CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

HALOBETASOL PROPIONATE AND TAZAROTENE (DUOBRII)

(Bausch Health, Canada Inc.)

Indication: Psoriasis, moderate-to-severe plaque

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AE	adverse event
BD	betamethasone dipropionate
BSA	body surface area
CAL	calcipotriol
CAPP	Canadian Association of Psoriasis Patients
CPN	Canadian Psoriasis Network
CSPA	Canadian Skin Patient Alliance
DLQI	Dermatology Life Quality Index
EQ-5D	EuroQol 5-Dimensions
HP	halobetasol propionate
HPA	hypothalamic pituitary adrenal
HRQoL	health-related quality of life
ICC	intraclass correlation coefficient
IGA	Investigator's Global Assessment
IL	interleukin
ITT	intention to treat
LOCF	last observation carried forward
MCMC	Markov chain Monte Carlo
MID	minimal important difference
NMA	network meta-analysis
PASI	Psoriasis Area and Severity Index
PGA	Physician's Global Assessment
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
TAZ	tazarotene
TNF	tumour necrosis factor
VDA	vitamin D analogue
WDAE	withdrawal due to adverse event
w/w	weight by weight

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Halobetasol propionate (0.01% w/w) and tazarotene (0.045% w/w) lotion (Duobrii) topical antipsoriatic agent
Indication	Improving the signs and symptoms of plaque psoriasis in adult patients with moderate to severe plaque psoriasis
Reimbursement request	As per indication
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	June 9, 2020
Sponsor	Bausch Health, Canada Inc.

NOC = Notice of Compliance; w/w = weight by weight.

Source: CADTH Common Drug Review submission for halobetasol propionate and tazarotene.[1]

Introduction

Plaque psoriasis is a chronic, inflammatory skin disease characterized by the presence of erythematous inflammatory plaques.[2,3] The plaques may be itchy or painful and are usually covered by silver, flaking scales. In addition to the overt dermatological symptoms, plaque psoriasis is often associated with psychosocial symptoms that can impact various aspects of social functioning including interpersonal relationships and performance at school or work.[3] The estimated number of Canadians living with psoriasis is approximately one million and plaque psoriasis is the most common form, representing approximately 90% of cases.[4,5]

The severity of psoriasis is classified as mild, moderate, or severe using criteria such as body surface area (BSA) or scores on the Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI). The Canadian Guidelines for the Management of Plaque Psoriasis provide two definitions for each measure of disease severity: definitions used in clinical trials and definitions for clinical practice.[4] In clinical trials, moderate-to-severe psoriasis is defined by a lower limit of 10% BSA and the same limits have been used to define *severe* psoriasis.[4] The guidelines also highlight that despite the literature available, there is a lack of consensus regarding how disease severity should be defined. This was affirmed by the clinical expert on this review.

In patients with plaque psoriasis, topical agents (such as corticosteroids, vitamin D_3 analogues, and retinoids) are the most widely used treatments for the mild form of the disease. Combination therapy may also be considered, which is typically more efficacious than monotherapy.[4] The Canadian guidelines define moderate-to-severe psoriasis, clinically, by the inability to be controlled by topical therapy; however, it also states that topical agents used to treat mild psoriasis may still be useful adjunct therapy to systemic therapies or phototherapy. According to the clinical expert consulted for this review, if adequate improvement cannot be achieved with topical therapy and/or phototherapy, the systemic therapies such as cyclosporine, methotrexate, or biologic agents are considered.[4,6] With a variety of treatments available, the approach to treating plaque

psoriasis is heavily patient-centred where the goals of therapy may differ from patient to patient. It is widely accepted that an effective treatment for plaque psoriasis is also one that a patient is willing to work with.[4,7,8] The patient-centred approach was aligned with feedback from the clinical expert consulted for this review.

The drug under review, halobetasol propionate (HP) and tazarotene (TAZ) lotion (Duobrii), is a combination product composed of a topical superpotent corticosteroid (0.01% weight by weight [w/w] HP) and a retinoid product (0.045% w/w TAZ).[9] In Canada, HP/TAZ is indicated for improving the signs and symptoms of plaque psoriasis in adult patients with moderate-to-severe plaque psoriasis.[9] It is recommended that HP/TAZ is applied in a thin layer to the affected area once a day, and the total dosage should not exceed 50 g per week. If no improvement is seen within 12 weeks of treatment, reassessment of the diagnosis may be necessary.[9] The sponsor is requesting that HP/TAZ be reimbursed as per the indication reviewed by CADTH. The objective of this report is to perform a systematic review of the beneficial and harmful effects of 0.01% w/w HP and 0.045% w/w TAZ topical lotion for improving the signs and symptoms of plaque psoriasis in adult patients with moderate-to-severe plaque psoriasis.

Stakeholder Engagement

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from a clinical expert consulted by CADTH for the purpose of this review.

Patient Input

Three patient groups, the Canadian Psoriasis Network (CPN), the Canadian Skin Patient Alliance (CSPA), and the Canadian Association of Psoriasis Patients (CAPP), submitted a coordinated patient input response for the review of HP/TAZ for moderate-to-severe plaque psoriasis. All three patient groups aim to educate and advocate for patients with psoriatic disease and their caregivers with the ultimate goal of improving care and quality of patient life.

Information for this submission was collected through three surveys. First, a survey distributed by CPN which resulted in 61 responses distributed across eight provinces. Second, a survey distributed by CAPP about treatment gaps which resulted in 212 responses distributed across all the provinces. Third, a survey distributed by CPN and CAPP targeting people who had experience with HP/TAZ, which resulted in three responses.

The patient groups describe the experience of living with this chronic disorder, saying that it has a significant impact on their quality of life. Patients also reported feelings of low self-esteem, depression, and avoidance of social activities. Challenges with current topical treatments patients experience include side effects, inconvenience, high cost, and loss of effectiveness after prolonged use. Patients who had experience with HP/TAZ therapy remarked that HP/TAZ manages their itching and appearance of plaques better than previous treatments.

The outcomes patients expect from a new treatment are improved efficacy in terms of resolution of plaques, itching, redness, burning sensation, bleeding, joint pain, general pain, and improvement in the emotional toll of the disease such as depression and/or anxiety,

and stigma. Moreover, patients expect a treatment which addresses all their symptoms or is curative.

Clinician Input

The clinical expert consulted by CADTH identified needs in topical therapy for plaque psoriasis that are not being met by the presently available medications in Canada. Adherence is a major issue in topical therapy for plaque psoriasis as patients are unlikely to use medications that leave a visible residue on exposed sites, stain clothing or skin, produce irritation, have an objectionable odour, or are difficult to spread onto plaques. They noted that using multiple topical agents improves efficacy, and that it is preferred as a combination preparation to enhance ease of use and adherence. An ideal treatment in plaque psoriasis would produce a sustained PASI 100 response or DLQI of zero in all patients with little or no risk of adverse effects. This treatment would be easily accessed by the patient and convenient to administer.

According to the clinical expert, HP/TAZ is an appropriate first choice of topical therapy for patients with relatively limited areas of psoriatic involvement, as the efficacy and safety of HP/TAZ in patients with more than 12% of BSA affected by plaque psoriasis has not been established.[9] They also felt it would be an appropriate adjunctive therapy in those patients who require systemic drugs. For use as monotherapy, the expert identified that HP/TAZ would be most suitable in patients with relatively limited areas of psoriasis, as the 50 g per week limitation would exclude use in patients with large areas of involvement. Further, they thought it would be challenging to identify patients who are more likely to exhibit a treatment response with HP/TAZ, but would expect those who have clearly documented lack of response to superpotent corticosteroids to do less well.

The clinical expert did not think it would be appropriate to recommend that patients try other treatments before initiating treatment with HP/TAZ. In clinical practice, the clinical expert felt that an informal combination of the view of the prescriber and the patient regarding improvement in the signs of psoriasis and area of involvement at four to eight weeks is most likely to be recorded in an assessment of treatment response. Three reasons that would influence treatment discontinuation were also identified, which included: lack of adequate disease response; presence of significant skin atrophy, folliculitis, irritation, suspected irritant, or allergic contact dermatitis; and the treatment being cost-prohibitive.

Last, the clinical expert felt that a dermatologist is not required to diagnose, treat, or monitor patients who might receive HP/TAZ. Significant prescribing by family doctors, nurse practitioners, and perhaps by other specialists (e.g., rheumatology and internal medicine) was anticipated.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two identical sponsor-submitted pivotal trials, Study 301 and Study 302, met the inclusion criteria for the systematic review. The two trials were multi-centre, double-blind, randomized, parallel-group studies comparing HP/TAZ to vehicle when applied once daily to adult patients with moderate-to-severe plaque psoriasis. To be eligible for inclusion, patients needed to have an area of plaque psoriasis that was appropriate for topical

treatment and covered a BSA of between 3% and 12% (inclusive). Patients were also required to have a clinical diagnosis of psoriasis at baseline with an Investigator's Global Assessment (IGA) score of 3 or 4. Patients were excluded if they had received prior treatment for plaque psoriasis and failed to respond, or if they received treatment for psoriasis within a specified amount of time. Additional details of the inclusion and exclusion criteria are available in Table 5.

Overall, 418 patients were included in the two studies. A total of 203 and 215 patients in Study 301 and Study 302, respectively, were randomized in a 2:1 ratio to receive HP/TAZ or vehicle lotion. Patients applied the study drug to the treatment area determined by the investigator once daily for eight weeks; a follow-up visit was scheduled four weeks after treatment cessation. Concomitant medications, including non-medicated cleansers, moisturizers, and sunscreens that were approved by the sponsor, were permitted for use on the treatment areas. In both studies, health-related quality of life (HRQoL) was assessed using the DLQI, skin clearance was assessed using the IGA and BSA affected by psoriasis, and the signs of psoriasis (erythema, plaque elevation, and scaling). Skin clearance and HRQoL are considered outcomes that are important to patients. Treatment adherence and productivity were not included as outcomes.

At baseline, patients were a mean age of 48.8 (standard deviation [SD] = 13.3) and 51.8 (SD = 14.3) years in Study 301 and Study 302, respectively. The majority of patients were male (61.0% to 69.1%) and White (80.1% to 92.6%) in the two studies. Most patients randomized to Study 301 and Study 302 had moderate disease (82.8% and 87.4%, respectively), indicated by an IGA score of three. The rest of the patients in both studies were classified as having severe disease by an IGA score of four. The percent BSA affected by psoriasis was a mean 6.2% (SD = 2.9%) and 5.6% (SD = 2.6%) for patients in Study 301 and Study 302, respectively. Overall, the disease characteristics of patients in both of the pivotal trials were similar between the HP/TAZ and vehicle treatment groups, with a few differences to note. In Study 301, patients randomized to vehicle had [redacted] than patients receiving HP/TAZ [redacted]. In Study 302, patients randomized to HP/TAZ, the mean (SD) size of the target lesion for treatment was [redacted], and the erythema signs of psoriasis for the target lesion were [redacted]

Efficacy Results

HRQoL was assessed using the DLQI, which was included as an exploratory outcome in both trials. At the week 8 (end of treatment) study visit, the DLQI score for patients in Study 301 had [redacted] in the HP/TAZ and vehicle treatment groups, respectively. In Study 302, the mean (SD) change from baseline in the DLQI score was [redacted] patients in the HP/TAZ and vehicle treatment groups, respectively. In the absence of formal statistical testing, no conclusions can be made about whether DLQI was actually reduced in either group or whether there were any differences in DLQI between the two treatment groups.

Skin clearance was assessed using the IGA score and percentage of BSA affected by plaque psoriasis in both of the pivotal trials. The primary end point was treatment success at week 8, defined by at least a two-grade improvement from baseline in the IGA score in addition to an IGA score of clear or almost clear. In Study 301, 35.8% and 7.0% of patients treated with HP/TAZ and vehicle, respectively, had treatment success at week 8. In Study

302, 45.3% and 12.5% of patients treated with HP/TAZ and vehicle, respectively, had treatment success at week 8. In both trials, the difference between HP/TAZ and vehicle in the proportion of patients achieving treatment success ($P < 0.001$) was in favour of HP/TAZ. Treatment success based on the IGA was assessed at week 12, 6, 4, and 2 as secondary end points, which were analyzed following a gated sequential testing procedure in that order. The difference between HP/TAZ and vehicle in the proportion of patients with treatment success was in favour of HP/TAZ ($P < 0.05$) at week 12, 6, and 4 in both studies. A descriptive subgroup analysis of treatment success based on the IGA at week 8, by baseline disease severity, was reported in both trials. None of the patients in the vehicle treatment groups with severe disease based on the IGA at baseline achieved treatment success. The proportion of patients with treatment success at week 8 was numerically greater for the HP/TAZ groups than vehicle for patients with both moderate and severe disease at baseline. The latter is consistent with the primary analysis; however, no firm conclusions can be drawn about any of the subgroups in the absence of formal pre-specified testing. The subgroup analyses are also limited by their sample size, as less than 20% of the overall population in each of the two trials were included in the subgroup analysis of patients with severe disease at baseline.

Productivity and treatment adherence were not evaluated as efficacy outcomes in any of the clinical trials included in the review, but dosing compliance was reported. Based on the intention-to-treat (ITT) population and compliance defined by using between 80% and 120% of the expected applications of the study drug while enrolled in the study, [redacted] of patients were compliant with the study medication.

Harms Results

The percentage of patients that reported at least one adverse event (AE) up to the week 8 study visit in Study 301 and Study 302 was 36.8% and 35.0% for HP/TAZ groups and 19.4% and 23.3% for vehicle groups, respectively. At week 8, serious AEs were only reported by three (2.3%) patients in the HP/TAZ group in Study 301. No serious adverse events (SAEs) were reported in Study 302. The percentage of patients who stopped treatment due to AEs at week 8 was 7.5% and 5.1% in the HP/TAZ groups of Study 301 and Study 302, respectively, and 6.8% in the vehicle group of Study 302. There were no withdrawals due to adverse events (WDAEs) from the study drug in the vehicle group of Study 301. No deaths were reported in the two pivotal trials.

Of the notable harms included in the CADTH review protocol, pruritus was the most frequently occurring. It was reported among 3% of patients in the HP/TAZ treatment group of both Study 301 and Study 302, and 5.5% of patients in the vehicle treatment group of Study 302; pruritus was not reported in the vehicle group of Study 301. Skin atrophy and folliculitis was also reported and only occurred in the HP/TAZ treatment groups (skin atrophy, 3.0% and 0.7% and folliculitis, 1.5% and 2.2% in Study 301 and Study 302, respectively). In addition, events of burning sensation, skin irritation, and hypersensitivity were reported in both treatment groups in a small percentage of patients (≤ 1.5%). Severe dryness and hypothalamic pituitary adrenal (HPA) axis suppression were also included as notable harms in the CADTH review protocol, but neither occurred in either study.

Table 2: Summary of Key Results From Pivotal and Protocol Selected Studies (ITT Set Unless Otherwise Indicated)

	Study 301		Study 302	
	HP/TAZ N = 135	Vehicle N = 68	HP/TAZ N = 141	Vehicle N = 74
DLQI score[a]				
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
n, week 8	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment (week 8), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment success[b,c] by IGA				
Week 8				
Treatment success (% of patients)	35.76	6.98	45.33	12.51
Treatment failure (% of patients)	64.24	93.02	54.67	87.49
P value	< 0.001		< 0.001	
Week 12				
Treatment success (% of patients)	33.25	8.51	33.35	8.84
Treatment failure (% of patients)	66.75	91.49	66.65	91.16
P value	< 0.001		< 0.001	
Week 6				
Treatment success (% of patients)	37.84	6.67	37.53	8.24
Treatment failure (% of patients)	62.16	93.33	62.47	91.76
P value	< 0.001		< 0.001	
Week 4				
Treatment success (% of patients)	24.86	9.33	26.96	1.36
Treatment failure (% of patients)	75.14	90.67	73.04	98.64
P value	0.008		< 0.001	
Week 2				
Treatment success (% of patients)	9.15	2.98	9.77	0
Treatment failure (% of patients)	90.85	97.02	90.23	100.00
P value	0.098		0.004	
Safety set at week 8	**N = 133**	**N = 67**	**N = 137**	**N = 73**
Harms, n (%)				
AEs	49 (36.8)	13 (19.4)	48 (35.0)	17 (23.3)
SAEs	3 (2.3)	0	0	0
WDAE (from treatment)	10 (7.5)	0	7 (5.1)	5 (6.8)
Deaths	0	0	0	0
Notable harms				
Pruritus	4 (3.0)	0	4 (2.9)	4 (5.5)
Thinning of skin (skin atrophy)	4 (3.0)	0	1 (0.7)	0
Folliculitis	2 (1.5)	0	3 (2.2)	0
Burning sensation	2 (1.5)	1 (1.5)	0	1 (1.4)

	Study 301		Study 302	
Skin irritation	1 (0.8)	1 (1.5)	1 (0.7)	0
Hypersensitivity events	0	0	1 (0.7)	1 (1.4)

AE = adverse event; DLQI = Dermatology Life Quality Index; HP/TAZ = halobetasol propionate and tazarotene; IGA = Investigator's Global Assessment; ITT = intention to treat; MCMC = Markov chain Monte Carlo; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

[a] Descriptive analyses only. Missing data were not imputed.

[b] *Treatment success* was defined as at least a two-grade improvement from baseline in the IGA score and an IGA score equal to clear or almost clear.

[c] Cochran-Mantel-Haenszel test stratified by analysis centre. Values were adjusted for multiple imputation (MCMC). A gated sequential testing procedure, where the testing process was terminated if a value that was not statistically significant was observed, was used for the secondary outcomes regarding treatment success by the IGA score in the following order: week 12, 6, 4, 2.

