value		< 0.001		NR	< 0.001		NR	< 0.001
sPGA 0 (Nonresponder Imputation)								
Prior Biologic Psoriasis Therapy								
Yes, N1	105	101	177	NR	90	157	NR	76
n (%)	45 (42.9)	0 (0.0)	67 (37.9)	NR	0 (0.0)	65 (41.4)	NR	0 (0.0)
P value		< 0.001		NR	< 0.001		NR	< 0.001
No, N1	117	119	435	NR	219	467	NR	239
n (%)	48 (41.0)	1 (0.8)	207 (47.6)	NR	2 (0.9)	164 (35.1)	NR	1 (0.4)
P value		< 0.001		NR	< 0.001		NR	< 0.001
Failure of Prior Biologic Psoriasis Therapies								
Yes, N1	44	41	85	NR	40	65	NR	24
n (%)	20 (45.5)	0 (0.0)	26 (30.6)	NR	0 (0.0)	22 (33.8)	NR	0 (0.0)
P value		< 0.001		NR	< 0.001		NR	0.003
No, N1	178	179	527	NR	269	559	NR	291
n (%)	73 (41.0)	1 (0.6)	248 (47.1)	NR	2 (0.7)	207 (37.0)	NR	1 (0.3)
P value		< 0.001		NR	< 0.001		NR	< 0.001
PSI Responder (Nonresponder Imputation)								

	AMAGINE-1		AMAGINE-2			AMAGINE-3		
Subgroup	**BDL 210 N = 222**	**PLB N = 220**	**BDL 210 N = 612**	**USK N = 300**	**PLB N = 309**	**BDL 210 N = 624**	**USK N = 313**	**PLB N = 315**
Prior Biologic Psoriasis Therapy								
Yes, N1	105	101	177	NR	90	157	NR	76
n (%)	66 (62.9)	1 (1.0)	112 (63.3)	NR	3 (3.3)	95 (60.5)	NR	5/76 (6.6)
P value		< 0.001		NR	< 0.001		NR	< 0.001
No, N1	117	119	435	NR	219	467	NR	239
n (%)	69 (59.0)	8 (6.7)	302 (69.4)	NR	18 (8.2)	287 (61.5)	NR	15 (6.3)
P value		< 0.001		NR	< 0.001		NR	< 0.001
Failure of Prior Biologic Psoriasis Therapies								
Yes, N1	44	41	85	NR	40	65	NR	24
n (%)	28 (63.6)	1 (2.4)	52 (61.2)	NR	1 (2.5)	34 (52.3)	NR	2 (8.3)
P value		< 0.001		NR	< 0.001		NR	0.086
No, N1	178	179	527	NR	269	559	NR	291
n (%)	107 (60.1)	8 (4.5)	362 (68.7)	NR	20 (7.4)	348 (62.3)	NR	18 (6.2)
P value		< 0.001		NR	< 0.001		NR	< 0.001

BDL 210 = brodalumab 210 mg; NR = not reported; PASI = Psoriasis Area and Severity Index; PLB = placebo; PSI = Psoriasis Symptom Inventory (total score); sPGA = static Physician's Global Assessment; USK = ustekinumab.
Note: N = number of patients randomized; N1 = number of patients who were randomized and had a valid measurement value at the specified week, after imputation; *P* value is for comparison between specified treatment groups, within each subgroup category, and is nominal without multiplicity adjustment. The *P* value was based on the Cochran–Mantel–Haenszel test stratified by total body weight at baseline (≤ 100 kg, > 100 kg), geographic region, and adjusting for within-subgroup baseline PASI score (≤ median, > median).
Source: AMAGINE-1 CSR,[6] AMAGINE-1 study,[10] AMAGINE-2 CSR,[7] AMAGINE-3 CSR,[8] AMAGINE-2 and -3 study.[11]

Table 18: Subgroup Analysis by Prior Biologic Therapy (Week 52)

	AMAGINE-1		AMAGINE-2		AMAGINE-3	
Subgroup	**BDL 210 N2 = 83**	**PLB N2 = 84**	**BDL 210 /BDL 210 N = 168**	**USK/ USK N = 289**	**BDL 210 /BDL 210 N = 171**	**USK/ USK N = 301**
sPGA Success						
Prior Biologic Therapy						
Yes, N3	40	43	NR	NR	NR	NR
n (%)	30 (75.0)	0 (0.0)	NR	NR	NR	NR
P value		< 0.001	NR	NR	NR	NR
No, N3	43	41	NR	NR	NR	NR
n (%)	39 (90.7)	0 (0.0)	NR	NR	NR	NR
P value		< 0.001	NR	NR	NR	NR
Failure of Prior Biologic Therapies						
Yes, N3	15	19	NR	NR	NR	NR
n (%)	12 (80.0)	0 (0.0)	NR	NR	NR	NR
P value		< 0.001	NR	NR	NR	NR
No, N3	68	65	NR	NR	NR	NR
n (%)	57 (83.8)	0 (0.0)	NR	NR	NR	NR
P value		< 0.001	NR	NR	NR	NR

BDL 210 = brodalumab 210 mg; NR = not reported; PLB = placebo; sPGA = static Physician's Global Assessment.
Note: N2 = number of patients re-randomized into withdrawal/maintenance phase; N3 = number of patients who were re-randomized and had a valid measurement value at the specified week, after imputation; % = n/N1* 100. The *P* value shows treatment difference between BDL and PLB within each subgroup category, and is nominal without multiplicity adjustment. The *P* value was based on the Cochran–Mantel–Haenszel test stratified by week 12 total body weight (≤ 100 kg, > 100 kg) and week 12 sPGA (0, ≥ 1). Patients who experienced return of disease through week 52 were imputed as nonresponders at the time of qualification. Nonresponder imputation was used to impute missing data. Treatment groups were defined as planned treatment for the withdrawal/maintenance phase.
Source: AMAGINE-1 CSR,[6] AMAGINE-1 study,[10] AMAGINE-2 CSR,[7] AMAGINE-3 CSR,[8] AMAGINE-2 and -3 study.[11]

Table 19: Subgroup Analysis by Body Weight (Week 12)

Subgroup	AMAGINE-1		AMAGINE-2			AMAGINE-3		
	BDL 210 N = 222	**PLB N = 220**	**BDL 210 N = 612**	**USK N = 300**	**PLB N = 309**	**BDL 210 N = 624**	**USK N = 313**	**PLB N = 315**
PASI 75 (Nonresponder Imputation)								
Baseline Body Weight (kg)								
≤ 100, N1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
> 100, N1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
PASI 100 (Nonresponder Imputation)								
Baseline Body Weight (kg)								
≤ 100, N1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	AMAGINE-1		AMAGINE-2			AMAGINE-3		
	BDL 210 N = 222	PLB N = 220	BDL 210 N = 612	USK N = 300	PLB N = 309	BDL 210 N = 624	USK N = 313	PLB N = 315
P value		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
> 100, N1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
sPGA Success (Nonresponder Imputation)								
Baseline Body Weight (kg)								
≤ 100, N1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
> 100, N1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
sPGA 0 (Nonresponder Imputation)								
Baseline Body Weight (kg)								
≤ 100, N1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
> 100, N1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
PSI Responder (Nonresponder Imputation)								
Baseline Body Weight (kg)								
≤ 100, N1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
> 100, N1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]

BDL 210 = brodalumab 210 mg; NR= not reported; PASI = Psoriasis Area and Severity Index; PLB = placebo; PSI = Psoriasis Symptom Inventory (total score); sPGA = static Physician's Global Assessment.
Note: N = number of patients randomized; N1 = number of patients who were randomized and had a valid measurement value at the specified week, after imputation; *P* value is for comparison between specified treatment groups within each subgroup category, and is nominal without multiplicity adjustment. The *P* value is based on the Cochran–Mantel–Haenszel test stratified by prior biologic use (yes, no), geographic region, and adjusting for within-subgroup baseline PASI score (≤ median, > median).
Source: AMAGINE-1 CSR,[6] AMAGINE-1 study,[10] AMAGINE-2 CSR,[7] AMAGINE-3 CSR,[8] AMAGINE-2 and -3 study.[11]

Table 20: Subgroup Analysis by Body Weight (Week 52)

	AMAGINE-1		AMAGINE-2		AMAGINE-3	
Subgroup	BDL [redacted]	PLB [redacted]	BDL 210 /BDL 210 [redacted]	USK/ USK [redacted]	BDL 210 /BDL 210 [redacted]	USK/ USK [redacted]
sPGA Success (Nonresponder Imputation)						
Baseline Body Weight (kg)						
≤ 100, N3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 100, N3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BDL 210 = brodalumab 210 mg; NR = not reported; PLB = placebo; PSI = Psoriasis Symptom Inventory (total score); sPGA = static Physician's Global Assessment.
Note: N2 = number of patients re-randomized into withdrawal/maintenance phase; N3 = number of patients who were re-randomized and had a valid measurement value at the specified week, after imputation; % = n/N1* 100. The *P* value is for comparison between each BDL dose group and withdrawal (PLB) group within each subgroup category, and is nominal without multiplicity adjustment. The *P* value is based on Cochran–Mantel–Haenszel test stratified by week 12 sPGA.
Source: AMAGINE-1 CSR,[6] AMAGINE-1 study,[10] AMAGINE-2 CSR,[7] AMAGINE-3 CSR,[8] AMAGINE-2 and -3.[11]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Dermatology Life Quality Index (DLQI)
- Short Form-36 (SF-36)
- EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L)
- Psoriasis Area and Severity Index (PASI)
- Psoriasis Symptom Inventory (PSI)
- Static Physician's Global Assessment (sPGA)

Findings

Table 21: Brief Descriptions of Instruments Used in the AMAGINE-1, -2, and -3 Trials

Instrument	Type	Evidence of Validity	MID/Benchmark[a]	References
DLQI	The DLQI is a 10-item, dermatology-specific quality of life questionnaire.	YES	Range: 2.2 to 6.9	Basra et al. (2008)[34] Finlay et al. (1994)[35] Shikiar et al. (2006)[32] Shikiar et al. (2003)[33] Mazzotti et al. (2003)[36]
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 individual domain scores can be calculated. It also provides 2 component summary scores: PCS and MCS. Scores range from 0 to 100, with higher scores indicating better health.	YES	Ranges: 2.57 to 3.91 points for PCS and 3.89 to 6.05 points for the MCS*	Frendl and Ware (2014)[39] Maruish (2011)[40] Mease et al. (2006)[41] Shikiar et al. (2006)[32]
EQ-5D-3L	The EQ-5D-3L is a generic, preference-based, health-related quality of life measure consisting of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.	YES	Index score: range 0.09 to 0.22 VAS range: 3.82 to 10.34	EuroQol Group (1990)[38] Brooks et al. (1996)[37] Shikiar et al. (2006)[32]
PASI	A single estimate of a patient's disease severity at a given time based on induration, erythema, and scaling.	YES	Benchmark: PASI 75 MID for actual scores: not identified	Ashcroft et al. (1999)[46] Carlin et al. (2004)[47] Feldman et al. (2004)[48] Gourraud et al. (2012)[49] Mattei et al. (2014)[50]
PSI	The PSI is an 8-item, psoriasis-specific, patient-reported outcome measurement that assesses the severity of psoriasis-related symptoms based on a 24-hour recall.	YES	Not identified	Strober et al. (2016)[28] Bushnell et al. (2013)[29] Viswanathan et al. (2017)[30]

Instrument	Type	Evidence of Validity	MID/Benchmark[a]	References
sPGA	The sPGA 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 5 that are then averaged over all lesions.	YES	Not identified	Weisman et al. (2003)[51] Chow et al. (2015)[25] Simpson et al. (2015)[26] Cappelleri et al. (2013)[52]

DLQI = Dermatology Life Quality Index; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; MID = minimal important difference; MCS = mental component summary; PASI = Psoriasis Area and Severity Index; PCS = physical component summary; sPGA = static Physician's Global Assessment; PSI = Psoriasis Symptom Inventory; SF-36 = Short Form (36) Health Survey.

[a] Relevant to the condition of plaque psoriasis.

Dermatology Life Quality Index

The DLQI is a widely used dermatology-specific quality of life (QoL) instrument. It is a 10-item questionnaire that measures the effect of having skin disease on six different aspects relating to QoL: symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment.[32,35] Each of the 10 questions is scored as 0, 1, 2, and 3 based on the following responses, respectively: "not at all," "a little," "a lot," or "very much." 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. 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).[32,35] The higher the score, the greater the degree of QoL impairment. The meanings of the DLQI scores in terms of the effect on a patient's life are as follows:[34]

- 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 based on reassessment 7 to10 days after the initial assessment (the correlation between overall DLQI scores was 0.99, $P < 0.0001$, and of individual question scores was 0.95 to 0.98, $P < 0.001$).[35] It has also shown good internal consistency reliability (with Cronbach's alpha coefficients ranging from 0.75 to 0.92 when assessed in 12 international studies),[34] construct validity (as 37 separate studies have mentioned correlation of the DLQI with either generic or dermatology-specific and disease-specific measures),[34] and responsiveness (the DLQI is reportedly able to detect changes over time in 17 different studies).[34] Similar measures of validity, reliability, and responsiveness of the DLQI have also been shown in evaluations of the use of the instrument specifically in adult patients with moderate-to-severe psoriasis.[33,36]

Estimates of the minimal important difference (MID) — that is, 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 to obtain the DLQI MID were not patient-based (i.e., Basra et al.[34] derived estimates from PASI and Physician's Global Assessment anchors, as well as a distribution-based approach); therefore, they do not necessarily identify the smallest difference that patients would consider important.

Limitations associated with the DLQI are as follows:

- Concerns have been identified regarding unidimensionality and the behaviour of items of the DLQI in different patient populations with psoriasis with respect to their equivalence across different cultures, ages, and genders.[34]
- The patient's emotional aspects may be underrepresented; 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 component of the SF-36 or the Hospital Anxiety and Depression scale.[34]
- The DLQI may lack sensitivity in detecting change from mild to severe psoriasis.[53]

Short Form (36) Health Survey

The SF-36 is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[40] 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).[40] For each of the eight domains, a subscale score can be calculated. The SF-36 also provides two component summaries, the physical component summaries (PCS) and the mental component summary (MCS), derived from aggregating the eight domains according to a scoring algorithm. The PCS and 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, while 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.[40]

A systematic review by Frendl and Ware[39] examined SF-36 concordance and its MID across many different indications in studies evaluating drug therapy effectiveness. The SF-36 was observed to be responsive (when compared with primary clinical measures) in patients with psoriasis in these studies. In addition, of the 10 psoriasis studies identified, PCS or MCS improvement of at least 3 points versus placebo was observed in 70% of these studies.

Based on anchor data, the developer of the SF-36 proposed the following minimal mean group differences for the individual domain scores: PF, 3; RP, 3; BP, 3; GH, 2; VT, 2; SF, 3; RE, 4; and MH, 3. It should be noted that these 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.[40] As these MID values were based on clinical and other non–patient-reported outcomes, they do not necessarily identify the smallest difference that patients would consider important.

The MID of the PCS and MCS was also estimated in a study involving patients with moderate-to-severe plaque psoriasis. This study provided results for an estimated MID for patient-reported SF-36 scores. The estimated MID was based on PASI and PGA anchor data: MID-1 (PASI 25 to PASI 49), MID-2 (PASI 50 to PASI 74), and MID-3 (difference between nonresponders and minimal responders on PGA) and supported by two distribution-based approaches that use the standard error of measurement and one-half of the standard deviation as an upper limit for the MID.[32] The estimated MID for PCS ranged from 2.57 to 3.91, which was consistent with previous research.[40] The most reasonable

estimates of the MID for the MCS ranged from 3.89 to 6.05. The use of non–patient-based anchor data to estimate the MIDs in this study should be noted as a limitation. Further, the PGA anchor produced results that were inconsistent with the two other anchors, two distributional based approaches, and previous estimates of the MID for the PCS reported in the literature.[40] As such, the results from PGA anchor were not reported in this appendix.

EuroQol 5-Dimensions 3-Levels Questionnaire

The EQ-5D-3L is a generic health-related quality of life (HRQoL) instrument that has been applied to a wide range of health conditions and treatments, including psoriasis.[37,38] The first of two parts of the EQ-5D-3L is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose one level that reflects their own health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D-3L index score) to self-reported health states from a set of population-based preference weights.[37,38] The second part is a 20 cm visual analogue scale (EQ-VAS) that has end points labelled 0 and 100, with anchors of "worst imaginable health state" and "best imaginable health state," respectively. Respondents are asked to rate their own health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their own health on that day. Hence, the EQ-5D-3L produces three types of data for each respondent:

- A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- A population preference-weighted health index score based on the descriptive system.
- A self-reported assessment of health status based on the EQ-VAS.

The EQ-5D-3L index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively.

A systematic review of the use of EQ-5D-3L for skin conditions, including psoriasis and psoriatic arthritis, assessed the validity and responsiveness of the instrument.[54] The EQ-5D-3L was deemed reliable as per known group comparisons in multiple studies; evidence of convergent validity was also provided based on a moderate or strong correlation between EQ-5D-3L and other skin-specific measures.[32,54] Further, all nine studies of the systematic review by Yang et al. (2015)[54] showed that the EQ-5D-3L was responsive to changes in HRQoL. A five-level version of the questionnaire (EQ-5D-5L) is now available, and may be preferable to the EQ-5D-3L for psoriasis patients; however, further research in this area is required.[55]

One study involving patients with moderate-to-severe psoriasis estimated the MID for the EQ-5D-3L using anchor-based and distributional approaches, as described for SF-36. The MID for the EQ-5D-3L index score ranged from 0.09 (for MID-3) to 0.22 (MID-2); the MID for the EQ-5D VAS ranged from 3.82 (MID-1) to 10.34 (MID-3).[32]

Psoriasis Area and Severity Index

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 of higher than 10 is considered severe. A 75% reduction in the PASI score (PASI 75) is the current benchmark for most clinical trials in psoriasis and is the criterion for the efficacy of new psoriasis treatments approved by the FDA.[47]

The PASI is calculated by dividing the body into four regions: head (h), upper extremities (u), trunk (t), and lower extremities (l). These account for 10%, 20%, 30%, and 40% of the total body surface area (BSA), respectively.[48] Each of these areas is assessed separately for erythema, induration, and scaling, and rated on a scale of 0 (none) to 4 (very severe). The extent of psoriatic involvement for each region 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[48]

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

A number of limitations of the PASI have been identified:

- The PASI has been criticized as not correlating the clinical extent of the disease with quality of life (QoL) and the psychological stress caused by psoriasis. The patient's measure of QoL is often worse than the physician-rated clinical severity.[56]
- There are significant inter-rater reliability issues regarding the measurement of BSA.[46,48] There has been some work regarding the development of imaging and analysis systems to objectively measure BSA.[57] PASI scores can vary substantially between experienced and inexperienced physicians, raising concerns for inter-rater reliability.[58]
- Improvements in PASI score are not linearly related to severity or improvements in psoriasis.[47,48] The extent of psoriatic involvement is measured using a scale of 1 to 6 and the areas corresponding to each score are non-linear.
- Some severe disease (clinically) may be scored low. For example, PASI 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 higher than 40 are rare).[46] The validity of this scale may be overrated, in part because of the skew toward lower scores.[49]
- Criterion validity is restricted by the lack of a "gold standard" measure of psoriatic severity.[59]
- 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 K16 expression, and reduction in epidermal thickness).[47]

Psoriasis Symptom Inventory

The PSI is a psoriasis-specific, patient-reported outcome used to assess the severity of psoriasis-related symptoms. The PSI includes eight items that assess itching, redness, scaling, burning, stinging, cracking, flaking, and pain, and are measured using 5-point Likert-type scales ranging from 0 (not at all severe) to 4 (very severe).[28-30] Individual scores are summed to create a total score ranging from 0 to 32, with higher scores indicating a more severe condition.[28] The PSI is available in two versions: a 24-hour recall version and a seven-day recall version that captures symptoms over a one-week period.[29] The 24-hour recall version was used in the AMAGINE trials.

The PSI was developed in accordance with the FDA guidance for development of patient-reported outcomes (PRO) instruments[60] to allow the use of the PSI to assess psoriasis-specific symptoms in clinical trials.[61] Convergent and discriminant validity were used to evaluate the construct validity of the PSI based on at least a moderate correlation and small correlation, respectively, to the DLQI (item and domain scores) and SF-36 version 2 (subscale and component summary scores).[29,30,62] Using this method, the PSI was shown to have construct validity.[29,30,62] The PSI is also considered reliable as per excellent test-retest (reported as greater than 0.70 in three studies) and internal consistency data (reported as greater than 0.90 in two studies)[29,30,62] and responsive based on the known groups approach, as it was able to detect a statistically significant difference when the mean PSI score had changed, compared with PASI and sPGA scores[30,62] and the patient global assessment.[29]

One of the limitations of the PSI is that the majority of the study populations included in the studies validating the instrument were white, potentially limiting the generalizability of the results. Another limitation is that an MID has not yet been identified for the PSI. Also of note, one study showed that the PSI total scores varied significantly by clinical indicators of psoriasis severity (PASI and sPGA scores), with mean scores significantly larger in patients rated by clinicians as having more severe psoriasis.[62]

Static Physician's Global Assessment

The Physician's Global Assessment (PGA) is a measure used by physicians to determine the patient's overall severity of disease and is available in both a dynamic and a static form (sPGA). The former is an assessment of the change from baseline; the latter is measured at a single point in time.[24] The static version was used in this study. Various PGAs have been used in psoriasis with different descriptions and scores.[58] The specific sPGA used in

the AMAGINE trials is an ordinal system that rates psoriatic lesions by induration, erythema, and scaling based on scales of 0 to 5.[26,52] The following table highlights the scoring for induration (I), erythema (E), and scaling (S).