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

Critical Appraisal

The trials included in this review were both double-blind randomized controlled trials (RCTs). Both trials used an acceptable method of randomization and concealment of treatment allocation, and there was no reason to suggest randomization or blinding was compromised. Overall, there were no major differences between the baseline disease characteristics that would have significantly impacted the efficacy results. In terms of prior medication use, the vehicle treatment groups [redacted]. The reason for [redacted] in the vehicle treatment groups is unknown.

The primary and secondary outcomes in both trials were treatment success, defined as at least a two-grade improvement from baseline in the IGA score and an IGA score of clear or almost clear (0 or 1). No evidence for the validity of the five-point IGA scale, which was used in the two trials, was identified for this review; however, the six-point Physician's Global Assessment (PGA), which is the same scale as the IGA, but the assessor is a physician rather than investigator, was available. There was evidence of reliability in terms of test-retest data and internal consistency, but the outcome is subjective and has poor inter-rater reliability.[12] The limitations of this scale introduce uncertainty to the interpretation of the primary and secondary outcomes, as well as the magnitude of observed treatment response. Also, HRQoL was evaluated using the DLQI, which is a validated disease-specific instrument. Between-group comparisons or formal statistical testing of the DLQI was not performed, therefore the conclusions that can be drawn based on this outcome are limited. An appropriate method was used to handle missing data (imputed using Markov chain Monte Carlo [MCMC]) and secondary outcomes of treatment success by IGA were controlled for multiplicity using a gated sequential testing procedure. Statistical testing was conducted for the improvement in the signs of psoriasis, but multiplicity was not controlled for this outcome. Statistical testing and imputation of missing data were not conducted for the BSA, preventing any conclusions that can be drawn from this data.

The two trials included several limitations regarding the generalizability of the results to the target population identified by the indication and Canadian clinical practice. The information available regarding disease severity of the patients who were included in the two trials may be more representative of Canadian patients with mild-to-moderate disease rather than moderate to severe. The mean percent BSA of patients at baseline in the two trials was between 5.5% and 6.5% for randomized patients, however, patients with a BSA as low as 3% were eligible for inclusion in the study. Definitions of disease severity are described in

the Canadian Guidelines for the Management of Plaque Psoriasis, which suggest a BSA of 5% is used as an upper limit for mild disease and a BSA of 10% is used as a lower limit for moderate-to-severe psoriasis.[4] However, the definitions of disease severity for psoriasis vary across international guidelines. For example, guidelines published by the American Academy of Dermatology and the National Psoriasis Foundation (US) defined disease severity by BSA involvement with less than 3% BSA considered mild, 3% to 10% BSA considered moderate, and greater than 10% BSA considered severe disease.[13,14] The clinical expert consulted by CADTH acknowledged that there is lack of consensus regarding the definition of disease severity, but was of the view that the patient populations in Study 301 and Study 302 were more mild than what would be expected in a population of Canadian patients with moderate-to-severe psoriasis. Further, the evidence reviewed is not aligned with the anticipated use of HP/TAZ in clinical practice. According to the clinical expert consulted by CADTH for this review, it is unlikely that HP/TAZ would be used as monotherapy in patients with moderate-to-severe disease. The clinical expert advised that a more likely use of HP/TAZ in this population would be as an adjunct therapy to systemic treatment; however, evidence of this was not identified. Lastly, there is no direct evidence of HP/TAZ compared to other topical treatments for psoriasis, despite the number of available treatments for this disease area. As such, the comparative effectiveness of HP/TAZ remains uncertain.

Indirect Comparisons

Description of Studies

[redacted]

Efficacy Results

[redacted]

[redacted]

Harms Results

[redacted]

Critical Appraisal

[redacted]

Other Relevant Evidence

Long-Term Safety Study (Study 303)

Description of Study

Study 303 is a 52-week, multi-centre, single-arm, open-label, long-term safety study conducted in adult patients with moderate-to-severe plaque psoriasis defined by an IGA score of 3 or 4. The study drug, HP/TAZ, was applied once daily for eight weeks and then as needed in four-week treatment cycles, depending on treatment success (defined with an IGA score of 0 or 1), which evaluation every four weeks. This four-week evaluation/treatment cycle could continue for up to one year. In total, 555 patients were entered into the study, with 503 that completing three months of the study, 391 completing six months, and 138 patients completing 12 months. Most participants were White (86%) and male (65.6%) and the mean age was 52 years. With respect to baseline disease characteristics, 86.5% of participants were classified with moderate psoriasis based on an IGA score of 3, and the mean percent BSA affected by psoriasis in all participants was 5.6% (SD = 2.65%). Study 303 was designed to evaluate safety of once daily use of

HP/TAZ topical therapy. Study 303 was not designed to assess the efficacy of HP/TAZ. IGA and percentage BSA were evaluated to determine treatment success and need for re-treatment. Descriptive statistics were performed to provide an overview of the efficacy and safety results.

Harms Results

In terms of safety, 57.1% of patients experienced an AE after HP/TAZ administration with the most common AEs falling into the categories of general disorders and administration site conditions (30.7%), and infections and infestations (23.5%). A total of 7.5% of patients withdrew due to AEs, and 90% of the reasons for WDAEs were application site reactions. Overall, there were no deaths, and 18 patients experienced a SAE; however, no SAE was more common in one group than the other. In terms of treatment-emergent local skin reactions of at least grade 3 severity, throughout the entire 12-month study period, the incidence of local skin reactions was 22.2% for itching, 6.9% for dryness, and 9.8% for burning/stinging.

Efficacy Results

Efficacy outcomes in Study 303 were presented with descriptive statistics and were only evaluated to determine the need for a four-week HP/TAZ treatment cycle. By week 8, [redacted] of patients had achieved an IGA score equating to clear or almost clear. By week 24 the mean percent BSA affected by psoriasis had [redacted].

Critical Appraisal

Overall, Study 303 identified long-term safety data that should be considered with extended use of HP/TAZ topical therapy. However, the outcomes are limited by the open-label, single-arm study design, as well as the external validity in terms of generalizability to the Canadian patient population in terms of demographics and disease severity.

Phase II RCT (Study 201)

Description of Study

Study 201 was included to supplement the review of HP/TAZ in terms of providing additional efficacy data on comparisons to monad HP and monad TAZ. Study 201 was a phase II, multi-centre, double-blind, randomized, parallel-group, vehicle-controlled RCT conducted in adult patients with moderate-to-severe plaque psoriasis defined by an IGA score of 3 or 4. Patients were randomized 2:2:2:1 to receive HP/TAZ lotion (n = 59), HP monad (0.01%) lotion (n = 63), TAZ monad (0.045%) lotion (n = 59), or vehicle lotion respectively (n = 31). The assigned study drug was applied topically to the affected area, once daily for eight weeks. Patients were followed up at four weeks post-treatment cessation, at week 12. None of the efficacy end points were designated as primary.

Efficacy Results

The efficacy of HP/TAZ was demonstrated with the proportion of patients which achieved treatment success at week 8, defined as a two-grade improvement from baseline in the IGA score and an IGA score equating to clear or almost clear. At week 8, 52.5% of patients in the HP/TAZ group achieved treatment success based on IGA compared with 33.3% of patients in the monad HP group, 18.6% of patients in the monad TAZ group, and 9.7% of patients in the vehicle group. Related to the psoriasis signs, at week 8, 54.2%, 67.8%, and

64.4% of patients achieved a two-grade improvement in erythema, plaque elevation, and scaling, respectively, in the HP/TAZ group.

Harms Results

In terms of safety, a larger proportion of patients experienced an AE in the HP/TAZ (33.9%) and monad TAZ (46.6%) group when compared to the other groups. The most common AEs within these groups were application site reactions. Five patients reported a SAE and no SAE occurred in more than one patient. A higher percentage of patients discontinued the study drug and/or withdrew from the study prematurely due to AEs in the monad TAZ groups (12.1%) when compared to the other groups.

Critical Appraisal

Key limitations of Study 201 related to internal validity include minor imbalances in baseline demographics and disease characteristics, the disproportionate discontinuation rate, and lack of multiplicity adjustment for efficacy outcomes. The key limitation associated with external validity is generalizability to the Canadian patient population in terms of demographics and disease severity.

Conclusions

Based on the available evidence, HP/TAZ demonstrated efficacy in adult patients with plaque psoriasis in terms of skin clearance based on the IGA. In the two trials included in the CADTH review, the difference between HP/TAZ and vehicle in the proportion of patients achieving treatment success (defined by at least a two-grade improvement from baseline in the IGA score in addition to an IGA score equal to clear or almost clear) at week 8 was statistically significant in favour of HP/TAZ ($P < 0.001$). HRQoL was identified as an outcome that is important to patients and was measured using the DLQI in both studies; however, no conclusions can be made regarding the effect of HP/TAZ on HRQoL due to the exploratory nature of the outcome and lack of statistical testing. In addition, HP/TAZ does not appear to be associated with any safety signals. Key limitations are the lack of comparative evidence, lack of long-term data, and generalizability of the patient population; of note, the patients included in Study 301 and Study 302 may not be representative of Canadian patients with moderate-to-severe plaque psoriasis.

In the absence of direct evidence, the sponsor submitted a network meta-analysis (NMA) with the purpose of evaluating the relative efficacy of topical therapies approved for the treatment of moderate-to-severe plaque psoriasis in Canada. The results of the NMA suggest that after eight weeks of treatment, both combination therapies (HP/TAZ and betamethasone dipropionate [BD] plus vitamin D analogue [VDA]) were superior to vehicle in achieving treatment success; however, the NMA was performed to examine the relative treatment effect between active topical therapies to vehicle, rather than between active therapies.

Introduction

Disease Background

Plaque psoriasis is a chronic, inflammatory skin disease caused in part by dysregulation of the immune system. It is a T cell-mediated disease primarily driven by pathogenic T cells that produce high levels of interleukin (IL)-17 and tumour necrosis factor alpha (TNF-alpha) in response to IL-23.[2] The estimated number of Canadians living with psoriasis is approximately one million.[5] The sponsor submitted an estimation of 2.49% for the prevalence of psoriasis in Canada based on two real-world database studies. Plaque psoriasis is the most common form and represents approximately 90% of cases.[4,5] Approximately 35% of patients with psoriasis have moderate-to-severe disease.[15]

Psoriasis is characterized by the presence of erythematous inflammatory plaques that may be itchy or painful and are usually covered by silver, flaking scales.[2,3] In addition to the overt dermatological symptoms, plaque psoriasis is often associated with psychosocial symptoms including poor self-esteem and may affect various aspects of social functioning including interpersonal relationships and performance at school or work.[3] According to patient input received for this review, participants also reported loss of sleep, negative effects on self-confidence, and problems with intimacy. Psoriasis is associated with several comorbid conditions including depressive symptoms, conditions associated with an increased risk of cardiovascular disease (such as type 2 diabetes, metabolic syndrome, and obesity), psoriatic arthritis, inflammatory bowel disease, and kidney disease.[4,16-22]

The severity of psoriasis may be classified as either mild, moderate, or severe using criteria such as BSA or scores on the PASI and DLQI. The Canadian Guidelines for the Management of Plaque Psoriasis provides two definitions for each measure of disease severity: definitions used in clinical trials and definitions for clinical practice.[4] These definitions have been summarized in Figure 1; however, the guidelines highlight that despite the literature available, there is a lack of consensus regarding how disease severity should be defined. This was affirmed by the clinical expert consulted by CADTH for this review.

Standards of Therapy

Plaque psoriasis requires lifelong treatment. Measures of treatment success in clinical practice may include clearance (absence of signs of disease), control (satisfactory response to therapy as defined by the patient and/or physician), and remission (suppression of signs and symptoms over time).[4] Clearance and symptom control have been identified as treatment outcomes that are important to patients.

In patients with plaque psoriasis, topical agents (such as corticosteroids, vitamin D analogues, and retinoids) are the most widely used treatments for the mild form of the disease. Of the available topical agents, corticosteroids are the most widely used treatment with higher potency agents being the most efficacious, but also having increased potential for AEs.[4] Anthralin and tars may also be used, but their use has declined as there are other treatments that are more acceptable to patients that have become available. In an effort to reduce side effects with long-term use of corticosteroids, the topical agents may be used intermittently by either reducing the dose or taking a drug holiday for a period of time.[7] Combination therapy may also be considered, which is typically more efficacious than

monotherapy.[4] For example, calcipotriol/betamethasone is more effective than either of the components alone; however AEs may be of concern.

Figure 1: Terms Used in Evaluating Plaque Psoriasis

Term	Definitions used in clinical trials	Definition for clinical practice, as applied in these Guidelines
Measures of disease severity		
Mild plaque psoriasis	Not commonly defined; the US National Psoriasis Foundation suggests BSA = 5% as an upper limit for mild disease[12]	Disease with a minimal impact on the patient's QoL; patient can achieve an acceptable level of symptomatic control by routine skin care measures and/or topical therapy
Moderate plaque psoriasis	The lower limit of moderate to severe psoriasis may be set at PASI = 8[13,14] or, in trials of biologics, typically higher Several biologics trials have used criteria as stringent as PASI ≥ 12 and BSA ≥ 10% to define the lower limit of "moderate to severe" psoriasis,[15,16] although the same limits have also been used to define "severe" psoriasis[17]	Disease that cannot be, or would not be expected to be, controlled to an acceptable degree by routine skin care measures and/or disease that significantly affects the patient's QoL, either because of the extent of the disease, the physical discomfort it causes (pain or pruritus), or the location where the disease manifests (e.g., the face, hands, feet, or genitals)
Severe plaque psoriasis	The Rule of Tens requires PASI ≥ 10 or DLQI ≥ 10 or BSA ≥ 10%[18] In some phototherapy trials, BSA ≥ 20% is the lower limit of severe disease[19,20]	Disease that cannot be, or would not be expected to be, satisfactorily controlled by topical therapy and that causes severe degradation of the patient's QoL

BSA = body surface area; DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area Severity Index; QoL = quality of life.

Source: Papp K, Gulliver W, Lynde C, Poulin Y, Ashkenas J, Canadian Psoriasis Guidelines Committee. Canadian Guidelines for the Management of Plaque Psoriasis: Overview. *J Cutan Med Surg*. 2011;15(4):210-219. Reprinted with a permission of the author. Source: Canadian Guidelines for the Management of Plaque Psoriasis.[4]

The Canadian guidelines for management of plaque psoriasis define moderate-to-severe psoriasis by the inability to be controlled by topical therapy, as previously described; however, it also states that topical agents used to treat mild psoriasis may still be used as adjunct therapy to systemic therapies or phototherapy for this population. Calcipotriol/betamethasone ointment is noted as an exception as it has demonstrated efficacy in patients with relatively severe disease (average baseline PASI score of 22.6).[4] According to the clinical expert consulted for this review, if it is clear that the patient presenting to a dermatologist with moderate-to-severe plaque psoriasis has not received appropriate topical therapy, nor an adequate trial of phototherapy, a trial of topical therapy alone or topical therapy combined with phototherapy may be offered. The clinical expert also noted that frequently a combination of topical agents, including corticosteroids, calcipotriol, and retinoids, is prescribed and if adequate improvement cannot be achieved with topical therapy and/or phototherapy, systemic therapies will be considered.[4,6]

Traditional systemic agents include cyclosporine and methotrexate, but long-term use may be limited by toxicity.[4] In Canada, there are several biologic agents approved for the treatment of psoriasis. The first biologic agents licensed to treat plaque psoriasis were TNF-alpha inhibitors (i.e., etanercept, infliximab, certolizumab, and adalimumab). While effective and associated with rapid disease control, these TNF-alpha inhibitors are associated with a number of safety concerns including serious infections (e.g., sepsis, reactivated tuberculosis, and viral infections), autoimmune conditions (e.g., lupus and demyelinating disorders), and malignancies such as lymphoma.[4,6] Newer biologic agents include the IL-23

inhibitors risankizumab and guselkumab, the IL-12/23 inhibitor ustekinumab, and the IL-17 inhibitors secukinumab, ixekizumab, and brodalumab. These agents have been associated with serious infections, potential activation of inflammatory bowel disease with IL-17 inhibitors, and suicidal ideation in the case of brodalumab. The clinical expert consulted for this review noted that assuming an effective biologic agent is chosen, treatment must be continued indefinitely for efficacy to continue. The clinical expert also noted that the majority of patients who are treated with biologics or non-biologic systemic agents will require ongoing topical therapy to treat disease that the systemic drug has not cleared.

Despite the variety of treatments available for patients across the spectrum of plaque psoriasis, an overarching theme presented throughout the literature, which was aligned with the opinion of the clinical expert on this review, is that an effective treatment for plaque psoriasis is also one that a patient is willing to work with.[4,7,8] Adherence is a significant issue associated with treating these patients, particularly those using topical therapies; therefore, finding a therapy that a patient is likely to use consistently and long-term is critical. An ideal therapy would produce remission without the need for continuous long-term administration or could be administered intermittently as needed as per feedback from the clinical expert consulted for this review. Lastly, the approach to treating plaque psoriasis is heavily patient-centred where the goals of therapy may differ from patient to patient. This was confirmed by the clinical expert who also noted that what the patient hopes to achieve, which can range from eliminating symptoms such as pruritus to total clearance, will have a significant influence on the clinical decisions regarding appropriate therapies.

Drug

HP/TAZ lotion (Duobrii) is a combination product composed of a topical corticosteroid, 0.01% w/w HP, and a retinoid product, 0.045% w/w TAZ.

HP is a superpotent corticosteroid[23] with anti-inflammatory, anti-pruritic, and vasoconstrictive actions.[9] The mechanism of action is unclear, but it has been suggested that it induces proteins that inhibit phospholipase A2. Phospholipase A2 is responsible for releasing arachidonic acid, which is a precursor to prostaglandins and leukotrienes and consequently leads to anti-inflammatory effects.[9,24] TAZ is a prodrug that is converted to tazarotenic acid, which regulates gene expression of retinoic acid receptors. There is uncertainty around the mechanism of action in psoriasis, although in vivo studies have shown TAZ to have a role in reducing cell proliferation and hyperplasia, suppressing inflammatory markers, and inhibiting the formation of elements of psoriatic scale. It also reduces markers related to epidermal hyperplasia and abnormal differentiation.[9]

In Canada, HP/TAZ is indicated for improving the signs and symptoms of plaque psoriasis in adult patients with moderate-to-severe plaque psoriasis.[9] It is recommended that HP/TAZ is applied in a thin layer to the affected area once a day, and the total dosage should not exceed 50 g per week. Treatment with HP/TAZ should be discontinued once control has been achieved, although it may be reinitiated intermittently as necessary. If no improvement is seen within 12 weeks of treatment, reassessment of the diagnosis may be necessary. Efficacy and safety of HP/TAZ has not been established in patients with more than 12% BSA affected by plaque psoriasis.[9]

The sponsor is requesting that HP/TAZ is reimbursed as per the indication reviewed by CADTH.

Table 3: Key Characteristics of HP/TAZ and Other Relevant Topical Therapies for the Treatment of Plaque Psoriasis

	HP/TAZ (Duobrii)	Topical corticosteroids (e.g., betamethasone, mometasone, clobetasol propionate)	Vitamin D analogues (e.g., calcitriol, calcipotriol)	Retinoids (e.g., tazarotene 0.05% and 0.1% w/w)	Combination treatments (e.g., betamethasone/ calcipotriene, calcipotriol/ betamethasone)
Mechanism of action	HP is a superpotent topical corticosteroid with anti-inflammatory, antipruritic, and vasoconstrictive actions TAZ is a retinoid prodrug that reduces cell proliferation and hyperplasia, and suppresses high levels of inflammatory markers in psoriatic epidermis	Via multiple mechanisms, act as an anti-inflammatory and immune suppressant	Calcipotriol is a nonsteroidal antipsoriatic agent that, like the active form of vitamin D, regulates cell proliferation and differentiation	Oral retinoids are thought to modulate keratinocyte proliferation and differentiation in addition to having anti-inflammatory effects[4]	Combination of calcipotriol hydrate as a synthetic vitamin D analogue and betamethasone propionate (corticosteroid)
Indication[a]	For improving the signs and symptoms of plaque psoriasis in adult patients with moderate-to-severe plaque psoriasis	Symptomatic relief of acute and chronic skin eruptions, where anti-inflammatory, anti-allergenic, and antipruritic activity is required Topical corticosteroids are widely used for many other causes of skin inflammation	Topical treatment of psoriasis Combination use with a moderate to very potent topical corticosteroid, cyclosporin A, or acitretin	Topical treatment of plaque psoriasis	Topical treatment of psoriasis vulgaris in adults
Route of administration	Topical (lotion)	Topical	Topical (available as a cream, ointment, and scalp solution)	Topical (gel or cream)	Topical (available as a gel, ointment, foam)
Recommended dose	Applied in a thin layer to the affected area once a day	Varies between drugs	Varies between drugs	Applied in a thin layer to affected area once a day	Varies between drugs
Serious adverse effects or safety issues	Reversible HPA axis suppression Infection Contraindicated in pregnant women, those who are	If used under an occlusive dressing, particularly over extensive areas, or on the face, scalp, axilla(e), scrotum, or when applied to the genitourinary tract or oral mucosa, or when	Carcinogenesis, serum calcium abnormalities, and renal impairment Contraindicated in patients with:	Skin irritation Contraindicated in patients with hypersensitivity to retinoic compounds,	Safety issues are similar to those listed for topical corticosteroids and vitamin D analogues

	HP/TAZ (Duobrii)	Topical corticosteroids (e.g., betamethasone, mometasone, clobetasol propionate)	Vitamin D analogues (e.g., calcitriol, calcipotriol)	Retinoids (e.g., tazarotene 0.05% and 0.1% w/w)	Combination treatments (e.g., betamethasone/ calcipotriene, calcipotriol/ betamethasone)
	hypersensitive, with viral skin lesions or skin infections, and seborrheic dermatitis	administered rectally, sufficient absorption may take place to give rise to adrenal suppression and other systemic effects Children may be at greater risk of developing systemic complications with the use of topical corticosteroids	• hypersensitivity to drug or formulation • hypercalcemia • systemic treatment of calcium homeostasis • renal impairment or ESRD • liver dysfunction	patients with seborrheic dermatitis, and pregnant women	
Other	Not recommended for use on face, scalp, axillae, or intertriginous areas Not to be used on eczematous skin or with occlusive dressings		Should not be applied to the eyes, lips, or facial skin (Silkis)		Calcipotriol/ betamethasone is not recommended for use on face, axillae, flexures, groin, or genitals

ESRD = end-stage; HP/TAZ = halobetasol propionate and tazarotene; w/w = weight by weight.

[a] Health Canada approved indication.

Source: Halobetasol propionate and tazarotene (Duobrii) Product Monograph,[9] Canadian Guidelines for the Management of Plaque Psoriasis,[4] Calcitriol (Silkis) Product Monograph,[25] Calcipotriol (Dovonex) Product Monograph,[26] Product Monographs for combination treatments (Dovobet and Enstilar).[27-29]

Stakeholder Engagement

Patient Group Input

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

About the Patient Groups and Information Gathered

One response to CADTH's call for patient input was received for the review of HP/TAZ. The response was a joint submission by CPN, CSPA, and CAPP.

All three patient groups are national, not-for-profit organizations that are dedicated to improving care and quality of life of patients living with psoriatic diseases. These organizations aim to do this by advocating and educating for psoriatic patients and their caregivers. The CSPA extends this mandate into patients living with all dermatological conditions, including psoriasis.

A disclosure of any conflicts of interest for all three organizations is available on the CADTH website. Information for this submission was collected through three surveys. First, a survey distributed by CPN through their membership list and social media channels, which resulted in 61 responses distributed across eight provinces. Second, a survey about gaps in topical treatments for psoriasis promoted by CAPP on their social media channels, which resulted in 212 responses distributed across all the provinces. Half (52.1%) of respondents were 55 years or older, while 46% were working age adults, 35% were from Ontario, 15.6% from Nova Scotia, and 14.2% from British Columbia. Third, a survey targeting people who had experience with HP/TAZ distributed by CPN and CAPP on both their social media channels, featured on CPN's website, and included in an e-newsletter by the National Psoriasis Foundation in the US. Last, this submission was informed through information gathered for a report titled "Journey to Stability," created by CPN and CAPP.

Disease Experience

The patient groups describe psoriasis as a chronic inflammatory skin condition which causes skin cells to regenerate approximately seven times faster than average. As a result, skin cells are not shed normally and instead pile up on the skin's surface creating sores or lesions, commonly called plaques. The patient groups describe inflamed, thick, silvery scales that can form on top of the plaques, which can be itchy and painful. Psoriasis can range from a few dandruff-like scales to widespread patches that cover large areas of skin. Patients with psoriasis experience periods of flares where the disease is aggravated, areas affected may become itchy and painful, and even crack and bleed. Afterwards, patients may go into a period of remission where symptoms are decreased. Many oscillate between these experiences throughout the course of their lives with the condition. Psoriasis usually affects the elbows, knees, scalp, palms of hands, soles of feet, nails, genitals, and torso.

Nearly half (44.8%) of the respondents to CAPP's survey indicated that they had lived with psoriasis for more than 20 years, while 25.2% lived with the disease for between 10 to 20 years, 16% for between five to 10 years, and nearly 14% for fewer than five years. Within CPN's survey, half of survey respondents (51%) identified their condition as "well-controlled," 30% said "poorly controlled," and 5% said "not controlled at all." The rest indicated that they fall somewhere in between.

Many patients reported feelings of low self-esteem, loss of sleep, anxiety, depression, fear of intimacy, and avoidance of social activities as part of their experience living with this condition. It was also reported that patients living with this condition feel like they have to "miss social events and refrain from wearing certain types of clothing." In addition, CPN's survey reported that people with psoriasis are at higher risk of certain health conditions compared to the general population, 46.7% of respondents experience joint pain, 23.2% experience depression, 13.3% live with heart disease, and 11.7% reported having diabetes.

CPN's survey also described the impact that psoriasis has on family members and caregivers. Three-fifths (61.2%) of respondents identified that family members experience worry related to their condition, 34.7% experience intimacy challenges, and 24.5% have avoided activities. Patients also reported feelings of stress, time issues, and frustration due to their condition and the effects on their family and interpersonal relationships, as their family had to "clean up plaques around the house after they fell off" and that they "didn't want people to see or even know about the more private areas where [they] have psoriasis."

Experience With Treatments

CAPP's survey informed that 85% of respondents were currently using topical treatments such as Dovobet (17.4%), BD (14.8%), clobetasol (11.4%), Enstilar (7.4%), Dovonex (6%), cortisone (5.4%), Diprosalic (percentage not available for latter treatments), Elidel, Lamisil, Lyderm, Ultravate, Fucidin, and tar. Responses also included non-prescription moisturizers, essential and coconut oils, Epsom salt baths, and other products. Several respondents indicated they have tried multiple products, and one-tenth (9.2%) of respondents came to their current topical treatment through their own trial and error. Of the 55 individuals who responded to a question about alternate psoriasis treatments they have used, 42.3% said they have used over-the-counter topicals, phototherapy (49.1%), oral medications (41.8%), and biologics (41.8%).

When questioned about what challenges patients experienced with their current topical treatments within CPN's survey, answers ranged from: inconvenient (e.g., greasy, time-consuming, 78.6%), experienced side effects (e.g., redness, soreness, thinning skin, pain/burning, 46.4%), and ineffective after prolonged use (46.4%). CAPP's survey informed that the most common reason for discontinuation of a topical treatment was: lack of efficacy (56.4%), side effects (13.7%), difficulty of use (8.5%), lack of efficacy after prolonged use (7.7%), cost (6%), and unavailability of the product (3.4%).

Patients also reported issues with the cost of treatment (50.3% of respondents felt that their topical was expensive) and ease of administration, for example, 10.9% felt that their topical was difficult to use and 48% felt that their topical was messy.

> The closest phototherapy is more than an hour away from where I live (in rural Manitoba) and I cannot afford the gas to go there the two or three times a week that I would need to — phototherapy worked best for me. I am trying to get some benefit from [the] tanning bed in town and there is some improvement…

Moreover, some patients' treatment options are limited due to contraindications: "As a cancer survivor, I can't take any biologics so my options are limited…" Notably, one-tenth of respondents indicated that they did not have any needs that have not been met by currently available treatments.

As there were no clinical trials for HP/TAZ conducted in Canada, responses from three patients who had experience with HP/TAZ currently residing in the US informed this submission. Two of the respondents were aged 45 to 54 years and had been living with psoriasis for more than 20 years. One respondent was aged 19 to 24 and had been living with psoriasis for less than one year. All three respondents identified itching and appearance of plaques (in no particular order) as the most important aspects of the disease to control. The respondent aged 19 to 24 also identified anxiety and/or social stigma, whereas one older respondent identified pain as additional important aspects of psoriasis to control. The respondents living with psoriasis for more than 20 years indicated that HP/TAZ did a better job of managing the appearance of plaques (number, size, thickness, and scaling) than previous treatments they have used, and there were no symptoms that HP/TAZ did not manage as well as other treatments. The respondent living with psoriasis for under one year indicated that it managed their itchiness better, and that it was easier to apply although it "takes longer to become efficacious [sic] when compared to other steroid treatments." This is in contrast to one of the respondents with psoriasis for more than 20 years who indicated that it "works fast." When asked "did you experience any side effects when using HP/TAZ?" the two respondents aged 45 to 54 experienced skin thinning, and the respondent aged 19 to 24 experienced stretch marks, skin irritation, and dryness.

Improved Outcomes

In a survey run by CPN, patients were asked "What aspects of psoriasis are the most important to control in your opinion?" and the majority (88.3%) of respondents selected the appearance of plaques, 81.5% selected redness, itching (76.7%), burning sensation (75%), joint pain (41.7%), general pain (26.7%), depression/anxiety (30%), stigma (25%), and bleeding (25%), and one-fourth selected related conditions such as diabetes and heart disease. Moreover, 61.2% of respondents to CAPP's survey indicated they wanted a topical treatment to address all their symptoms, or a cure.

Generally, the patient groups described the single most important outcome was the resolution of plaques. In terms of other specific outcomes and factors affecting their use of topical treatment, respondents to CAPP's survey indicated that the treatment should resolve symptoms faster, reduce side effects (e.g., thinning of the skin), "works better on scalps," work for both the rash and the pain, and be "a more effective natural approach." As previously noted, patients also stressed the importance of a treatment which had a better applicator, is not messy, greasy, or smelly, and is more affordable especially for patients which have to treat large areas of their body.

The effectiveness of treatments within individuals, and the way in which individuals view their condition varies. Thus, the needs of patients vary across the disease population and across the course of disease progression. The organizations stress that having access to a variety of treatments which are safe, effective, and affordable is of fundamental importance to patients. Currently, the symptoms of psoriasis are not being properly treated and there needs to be better new medicines to treat itchiness, redness, flakes, and other symptoms. However, patients ultimately want a cure for psoriasis.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical

appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by one clinical specialist with expertise in the diagnosis and management of plaque psoriasis.

Unmet Needs

The clinical expert identified a number of needs in topical therapy for plaque psoriasis that are not being met by the presently available medications in Canada. Adherence is a major issue in topical therapy for plaque psoriasis. Patients are unlikely to use medications that leave a visible residue on exposed sites, stain clothing or skin, produce irritation, have an objectionable odour, or are difficult to spread onto plaques. Efficacy is improved when multiple topical agents are used in plaque psoriasis. When using multiple agents, it is preferred that they be used in a combination preparation rather than as separate prescriptions. This greatly enhances the ease of use and improves adherence.

The clinical expert consulted by CADTH considered that an ideal treatment in plaque psoriasis would produce a sustained PASI 100 response in all patients with little or no risk of adverse effects. This treatment would be easily accessed by the patient and convenient to administer. The PASI 100 response would translate to a DLQI score of near zero. An ideal treatment would also benefit one or more of the comorbidities, particularly psoriatic arthritis. An ideal medication would produce remission without the need for continuous long-term administration or could be administered intermittently as required when the patient reaches a predetermined PASI score after interruption of therapy. Clearly, the ideal treatment is not currently available.

Place in Therapy

The clinical expert does not expect HP/TAZ to cause a shift in the current Canadian treatment paradigm for moderate and severe plaque psoriasis; however, they feel it will be a welcome addition to the lineup of currently available topical therapies. It may offer protection against the local and systemic adverse effects of superpotent topical corticosteroids. The clinical expert noted that it is efficacious and cosmetically elegant and will likely be well accepted by patients resulting in high levels of adherence. They also mentioned that the base allows convenient application to hairy areas, however, HP/TAZ is not recommended for use on the scalp.[9]

According to the clinical expert, HP/TAZ is an appropriate first choice of topical therapy for patients with relatively limited areas of psoriatic involvement, noting that the efficacy and safety of HP/TAZ in patients with more than 12% of BSA affected by plaque psoriasis has not been established.[30] They also felt it would be an appropriate adjunctive therapy in those patients who require systemic drugs.

The clinical expert did not think it would be appropriate to recommend that patients try other treatments before initiating treatment with HP/TAZ. They believe that HP/TAZ would be an appropriate choice of first topical agent in all patients with plaque psoriasis, excluding pregnant women and children and those who have facial and/or intertriginous involvement only. Of note, HP/TAZ is contraindicated in pregnant women and there is no evidence to support its use in children. Further, HP/TAZ is not recommended for use on the face or intertriginous areas.

Patient Population

In the opinion of the clinical expert consulted for this review, HP/TAZ would be most suitable as monotherapy for patients with relatively limited areas of psoriasis, noting that the 50 g per week limitation would exclude use in patients with large areas of involvement. HP/TAZ would also be appropriate for patients on systemic therapy, both biologics and non-biologics, who have residual plaques, or those who have previously been completely controlled with systemics and are now having flares.

Patients best suited for treatment with HP/TAZ would be recognized by clinical examination by a dermatologist. Psoriasis is generally not a challenging diagnosis for a dermatologist, so misdiagnosis is unlikely at the level of the dermatologist. No lab testing is required to make the diagnosis and routine lab testing will not be required to follow a patient on HP/TAZ.

The clinical expert anticipated that HP/TAZ will be prescribed in Canada for the treatment of mild psoriasis by family physicians and nurse practitioners. In that setting, they would anticipate some instances of misdiagnosis or inappropriate prescribing of HP/TAZ.

The clinical expert suggested that patients who would be least suitable for treatment with HP/TAZ are those who have a history of suspected hypersensitivity to HP or TAZ, as well as children and pregnant women. Treatment with HP/TAZ would not be appropriate for use as monotherapy in patients with large areas of plaque psoriasis where the 50 g per week limit would be insufficient. It would also not be appropriate in psoriasis with eczematous features, pustular psoriasis, or erythrodermic psoriasis. It would not be appropriate for use on the face or intertriginous areas.

The clinical expert does not think it would be possible to identify patients who are more likely to exhibit a response to treatment with HP/TAZ accurately. They would expect those who have a clearly documented lack of response to superpotent corticosteroids to do less well.

Assessing Response to Treatment

The clinical expert stated that the outcomes used in clinical practice are not aligned with the outcomes typically used in clinical trials. It is unlikely that PASI, IGA, and DLQI scores will be calculated and recorded in clinical practice. What is more likely to be recorded is an informal combination of the prescriber's and patient's view of improvement in erythema, scaling, thickness, area of involvement, and pruritus at four to eight weeks. It is expected that many patients with mild psoriasis for whom a dermatologist prescribes HP/TAZ will actually be sent back to the referring physician for continued follow-up.