Table 22: Scoring System for the static Physician's Global Assessment

Score	Induration	Erythema	Scaling
0	No evidence of plaque elevation	No evidence of erythema, although hyperpigmentation may be present	No evidence of scaling
1	Minimal plaque elevation (~ 0.5 mm)	Faint erythema	Minimal; occasional fine scale over less than 5% of lesions
2	Mild plaque elevation (~ 1 mm)	Light red coloration	Mild; fine scale predominates
3	Moderate plaque elevation (~ 1.5 mm)	Moderate red coloration	Moderate; coarse scale predominates
4	Marked plaque elevation (~ 2 mm)	Bright red coloration	Marked; thick, non-tenacious scale predominates
5	Severe plaque elevation (~ 2.5 mm)	Dusky to deep red coloration	Severe; very thick tenacious scale predominates

Source: Chow et al. and Cappelleri et al.[25,52]

The sum of the three scales are added and then divided by three (I + E + S/3) to obtain a final sPGA score as follows:[25]

- 0 = clear; except for residual discoloration
- 1 = almost clear; lesions have individual scores for induration, erythema, and scaling (IES) of at least 1
- 2 = mild; lesions have individual scores for IES of at least 2
- 3 = moderate; lesions have individual scores for IES of at least 3
- 4 = marked; lesions have individual scores for IES of at least 4
- 5 = severe; lesions have individual scores for IES of at least 5.

The PGA is more subjective than the PASI in that there is no attempt to quantify the individual elements of plaque morphology or BSA involvement.[48,51] There have also been fewer studies using PGA than PASI. This outcome is considered reliable using test-retest data (1% to 3% variability[51] and ICC = 0.8[52]) and internal consistency (Cronbach's alpha > 0.8 consistently from week 2 measurements onwards).[52] However, inter-rater reliability due to variability, especially in untrained observers, is poor.[51] Many studies now employ only the final value of clear or almost clear as treatment success. Although it would seem that the PGA is less likely to be open to interpretation, different studies have used different definitions of clear or almost clear, making comparisons between treatments difficult.[24,51] Construct and content validity are considered strong within a study, but comparison with other studies, as well as relationships to other methods, are problematic due to the variability in data collection, analysis, and reporting method.[51] A MID in patients with plaque psoriasis was not identified.

Conclusion

The DLQI is a dermatology-specific QoL measure that has been validated for use in the psoriasis patient population, with an estimated MID in the range of 2.2 to 6.9.[26,34] The SF-36, a general health instrument, was observed to be responsive (when compared with primary clinical measures) in patients with psoriasis. An estimate for the MID was also provided by a study specific to patients with moderate-to-severe psoriasis, which supported an MID of 2.57 to 3.91 for the PCS and an MID of 3.89 to 6.05 for the MCS.[32] The EQ-5D-3L is a generic HRQoL instrument that has been used for various health conditions, including psoriasis. Assessments of the EQ-5D-3L demonstrated validity, reliability, and responsiveness in patients with psoriasis, with an MID ranging from 0.09 to 0.22 for the EQ-5D-3L index score and 3.82 to 10.43 for the VAS score.[32,54] The PASI is the most widely used instrument in psoriasis trials that assesses and grades the severity of psoriatic lesions and the patient's response to treatment. This outcome is considered reliable using test-retest data and internal consistency; however, inter-rater reliability due to variability is poor, particularly in untrained observers.[51] A MID was not identified for PASI; however, the current benchmark for most clinical trials for PASI is a 75% reduction in the PASI score (PASI 75).[47] Like the PASI, the PSI is a psoriasis-specific instrument, but it is patient-reported. It is used to assess the severity of psoriasis-related symptoms and has been validated in patients with moderate-to-severe psoriasis; however, an MID has not been established.[29,30,62] Lastly, the sPGA is validated, reliable, and easy to use, but it cannot measure the extent of psoriasis, may not be able to discriminate small changes in severity, and an MID has not been identified.[63]

Appendix 6: Summary of Other Studies

Objective

To summarize the results of the open-label long-term phase of AMAGINE-1, AMAGINE-2, and AMAGINE-3 (up to week 96). The following summary is based on unpublished data from the clinical study report of each trial.[6-8]

Trial Description

[redacted]

Results

Patient Disposition

[redacted]

Safety Results

[redacted]

[redacted]

Table 23: Exposure-Adjusted Rates of Adverse Events Through Long-term Phase

	AMAGINE-1		AMAGINE-2		AMAGINE-3	
AEs	**Overall BDL 210[a]** [redacted]	**All BDL** [redacted]	**Overall BDL 210[a]** [redacted]	**All BDL** [redacted]	**Overall BDL 210[a]** [redacted]	**All BDL** [redacted]
Subject-yrs[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All TEAEs, n (r)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Common AEs (r > 5 in Any Group)						
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
URTI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs						
All TEAEs, n (r)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
r > 1						
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study Discontinuation						
WDAEs, n (r)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatal						
n (r)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Notable Harms						
Infection (and infestation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection-site reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IBD(S)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Suicidal ideation/ attempt	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitive reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	AMAGINE-1		AMAGINE-2		AMAGINE-3	
AEs	**Overall BDL 210[a]** [redacted]	**All BDL** [redacted]	**Overall BDL 210[a]** [redacted]	**All BDL** [redacted]	**Overall BDL 210[a]** [redacted]	**All BDL** [redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms (benign, malignant and unspecified)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; BDL = brodalumab; IBD(S) = inflammatory bowel disease (syndrome); NR = not reported; q.2.w. = every 2 weeks; SAE = serious adverse events; TEAE = treatment-emergent adverse event, URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.
Note: N = Number of subjects randomized and received at least one dose of BDL; n = Number of adverse events; r = exposure-adjusted event rate per 100 patient-years(n/Patient-yr*100). Multiple occurrences of the same event for a patient are counted as multiple events. Treatment groups are as treated after first dose of active BDL.
[a] Overall 210 mg q.2.w. = at least 75% of the doses were 210 mg and none were 140 mg.
[b] Subj-yr = Total subject- years of exposure through the data cut-off date.
Source: AMAGINE-1 CSR,[6] AMAGINE-1 study,[10] AMAGINE-2 CSR,[7] AMAGINE-3 CSR,[8] AMAGINE-2 and -3 study.[11]

Summary

[redacted]

Appendix 7: Summary of Indirect Comparisons

Introduction and Background

Given the absence of head-to-head studies that have compared brodalumab (BDL) against most other relevant biologics used to treat moderate-to-severe plaque psoriasis in adult patients, the objective of this appendix is to summarize and critically appraise the evidence available regarding the comparative efficacy and safety of BDL versus other treatments through indirect treatment comparison (ITC).

Methods

The manufacturer submitted one ITC,[64] which was reviewed, summarized, and critically appraised. CADTH Common Drug Review (CDR) conducted an independent literature search for published ITCs that compared BDL with other relevant comparators for the treatment of moderate-to-severe plaque psoriasis in adult patients; one additional publication was identified.[65] Another network meta-analysis (NMA) by Sbidian et al.[66] was identified; however, that NMA was not summarized or critically appraised in this appendix because both doses of BDL (140 mg every two weeks and 210 mg every two weeks) were grouped together as a single arm; hence, the relative effect of BDL 210 mg every two weeks compared with other biologics was not reported.

Description of Indirect Treatment Comparisons Identified

Table 24 presents the population, interventions, comparisons, and outcomes — as well as the patients, intervention, comparator, outcomes, study design criteria — for each ITC identified.

Table 24: Populations, Interventions, Comparisons, Outcomes, and Study Design Criteria for Study Inclusion

	Manufacturer-Sponsored and Submitted ITC 2017[64]	Sawyer et al. (2018)[65]
Population	[redacted]	Adult patients with moderate-to-severe chronic plaque-type psoriasis
Intervention	[redacted]	• adalimumab • apremilast • brodalumab • etanercept • infliximab • ixekizumab • secukinumab • ustekinumab
Comparators	[redacted]	Any comparator, including placebo and unlicensed doses of biological and non-biological systemic therapies
Outcomes	[redacted]	• PASI 50 • PASI 75 • PASI 90

	Manufacturer-Sponsored and Submitted ITC 2017[64]	Sawyer et al. (2018)[65]
	[redacted]	• PASI 100
Study Design	[redacted]	RCTs
Other	[redacted]	Published in English

ITC = indirect treatment comparison; PASI = Psoriasis Area and Severity Index; RCT = randomized controlled trial.
Source: Manufacturer-supplied indirect comparison,[64] Sawyer et al.[65]

Review and Appraisal of Indirect Treatment Comparisons

Review of the Manufacturer-Sponsored Indirect Treatment Comparison[64]

Objectives and Rationale for the Manufacturer-Sponsored Indirect Treatment Comparison

[redacted]

Methods for the Manufacturer-Sponsored Indirect Treatment Comparison

Study Eligibility and Selection Process

[redacted]

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Data Extraction

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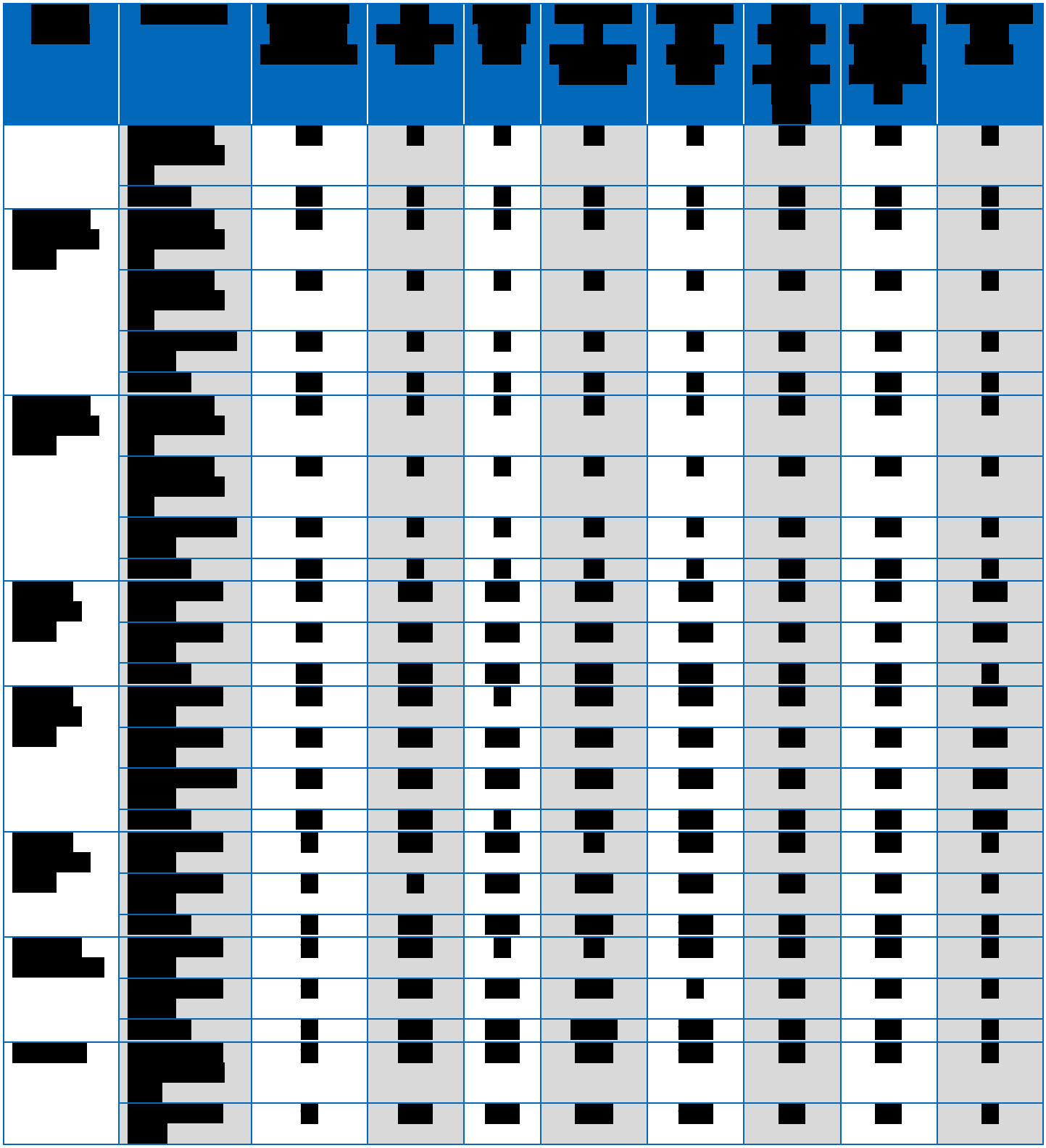