A clinically meaningful response to treatment judged at four to eight weeks would require joint input from the patient and the clinician. Response would not generally be graded on a formal scale, but rather be an assessment as to whether there has been a significant improvement in the appearance of the plaques (area, scaling, thickness, and redness) and a reduction in pruritus and/or pain. There would also be observations of atrophy, irritation, and folliculitis.

It is very likely that there would be considerable variability in the assessment of response from clinician to clinician. As well, patients vary significantly in their expectations of response to topical therapy.

Ideally, when any superpotent topical corticosteroid is prescribed, the first follow-up assessment should take place at or before one month. Given the severe shortage of dermatologists in Canada, many patients will be returned to the care of their family physician and will not be followed by the dermatologist. For those patients who will remain under the care of a dermatologist, it is unlikely that a follow-up appointment can be booked prior to eight weeks after starting HP/TAZ.

Discontinuing Treatment

The clinical expert stated three factors that would influence the decision to stop the treatment, including lack of adequate disease response; presence of significant skin atrophy, folliculitis, irritation, suspected irritant, or allergic contact dermatitis; and the treatment being cost-prohibitive (i.e., the patient cannot afford continued use of HP/TAZ).

Prescribing Conditions

As per input from the clinical expert, the drug under review would be dispensed by the patient's community pharmacist who would likely offer some written information with the medication. The drug would be applied by the patient, generally in the patient's home.

The clinical expert did not feel that a dermatologist would be required to diagnose, treat, or monitor patients who might receive HP/TAZ. The clinical expert anticipates significant prescribing by family doctors, nurse practitioners, and perhaps by other specialists (e.g., rheumatology and internal medicine).

Additional Considerations

The clinical expert noted that HP/TAZ is unlikely to be used as monotherapy in patients with moderate-to-severe plaque psoriasis and is more likely to be an adjunct to systemic therapy. It is appropriate as monotherapy in mild psoriasis and thus, significant prescribing by non-dermatologists is anticipated.

Clinical Evidence

The clinical evidence included in the review of HP/TAZ is presented in three sections. The first section, the systematic review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section includes indirect evidence from the sponsor and indirect evidence selected from the literature that met the selection criteria specified in the review. The third section includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of 0.01% w/w HP/TAZ topical lotion for improving the signs and symptoms of plaque psoriasis in adult patients with moderate-to-severe plaque psoriasis.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 4.

Of note, the systematic review protocol presented below was established prior to the granting of a Notice of Compliance from Health Canada.

Table 4: Inclusion Criteria for the Systematic Review

Patient population	Adults with moderate-to-severe plaque psoriasis Subgroups: HP/TAZ used as adjunct therapy vs. monotherapy disease severity (e.g., moderate vs. severe) previous experience with treatments for plaque psoriasis (topical or systemic)
Intervention	0.01% w/w halobetasol propionate and 0.045% w/w tazarotene lotion, applied in a thin layer to the affected area once daily
Comparators	Topical treatments as monotherapy, as a combination therapy, or used sequentially: corticosteroids, vitamin D analogues, retinoids Phototherapy as monotherapy or in combination with topical treatment
Outcomes	**Efficacy outcomes:** HRQoL[a] (e.g., DLQI, SF-36, EQ-5D) skin clearance/psoriasis score (e.g., PASI response, IGA) psoriasis-related signs and symptoms[a] (e.g., PSI) productivity treatment adherence **Harms outcomes:** AEs,[a] SAEs, WDAEs, mortality Notable harms: HPA axis suppression (secondary glucocorticoid insufficiency, adrenal hypercorticism [Cushing syndrome, hyperglycemia, glycosuria]), hypersensitivity events, skin irritation[a] (e.g., burning or stinging, itching, severe dryness), thinning of skin,[a] folliculitis
Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimensions; HP = halobetasol propionate; HPA = hypothalamic pituitary adrenal; HRQoL = health-related quality of life; IGA = Investigator's Global Assessment; PASI = Psoriasis Area Severity Index; PSI = Psoriasis Symptom Inventory; RCT = randomized controlled trial; SAE = serious adverse event; SF-36 = Short Form (36) Health Survey; TAZ = tazarotene; vs. = versus; w/w = weight by weight; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist (https://www.cadth.ca/resources/finding-evidence/press 2016).[31]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Monoferric (iron isomaltoside). Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International

Clinical Trials Registry Platform (ICTRP) search portal. No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on February 12, 2020. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on June 17, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[32] Health Technology Assessment (HTA) Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (free). Google was used to search for additional internet-based materials. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 1 for more information on the grey literature search strategy.

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

Findings From the Literature

A total of two studies were identified for inclusion in the systematic review (Figure 2). The included studies are summarized in Table 5. A list of excluded studies is presented in Appendix 2.

Figure 2: Flow Diagram for Inclusion and Exclusion of Studies

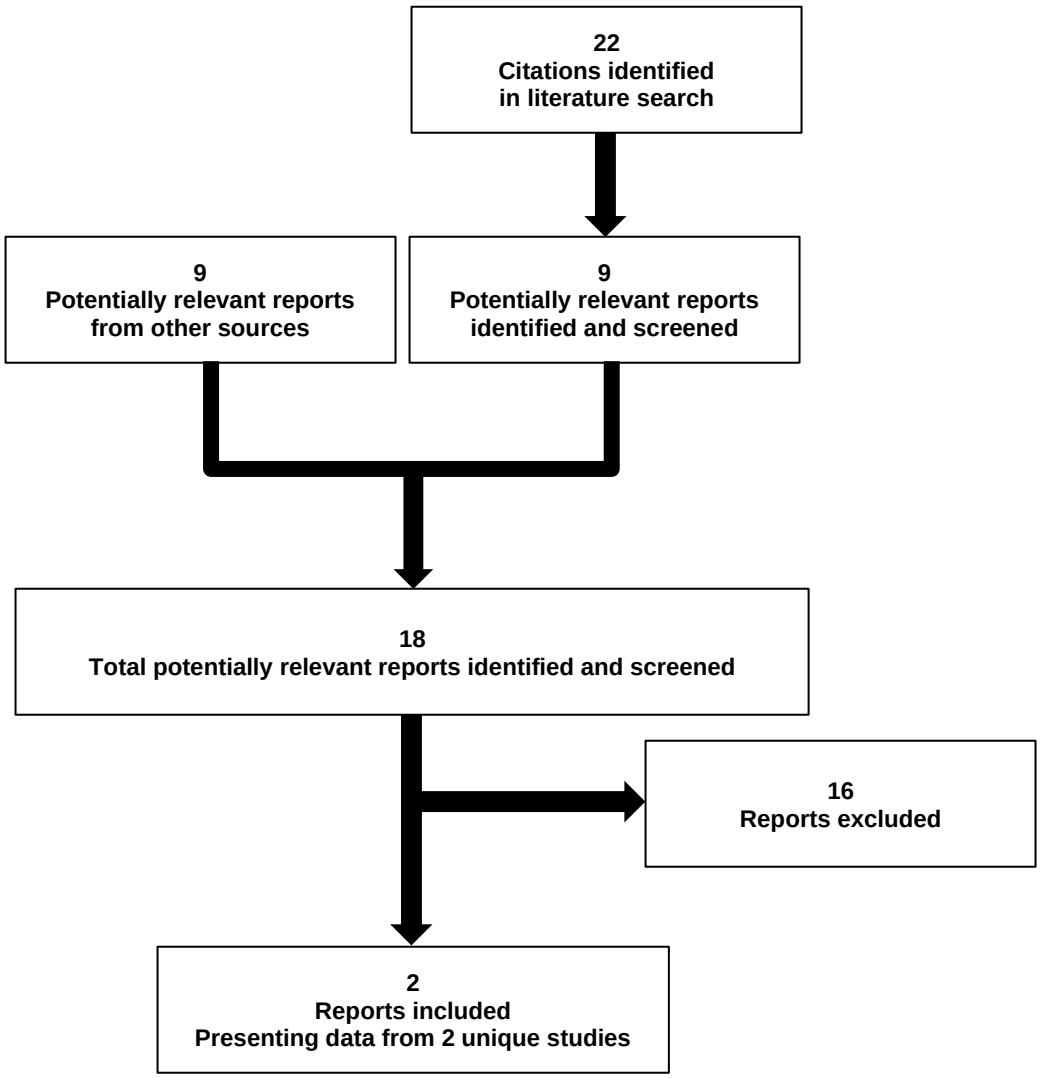

Table 5: Details of Included Studies

	Study 301	Study 302
Designs and populations		
Study design	Double-blind, multi-centre, vehicle-controlled, phase III RCT	
Locations	16 sites in the US	
Randomized (N)	203	215

Inclusion criteria	• ≥ 18 years
	• Had an area of plaque psoriasis appropriate for topical treatment that covered a BSA[a] of 3% to 12%
	• Willing and able to avoid prolonged exposure of treatment area to UV radiation
	• Clinical diagnosis of psoriasis at baseline with an IGA score[a] of 3 or 4
	• Had a target lesion that:
	  ○ measured 16 cm^2 to 100 cm^2
	  ○ scored ≥ 3 for at least two of three of psoriasis signs (erythema, plaque elevation, and scaling) with a sum of the three scores at least 8; no signs could have a score of 0 or 1
	  ○ was not located on excluded areas or areas covering bony prominences (e.g., elbows and knees)
	• In good general health[b]	

Exclusion criteria	• Had spontaneously improving or rapidly deteriorating plaque psoriasis or pustular psoriasis, as determined by the investigator • Presented with psoriasis that was treated with prescription medication and failed to respond to treatment, even partially or temporarily, as determined by the investigator • Presented with any concurrent skin condition that could interfere with the evaluation of treatment areas • Had received treatment with any investigational drug or device within 60 days or 5 drug half-lives prior to baseline visit, or currently in another clinical study • Received treatment with topical antipsoriatic drug within 14 days prior to baseline • Had used phototherapy, photochemotherapy, or non-biologic systemic psoriasis therapy within 4 weeks prior to baseline • Had used biologics known to affect psoriasis within 3 months of baseline visit • Had prolonged exposure to UV radiation within 4 weeks prior to baseline or intending to during study period • Was pregnant, nursing an infant, or planning pregnancy during study period • Had underlying disease[c] deemed uncontrolled and a safety concern by the investigator	
Drugs		
Intervention	HP/TAZ lotion applied topically to the affected area once daily for 8 weeks Note: up to a maximum weekly dose of 50 g	
Comparator(s)	Vehicle lotion applied topically to the affected area once daily for 8 weeks	
Duration		
Phase		
Double-blind	8 weeks	
Follow-up	4 weeks	
Outcomes		
Primary end point	Percentage of patients with treatment success at week 8, defined as at least a 2-grade improvement from baseline in IGA score and an IGA score equal to clear or almost clear	
Secondary and exploratory end points	**Secondary:** • Percentage of patients with treatment success at week 12, 6, 4, and 2 **Exploratory:** • Percentage of patients with at least a 2-grade improvement from baseline in the score for each of the signs of psoriasis (erythema, plaque elevation, and scaling) at week 8, 12, 6, 4, and 2	

	Study 301	Study 302
	• Change from baseline in DLQI • Percentage of patients with at least a 2-grade improvement from baseline in IGA score • BSA and percentage change from baseline in BSA	
Notes		
Publications	None	None

BSA = body surface area; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; HP = halobetasol propionate; IGA = Investigator's Global Assessment; QTcF = corrected QT interval by Fredericia; RCT = randomized controlled trial; TAZ = tazarotene; UV = ultraviolet.

Note: One additional report was included (CDR submission).[1]

[a] The face, scalp, palms, soles, axillae, and intertriginous areas were excluded from the calculation of BSA involvement or IGA score.

[b] Based on the subject's medical history and a physical examination, with screening hematology and serum chemistry laboratory values and ECGs within normal range or not clinically significant as determined by the investigator.

[c] Examples of underlying disease included: uncontrolled diabetes, cardiac disease, and/or QTcF > 500 ms.

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

Description of Studies

The two identically designed pivotal trials submitted by the sponsor, Study 301 (N = 203) and Study 302 (N = 215), met the inclusion criteria for the systematic review. Details of the included studies and study designs are provided in Table 5.

The objective of Study 301 and Study 302 was to evaluate the safety and efficacy of topical HP/TAZ in comparison to vehicle when applied once daily to adult patients with moderate-to-severe plaque psoriasis. Overall, 418 patients were included in the two studies. Each of the pivotal trials included 16 study sites, all of which were located in the US and carried out between August 2015 and November 2016.

The two trials were multi-centre, double-blind, randomized, parallel-group studies comparing HP/TAZ to vehicle. Following a screening visit that occurred between one and 35 days prior to randomization, patients were randomized in a 2:1 ratio to receive HP/TAZ or vehicle. The method of randomization used involved a unique subject number assigned to patients by the investigational centre that was used to assign patients to a study drug kit that was dispensed by an interactive response technology system. Randomization was not stratified.

The area affected by plaque psoriasis that would be treated was determined by the investigator at baseline, and patients were to treat this area with the study drug once daily for eight weeks. There were four on-treatment post-baseline study visits that occurred at week 2, 4, 6, and 8. Patients were also asked to return for a follow-up visit four weeks after treatment cessation at week 12. Patients who discontinued early were asked to complete all week 8 assessments as appropriate before starting any alternative therapy for psoriasis.

Populations

Inclusion and Exclusion Criteria

A list of key inclusion and exclusion criteria is available in Table 5.

To be eligible for participation in Study 301 and Study 302, patients were required to have an area of plaque psoriasis that was appropriate for topical treatment and covered a BSA of

between 3% and 12% (inclusive). Patients were also required to have a clinical diagnosis of psoriasis at baseline with an IGA score of 3 or 4. The calculation of BSA and IGA did not include the face, scalp, palms, soles, axillae, and intertriginous areas. The patient needed to have a target lesion that measured between 16 cm^2 and 100 cm^2 (inclusive), was not located on areas covering bony prominences, and met the psoriasis signs scoring criteria noted in Table 5.

Patients were excluded from Study 301 and Study 302 if they presented with psoriasis that was treated with and failed to respond to prescription medication, even partially or temporarily. Patients were also excluded if they had received treatment with: any topical antipsoriatic drug within 14 days prior to the study baseline visit; had used phototherapy, photochemotherapy, or non-biologic systemic therapies for psoriasis within four weeks of the study baseline visit; and biologics known to affect psoriasis within three months of baseline visit.

Baseline Characteristics

The baseline characteristics for randomized patients in Study 301 and Study 302 are summarized in Table 6. Patients were a mean age of 48.8 (SD = 13.3) and 51.8 (SD = 14.3) years in Study 301 and Study 302, respectively. The majority of patients were male (67.0% and 63.3%) and White (89.7% and 81.9%) in Study 301 and Study 302, respectively, and 32.0% in Study 301 and 23.3% in Study 302 were Hispanic or Latino. In Study 301, a greater proportion of patients randomized to vehicle were male (69.1% vs. 65.9%) and Black or African American (6.7% vs. 2.9%), and a smaller proportion of patients randomized to vehicle were Hispanic or Latino (29.4% vs. 33.3%). In Study 302, a greater proportion of patients randomized to vehicle were male (67.6% vs. 61.0%), White (85.1% vs. 80.1%), and Black or African American (9.5% vs. 6.4%), and a smaller proportion were Asian (4.1% vs. 9.2%).

At baseline, most of the patients randomized to Study 301 and Study 302 had moderate disease (82.8% and 87.4%, respectively), indicated by an IGA score of 3. The rest of the patients in both studies were classified as having severe disease by an IGA score of 4. Percent BSA affected by psoriasis was a mean of 6.2% (SD = 2.9%) and 5.6% (SD = 2.6%) for patients in Study 301 and Study 302, respectively, which was also similar between treatment groups. Overall, the disease characteristics of patients in both pivotal trials were similar between the HP/TAZ and vehicle treatment groups, with a few differences to note. In Study 301, patients randomized to vehicle had [redacted] than patients receiving HP/TAZ [redacted]. In Study 302, patients randomized to HP/TAZ, the mean (SD) size of the target lesion for treatment was [redacted], and the erythema signs of psoriasis for the target lesion were [redacted].

Table 6: Summary of Baseline Characteristics (ITT Set)

Characteristic	Study 301		Study 302	
	HP/TAZ N = 135	Vehicle N = 68	HP/TAZ N = 141	Vehicle N = 74
Demographic characteristics				
Age, mean (SD)	48.1 (13.3)	50.0 (13.3)	51.8 (14.8)	51.8 (13.2)
Sex (% male), n (%)	89 (65.9)	47 (69.1)	86 (61.0)	50 (67.6)
Ethnicity				
Hispanic or Latino	45 (33.3)	20 (29.4)	33 (23.4)	17 (23.0)
Not Hispanic or Latino	90 (66.7)	48 (70.6)	108 (76.6)	57 (77.0)
Race				
White	119 (88.1)	63 (92.6)	113 (80.1)	63 (85.1)
Black or African American	9 (6.7)	2 (2.9)	9 (6.4)	7 (9.5)
Asian	3 (2.2)	2 (2.9)	13 (9.2)	3 (4.1)
Other	4 (3.0)	1 (1.5)	6 (4.3)	1 (1.4)
BMI, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline disease characteristics				
IGA score, n (%)				
3 = moderate	112 (83.0)	56 (82.4)	125 (88.7)	63 (85.1)
4 = severe	23 (17.0)	12 (17.6)	16 (11.3)	11 (14.9)
Percentage BSA affected by psoriasis				
Mean (SD)	6.5 (2.98)	5.5 (2.58)	5.4 (2.64)	5.9 (2.51)
Median (range)	6.0 (3 to 12)	5.0 (3 to 12)	4.0 (3 to 12)	5.0 (3 to 12)
Size of target lesion (cm^2)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Signs				
Erythema (target lesion)				
2 = mild	[redacted]	[redacted]	[redacted]	[redacted]
3 = moderate	[redacted]	[redacted]	[redacted]	[redacted]
4 = severe	[redacted]	[redacted]	[redacted]	[redacted]
Plaque elevation (target lesion)				
2 = mild	[redacted]	[redacted]	[redacted]	[redacted]
3 = moderate	[redacted]	[redacted]	[redacted]	[redacted]
4 = severe	[redacted]	[redacted]	[redacted]	[redacted]
Scaling (target lesion)				
2 = mild	[redacted]	[redacted]	[redacted]	[redacted]
3 = moderate	[redacted]	[redacted]	[redacted]	[redacted]
4 = severe	[redacted]	[redacted]	[redacted]	[redacted]

BMI = body mass index; BSA = body surface area; HP = halobetasol propionate; IGA = Investigator's Global Assessment; ITT = intention to treat; SD = standard deviation; TAZ = tazarotene.

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

A summary of prior medication used by the patients included in Study 301 and Study 302 is available in Table 7. The most common medications previously used in Study 301 and Study 302 were [redacted]

Table 7: Prior Medication Use (ITT Set)

	Study 301		Study 302	
	HP/TAZ N = 135	Vehicle N = 68	HP/TAZ N = 141	Vehicle N = 74
Patient history of prior medication use, n (%)				
[redacted]				

HP = halobetasol propionate; ITT = intention to treat; TAZ = tazarotene; [redacted].

[redacted]

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

Interventions

Patients enrolled in Study 301 and Study 302 were randomized in a 2:1 ratio to receive HP/TAZ (HP 0.01%, TAZ 0.045%) lotion or vehicle lotion, respectively. All patients were to apply the study drug once daily to the affected area for eight weeks, with a maximum weekly usage of 50 g. The affected area was determined by the investigator at baseline. Study drug was to be applied as a thin layer to the entire selected treatment area as indicated on a body diagram, and patients were instructed to avoid or minimize exposure to direct sunlight and artificial ultraviolet light sources during the study. The investigator instructed patients on how to apply the study drug to affected treatment areas at the baseline visit. Patients were also provided with written instructions. Further, patients were asked to refrain from applying study drug on the day of a clinic visit in order to observe their study drug application technique and retrain if necessary. Both HP/TAZ and vehicle lotion were packaged and labelled identically and dispensed in tube containers of 45 g, two at a time.

Certain concomitant treatments were permitted during the two pivotal studies. A summary of concomitant medication use is available in Table 8. Non-medicated cleansers, moisturizers, and sunscreens that were approved by the sponsor were permitted for use on the treatment areas during Study 301 and Study 302. Patients could treat areas that were excluded from the trials, such as the face, scalp, axillae, and intertriginous areas, with over-the-counter 1% hydrocortisone cream, tar shampoos, or moisturizers that were permitted. Palms of the hands and soles of the feet were not included in assessments of BSA or IGA for the studies, but patients were permitted to use study drug to treat these areas and could be evaluated by the investigator for improvement.

Table 8: Concomitant Medication Use (ITT Set)

	Study 301		Study 302	
	HP/TAZ N = 135	Vehicle N = 68	HP/TAZ N = 141	Vehicle N = 74
Concomitant medication use, n (%)				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

	Study 301		Study 302	
	HP/TAZ N = 135	Vehicle N = 68	HP/TAZ N = 141	Vehicle N = 74
[redacted]				
[redacted]				
[redacted]				
[redacted]				

HP = halobetasol propionate; ITT = intention to treat; TAZ = tazarotene.

[redacted]

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

If a patient was using a concomitant therapy that may interfere with the interpretation of study results, they were discontinued from the concomitant product rather than withdrawn from the study. Topical treatments (other than those previously described) were not permitted.

The investigators were to try to minimize study drug interruptions; however, if signs or symptoms of the treatment areas developed while being treated with study drug that impacted daily activities or caused discomfort during application, a "drug holiday," or temporary interruption of study drug, could be implemented. An effort was made to limit the drug holidays to four days, but if they exceeded this limit, further use of study drug was reconsidered. The use of study drug could also be delayed or halted at any time due to safety evaluations of concern.

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 5. These end points are further summarized in this section. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4.

Dermatology Life Quality Index

The DLQI is a widely used dermatology-specific HRQoL instrument designed to assess the impact of skin disease.[33] It is a ten-item questionnaire that covers six domains: symptoms and feeling, daily activities, leisure, work and school, personal relationships, and bother with psoriasis treatment. A four-point Likert scale is used to measure how much the skin disease affects a patient's life over the past week, in which *not at all* or *not relevant* are scored as 0, *a little* is scored as 1, *a lot* is scored as 2, and *very much* is scored as 3. The overall DLQI score is a numeric score derived from a sum of the 10 items, for a total score that ranges from zero to 30. A lower score indicates greater HRQoL. At least 80% of the questions must be answered for a score to be reported.[33,34] The final numeric score translates to the effect of the patient's disease on their HRQoL where 0 to 1 indicates no effect, 2 to 5 indicates a small effect, 6 to 10 indicates a moderate effect, 11 to 20 indicates a very large effect, and 21 to 30 indicates an extremely large effect.

There is evidence of validity, reliability, and responsiveness of the DLQI in patients with psoriasis, as described in Appendix 4. In addition, multiple sources in the literature report a

within-group minimal important difference (MID) for patients with psoriasis, which ranges from 2.2 to 6.9.

The DLQI was used to assess patient's HRQoL at baseline, week 4, 8, and 12, and the mean (SD) change from baseline was reported as an exploratory outcome.

Investigator's Global Assessment

The IGA is a subjective measurement of the clinical signs of psoriasis. In the two studies under review, a five-point, static version of the IGA was used.[10,11] To generate the IGA score, psoriatic lesions are graded for erythema, thickness, and scaling based on a scale of 0 to 4, that are then averaged across all lesions to obtain a single estimate of the patient's overall severity of disease at a given point in time. The three items are given equal weighting. The sum of the three scales are added and then divided by three [$(E + I + S)/3$] for a final IGA score of 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), or 4 (severe) corresponding to increasing severity of disease. Although the five-point static IGA scale was used in the pivotal trials to evaluate treatment efficacy, there are no studies evaluating validity, reliability, and responsiveness of this five-point scale. However, the six-point IGA scale has been validated in terms of its validity and reliability. No MID for the IGA in patients with psoriasis has been identified in the literature.

The IGA score was used to describe the severity of psoriasis of the treatable areas in Study 301 and Study 302. The face, scalp, palms, soles, axillae, and intertriginous areas were excluded from the IGA assessment. The primary outcome was the percentage of patients with treatment success at week 8, where treatment success was defined as at least a two-grade improvement from baseline in the IGA score and an IGA score of clear or almost clear (0 or 1). This definition of treatment success was used at weeks 2, 4, 6, and 12 as a secondary outcome. In addition, the percentage of patients with at least a two-grade improvement form baseline in the IGA score was reported as an exploratory outcome.

Body Surface Area

BSA is used to determine the extent of psoriasis coverage within a patient. The 1% rule was used to calculate BSA in the HP/TAZ pivotal trials. This estimation uses a flat palm in which the subject's palm represents approximately 1% of the total BSA. The subject or investigator then uses their flat palm to estimate the percentage BSA affected by psoriasis.[35] The BSA calculation in the pivotal trials did not include areas of the face, scalp, palms, soles, axillae, and other intertriginous areas.[10,11] It is generally accepted that if a patient presents with an affected BSA of 0% to 3% or less this is considered low BSA affected, 3% to 10% or less is considered medium BSA affected, and an affected BSA of greater than 10% is considered a high amount of BSA involvement.[36]

Evidence of a MID for reduction in BSA was not identified in the literature for patients with psoriasis. The clinical expert consulted by CADTH for this review indicated that a one-third reduction in BSA is a clinically important difference for patients.

The BSA was used to assess patients at baseline, week 2, 4, 6, 8, and 12 and the mean (SD) change from baseline was reported as an exploratory outcome.

Psoriasis Signs

The signs of psoriasis, which include erythema, plaque elevation, and scaling, were assessed for the selected target lesion in the two pivotal trials. Each of the signs are evaluated using a subjective scale that ranges from 0 or *none* (no signs of psoriasis) to 4 or

severe. According to the sponsor, the results from the psoriasis signs scale are used to detect specific changes of a patient's lesions. In addition, they have suggested there are many similar scales that are widely used for psoriasis as erythema, plaque elevation, and scaling are basic characteristics of psoriasis lesions. Currently, there is no further information on the construct of the grading for this assessment, including evidence on its validity, reliability, responsiveness to change, and clinical relevance. The clinical expert consulted by CADTH for this review indicated that a decrease of two points in any of the signs of psoriasis would be considered a clinically important outcome for patients.

The signs of psoriasis were used as an exploratory outcome in Study 301 and Study 302. Similar to the IGA score, the psoriasis signs were used to describe treatment success, defined as at least a two-grade improvement from baseline for each of the three signs for the target lesion. To help distinguish this outcome from treatment success by IGA, treatment success based on the signs of psoriasis will be referred to as "improvement in the signs of psoriasis" throughout the report. The percentage of patients with an improvement in the signs of psoriasis was reported at weeks 2, 4, 6, 8, and 12. Additionally, a summary of the score for each of the signs of psoriasis was reported.

Harms

Treatment-emergent AEs, or those that occurred between, on, or after the date of first study drug application, were summarized at week 8 (end-of-treatment period) and at week 12 (follow-up period). Serious AEs, WDAEs, and deaths were also reported.

In addition, the frequency of local skin reactions summarized by treatment group and visit were reported as a measure of tolerability. Itching and burning/stinging were patient reported based on a 24-hour recall period and dryness was assessed by the investigator. Local skin reactions that required use of concomitant therapy or study drug interruption or discontinuation were reported as an AE.

Statistical Analysis

In both trials, the primary outcome (percentage of patients with treatment success) was analyzed using Cochran-Mantel-Haenszel tests stratified by analysis centre to compare HP/TAZ to vehicle. Missing efficacy data were primarily handled using the MCMC multiple imputation method. Sensitivity analyses of the primary outcome were conducted using the last observation carried forward (LOCF) method and repeated measures analysis on observed data.

The secondary outcomes (IGA treatment success) and exploratory outcomes related to improvement in the signs of psoriasis were analyzed using the same Cochran-Mantel-Haenszel model as the primary outcome. Missing data for these outcomes was also handled using the MCMC multiple imputation method.

A gated sequential testing procedure, where the testing process was terminated if a value that was not statistically significant was observed, was used for the secondary outcomes regarding treatment success by the IGA score. The order was as follows: the percentage of patients who show two or greater grade improvement in the IGA score, and reach clear or almost clear at week 12 for HP/TAZ versus vehicle, followed by the same outcome and comparison at week 6, week 4, and finally week 2. Aside from these secondary outcomes and the primary outcome, none of the other outcomes were adjusted for multiplicity.

Only descriptive statistics were reported for the remaining exploratory efficacy outcomes (DLQI, two-grade improvement from baseline in IGA score, and BSA outcomes) and missing data were not imputed. For per-protocol analyses, a LOCF approach was used to impute missing values. Data were not imputed for missing safety data.

Each trial was estimated to have greater than 95% power to detect a statistically significant outcome for a two-sided test with an alpha level of 0.05 based on a total of 140 patients in the HP/TAZ group and 70 patients in with vehicle group. The power calculations were based on observed IGA efficacy data at week 8 using the ITT analysis set from the phase II study for HP/TAZ (Study 201).

Subgroup analyses for the primary outcome (ITT population) were conducted and descriptive statistics were reported. The following subgroups were included: baseline IGA, sex, age (less than vs. greater than the median age of patients), ethnicity, and race. The subgroup analyses appear to be pre-planned, although treatment randomization was not stratified by any of these subgroups at baseline.

Table 9: Statistical Analysis of Efficacy Endpoints

End point	Statistical model	Adjustment factors	Sensitivity analyses
Study 301 and Study 302			
Primary end point: Treatment success[a] by IGA at week 8	Cochran-Mantel-Haenszel, stratified by analysis centre	No adjustments for covariates[b] (no analyses were performed that included covariates) Missing data were handled using multiple imputation (MCMC) The secondary end points follow a gated sequential procedure in the following order: week 12, 6, 4, 2	LOCF Repeated measures analysis on observed data
Secondary end points: Treatment success[a] by IGA at week 12, 6, 4, and 2			None
Exploratory end points: Improvement in signs of psoriasis[c]	Cochran-Mantel-Haenszel, stratified by analysis centre	No adjustments for covariates (no analyses were performed that included covariates) Missing data were handled using multiple imputation (MCMC) No adjustments for multiplicity	None
Exploratory end points: DLQI,[d] IGA,[e] BSA,[f]	Summarized using descriptive statistics		

BSA = body surface area; DLQI = Dermatology Life Quality Index; IGA = Investigator's Global Assessment; LOCF = last observation carried forward; MCMC = Markov chain Monte Carlo.

[a] *Treatment success* was defined as at least a two-grade improvement from baseline in IGA score and an IGA score equal to clear or almost clear.

[b] No analyses were performed that included covariates.

[c] Improvement equalled the percentage of patients with at least a two-grade improvement from baseline for each of the signs for the target lesion.

[d] Change from baseline.

[e] IGA by study visit and change from baseline.

[f] BSA by study visit and percentage of patients with at least a two-grade improvement from baseline.

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

Analysis Populations

All patients who were randomized and dispensed study drug were included in the ITT analysis set.

The per-protocol analysis set included all subjects in the ITT set who completed the week 8 study visit without any major protocol violations, which included: violating inclusion/exclusion criteria, use of an interfering concomitant medication, not attending the week 8 visit, missing more than one visit between baseline and week 8, not being compliant with the dosing regimen, and attending the week 8 study visit more or less than five days from the intended visit date.

The safety analysis set was defined by subjects who were randomized, received at least one confirmed dose of study drug, and completed at least one post-baseline safety assessment.

The ITT analysis set was used for the primary evaluation of efficacy and the per-protocol set was used for supportive analyses. The safety set was used for all safety analyses.

Results

Patient Disposition

A summary of patient disposition including the number of patients included in each analysis set is presented in Table 10.

The number of patients screened for Study 301 and Study 302 was not reported. A total of 83.3% of randomized patients completed Study 301 and 84.2% of patients completed Study 302. Overall, study discontinuation rates were 16.7% and 15.8% in Study 301 and Study 302, respectively. Reasons for discontinuation were similar between the two treatment groups in both studies, with the exception of discontinuation due to AEs in Study 301, which was reported as 4.4% of patients treated with HP/TAZ and 0% for patients who received vehicle. The most common reasons for discontinuation from study were patient request (6.9% in Study 301 and 7.0% in Study 302), lost to follow-up (4.9% and 2.5%, respectively), and AEs (3.0% and 4.2%, respectively). Discontinuation rates were also similar across the two pivotal trials.

Table 10: Patient Disposition (All Randomized Patients)

	Study 301		Study 302	
	HP/TAZ	Vehicle	HP/TAZ	Vehicle
Screened, N	Not reported		Not reported	
Randomized, n	135	68	141	74
Completed study, n (%)	112 (83.0)	57 (83.8)	120 (85.1)	61 (82.4)
Discontinued from study, n (%)	23 (17.0)	11 (16.2)	21 (14.9)	13 (17.6)
Reason for discontinuation, n (%)				
Adverse event	6 (4.4)	0	5 (3.5)	4 (5.4)
Lost to follow-up	6 (4.4)	4 (5.9)	3 (2.1)	2 (2.7)
Protocol violation	1 (0.7)	0	2 (1.4)	0
Patient request	7 (5.2)	7 (10.3)	10 (7.1)	5 (6.8)

	Study 301		Study 302	
Worsening condition	2 (1.5)	0	1 (0.7)	2 (2.7)
Other	1 (0.7)	0	0	0
ITT, n	135	68	141	74
PP,[a] n	117	55	112	65
Safety, n	133	67	137	73

HP/TAZ = halobetasol propionate and tazarotene; ITT = intention to treat; PP = per protocol.

[a] Data are for the week 8 PP population. Data for the week 12 PP population is also available (HP/TAZ = 111, vehicle = 62).

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

Exposure to Study Treatments

A summary of exposure to study drug during Study 301 and Study 302 is provided in Table 11.

The amount of study drug used, number of days exposed to study drug, and total number of applications of study drug were [redacted] in Study 301. Patients used about [redacted]. The number of days exposed to study drug and number of applications were [redacted]. Patients receiving HP/TAZ used [redacted] and patients receiving vehicle used [redacted].

Table 11: Exposure to Study Drug (Safety Set)

	Study 301		Study 302	
	HP/TAZ N = 133	Vehicle N = 67	HP/TAZ N = 137	Vehicle N = 73
Amount of study drug used (g)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Number of days exposed				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Number of applications				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]

HP/TAZ = halobetasol propionate and tazarotene; SD = standard deviation.

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

Compliance was defined by using between 80% and 120% of the expected applications of study drug while enrolled in the study. Briefly, based on the ITT population, [redacted] of patients receiving HP/TAZ [redacted] of patients receiving vehicle were compliant in Study 301. In Study 302, [redacted] of patients treated with HP/TAZ and vehicle, respectively, were compliant. Data related to extent of exposure was summarized earlier in Table 11.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below. See Appendix 3 for detailed efficacy data.