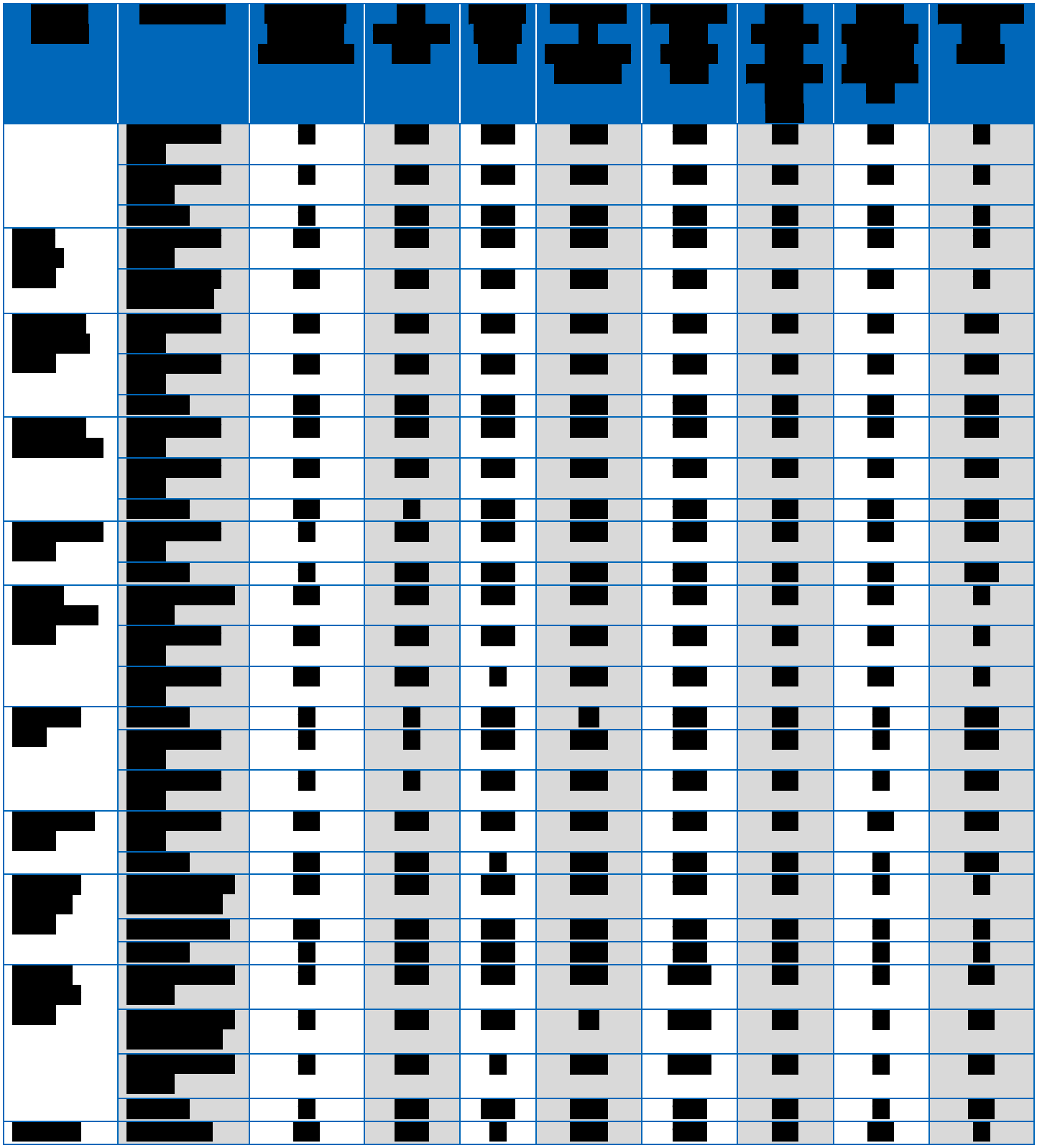

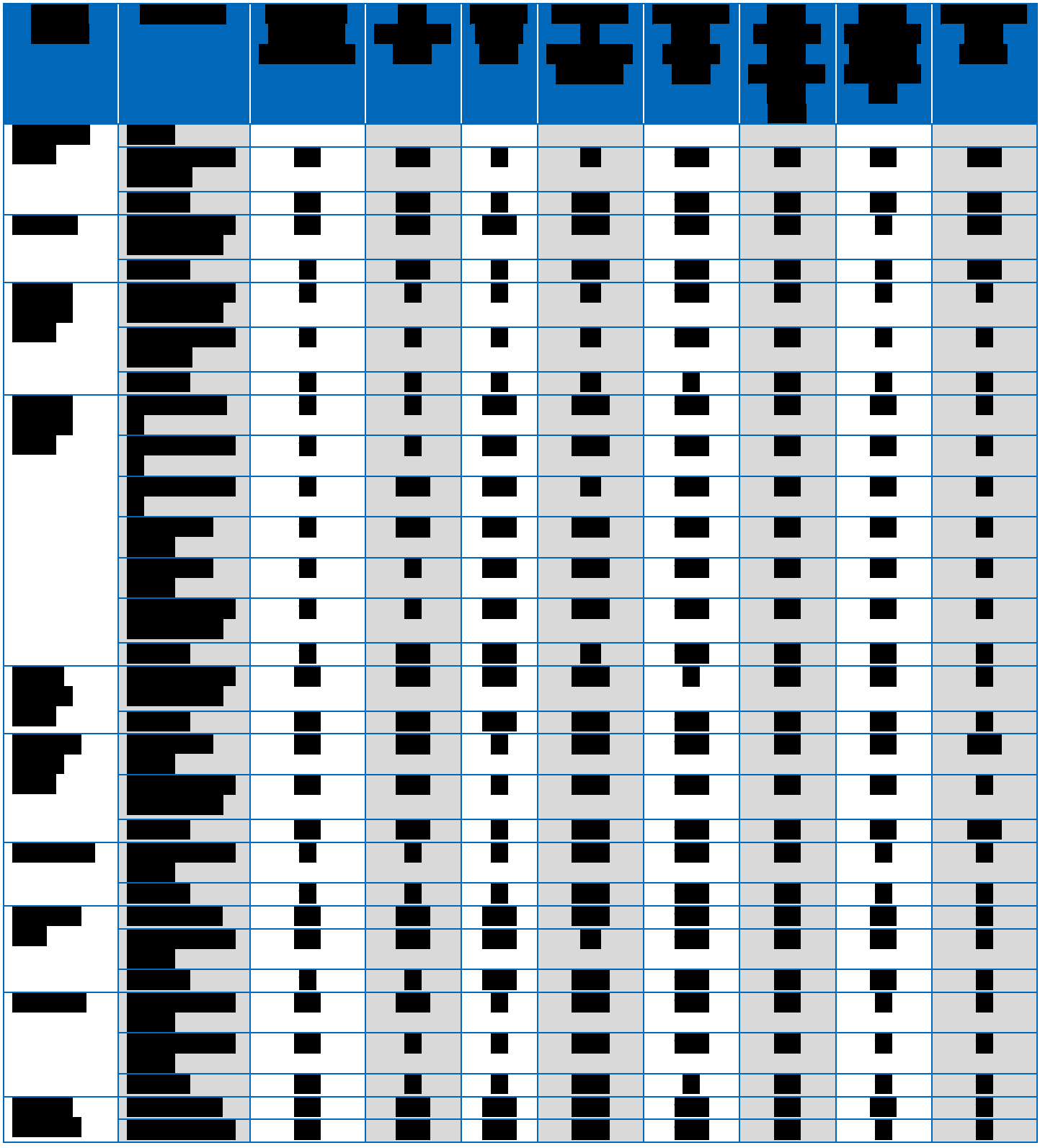

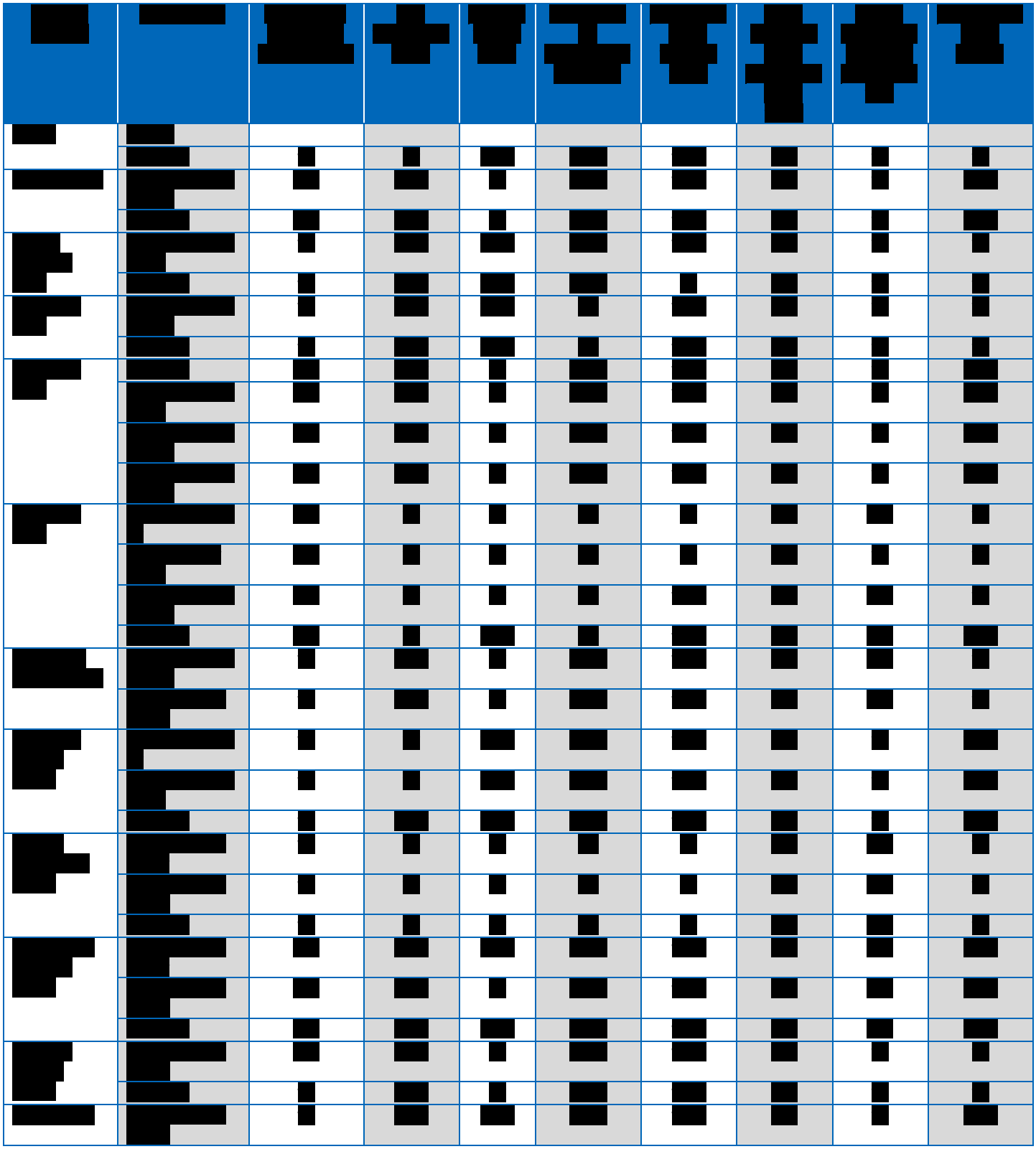

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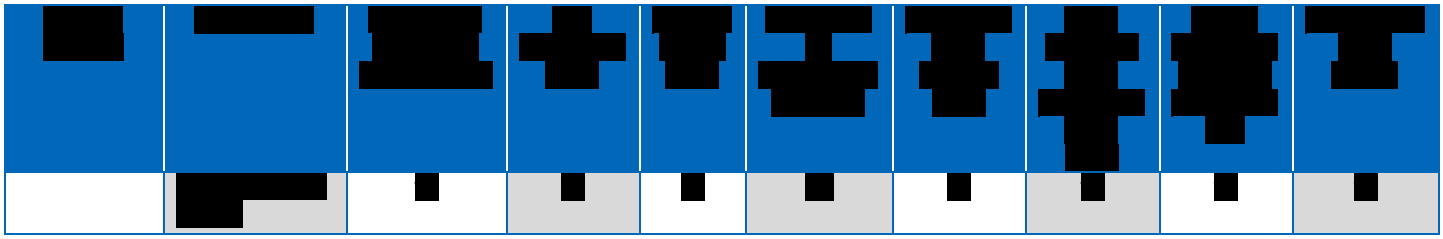

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Comparators

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Outcomes

[redacted]

Quality Assessment of Included Studies

[redacted]

Evidence Network

[redacted]

Indirect Comparison Methods

[redacted]

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Results

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Critical Appraisal

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Review of IDC by Sawyer et al. (2018)[65]

Objectives and Rationale for Indirect Treatment Comparison by Sawyer et al. (2018)[65]

The objective of the systematic review and NMA by Sawyer et al. (2018)[65] was to compare BDL with other biological therapies and apremilast, indicated for the treatment of moderate-to-severe psoriasis, by estimating the relative treatment effects for pairs of therapies not compared directly.

Methods for Indirect Treatment Comparison by Sawyer et al. (2018)[65]

Study Eligibility and Selection Process

English-language randomized controlled trials (RCTs) were eligible to be included in the systematic review if they met the following a priori inclusion criterion: adult patients with moderate-to-severe plaque psoriasis. Studies that included patients with both psoriasis and psoriatic arthritis were excluded.

Studies that examined adalimumab, apremilast, BDL, etanercept, infliximab, ixekizumab, secukinumab, or ustekinumab (USK) and involved any comparator — including placebo and unlicensed doses of biological and non-biological systemic therapies — were included. With the exception of BDL 140 mg every two weeks, only doses of biological therapies licensed by the European Medicines Agency (EMA) and regimens recommended by the National Institute of Health and Care Excellence (NICE) were included in the base-case analysis. Conventional systemic therapies, as well as other doses of licensed biological therapies, were included in a sensitivity analysis.

Outcomes of interest were the proportion of patients achieving PASI 50, PASI 75, PASI 90, and PASI 100 at the end of the induction period for each therapy.

Appropriate systematic review methods were employed in assessing study inclusion eligibility. The literature search was conducted for articles published from 2000 to 31 August 2016 and included multiple databases (Embase, MEDLINE, and Cochrane Library databases). In order to identify additional studies, the bibliography of each relevant article

was cross-referenced with the search results. Also, abstracts of relevant disease-specific and health economics and outcomes research congresses were searched. Two reviewers independently screened titles, abstracts, and full-text articles for inclusion. Disagreements were resolved by a third reviewer.

Data Extraction

For each study included in the review, study design details, patient information, intervention information and efficacy, and safety outcomes were extracted. A total of 54 RCTs were included in the NMA. In comparison with the manufacturer-submitted NMA, 12 new trials were included in the NMA by Sawyer et al. (2018). Select study and patient characteristics for these 12 trials are presented in Table 25. In addition, three RCTs (van de Kerkhof 2008,[67] Gottlieb 2003,[68] and LIBERATE[70]) that were included in the manufacturer-submitted systematic review but excluded from the NMA analyses were included in the NMA by Sawyer et al. (2018). Conversely, four trials (reSURFACE2 [Reich et al. 2017],[77] IXORA-S [Reich et al. 2017],[78] VOYAGE-1 [Blauvelt et al. 2016],[79] VOYAGE-2 [Reich et al. 2016][80]) that were included in the manufacturer-submitted NMA were not included in the NMA by Sawyer et al. (2018). The inclusion criteria for the included trials were comparable in terms of the diagnostic criteria for moderate-to-severe plaque psoriasis using body surface area (BSA) involvement and Psoriasis Area and Severity Index (PASI) score, as well as in terms of prior exposure to conventional systemic therapies or phototherapy.

The mean age was generally consistent across trials (ranging between 39 and 57 years of age). Differences between trials were evident in the baseline body weight of patients (treatment arm range: 67.0 kg to 97 kg), the duration of psoriasis (treatment arm range: 11.0 years to 23.5 years), percentage of prior biologic use (treatment arm range: 0% to 53%), baseline PASI scores (treatment arm range: 13.1 to 33.1), mean BSA involved (treatment arm range: 12% to 50%), and baseline Dermatology Life Quality Index (DLQI) scores (treatment arm range: 8.4 to 16.1) (Table 25). Some studies did not report the baseline characteristics of interest.

Table 25: Included Studies and Select Patient Characteristics Included in Sawyer et al. (2018)[65]

Author (Year)	Treatment	Number of Patients Randomized	Age (Years), Mean	Weight (kg), Mean	Duration of Psoriasis (Years)	Baseline PASI Score, Mean	Body Surface Area Involved (%), Mean	Prior Biologic Therapy Exposure (%)	Baseline DLQI Score
Goldminz et al. (2015)	Adalimumab 40 mg q.2.w.	15	50.5	NR	17.3	16.8	NR	40%	NR
	Methotrexate	15	50.3	NR	21.5	15.9	NR	27%	NR
Bissonnette et al. (2013)	Placebo	10	57.4	94.8	NR	13.1	13%	NR	NR
	Adalimumab 40 mg q.2.w.	20	56.1	95.1	NR	11.6	12%	NR	NR
PSOR-005, Papp et al. (2012)	Placebo	88	44.1	90.4	19.6	18.1	21%	NR	10.7
	Apremilast 20 mg b.i.d.	87	44.6	89.9	19.2	18.5	21%	NR	11.6
	Apremilast 30 mg b.i.d.	88	44.1	91.4	19.2	19.1	25%	NR	10.6
ESTEEM 1 Papp et al. (2015)	Placebo	282	46.5	93.7	18.7	19.4	25%	28%	12.1
	Apremilast 30 mg b.i.d.	562	45.8	93.2	19.8	18.7	24%	29%	12.7
ESTEEM 2 Paul et al. (2015)	Placebo	137	45.7	90.5	18.7	20.0	28%	32%	NR
	Apremilast 30 mg b.i.d.	274	45.3	91.4	17.9	18.9	26%	34%	NR
Papp et al. (2013)	Placebo	87	43.7	NR	NR	18.9	28%	NR	NR
	Apremilast 20 mg b.i.d.	85	48.4	NR	NR	20.9	31%	NR	NR
PRISTINE Strohal et al. (2013)	Etanercept 50 mg q.w.	137	43.9	86.6	16.6	20.9	33%	NR	15
	Etanercept 50 mg b.i.d.	136	44.0	83.7	18.1	21.4	33%	NR	14.1
RESTORE1 Barker et al. (2011)	Infliximab 5 mg/kg	653	44.1	84.5	18.8	21.4	32%	8%	13.5
	Methotrexate	215	41.9	83.8	17.0	21.1	31%	8%	13.8

Author (Year)	Treatment	Number of Patients Randomized	Age (Years), Mean	Weight (kg), Mean	Duration of Psoriasis (Years)	Baseline PASI Score, Mean	Body Surface Area Involved (%), Mean	Prior Biologic Therapy Exposure (%)	Baseline DLQI Score
SCULPTURE Mrowietz et al. (2015)	Secukinumab 150 mg	482	45.3	85.2	17.2	24.0	36%	27%	NR
	Secukinumab 300 mg	484	46.7	85.1	17.4	23.3	34%	29%	NR
CNTO 1275 Krueger et al. (2007)	Placebo	64	44.0	92.8	16.9	19.9	27%	NR	12
	Ustekinumab 45 mg	64	45.0	92.8	19.8	18.9	27%	NR	12.6
	Ustekinumab 90 mg	64	44.0	91.9	17.3	19.0	27%	NR	10.5
Caproni et al. (2009)	Etanercept 50 mg b.i.d.	30	28 to 67	NR	NR	21.54	NR	NR	NR
	Acitretin	30	31 to 65	NR	NR	22.25	NR	NR	NR
Gisondi et al. 2008)	Etanercept 25 mg b.i.d.	22	55.3	79.5	23.5	11.0	13%	NR	NR
	Acitretin	20	55.0	78.4	18.9	10.4	11%	NR	NR

b.i.d. = twice daily; DLQI = Dermatology Life Quality Index; NR = not reported; PASI = Psoriasis Area and Severity Index; q.w. = weekly; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks.