Health-Related Quality of Life

In both Study 301 and Study 302, HRQoL was evaluated as an exploratory outcome and assessed at week 4, 8, and 12 using the DLQI. This was the only measure of HRQoL included in the two studies. The DLQI scores at baseline and week 8, and change from baseline scores, are presented in Table 12. Data at week 8 was missing for 12% and 16% of patients in Study 301 and Study 302, respectively. The corresponding results for week 4 and week 12 are available in Appendix 3 (Table 43).

At the week 8 (end-of-treatment) study visit, the DLQI score for patients in Study 301 had [redacted] by a mean (SD) [redacted] in the HP/TAZ and vehicle treatment groups, respectively. In Study 302, the mean (SD) change from baseline in the DLQI score was [redacted] in the HP/TAZ and vehicle treatment groups, respectively. In the absence of formal statistical testing, no conclusions can be made as to whether DLQI was actually reduced in either group or whether there were any differences in DLQI between the two treatment groups.

Table 12: Change From Baseline in DLQI Score (ITT Set)

	Total N	Baseline	End-of-treatment time point (week 8)		
		Mean (SD)	n	Mean (SD)	Mean change from baseline (SD)
Study 301					
HP/TAZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vehicle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study 302					
HP/TAZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vehicle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DLQI = Dermatology Life Quality Index; HP/TAZ = halobetasol propionate and tazarotene; ITT = intention to treat; SD = standard deviation.

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

Skin Clearance

Skin clearance was assessed by the proportion of patients achieving treatment success by the IGA and BSA affected by plaque psoriasis in both of the pivotal trials. The IGA score by study visit was also reported and is available following the presentation of treatment success by IGA.

Treatment Success by IGA

The primary end point was treatment success at week 8, defined by at least a two-grade improvement from baseline in the IGA score in addition to an IGA score equal to clear or almost clear. This definition of treatment success was also assessed at week 12, 6, 4, and 2 as secondary end points. A summary of this data is available in Table 13. At week 8, 35.8% and 7.0% of patients treated with HP/TAZ and vehicle, respectively, had treatment success in Study 301. In Study 302, 45.3% and12.5% of patients treated with HP/TAZ and vehicle, respectively, had treatment success. In both trials, the difference between HP/TAZ

and vehicle in the proportion of patients achieving treatment success (P < 0.001) was in favour of HP/TAZ. Two sensitivity analyses were carried out for the primary outcome: imputing missing values using LOCF and a repeated measures analysis on observed data. In both trials, the sensitivity analyses were consistent with the primary analysis.

The secondary end points were analyzed following a gated sequential testing procedure, beginning with treatment success at week 12, followed by week 6, 4, and finally week 2. The results are available in Table 13. Of note, week 8 was the last visit where the patient received study drug and week 12 was a post-treatment follow-up visit. The difference between HP/TAZ and vehicle in the proportion of patients with treatment success was in favour of HP/TAZ (P < 0.05) at week 12, 6, and 4 in both studies. The difference in favour of HP/TAZ was also observed at week 2 in Study 302 (P = 0.004), but not in Study 301 (P = 0.098).

Table 13: Treatment Success by IGA (ITT Set)

	Study 301		Study 302	
	HP/TAZ N = 135	Vehicle N = 68	HP/TAZ N = 141	Vehicle N = 74
Primary end point, treatment success[a] at week 8				
Treatment success (% of patients)	35.76	6.98	45.33	12.51
Treatment failure (% of patients)	64.24	93.02	54.67	87.49
P value	< 0.001		< 0.001	
Secondary end points				
Treatment success[a] at week 12				
Treatment success (% of patients)	33.25	8.51	33.35	8.84
Treatment failure (% of patients)	66.75	91.49	66.65	91.16
P value	< 0.001		< 0.001	
Treatment success[a] at week 6				
Treatment success (% of patients)	37.84	6.67	37.53	8.24
Treatment failure (% of patients)	62.16	93.33	62.47	91.76
P value	< 0.001		< 0.001	
Treatment success[a] at week 4				
Treatment success (% of patients)	24.86	9.33	26.96	1.36
Treatment failure (% of patients)	75.14	90.67	73.04	98.64
P value	0.008		< 0.001	
Treatment success[a] at week 2				
Treatment success (% of patients)	9.15	2.98	9.77	0
Treatment failure (% of patients)	90.85	97.02	90.23	100.00
P value	0.098		0.004	

HP/TAZ = halobetasol propionate and tazarotene; IGA = Investigator's Global Assessment; ITT = intention to treat; MCMC = Markov chain Monte Carlo.

Note: For all end points, Cochran-Mantel-Haenszel test was stratified by analysis centre. Missing values were imputed using multiple imputation (MCMC).

[a] *Treatment success* was defined as at least a two-grade improvement from baseline in the IGA score and an IGA score equal to clear or almost clear.

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

A subgroup analysis by disease severity at baseline was performed for the primary end point in both trials (Table 14). Since no formal testing was carried out for this subgroup, the results are descriptive in nature. The proportion of the subgroup patients with moderate disease (IGA = 3) who achieved treatment success at week 8 was 34.9% and 8.5% for the HP/TAZ and vehicle treatment groups in Study 301, respectively, and 47.6% and 14.7% for the HP/TAZ and vehicle treatment groups in Study 302, respectively. The proportion of patients with treatment success in either treatment group was numerically similar to the results for the overall treatment population for both trials (Study 301: HP/TAZ 35.8% and vehicle 7.0%; Study 302: HP/TAZ 45.3% and vehicle 12.5%). For patients with severe disease (IGA = 4), the proportion of patients treated with HP/TAZ that achieved treatment success at week 8 was numerically similar to that of the overall population in Study 301 (40.1% vs. 35.76%). In Study 302, the treatment success among patients with severe disease who were treated with HP/TAZ was numerically less than the overall population (27.7% vs. 45.33%). In both trials, none of the patients in the vehicle group with severe disease achieved treatment success at week 8.

Table 14: Subgroup Analysis by Disease Severity (ITT Set)

	Study 301		Study 302	
	HP/TAZ N = 135	Vehicle N = 68	HP/TAZ N = 141	Vehicle N = 74
Treatment success by IGA at week 8				
Baseline IGA = 3				
Patients included in analysis, n	112	56	125	63
Treatment success[a] (% of patients)	34.9	8.5	47.6	14.7
Treatment failure (% of patients)	65.1	91.5	52.4	85.3
Baseline IGA = 4				
Patients included in analysis, n	23	12	16	11
Treatment success[a] (% of patients)	40.1	0	27.7	0
Treatment failure (% of patients)	59.9	100.0	72.3	100

HP/TAZ = halobetasol propionate and tazarotene; IGA = Investigator's Global Assessment; ITT = intention to treat; MCMC = Markov chain Monte Carlo.

Note: Missing values were imputed using multiple imputation (MCMC).

[a] *Treatment success* was defined as at least a two-grade improvement from baseline in the IGA score and an IGA score equal to clear or almost clear.

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

IGA Score by Study Visit

The IGA score by study visit was descriptively reported in Study 301 and Study 302 and the results have been presented in Table 15. Since this outcome was exploratory and not formally tested, no formal conclusions can be made based on these results.

As per the inclusion criteria of the two trials, the disease severity of all patients was moderate or severe (IGA score of 3 or 4) at baseline. In Study 301, the proportion of patients with an IGA score of 0 or 1 at week 4 was 24.9% for patients randomized to HP/TAZ and 9.3% of patients randomized to vehicle. At week 8, 35.8% and 7.0% of patients treated with HP/TAZ and vehicle, respectively, had an IGA score of 0 or 1. At week 12 (four weeks following end of treatment), the proportion of patients with an IGA score of 0 or 1 in the HP/TAZ and vehicle treatment groups was 33.3% and 8.5%, respectively.

In Study 302, the proportion of patients with an IGA score of 0 or 1 at week 4 was 27.0% for patients randomized to HP/TAZ and 1.4% of patients randomized to vehicle. At week 8, 45.3% and 12.5% of patients treated with HP/TAZ and vehicle, respectively, had an IGA score of 0 or 1. At week 12, the proportion of patients with an IGA score of 0 or 1 in the HP/TAZ and vehicle treatment groups was 33.4% and 8.8%, respectively.

Table 15: IGA Score by Study Visit (ITT Set)

			% of patients					
		N at baseline	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12
Study 301								
HP/TAZ N = 135	0 = Clear	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1 = Almost clear	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2 = Mild	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3 = Moderate	112	83.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4 = Severe	23	17.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vehicle N = 68	0 = Clear	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1 = Almost clear	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2 = Mild	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3 = Moderate	56	82.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4 = Severe	12	17.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study 302								
HP/TAZ N = 141	0 = Clear	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1 = Almost clear	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2 = Mild	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3 = Moderate	125	88.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4 = Severe	16	11.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vehicle N = 74	0 = Clear	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1 = Almost clear	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2 = Mild	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3 = Moderate	63	85.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4 = Severe	11	14.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HP/TAZ = halobetasol propionate and tazarotene; IGA = Investigator's Global Assessment; ITT = intention to treat.

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

Percentage BSA and percentage change from baseline in BSA at week 8 are presented in Table 16. The corresponding results from week 2 through week 12 are available in Appendix 3 (Table 44). The BSA outcomes were included as exploratory end points in both trials and only descriptive statistics were presented for this outcome. At week 8, data were missing for 12% and 15% of patients in Study 301 and Study 302, respectively, and missing data were not imputed.

Patients in the HP/TAZ and vehicle treatment groups in Study 301 had a mean 6.5% (SD = 3.0%) and 5.5% (SD = 2.6%) of their BSA affected by psoriasis at baseline. At week 8, the percent BSA affected by psoriasis had decreased to a mean of 4.4% (SD = 3.3%) and 5.3% (SD = 3.7%), respectively, which corresponded to a 32.8% (SD = 40.8%) change for the HP/TAZ group and a 2.3% (SD = 83.0%) change for the vehicle group. In Study 302, the

mean percent of BSA affected by psoriasis at baseline was 5.4% (SD = 2.6%) and 5.9% (SD = 2.5%) for the HP/TAZ and vehicle treatment groups. This corresponded to a mean change of 42.5% (SD = 37.7%) and 8.3% (SD = 27.2%) for the two treatment groups, respectively.

Table 16: Percentage BSA Affected by Psoriasis (ITT Set)

	Total N	Baseline	End-of-treatment time point (week 8)		
		Mean (SD)	n	Mean (SD)	% change from baseline, mean (SD)
Study 301					
HP/TAZ	135	6.5 (3.0)	120	4.4 (3.3)	–32.8 (40.8)
Vehicle	68	5.5 (2.6)	59	5.3 (3.7)	–2.3 (83.0)
Study 302					
HP/TAZ	141	5.4 (2.6)	120	2.9 (2.3)	–42.5 (37.7)
Vehicle	74	5.9 (2.5)	62	5.4 (3.0)	–8.3 (27.2)

BSA = body surface area; HP/TAZ = halobetasol propionate and tazarotene; ITT = intention to treat; SD = standard deviation.

Note: Assessment of BSA affected by psoriasis did not include areas of the face, scalp, palms, soles, axillae, and other intertriginous areas.

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

Psoriasis-Related Signs and Symptoms

Improvement in the signs and symptoms of psoriasis (erythema, plaque elevation, and scaling) was reported as an exploratory outcome and not adjusted for multiplicity in Study 301 or Study 302. Improvement in the signs of psoriasis was a measure of treatment success, which was defined as at least a two-grade improvement from baseline for each of the three signs of psoriasis, and it was assessed at week 2, 4, 6, 8, and 12. The results are available in Table 17. A summary of the severity of the signs of psoriasis individually and by visit are also available in Appendix 3 (Table 45, Table 46, and Table 47).

In Study 301, [redacted] in the signs of psoriasis at week 8 was reported for [redacted] of patients in the HP/TAZ and vehicle treatment groups, respectively. At week 12 in Study 301, [redacted] in the signs of psoriasis was reported for [redacted] of patients in the HP/TAZ treatment group and [redacted] of patients in the vehicle treatment group. In Study 302, [redacted] in the signs of psoriasis at week 8 was reported for [redacted] of patients in the HP/TAZ and vehicle treatment groups, respectively, and at week 12, [redacted] in the signs of psoriasis was reported for [redacted] of patients in the HP/TAZ and vehicle treatment groups, respectively.

Table 17: Improvement in the Signs of Psoriasis by Study Visit (ITT Set)

	Study 301		Study 302	
	HP/TAZ N = 135	Vehicle N = 68	HP/TAZ N = 141	Vehicle N = 74
Treatment success[a] measured by an improvement in the signs of psoriasis				
Week 2				
Success (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
Failure (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]	[redacted]		[redacted]	

	Study 301		Study 302	
	HP/TAZ N = 135	Vehicle N = 68	HP/TAZ N = 141	Vehicle N = 74
Week 4				
Success (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
Failure (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]	[redacted]		[redacted]	
Week 6				
Success (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
Failure (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]	[redacted]		[redacted]	
Week 8				
Success (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
Failure (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]	[redacted]		[redacted]	
Week 12				
Success (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
Failure (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]	[redacted]		[redacted]	

HP/TAZ = halobetasol propionate and tazarotene; ITT = intention to treat; MCMC = Markov chain Monte Carlo.

[a] Treatment success defined by the percentage of patients with at least a two-grade improvement from baseline for each sign of psoriasis (erythema, plaque elevation, and scaling).

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Note: For all end points, Cochran-Mantel-Haenszel test stratified by analysis centre. Missing values were imputed using multiple imputation (MCMC).

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

Productivity

Data related to productivity was not assessed in Study 301 or Study 302.

Treatment Adherence

Treatment adherence was not explicitly measured as an efficacy outcome, but dosing compliance was reported as a safety assessment and has been presented in-text following Table 11 in the Exposure to Study Treatments section of this report.

Harms

Only those harms identified in the review protocol are reported below. See Table 18 for detailed harms data that were reported up until the week 8 study visit.

Adverse Events

In Study 301, the percentage of patients that reported at least one AE was 36.8% and 19.4% for the HP/TAZ treatment group and vehicle treatment group, respectively. In Study 302, 35.0% and 23.3% of patients in the HP/TAZ and vehicle treatment groups, respectively, reported at least one AE. The most commonly reported AE in both studies was contact dermatitis, which only occurred in patients in the HP/TAZ treatment groups (5.3% in Study 301 and 9.5% in Study 302).

Serious Adverse Events

At week 8, SAEs were reported by three (2.3%) patients in the HP/TAZ group in Study 301. No SAE was observed in more than one patient. No SAEs were reported in Study 302.

Withdrawals Due to Adverse Events

Overall, 7.5% of patients in the HP/TAZ treatment group and zero patients in the vehicle treatment group reported a WDAE in Study 301. In Study 302, 5.1% of patients in the HP/TAZ group and 6.8% of patients in the vehicle group reported a WDAE. The most common reason for WDAE was contact dermatitis, which only occurred in the HP/TAZ treatment groups (2.3% of patients in Study 301 and 1.5% of patients in Study 302).

Mortality

No deaths were reported in either of the two pivotal trials.

Notable Harms

Of the notable harms included in the CADTH review protocol, pruritus was the most frequently occurring. In Study 301, it was reported among 3.0% of patients in the HP/TAZ treatment group and zero patients in the vehicle treatment group. In Study 302, pruritus was reported by 2.9% and 5.5% of patients in the HP/TAZ and vehicle treatment groups, respectively. Skin atrophy and folliculitis were also reported in both studies. In Study 301, skin atrophy and folliculitis were reported in 3.0% and 1.5%, respectively, of patients in the HP/TAZ treatment group, and zero patients in the vehicle treatment group. In Study 302, skin atrophy was reported in 0.7% of patients in the HP/TAZ treatment group and folliculitis was reported in 2.2% of the HP/TAZ group. Neither harm was reported in the vehicle treatment group in Study 302. In addition, events of burning sensation and skin irritation were reported in a small percentage of patients (≤ 1.5%) in both treatment groups of Study 301. Hypersensitivity was reported in one patient in each of the HP/TAZ and vehicle treatment groups of Study 302, as well as one skin irritation AE in the HP/TAZ group and one burning sensation AE in the vehicle treatment group. Severe dryness and HPA axis suppression were also included as notable harms in the CADTH review protocol, but neither harm was reported on in either study.