Source: Sawyer L, Fotheringham I, Wright E, Yasmeen N, Gibbons C, Holmen Moller A. The comparative efficacy of brodalumab in patients with moderate-to-severe psoriasis: a systematic literature review and network meta-analysis. *J Dermatolog Treat.* 2018:1-12. (CC BY-NC-ND 4.0).[6.5]

Comparators

Comparators and their dosage regimens were appropriate for Canadian decision-makers. All comparators were biologics or apremilast; therefore, they would be considered appropriate in terms of when they would be used in the treatment algorithm. However, a new biologic (guselkumab) that was recently approved in Canada for the treatment of adult patients with moderate-to-severe plaque psoriasis was not included in this NMA.

Outcomes

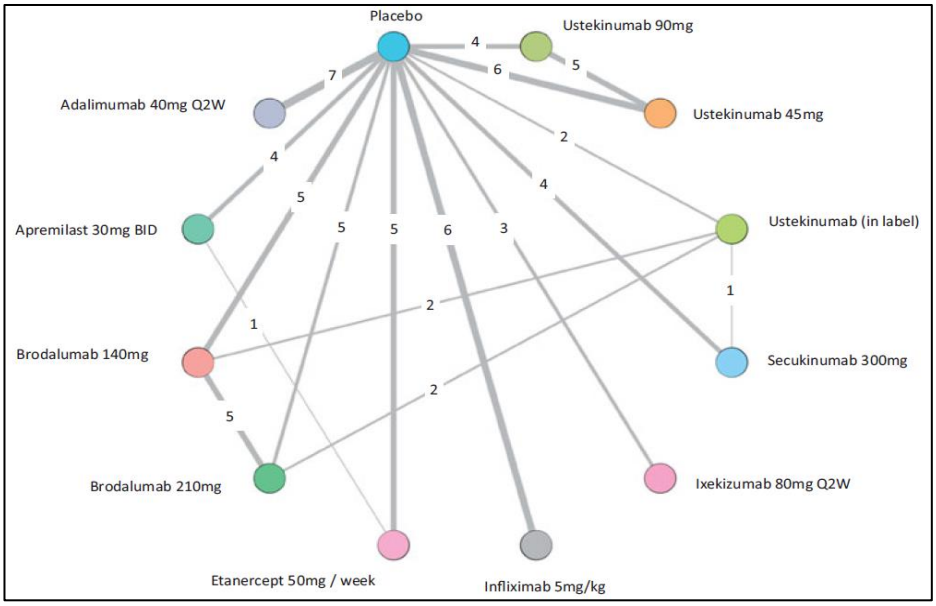
The NMA assessed PASI 50, PASI 75, PASI 90, and PASI 100. The base-case analysis of PASI responses comprised 41 studies involving 17,959 patients. Key efficacy outcomes of interest that were identified in the CDR review protocol — such as DLQI and global assessment — were not reported in the NMA. Similarly, key safety outcomes — adverse events (AEs), serious adverse events (SAEs), and withdrawals due to adverse events (WDAEs) — were not reported in this NMA.

Quality Assessment

The concise critical appraisal checklists provided by NICE in the Single Technology Appraisal user guide was used to assess the methodological quality of included studies. The potential risk of bias was determined by assessing the heterogeneity of study and patient characteristics as well as treatment and outcome characteristics. Randomization was judged as carried out appropriately in 50 studies and not clear in four studies. Concealment of treatment allocation was judged to be adequate in 39 studies, not clear in 14 studies, and not carried out appropriately in one study. One study had a judgment of unclear for similarity between groups; 53 studies had their demographics and disease characteristics judged as balanced between the groups. Two studies were assessed as having a high risk of bias due to inadequate blinding of participants and outcome assessors; 41 studies were judged adequate for blinding of participants and outcome assessors; four studies were judged as partly blinded; and seven studies were judged as not clear for the blinding of participants and outcome assessors. All studies except one were judged to be at low risk of bias with regard to selective outcome reporting. Discontinuation between groups was not similar in 13 studies, and it was unclear in five studies. The remaining 36 had similar between-group discontinuation due to AEs. Overall, it was judged that the risk of bias for most studies evaluated was low.

Evidence Network

Figure 4: Evidence Network for Base-Case Analysis of PASI Response

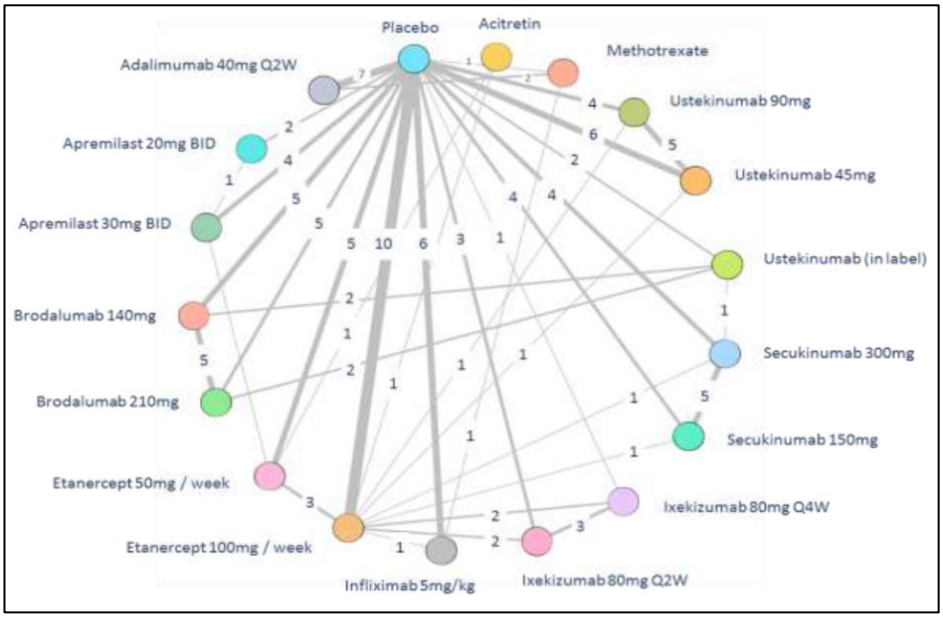


b.i.d. = twice daily; PASI = Psoriasis Area and Severity Index; q.2.w. = every 2 weeks.

Note: Lines connecting therapies represent direct comparisons observed in a clinical trial; the numbers and thicknesses of the lines represent how many trials measured the contrast.

Source: Sawyer L, Fotheringham I, Wright E, Yasmeen N, Gibbons C, Holmen Moller A. The comparative efficacy of brodalumab in patients with moderate-to-severe psoriasis: a systematic literature review and network meta-analysis. *J Dermatolog Treat.* 2018:1-12. (CC BY-NC-ND 4.0).[65]

Figure 5: Evidence Network for PASI Response Sensitivity Analysis



b.i.d. = twice daily; PASI = Psoriasis Area and Severity Index; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks.
Note: Lines connecting therapies represent direct comparisons observed in a clinical trial; the numbers and thicknesses of the lines represent how many trials measured the contrast.
Source: Sawyer L, Fotheringham I, Wright E, Yasmeen N, Gibbons C, Holmen Moller A. The comparative efficacy of brodalumab in patients with moderate-to-severe psoriasis: a systematic literature review and network meta-analysis. *J Dermatolog Treat.* 2018:1-12. (CC BY-NC-ND 4.0).[65]

Meta-Analysis and Indirect Comparison for Indirect Treatment Comparison by Sawyer et al. (2018)[65]

All NMAs were performed using WinBUGS version 1.4 statistical software with non-informative priors. An initial burn-in of at least 20,000 simulations was used. Convergence was confirmed through visual inspection of the Brook-Gelman-Rubin diagnostic and history plots. In order to estimate the sampled parameters, 50,000 simulations on three chains were undertaken. Results were calculated as risk ratios for brodalumab 210 mg every two weeks compared with each therapy, and for each treatment compared with placebo.

PASI response was modelled as a discrete dependent variable. No adjustments were made to address between-study differences in potential effect modifiers. Another model that included an adjustment for placebo arm response rates was tested. Placebo arm response rates varied considerably among the included psoriasis trials. Given that this is potentially a source of significant bias in cross-trial comparisons of treatment outcomes, a model that adjusts for placebo arm response rate may account for heterogeneity across trials and potentially improve the model fit. This adjustment for the placebo arm response rates was done in accordance with methods recommended by the NICE Decision Support Unit.[81-83] The estimated reference arm adjustment coefficient (beta) in the adjusted model was statistically significantly different from zero; it was estimated to be 0.642 (median; 95% credible interval [CrI], −0.835 to −0.438), indicating that the placebo-adjusted model reduced unexplained heterogeneity and improved the model in comparison with the unadjusted model. The 95% CrI of the random effect(s) was narrower in the adjusted model

relative to the unadjusted model, indicating a reduction in the between-study heterogeneity, which was captured by the adjustment coefficient.

For both adjusted and unadjusted models, results were generated using random- and fixed-effects and were compared for goodness of fit to the data using the total residual deviance statistic (deviance information criterion, or DIC). The total residual deviance statistic was similar between the two models; the DIC for the unadjusted model was lower than the DIC for the adjusted model. While a lower DIC implies a better model fit,[81] the placebo-adjusted model was considered by the authors to be more appropriate than the unadjusted model due to the statistical advantages of the placebo-adjusted model in terms of the observed heterogeneity of PASI response rates across the included trials and goodness of fit. Inconsistency in the direct evidence was assessed using a random-effects, unrelated mean-effects model. No significant inconsistency was reported in the base case or sensitivity analysis networks.

A sensitivity analysis was performed to assess the impact of including additional indirect evidence through the inclusion of data for unlicensed or unapproved doses of biological therapies, and for the inclusion of conventional systemic therapies.

Results of Indirect Treatment Comparison by Sawyer et al. (2018)[65]

Psoriasis Area and Severity Index 50, 75, 90, and 100 Responses

All biological therapies and apremilast had significantly higher PASI 50, 75, 90, and 100 responses than placebo. BDL 210 mg every two weeks had significantly higher PASI 50, 75, 90, and 100 responses than adalimumab 40 mg every two weeks, apremilast 30 mg twice daily, etanercept 50 mg once weekly, and USK (45 mg, 90 mg, and weight-based dosage), and had significantly higher PASI 50, 75, 90, and 100 responses than infliximab 5 mg/kg and secukinumab 300 mg when controlling for cross-trial variation in placebo responses. No statistically significant difference was found between BDL 210 mg every two weeks and ixekizumab 80 mg every two weeks in both the adjusted and unadjusted models. Results are presented in Table 26 through Table 29.

In the sensitivity analysis that assessed the impact of including additional indirect evidence through the inclusion of data for unlicensed or unapproved doses of biological therapies and conventional systemic therapies, a total of 54 trials involving 25,838 patients were included. Results after including conventional systemics like acitretin and methotrexate, as well as unlicensed doses of biologics, were generally similar to the base-case analysis. Results are presented in Table 26 through Table 29.

Table 26: Base-Case and Sensitivity Analysis for PASI 100 Response NMA Results in Sawyer et al. (2018)[65]

	Base Case		Sensitivity Analysis	
Treatment	**Adjusted Model Median Risk Ratio (95% CrI)**	**Unadjusted Model Median Risk Ratio (95% CrI)**	**Adjusted Model Median Risk Ratio (95% CrI)**	**Unadjusted Model Median Risk Ratio (95% CrI)**
Brodalumab 210 mg vs.				
Placebo	***313.8 (227 to 438.2)***	***298.8 (224.6 to 402.2)***	***378 (277.4 to 522.8)***	***357.9 (271.90 to 475.2)***
Adalimumab 40 mg q.2.w.	***2.38 (1.94 to 3.04)***	***2.96 (2.16 to 4.23)***	***2.39 (1.93 to 3)***	***2.77 (2.03 to 3.91)***
Apremilast 30 mg b.i.d.	***13.31 (9.73 to 18.73)***	***16.51 (10.73 to 26.99)***	***14.51 (10.42 to 20.64)***	***18.73 (12.06 to 30.28)***
Etanercept 50 mg q.w.	***8.28 (6.17 to 11.29)***	***7.57 (5.04 to 11.83)***	***10.07 (7.56 to 13.59)***	***9.68 (6.72 to 14.33)***
Infliximab 5 mg/kg	***1.42 (1.17 to 1.76)***	1.24 (0.93 to 1.7)	***1.56 (1.28 to 1.91)***	***1.52 (1.15 to 2.03)***
Ixekizumab 80 mg q.2.w.	0.99 (0.84 to 1.18)	0.91 (0.73 to 1.16)	0.97 (0.82 to 1.16)	0.87 (0.71 to 1.08)
Secukinumab 300 mg	***1.33 (1.12 to 1.59)***	1.22 (0.99 to 1.53)	***1.37 (1.15 to 1.64)***	***1.23 (1 to 1.53)***
Ustekinumab 45 mg	***2.11 (1.76 to 2.6)***	***1.88 (1.47 to 2.5)***	***2.27 (1.87 to 2.8)***	***2.08 (1.62 to 2.71)***
Ustekinumab 90 mg	***1.83 (1.5 to 2.28)***	***1.58 (1.23 to 2.09)***	***1.98 (1.62 to 2.47)***	***1.74 (1.36 to 2.27)***
Ustekinumab (label dose)	***2.14 (1.79 to 2.6)***	***2.15 (1.76 to 2.68)***	***2.21 (1.82 to 2.71)***	***2.19 (1.78 to 2.76)***
Apremilast 20 mg b.i.d.	NA	NA	***21.73 (12.56 to 39.82)***	***37.12 (17.93 to 82.26)***
Etanercept 100 mg q.w.	NA	NA	***5.13 (4.26 to 6.21)***	***4.63 (3.64 to 5.98)***
Ixekizumab 80 mg q.4.w.	NA	NA	1.18 (0.99 to 1.43)	1.05 (0.84 to 1.33)
Secukinumab 150 mg	NA	NA	***2.29 (1.86 to 2.88)***	***2.02 (1.57 to 2.66)***
Methotrexate	NA	NA	***10.63 (6.85 to 17.1)***	***12.25 (7.17 to 22.95)***
Acitretin	NA	NA	***26.49 (8.44 to 109.6)***	***24.68 (7.74 to 100.3)***

b.i.d. = twice daily; CrI = credible interval; NA = not applicable; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; q.w. = every week; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; vs. = versus.
Note: Risk ratios in bold indicate significant differences.
Source: Sawyer L, Fotheringham I, Wright E, Yasmeen N, Gibbons C, Holmen Moller A. The comparative efficacy of brodalumab in patients with moderate-to-severe psoriasis: a systematic literature review and network meta-analysis. *J Dermatolog Treat.* 2018:1-12. (CC BY-NC-ND 4.0).[65]

Table 27: Base-Case and Sensitivity Analysis for PASI 90 Response NMA Results in Sawyer et al. (2018)[65]

Treatment	Base Case		Sensitivity Analysis	
	Adjusted Model Median Risk Ratio (95% CrI)	Unadjusted Model Median Risk Ratio (95% CrI)	Adjusted Model Median Risk Ratio (95% CrI)	Unadjusted Model Median Risk Ratio (95% CrI)
Brodalumab 210 mg vs.				
Placebo	***56.46 (43.98 to 72.99)***	***54.95 (43.91 to 69.41)***	***63.37 (50.01 to 81.2)***	***61.54 (49.71 to 76.7)***
Adalimumab 40 mg q.2.w.	***1.64 (1.46 to 1.91)***	***1.89 (1.56 to 2.38)***	***1.64 (1.45 to 1.88)***	***1.8 (1.50 to 2.24)***
Apremilast 30 mg b.i.d.	***5.22 (4.2 to 6.61)***	***6.14 (4.53 to 8.73)***	***5.46 (4.35 to 6.97)***	***6.62 (4.86 to 9.34)***
Etanercept 50 mg q.w.	***3.74 (3.07 to 4.61)***	***3.54 (2.69 to 4.82)***	***4.22 (3.49 to 5.17)***	***4.15 (3.24 to 5.43)***
Infliximab 5 mg/kg	***1.21 (1.09 to 1.36)***	1.12 (0.96 to 1.34)	***1.27 (1.14 to 1.42)***	***1.26 (1.08 to 1.48)***
Ixekizumab 80 mg q.2.w.	0.99 (0.92 to 1.09)	0.95 (0.85 to 1.08)	0.99 (0.91 to 1.08)	0.93 (0.84 to 1.04)
Secukinumab 300 mg	***1.16 (1.07 to 1.28)***	1.12 (1.00 to 1.26)	***1.18 (1.08 to 1.3)***	***1.12 (1.00 to 1.26)***
Ustekinumab 45 mg	***1.53 (1.37 to 1.72)***	***1.43 (1.24 to 1.69)***	***1.59 (1.42 to 1.79)***	***1.51 (1.31 to 1.77)***
Ustekinumab 90 mg	***1.4 (1.25 to 1.59)***	***1.29 (1.12 to 1.51)***	***1.46 (1.31 to 1.66)***	***1.36 (1.18 to 1.58)***
Ustekinumab (label dose)	***1.54 (1.39 to 1.73)***	***1.55 (1.37 to 1.78)***	***1.56 (1.39 to 1.77)***	***1.56 (1.38 to 1.8)***
Apremilast 20 mg b.i.d.	NA	NA	***7.29 (4.94 to 11.29)***	***10.91 (6.43 to 19.71)***
Etanercept 100 mg q.w.	NA	NA	***2.67 (2.39 to 3)***	***2.51 (2.16 to 2.96)***
Ixekizumab 80 mg q.4.w.	NA	NA	1.09 (0.99 to 1.21)	1.03 (0.91 to 1.16)
Secukinumab 150 mg	NA	NA	***1.6 (1.41 to 1.83)***	***1.49 (1.29 to 1.75)***
Methotrexate	NA	NA	***4.39 (3.26 to 6.1)***	***4.89 (3.38 to 7.63)***
Acitretin	NA	NA	***8.41 (3.74 to 24.3)***	***8.07 (3.56 to 23)***

b.i.d. = twice daily; CrI = credible interval; NA = not applicable; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; q.w. = every week; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; vs. = versus.
Note: Risk ratios in bold indicate significant differences.
Source: Sawyer L, Fotheringham I, Wright E, Yasmeen N, Gibbons C, Holmen Moller A. The comparative efficacy of brodalumab in patients with moderate-to-severe psoriasis: a systematic literature review and network meta-analysis. *J Dermatolog Treat.* 2018:1-12. (CC BY-NC-ND 4.0).[65]

Table 28: Base-Case and Sensitivity Analysis for PASI 75 Response NMA Results in Sawyer et al. (2018)[65]

Treatment	Base Case		Sensitivity Analysis	
	Adjusted Model Median Risk Ratio (95% CrI)	Unadjusted Model Median Risk Ratio (95% CrI)	Adjusted Model Median Risk Ratio (95% CrI)	Unadjusted Model Median Risk Ratio (95% CrI)
Brodalumab 210 mg vs.:				
Placebo	***16.48 (13.56 to 20.18)***	***16.25 (13.57 to 19.63)***	***16.85 (14.05 to 20.39)***	***16.61 (14.01 to 19.8)***
Adalimumab 40 mg q.2.w.	***1.31 (1.22 to 1.42)***	***1.43 (1.27 to 1.64)***	***1.29 (1.21 to 1.39)***	***1.37 (1.23 to 1.55)***
Apremilast 30 mg b.i.d.	***2.77 (2.39 to 3.26)***	***3.12 (2.52 to 4.02)***	***2.76 (2.37 to 3.26)***	***3.17 (2.56 to 4.05)***
Etanercept 50 mg q.w.	***2.2 (1.94 to 2.53)***	***2.13 (1.78 to 2.63)***	***2.32 (2.05 to 2.65)***	***2.31 (1.96 to 2.77)***
Infliximab 5 mg/kg	***1.1 (1.04 to 1.17)***	1.06 (0.98 to 1.16)	***1.12 (1.07 to 1.19)***	***1.12 (1.04 to 1.22)***
Ixekizumab 80 mg q.2.w.	1.00 (0.96 to 1.04)	0.98 (0.92 to 1.04)	0.99 (0.96 to 1.04)	0.97 (0.92 to 1.02)
Secukinumab 300 mg	***1.08 (1.03 to 1.13)***	1.06 (1.00 to 1.12)	***1.08 (1.04 to 1.14)***	***1.05 (1 to 1.12)***
Ustekinumab 45 mg	***1.25 (1.18 to 1.34)***	***1.21 (1.12 to 1.33)***	***1.27 (1.2 to 1.35)***	***1.24 (1.15 to 1.35)***
Ustekinumab 90 mg	***1.19 (1.12 to 1.28)***	***1.14 (1.06 to 1.25)***	***1.21 (1.14 to 1.29)***	***1.17 (1.09 to 1.26)***
Ustekinumab (label dose)	***1.26 (1.19 to 1.35)***	***1.27 (1.18 to 1.38)***	***1.25 (1.18 to 1.34)***	***1.26 (1.17 to 1.37)***
Apremilast 20 mg b.i.d.	NA	NA	***3.37 (2.58 to 4.6)***	***4.52 (3.11 to 6.98)***
Etanercept 100 mg q.w.	NA	NA	***1.72 (1.62 to 1.85)***	***1.67 (1.53 to 1.85)***
Ixekizumab 80 mg q.4.w.	NA	NA	1.04 (1 to 1.09)	1.01 (0.96 to 1.07)
Secukinumab 150 mg	NA	NA	***1.27 (1.19 to 1.37)***	***1.22 (1.13 to 1.34)***
Methotrexate	NA	NA	***2.38 (1.96 to 2.97)***	***2.58 (2.02 to 3.5)***
Acitretin	NA	NA	***3.73 (2.14 to 8.09)***	***3.65 (2.09 to 7.83)***

b.i.d. = twice daily; CrI = credible interval; NA = not applicable; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; q.w. = every week; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; vs. = versus.
Note: Risk ratios in bold indicate significant differences.
Source: Sawyer L, Fotheringham I, Wright E, Yasmeen N, Gibbons C, Holmen Moller A. The comparative efficacy of brodalumab in patients with moderate-to-severe psoriasis: a systematic literature review and network meta-analysis. *J Dermatolog Treat.* 2018:1-12. (CC BY-NC-ND 4.0).[65]