Table 18: Summary of Harms, up to Week 8 Study Visit (Safety Set)

	Study 301		Study 302	
	HP/TAZ N = 133	Vehicle N = 67	HP/TAZ N = 137	Vehicle N = 73
Patients with ≥ 1 AE				
n (%)	49 (36.8)	13 (19.4)	48 (35.0)	17 (23.3)
Most common events,[a] n (%)				
Contact dermatitis	7 (5.3)	0	13 (9.5)	0
Application site pain	5 (3.8)	0	2 (1.5)	1 (1.4)
Nasopharyngitis	4 (3.0)	2 (3.0)	1 (0.7)	2 (2.7)
Upper respiratory tract infection	4 (3.0)	1 (1.5)	—	—
Pruritus	4 (3.0)	0	4 (2.9)	4 (5.5)
Skin atrophy	4 (3.0)	0	—	—
Folliculitis	2 (1.5)	0	3 (2.2)	0

	Study 301		Study 302	
	HP/TAZ N = 133	Vehicle N = 67	HP/TAZ N = 137	Vehicle N = 73
Otitis media	2 (1.5)	0	—	—
Pneumonia	2 (1.5)	0	—	—
Skin burning sensation	2 (1.5)	1 (1.5)	—	—
Psoriasis	2 (1.5)	0	2 (1.5)	2 (2.7)
Excoriation	2 (1.5)	0	3 (2.2)	0
Skin abrasion	2 (1.5)	0	—	—
Seasonal allergy	2 (1.5)	0	—	—
Peripheral swelling	0	2 (3.0)	—	—
Headache	0	2 (3.0)	—	—
Burning sensation (nervous system)	—	—	4 (2.9)	2 (2.7)
Rash	—	—	3 (2.2)	0
Influenza	—	—	2 (1.5)	0
Sinusitis	—	—	2 (1.5)	0
Pain	—	—	2 (1.5)	0
Aspartate aminotransferase increased	—	—	2 (1.5)	2 (2.7)
Alanine aminotransferase increased	—	—	2 (1.5)	1 (1.4)
Patients with ≥ 1 SAE				
n (%)	3 (2.3)	0	0	0
SAEs by preferred term, n (%)				
Cellulitis staphylococcal	1 (0.8)	0	—	—
Pneumonia, asthma exacerbation[b]	1 (0.8)	0	—	—
Anemia	1 (0.8)	0	—	—
Patients who stopped treatment due to AEs[c]				
n (%)	10 (7.5)	0	7 (5.1)	5 (6.8)
AEs by preferred term, n (%)				
Contact dermatitis	3 (2.3)	0	2 (1.5)	0
Psoriasis	2 (1.5)	0	1 (0.7)	2 (2.7)
Skin burning sensation	2 (1.5)	0	0	1 (1.4)
Hypersensitivity	1 (0.8)	0	1 (0.7)	1 (1.4)
Pruritus	—	—	0	3 (4.1)
Anemia	1 (0.8)	0	—	—
Cellulitis staphylococcal	1 (0.8)	0	—	—
Folliculitis	1 (0.8)	0	—	—
Blister	1 (0.8)	0	—	—
Scab	1 (0.8)	0	—	—
Skin irritation	1 (0.8)	0	—	—
Application site dermatitis	—	—	1 (0.7)	0
Application site pain	—	—	1 (0.7)	1 (1.4)
Influenza	—	—	1 (0.7)	0

	Study 301		Study 302	
	HP/TAZ N = 133	Vehicle N = 67	HP/TAZ N = 137	Vehicle N = 73
Deaths				
n (%)	0	0	0	0
Notable harms				
AEs of interest,[d] n (%)				
Pruritus	4 (3.0)	0	4 (2.9)	4 (5.5)
Thinning of skin (skin atrophy)	4 (3.0)	0	1 (0.7)	0
Folliculitis	2 (1.5)	0	3 (2.2)	0
Burning sensation	2 (1.5)	1 (1.5)	0	1 (1.4)
Skin irritation	1 (0.8)	1 (1.5)	1 (0.7)	0
Hypersensitivity events	0	0	1 (0.7)	1 (1.4)
HPA axis suppression[e]	—	—	—	—
Severe dryness	—	—	—	—

AE = adverse event; HP/TAZ = halobetasol propionate and tazarotene; HPA = hypothalamic pituitary adrenal; SAE = serious adverse event.

[a] Frequency of two or more patients in any treatment group. AEs that were not reported in at least two patients in any treatment group are indicated by an em dash (—).

[b] One patient reported two SAEs: cellulitis staphylococcal (1) and asthma (1).

[c] Includes patients with a treatment-emergent AE leading to permanent withdrawal of study drug and/or early study discontinuation.

[d] The AEs for pruritus and folliculitis in both studies are also reported as some of the most common events. The AEs reported for skin atrophy in Study 301 are also reported as one of the most common events.

[e] Includes secondary glucocorticoid insufficiency and adrenal hypercorticism (Cushing syndrome, hyperglycemia, glycosuria).

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

Local signs and symptoms were assessed as a measure of tolerability and summarized as the proportion of patients with a treatment-emergent grade 3 (severe) local skin reaction. This was defined as follows: itching = intense itching that may interrupt daily activities and/or sleep, dryness = marked roughness, and burning/stinging = hot burning sensation that causes definite discomfort and may interrupt daily activities and/or sleep. In Study 301, the proportion of patients in the HP/TAZ and vehicle treatment groups with a severe treatment-emergent skin reaction was: itching, 17.4% versus 19.4%; dryness, 2.3% versus 10.4%; and burning/stinging, 10.6% versus 14.9%. In Study 302, severe treatment-emergent skin reactions were reported as follows for the HP/TAZ treatment group compared to vehicle: itching, 11.7% versus 21.9%; dryness, 5.1% versus 16.4%; and burning/stinging, 5.8% versus 13.7%. In addition, skin atrophy and folliculitis were reported for 3.3% and 2.5%, respectively, of patients receiving HP/TAZ in Study 301 and 2.5% and 3.3%, respectively, in Study 302, compared to 0% of patients receiving vehicle in both studies.

Critical Appraisal

Internal Validity

Both trials used an acceptable method of randomization and concealment of treatment allocation. An interactive response technology system was used to randomize patients and randomization was not stratified. The two trials were double blind and vehicle controlled, where the HP/TAZ lotion and the vehicle lotion were identically packaged and labelled. Blinding was not identified as an issue in either of the two trials.

At baseline, there were some differences between the treatment groups in terms of demographic characteristics of patients in the two trials, such as a higher proportion of males in the vehicle group of Study 302 (67.6% vs. 61.0%) and a higher proportion of White patients in the vehicle group in both studies (301, 92.5% vs. 88.1%, and 302, 85.1% vs. 80.1%); however, demographic differences were not expected to affect treatment efficacy according to the clinical expert consulted for this review. As for the disease characteristics of patients at baseline, they appeared to be similar between treatment groups in Study 301 overall, with some slight differences in severity of the signs of psoriasis. In Study 302, the patients in the HP/TAZ group appeared to have milder disease in terms of IGA (11.3% had severe disease compared to 14.9% in the vehicle group), and a [redacted]target lesion (the mean [SD] size for HP/TAZ was [redacted]; vehicle was [redacted]). These differences are minor but should be considered when interpreting the efficacy results in both trials due to potential bias in the results in favour of the HP/TAZ groups. In terms of prior medication use, the vehicle treatment groups included a [redacted] of patients that reported prior use of [redacted].

The pivotal trials were designed to compare HP/TAZ lotion to vehicle lotion, administered once daily to the affected area (which was determined by the investigator) for eight weeks, with a maximum weekly usage of 50 g. Concomitant treatments were permitted in the two studies and was similar between treatment groups in the two trials overall. Therefore, it was unlikely to have a differential impact on treatment efficacy; however, patients who had used concomitant therapy that could interfere with the interpretation of the study results were discontinued from the concomitant product rather than withdrawn from study. Specific details about the number of patients who violated the protocol that continued in the two studies was not available and therefore the impact of this issue on the results is uncertain.

Exclusion criteria regarding the use of prior treatment with certain therapies for psoriasis was implemented in the two trials, as noted in the Populations section of this report. The clinical expert consulted on this review noted that the washout period for phototherapy and biologics was too short to be certain that they did not have an impact on treatment effect. In the trials, patients were excluded if they had used phototherapy within four weeks prior to baseline, and if they had used biologics within three months of the baseline visit. The clinical expert suggested that for older therapies such as etanercept, adalimumab, and infliximab, three months is a sufficient washout period; however, a more appropriate washout period would have been eight weeks for phototherapy and four to six months for therapies such as ustekinumab, tildrakizumab, guselkumab, and risankizumab, as per a longer half-life with these therapies. The British Association of Dermatologists guidelines for biologic therapy for psoriasis also notes a washout period of three months or four times the terminal half-life for biologics, whichever is greater.[37] Reported prior use of [redacted] and likely not of concern for the two trials; [redacted]. Types of [redacted] that patients reported having previously used included: [redacted].

The primary outcome in both trials was treatment success at week 8, defined as at least a two-grade improvement from baseline in the IGA score and an IGA score of clear or almost clear (0 or 1). The secondary outcomes used the same definition of treatment success for

week 2, 4, 6, 8, and 12. There is evidence regarding the validity and reliability of the six-point PGA scale (the same scale as the IGA, but the assessor is a physician rather than investigator) in the literature, but no evidence was identified regarding the five-point IGA scale used in the two studies. A MID was not identified in the literature for either version of the IGA scale. Further, the IGA has been shown to be reliable based on test-retest data and internal consistency, but is also a subjective measure that has demonstrated poor inter-rater reliability.[12] The limitations of this scale introduce uncertainty to the interpretation of the primary and secondary outcomes, as well as the magnitude of observed treatment response. The two trials also assessed the improvement in the signs of psoriasis and the percentage BSA affected by psoriasis. A MID was not identified for either outcome and only evidence of reliability was available for the BSA. The DLQI was used to evaluate HRQoL in the two trials. The DLQI is a widely used instrument that captures different aspects of patients' lives that are affected by skin disease and is considered valid and reliable, with an estimated MID in the range of 2.2 to 6.9.[34,38] It has also shown good internal consistency reliability (with Cronbach alpha coefficients ranging from 0.75 to 0.92).[38]

The primary and secondary outcomes were controlled for multiplicity using a gatekeeping sequential procedure. Statistical testing was also conducted for the signs of psoriasis, but this should be interpreted considering the potential for risk of increased type I error. The DLQI and BSA outcomes were outside statistical testing procedures and reported descriptively without between-group comparisons, therefore conclusions that can be drawn from this data are limited. Missing data were imputed for the primary, secondary, and signs of psoriasis (treatment success) outcomes using the MCMC multiple imputation method, which is considered an appropriate approach. Missing data were not imputed for the DLQI and BSA outcomes, where between 12% and 16% of data were missing at week 8. Sensitivity analyses were conducted on the primary outcome using the LOCF method for missing data and a repeated measures analysis on observed data, and both were consistent with the primary analysis. As such, missing data were unlikely to be an issue for the analysis of treatment success by the IGA.

Subgroup analyses by various demographic characteristics that appear to be pre-planned were performed, but treatment randomization was not stratified by any of the subgroups at baseline and only descriptive results were provided. Further, the sample size of patients with severe disease was very small, including less than 20% of the overall population (17.2% and 12.6% of patients in Study 301 and Study 302, respectively, had severe disease). Thus, any conclusions that can be drawn regarding efficacy by baseline disease severity are limited. The CADTH review protocol included two additional subgroups of interest, namely, patients that used HP/TAZ as adjunct therapy compared to monotherapy, and patients with previous experience with treatments for plaque psoriasis (topical or systemic); however, no evidence was identified regarding these subgroups at the time of this review.

External Validity

The two trials include a number of limitations regarding generalizability to the target population identified by the indication and Canadian clinical practice.

All of the study centres were located in the US and the demographic characteristics of patients included in the two trials differ from what would be seen in practice in Canada. More specifically, there is a higher proportion of Hispanic and Black/African American patients, and a lower proportion of Asian patients than what is typically seen in Canadian

clinical practice. There is also a higher proportion of male patients included in the clinical trials.

The disease severity of the patients enrolled is one issue for generalizing the results of the trials to the target population identified in the indication for HP/TAZ. Overall, the information available regarding disease severity of the patients who were included in the two trials appear to describe Canadian patients with mild-to-moderate disease rather than moderate to severe. Definitions of disease severity used in clinical trials available in the Canadian Guidelines for the Management of Plaque Psoriasis, which have suggested that a BSA of 5% is used as an upper limit for mild disease, and a BSA of 10% is used as a lower limit for moderate-to-severe psoriasis.[4] The mean percent BSA of patients at baseline in the two trials was between 5.5% and 6.5% on average with upper and lower limits of 12% and 3%. However, the definitions of disease severity for psoriasis vary across international guidelines. For example, guidelines published by the American Academy of Dermatology and the National Psoriasis Foundation (US) defined disease severity by BSA involvement as less than 3% BSA considered mild, 3% to 10% BSA considered moderate, and greater than 10% BSA considered severe disease.[13,14] The clinical expert consulted by CADTH acknowledged that there is lack of consensus regarding the definition of disease severity, but was of the view that the patient population in Study 301 and Study 302 was milder than what would be expected in a population of Canadian patients with moderate-to-severe psoriasis. CADTH acknowledges that patients were defined as having moderate or severe plaque psoriasis based on a baseline IGA score of at least 3; however, this was measured by the investigator or evaluator and the subjective nature of this scale and poor inter-rater reliability introduce uncertainty to this measure. Further, patients who had been treated with prescription medication and failed to respond to treatment, partially or temporarily, were excluded from the pivotal trials. Based on input from the clinical expert consulted by CADTH for this review, it is unlikely that a patient would present to care with moderate-to-severe psoriasis having not tried and failed to respond to prior treatment.

The intervention and method of administration in the clinical trials was consistent with the recommended dosing for HP/TAZ.[9] The clinical expert consulted for this review also noted that in clinical practice, once a patient had achieved an IGA score of 0 or 1, treatment would be reduced or stopped. The use of certain concomitant medications was permitted during the two trials, which may be aligned with what patients do in clinical practice; however, concomitant use of phototherapy or systemic therapy was not permitted in the trials. Most patients with moderate-to-severe psoriasis would likely be treated with phototherapy or systemic treatment as per the clinical definition of moderate or severe plaque psoriasis which describes disease that cannot be, or would not be expected to be, satisfactorily controlled by routine skin care measures or topical therapy, respectively.[4] To this point, it is unlikely that HP/TAZ would be used as monotherapy in patients with moderate-to-severe disease, which was confirmed by the clinical expert consulted for this review. Further, a more likely use of HP/TAZ in this population would be as an adjunct therapy to systemic treatment; however, evidence of this was not identified. This is a limitation to the generalizability of the clinical trial results for HP/TAZ.

According to feedback from the clinical expert, patients are assessed very informally in clinical practice with a focus on HRQoL and broadly on signs and symptoms of disease. Specific, structured questionnaires and scales are not typically used in clinical practice, but the goal of the assessment is similar, therefore, some of the outcomes used in the trials are relevant to clinical practice, but others such as the signs of psoriasis and percentage BSA affected by psoriasis are less relevant. The primary efficacy outcome was assessed after

receiving treatment with study drug for eight weeks. As per feedback from the clinical expert consulted for this review, all patients issued a first prescription of a superpotent corticosteroid, including HP/TAZ, should be assessed after approximately four weeks for treatment response and safety-related issues, and a decision to continue or change treatment would be made at that time. The clinical expert acknowledged that the availability of a dermatologist for a four-week follow-up visit varies between practices; however, four weeks was still noted as an ideal follow-up time frame. The four-week end-of-treatment follow-up period was noted as being adequate to assess recurrence of disease.

Evidence comparing the use of HP/TAZ to other treatments for plaque psoriasis was limited to the sponsor-submitted NMA as no direct comparisons with active comparators were identified, despite the number of available treatments for this disease area. Further, the lack of direct comparative evidence is a major limitation of these trials and in the evaluation of HP/TAZ in the Canadian context. As such, the comparative effectiveness of HP/TAZ remains uncertain.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

As there was no direct evidence comparing HP/TAZ to other topical therapies for plaque psoriasis, a review of indirect evidence was undertaken. The aim of this section is to provide an overview and critical appraisal of the published and unpublished indirect evidence available for the assessment of the comparative efficacy and harms of HP/TAZ to the available topical pharmacologic therapies in patients with plaque psoriasis.

CADTH conducted a literature search to identify potentially relevant indirect treatment comparisons (ITCs) in patients with plaque psoriasis, in addition to reviewing the sponsor's CADTH Common Drug Review submission. Multiple databases were searched using a combination of MeSH and keywords. Details of the search strategy can be found in Appendix 1. No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Titles, abstracts, and full text articles were screened for inclusion by one reviewer based on the population, intervention, comparator, and outcome criteria outlined in Table 19. No potentially relevant ITCs were identified in the literature search.

One sponsor-submitted ITC was included in this review.[39] This ITC was used to inform the pharmacoeconomic model.

Description of Indirect Comparison(s)

[redacted]

Methods of Sponsor-Submitted NMA

Objectives

[redacted]

Study Selection Methods

[redacted]

Table 19: Study Selection Criteria and Methods for Sponsor-Submitted NMA

	Sponsor-submitted NMA
Population	[redacted]
Intervention	[redacted]
Comparator	[redacted]

	Sponsor-submitted NMA
	[redacted]
Outcome	[redacted]
Study design	[redacted]
Publication characteristics	[redacted]
Exclusion criteria	[redacted]
Databases searched	[redacted]
Selection process	[redacted]
Data extraction process	[redacted]
Quality assessment	[redacted]

NMA = network meta-analysis.

Source: Sponsor-submitted NMA.[39]

ITC Analysis Methods

[redacted]

Table 20: [redacted]

Table 20 contained confidential information and was removed at the request of the sponsor.

Source: Sponsor-submitted NMA.[39]

[redacted]

Table 21: ITC Analysis Methods

	[redacted]	[redacted]
ITC methods	[redacted]	
Priors	[redacted]	[redacted]
Assessment of model fit	[redacted]	[redacted]
Assessment of consistency	[redacted]	[redacted]
Assessment of convergence	[redacted]	[redacted]
Outcomes	[redacted]	[redacted]
Follow-up time points	[redacted]	
Construction of nodes	[redacted]	

Sensitivity analyses		
Subgroup analysis		
Methods for pairwise meta-analysis		

ITC = indirect treatment comparisons; NMA = network meta-analysis.

Source: Sponsor-submitted NMA.[39]

Results of Sponsor-Submitted NMA

Summary of Included Studies

Figure 3:

Figure 3 contained confidential information and was removed at the request of the sponsor.

Source: Sponsor-submitted NMA.[39]

Figure 4:

Figure 4 contained confidential information and was removed at the request of the sponsor.

Source: Sponsor-submitted NMA.[39]

[redacted]

Table 22: Study Characteristics of Publications Included in NMA

Table 23 contained confidential information and was removed at the request of the sponsor.

[redacted]

Source: Reproduced from sponsor-submitted NMA.[39]

Table 23: Patient Characteristics of Publications Included in NMA

Table 24 contained confidential information and was removed at the request of the sponsor.