Table 29: Base-Case and Sensitivity Analysis for PASI 50 Response NMA Results in Sawyer et al. (2018)[65]

Treatment	Base Case		Sensitivity Analysis	
	Adjusted Model Median Risk Ratio (95% CrI)	Unadjusted Model Median Risk Ratio (95% CrI)	Adjusted Model Median Risk Ratio (95% CrI)	Unadjusted Model Median Risk Ratio (95% CrI)
Brodalumab 210 mg vs.:				
Placebo	***7.1 (6.1 to 8.32)***	***7.05 (6.11 to 8.2)***	***6.99 (6.07 to 8.1)***	***6.95 (6.07 to 8)***
Adalimumab 40 mg q.2.w.	***1.15 (1.11 to 1.21)***	***1.21 (1.14 to 1.32)***	***1.13 (1.1 to 1.18)***	***1.17 (1.11 to 1.26)***
Apremilast 30 mg b.i.d.	***1.86 (1.68 to 2.09)***	***2.03 (1.75 to 2.43)***	***1.83 (1.65 to 2.05)***	***2.02 (1.74 to 2.4)***
Etanercept 50 mg q.w.	***1.59 (1.46 to 1.75)***	***1.56 (1.39 to 1.8)***	***1.63 (1.5 to 1.77)***	***1.63 (1.46 to 1.84)***
Infliximab 5 mg/kg	***1.05 (1.02 to 1.08)***	1.03 (0.99 to 1.08)	***1.06 (1.03 to 1.09)***	***1.05 (1.02 to 1.1)***
Ixekizumab 80 mg q.2.w.	1.00 (0.98 to 1.02)	0.99 (0.96 to 1.02)	1 (0.98 to 1.02)	0.99 (0.97 to 1.01)
Secukinumab 300 mg	***1.04 (1.02 to 1.06)***	1.03 (1.00 to 1.06)	***1.04 (1.02 to 1.06)***	***1.02 (1 to 1.05)***
Ustekinumab 45 mg	***1.12 (1.09 to 1.16)***	***1.1 (1.06 to 1.16)***	***1.12 (1.09 to 1.16)***	***1.11 (1.07 to 1.16)***
Ustekinumab 90 mg	***1.09 (1.06 to 1.13)***	***1.07 (1.03 to 1.12)***	***1.1 (1.07 to 1.14)***	***1.08 (1.04 to 1.12)***
Ustekinumab (label dose)	***1.13 (1.09 to 1.17)***	***1.13 (1.09 to 1.19)***	***1.12 (1.08 to 1.16)***	***1.12 (1.08 to 1.18)***

Treatment	Base Case		Sensitivity Analysis	
	Adjusted Model Median Risk Ratio (95% CrI)	Unadjusted Model Median Risk Ratio (95% CrI)	Adjusted Model Median Risk Ratio (95% CrI)	Unadjusted Model Median Risk Ratio (95% CrI)
Apremilast 20 mg b.i.d.	NA	NA	***2.1 (1.75 to 2.62)***	***2.6 (1.99 to 3.58)***
Etanercept 100 mg q.w.	NA	NA	***1.35 (1.29 to 1.4)***	***1.32 (1.25 to 1.41)***
Ixekizumab 80 mg q.4.w.	NA	NA	1.02 (1 to 1.04)	1.01 (0.98 to 1.03)
Secukinumab 150 mg	NA	NA	***1.13 (1.09 to 1.17)***	***1.11 (1.06 to 1.16)***
Methotrexate	NA	NA	***1.65 (1.46 to 1.92)***	***1.75 (1.49 to 2.16)***
Acitretin	NA	NA	***2.25 (1.54 to 3.97)***	***2.23 (1.52 to 3.9)***

b.i.d. = twice daily; CrI = credible interval; NA = not applicable; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; q.w. = every week; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; vs. = versus.
Note: Risk ratios in bold indicate significant differences.
Source: Sawyer L, Fotheringham I, Wright E, Yasmeen N, Gibbons C, Holmen Moller A. The comparative efficacy of brodalumab in patients with moderate-to-severe psoriasis: a systematic literature review and network meta-analysis. *J Dermatolog Treat.* 2018:1-12. (CC BY-NC-ND 4.0).[65]

Critical Appraisal of Indirect Treatment Comparison by Sawyer et al. (2018)[65]

The Sawyer et al.[65] rationale for conducting the ITC (i.e., the absence of head-to-head studies comparing BDL with most other relevant biologics or apremilast) and the objectives of the ITC (to compare the efficacy of BDL 210 mg with approved biologics for the treatment of moderate-to-severe chronic plaque psoriasis) were clearly reported. A comprehensive systematic review was performed with a two-stage, dual-selection process in which articles were first selected based on titles and abstracts, then full-text articles were retrieved and ascertained for their inclusion criteria. Risk of bias was assessed using the concise critical appraisal checklists provided by NICE in the Single Technology Appraisal user guide. Detailed results of these assessments were provided. The inclusion and exclusion criteria used for screening were provided and list of included references with accompanying reasons were reported; however, a list of excluded studies was not reported. A figure of the network was provided.

Similar to the manufacturer-submitted NMA, there was a lack of reporting in the majority of studies regarding at least one of the domains related to risk of bias. Many studies were lacking sufficient information to ascertain their true validity. This lack of verification regarding the risk of bias of the trials might have affected the results of the NMA and may have led to increased uncertainty surrounding the NMA conclusions.

Sawyer et al.[65] conducted both adjusted and unadjusted NMAs, in which the adjusted model reduced unexplained heterogeneity and improved the model. Given the variation in placebo response, the authors stated that the results from the adjusted model were preferred over those of the unadjusted model. Adjusting for the variation in response rates in the placebo groups across trials also seems to be the approach preferred by NICE versus the unadjusted analysis.[13,74] While adjusting for placebo response might be the preferred approach, there are limitations to the approach, because there is an assumption that study and patient characteristics (that are effect modifiers of the relative treatment effect) are also prognostic factors of the outcome with placebo.[75,76] Given that the extent to which placebo response is an adequate proxy for specific characteristics or effect modifiers is unclear, uncertainty remains in such an analysis.

Other limitations included the inconsistent or absent reporting of key data in the included studies and the fact that only English-language articles were included. Missing key articles has the potential to reduce the confidence in the results. In addition, while the induction periods are important in the treatment of patients with moderate-to-severe chronic plaque psoriasis, NMA analyses on longer durations would be beneficial to ascertain the long-term efficacy and tolerability of the various biologics. However, it is acknowledged that many (if not the majority) of the trials for psoriasis drug treatments are not adequately designed to evaluate long-term comparative efficacy and safety, which may have precluded an indirect analysis of such data.

The NMA results presented were PASI response rates, which is an appropriate outcome for patients with moderate-to-severe psoriasis. However, the ITC did not include any safety or harm outcomes, nor did it include health-related quality of life (HRQoL) data.

Sawyer et al.[65] indicated that an assessment of inconsistency was undertaken; however, results of such assessment were not provided.

In the base-case analysis, etanercept 50 mg per week was used. However, the recommended dose in Canada is 50 mg twice weekly, meaning the dose used in the base-case analyses is lower than that recommended in Canada. This might have resulted in a lower response for etanercept than if data for etanercept twice weekly were included.

Sawyer et al.[65] did not include the recently approved biologic guselkumab, which is an interleukin (IL)-23 inhibitor. As a result, the relative risks involved in achieving PASI responses with BDL 210 mg every two weeks compared with guselkumab are unknown.

Discussion

A summary and critical appraisal of two NMAs were included in this appendix. One was submitted by the manufacturer[64] and the other was done by Sawyer et al.[65] [redacted] The NMA by Sawyer et al.[65] reported that the relative risk of achieving PASI 50, 75, 90, and 100 responses with BDL 210 mg every two weeks was statistically greater than with adalimumab 40 mg every two weeks, apremilast 30 mg twice daily, etanercept 50 mg once weekly, and USK (45 mg, 90 mg, and weight-based dosage), and that the relative risk of achieving PASI 50, 75, 90, and 100 responses was statistically greater than with infliximab 5 mg/kg and secukinumab 300 mg when controlling for cross-trial variation in placebo responses. No statistical difference was found between BDL 210 mg every two weeks and ixekizumab 80 mg every two weeks in either the adjusted or unadjusted models.[65]The clinical expert indicated that the lack of difference between BDL and ixekizumab is unsurprising given their similar mechanism of action; for the same reason, a difference between BDL and secukinumab would not be expected. The main limitation of Sawyer et al.[65] is that it did not include the recently approved biologic guselkumab, an IL-23 inhibitor. Hence the relative risk in achieving PASI responses with BDL compared with guselkumab is unknown from this ITC. [redacted] In addition, given that the NMA was conducted on PASI scores at the induction periods (which is

understandable), there nonetheless remains uncertainty around the long-term efficacy and tolerability of the various biologics, in particular between BDL and guselkumab.

Conclusion

Two ITCs — one submitted by the manufacturer and one undertaken by Sawyer et al. (funded by Leo Pharma) — were summarized and critically appraised in this review. Results of the adjusted NMA conducted by Sawyer et al. (which controls for differences in placebo response across trials) suggests that over short-term induction treatment periods (ranging from 10 to16 weeks), the relative risk of achieving PASI 50, PASI 75, PASI 90, and PASI 100 responses is statistically greater for BDL than for adalimumab, apremilast, etanercept, USK, infliximab, and secukinumab in patients with moderate-to-severe chronic plaque psoriasis. BDL and ixekizumab appear to result in similar PASI responses after short-term induction treatment, based on the results of [redacted], while the comparative efficacy of BDL versus guselkumab is less certain given that it was not included in the ITC conducted by Sawyer et al. In addition, the relative efficacy of BDL in comparison with other biologics beyond the short-term induction periods remains unknown. Safety outcomes and HRQoL data were not evaluated in the ITCs; therefore, the comparative safety and HRQoL data of BDL versus other treatments for moderate-to-severe chronic plaque psoriasis has yet to be fully evaluated. These results seem to support BDL as another treatment option that is at least as efficacious as other newer biologics. However, there is uncertainty around the relative efficacy of BDL when compared with guselkumab.

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