[redacted]

Source: Reproduced from sponsor-submitted NMA.[39]

Results

[redacted]

Table 24: [redacted]

	Relative treatment effects: RR (95% CrI)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

CrI = credible interval; RR = relative risk.

Source: Sponsor-submitted NMA.[39]

[redacted]

Table 25: [redacted]

	Relative treatment effects: RR (95% CrI)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

CrI = credible interval; RR = relative risk.

Source: Sponsor-submitted NMA.[39]

Critical Appraisal of Sponsor-Submitted NMA

[redacted]

[redacted]

[redacted]

[redacted]

Summary

There are no head-to-head trials comparing HP/TAZ lotion to other topical pharmacological therapies for patients with plaque psoriasis. [redacted]

[redacted]

Other Relevant Evidence

This section includes two additional relevant studies included in the sponsor's submission to CADTH that were considered to address important gaps in the evidence included in the systematic review. Study 303 is a long-term safety study which has been summarized to provide evidence regarding the long-term safety and efficacy of topical HP/TAZ therapy in the treatment of moderate-to-severe plaque psoriasis following once daily, eight-week treatment courses in patients followed up to one year. Study 201 is a phase II RCT designed to provide evidence regarding the safety, tolerability, and efficacy of HP/TAZ lotion applied once daily in comparison with its monads and vehicle in the treatment of moderate-to-severe plaque psoriasis.

Long-Term Safety Study: Study 303

Methods

Study 303 was a 52-week, multi-centre, open-label, single-arm study to assess the long-term safety of HP/TAZ lotion in adult patients with moderate-to-severe plaque psoriasis, defined with an IGA score of 3 or 4. There were a total of 46 study sites which were all located in the US. All patients in the study received HP/TAZ lotion once daily.

Populations

The inclusion and exclusion criteria were similar to Study 301 and Study 302. The only exception pertained to the inclusion criteria, where patients did not need to present with a target lesion which measured between 16 cm^2 to 100 cm^2 for evaluation for changes in psoriasis signs (erythema, plaque elevation, and scaling).

A summary of the baseline demographics and disease characteristics are summarized in Table 26. Most participants were White (86%), male (65.6%), and the mean age was 52 years. With respect to baseline disease characteristics, 86.5% of participants were classified with moderate psoriasis with an IGA score of 3, and the mean percent BSA affected by psoriasis of all participants was 5.6% (SD = 2.65%). The baseline demographics and disease characteristics were similar to the pivotal trials, and Study 201.

Table 26: Summary of Baseline Characteristics (Safety Set)

Characteristic	HP/TAZ N = 550
Demographic characteristics	
Age, mean (SD)	51.9 (14.06)
Male, n (%)	361 (65.6%)
Ethnicity	
Hispanic or Latino	141 (25.6%)

Characteristic	HP/TAZ N = 550
Not Hispanic or Latino	409 (74.4%)
Race	
White	473 (86%)
Black or African American	46 (8.4%)
Asian	15 (2.7%)
Other	4 (0.7%)
Baseline disease characteristics	
IGA score, n (%)	
3 = moderate	476 (86.5%)
4 = severe	74 (13.5%)
Percentage BSA affected by psoriasis	
Mean (SD)	5.6 (2.65)
Median (range)	5 (3 to 12)

BSA = body surface area; HP/TAZ = halobetasol propionate and tazarotene; IGA = Investigator's Global Assessment; SD = standard deviation.

Source: Clinical Study Report for Study 303.[40]

Interventions

All study patients received HP/TAZ applied to affected areas once daily for eight weeks, and then as needed in four-week periods up to one year. After the initial eight-week application period, patients were evaluated for treatment success, defined as an IGA score of 0 or 1. Patients who were considered a treatment failure at week 8, continued applying HP/TAZ therapy for an additional four-week period. Patients were discontinued from the study if they had not achieved a 1-point improvement in IGA from baseline by week 12. Patients were evaluated every four weeks for one year.

Patients who achieved treatment success at week 8, were re-evaluated four weeks later, for disease worsening. If disease worsening occurred, patients were instructed to apply once daily HP/TAZ therapy for another four-week period, after which they were re-evaluated for treatment success. Patients who achieved treatment success at any visit could undergo periods of non-treatment until they no longer were a treatment success, in which case they would undergo a four-week treatment again.

Patients were discontinued from the study if they had remained on continuous treatment for 24 weeks and did not achieve an IGA score equating to clear or almost clear.

Outcomes

Study 303 was designed to evaluate safety outcomes related to topical HP/TAZ once daily therapy. Of interest to the current review, were the occurrence of new and ongoing AEs, the percentage of patients who experienced a local skin reaction or hypersensitivity event, and harms related to HPA axis suppression.

Study 303 was not designed to assess the efficacy of HP/TAZ. IGA and percentage BSA were evaluated to determine treatment success and need for re-treatment. The following efficacy outcomes were summarized with descriptive statistics: treatment success based on IGA at week 8, time to first treatment success, and the percentage BSA affected by

psoriasis. In the efficacy tabulations, a subject was considered a treatment success if their IGA score equated to clear or almost clear.

Statistical Analysis

Descriptive statistics were performed to provide an overview of the efficacy and safety results. All summaries were presented for the safety analysis set, except for the patient disposition. The safety analysis set included all patients which received one dose of HP/TAZ lotion and had one post-baseline safety evaluation. No imputations were made for missing data.

Patient Disposition

The patient disposition for Study 303 has been summarized in Table 27. Of the 555 patients included in the study, 24.5% of patients completed the 52-week study, including the end of study visit. The discontinuation rate was 9.4%, 29.5%, and 75.1%, at three, six, and 12 months, respectively. Five patients were excluded from the safety population due to not presenting for a post-baseline safety evaluation. The most common reason for discontinuing the study was lack of efficacy at six months (20.9%) followed by patient request (15.7%).

Table 27: Patient Disposition (ITT Set)

	HP/TAZ
Screened	Not reported
Total, N	555
Completed study, n (%)	
Completed 3 months on study	503 (90.6%)
Completed 6 months on study	391 (70.5%)
Completed 12 months on study	138 (24.9%)
Discontinued study, n (%)	
Patient request	87 (15.7%)
Adverse event	33 (5.9%)
Protocol violation	6 (1.1%)
Worsening condition	16 (2.9%)
Lack of efficacy at 3 months	26 (4.7%)
Lack of efficacy at 6 months	116 (20.9%)
Sponsor request	39 (7.0%)
Other	46 (8.3%)
ITT, N	555
Safety, N	550

HP = halobetasol propionate; ITT = intention to treat; TAZ = tazarotene.

Source: Clinical Study Report for Study 303.[40]

Exposure to Study Treatments

The duration of exposure to study drug is summarized in Table 28. The mean amount of study drug applied was [redacted], with a mean duration [redacted], and a mean application of [redacted]. Treatment compliance was not assessed.

Table 28: Exposure to Study Drug (Safety Set)

	HP/TAZ N = 550
Total amount of study drug used (g)	
n	[redacted]
Mean (SD)	[redacted]
Median (range)	256.5 (6.2 to 1,806.4)
Total number of days exposed	
n	[redacted]
Mean (SD)	[redacted]
Median (range)	172 (3 to 380)
Total number of applications	
n	[redacted]
Mean (SD)	[redacted]
Median (range)	164 (3 to 371)

HP = halobetasol propionate; SD = standard deviation; TAZ = tazarotene.

Source: Clinical Study Report for Study 303.[40]

Harms

Local Skin Reactions

A summary of the treatment-emergent local skin reactions of at least grade 3 severity following HP/TAZ application is provided in Table 29. Throughout the entire 12-month study period, the incidence of local skin reactions was 22.2% for itching, 6.9% for dryness, and 9.8% for burning/stinging.

Table 29: Subject Proportion of Local Skin Reactions Grade 3 or Greater (Safety Set)

	HP/TAZ N = 550
Itching, n (%)	122 (22.2%)
Dryness, n (%)	38 (6.9%)
Burning/stinging, n (%)	54 (9.8%)

HP/TAZ = halobetasol propionate and tazarotene.

Source: Clinical Study Report for Study 303.[40]

Harms

A summary of the harms reported for Study 303 has been provided in Table 30. Overall, more than half (57.1%) of subjects experienced a treatment-emergent AE after HP/TAZ administration. The most common AEs reported were general disorders and administration site conditions (30.7%), and infections and infestations (23.5%); both these categories of AEs decreased in prevalence throughout the latter portions of the study. Eighteen patients experienced a SAE, and no SAE was observed in more than one patient.

WDAEs, deaths, and notable harms are also reported in Table 30. WDAEs occurred in 7.5% of patients throughout the entire study period, with the highest proportion (5.7%) occurring in the first three months. Within this quarter, application site reactions made up 90% of the reasons for withdrawals. There were no deaths reported in Study 303. Regarding the notable harms, there were two patients which experienced folliculitis, two patients which experienced hyperglycemia, 14 patients which experienced skin burning or stinging, and four patients which experienced skin atrophy.

Table 30: Summary of Harms, up to Week 52 Study Visit (Safety Set)

	0 to 12 weeks N = 527	> 12 to 24 weeks N = 392	> 24 to 36 weeks N = 239	> 36 weeks to EOS N = 219	Total N = 550
Patients with ≥ 1 AE					
n (%)	223 (42.3%)	130 (33.2%)	61 (25.5%)	43 (19.6%)	314 (57.1%)
AEs by preferred term,[a] n (%)					
Application site dermatitis	39 (7.4%)	20 (5.1%)	7 (2.9%)	3 (1.4%)	59 (10.7%)
Application site pruritus	22 (4.2%)	6 (1.5%)	4 (1.7%)	2 (0.9%)	33 (6.0%)
Application site pain	25 (4.7%)	2 (0.5%)	1 (0.4%)	1 (0.5%)	29 (5.3%)
Application site irritation	11 (2.1%)	4 (1.0%)	3 (1.3%)	1 (0.5%)	14 (2.5%)
[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]
Patients with ≥ 1 SAE					
n (%)	6 (1.1%)	5 (1.3%)	5 (2.1%)	2 (0.9%)	18 (3.3%)
Patients who stopped treatment due to AEs					
n (%)	30 (5.7%)	9 (2.3%)	2 (0.8%)	0	41 (7.5%)
Deaths					
n (%)	0	0	0	0	0
Notable harms					
AE of interest, n (%)					
Folliculitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HPA axis suppression[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	0 to 12 weeks N = 527	> 12 to 24 weeks N = 392	> 24 to 36 weeks N = 239	> 36 weeks to EOS N = 219	Total N = 550
Skin burning or stinging	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin itching (pruritis)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe skin dryness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thinning of skin (skin atrophy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; EOS = end of study; HPA = hypothalamic pituitary adrenal; SAE = serious adverse event.

[a] Frequency of 3% or greater in any study period.

[b] Includes secondary glucocorticoid insufficiency and adrenal hypercorticism (Cushing's, hyperglycemia, glycosuria).

Source: Clinical Study Report for Study 303.[40]

Efficacy

IGA and Treatment Success Over Time

The IGA score and proportion of subjects which achieved treatment success by visit throughout Study 303 is summarized in Table 31. By week 8, [redacted] of patients had achieved an IGA score equating to clear or almost clear. Moreover, the proportion of patients which have achieved treatment success was [redacted] by week 24 and week 52, respectively.

Table 31: Summary of IGA and Treatment Success by Visit (Safety Set)

HP/TAZ	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0 = Clear	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 = Almost clear	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 = Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 = Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 = Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment success[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HP/TAZ	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0 = Clear	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 = Almost clear	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 = Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 = Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 = Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment success[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HP/TAZ = halobetasol propionate and tazarotene; IGA = Investigator's Global Assessment.

[a] *Treatment success* was defined as an IGA score equating to clear or almost clear.

Source: Clinical Study Report for Study 303.[40]

Time to First Treatment Success

The duration in which it took patients to achieve treatment success is summarized in Table 32. At week 8, [redacted] of patients achieved treatment success. Of note, [redacted] to achieve treatment success.

Table 32: Summary of Treatment Success and Number of Non-Medicating Weeks (Safety Set)

	HP/TAZ N = 550
Treatment success[a] at week 8, n (%)	[redacted]
Time to first treatment success,[a] n	[redacted]
2 weeks	[redacted]
4 weeks	[redacted]
8 weeks	[redacted]
12 weeks	[redacted]
16 weeks	[redacted]
20 weeks	[redacted]
24 weeks	[redacted]
28 weeks	[redacted]
32 weeks	[redacted]

HP = halobetasol propionate; IGA = Investigator's Global Assessment; TAZ = tazarotene.

[a] *Treatment success* was defined as an IGA score equating to clear or almost clear.

Source: Clinical Study Report for Study 303.[40]

Body Surface Area

The percentage BSA affected by psoriasis throughout the study is summarized in Table 33. At baseline, patients presented with a mean BSA of [redacted] by week 28, [redacted].

Table 33: Summary of Percentage BSA Affected by Psoriasis

HP/TAZ	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HP/TAZ	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSA = body surface area; HP/TAZ = halobetasol propionate and tazarotene; SD = standard deviation.

Source: Clinical Study Report for Study 303.[40]

Critical Appraisal

Internal Validity

The main limitations of the long-term safety study include the open-label and single-arm study design. The absence of an active comparator or vehicle group limits the certainty of conclusions on the safety of HP/TAZ topical therapy. Related to the open-label study

design, investigators and patients were aware of the study drug administered, which may bias the reporting of subjective outcomes such as safety.

External Validity

Related to the baseline characteristics, most participants were male (65.6%) with a high proportion of Hispanic or Latino participants (25.6%). The clinical expert noted that this is not typical of Canadian clinical practice where it is expected that 50% of patients are male with a much lower Hispanic or Latino population. The clinical expert did not expect that that would change drug efficacy.

The generalizability of this study is compromised by a lack of study centres within Canada, and the demographics of the population included in this study may not reflect the diversity of patients within Canada. Similar to the pivotal trials the severity of disease, the percentage BSA affected by psoriasis may be more representative of a mild-to-moderate plaque psoriasis population as per the Canadian Guidelines for the Management of Plaque Psoriasis.[4] Further, the clinical expert consulted by CADTH for this review viewed the patient population in Study 301 and Study 302 as milder than what would be expected in a population of Canadian patients with moderate-to-severe psoriasis. These guidelines state that moderate plaque psoriasis is defined with a lower limit of 10% BSA affected by psoriasis.[4] The demographics and disease severity of patients included in this trial limits the generalizability of these results to a Canadian population of patients with moderate-to-severe plaque psoriasis.

Summary

Study 303 demonstrated safety and tolerability of HP/TAZ intermittent treatment up to one year. Briefly, more than half (57.1%) of patients experienced an AE, and 18 (3.3%) patients experienced a SAE. Of the patients who stopped treatment due to AEs (7.5%), most did so due to application site reactions within the first three months. Overall, intermittent treatment with HP/TAZ once daily therapy seemed to be well-tolerated up to 52 weeks. There were no alarming safety signals observed. Descriptive statistics summarized for the IGA informed that most patients achieved their first treatment success at week 4, or week 8.

Other Relevant Studies: Phase II RCT

Methods

Study 201 was a phase II, multi-centre, double-blind, randomized, parallel-group, vehicle-controlled RCT designed to assess the safety, tolerability, and efficacy of HP/TAZ lotion applied once daily in comparison with its monads and vehicle in adult patients with moderate-to-severe plaque psoriasis.

Populations

To be eligible for Study 201, patients needed to be at least 18 years of age with a diagnosis of moderate-to-severe plaque psoriasis, defined with an IGA score of 3 or 4. Inclusion and exclusion criteria were identical to the pivotal trials.

The baseline demographics and disease characteristics are summarized in Table 34. The mean age ranged from 48.2 to 55.7 years across the treatment groups. The proportion of male participants ranged from 59.3% to 67.8%, and approximately 90% of participants were White. Related to baseline disease characteristics, the proportion of patients who had an IGA score of 3 ranged from 88.9% to 96.6%, and patients had a mean BSA affected by

psoriasis which ranged from 5.1% to 6%. Related to the psoriasis signs, there were imbalances in the proportion of patients across the treatment groups within the plaque elevation and scaling categories, however proportions of patients were well distributed within the erythema sub-category (Table 34).

Table 34: Summary of Baseline Characteristics (ITT Set)

Characteristic	HP/TAZ N = 59	Monad HP N = 63	Monad TAZ N = 59	Vehicle N = 31
Demographic characteristics				
Age, mean (SD)	48.2 (13.7)	54.2 (11.52)	55.7 (13.1)	52.4 (16.11)
Sex (% male), n (%)	35 (59.3%)	39 (61.9%)	40 (67.8%)	19 (61.3%)
Ethnicity				
Hispanic or Latino	14 (23.7%)	11 (17.5%)	11 (18.6%)	6 (19.4%)
Not Hispanic or Latino	45 (76.3%)	52 (82.5%)	48 (81.4%)	25 (80.6%)
Race				
White	56 (94.9%)	55 (87.3%)	55 (93.2%)	27 (87.1%)
Black or African American	3 (5.1%)	4 (6.3%)	2 (3.4%)	4 (12.9%)
Asian	0	3 (4.8%)	2 (3.4%)	0
Other	0	1 (1.6%)	0	0
Baseline disease characteristics				
IGA score, n (%)				
3 = moderate	57 (96.6%)	56 (88.9%)	54 (91.5%)	30 (96.8%)
4 = severe	2 (3.4%)	7 (11.1%)	5 (8.5%)	1 (3.2%)
Percentage BSA affected by psoriasis				
Mean (SD)	5.2 (2.32)	5.3 (2.58)	6.0 (2.95)	5.1 (1.97)
Median (range)	5 (3 to 12)	5 (3 to 12)	5 (3 to 12)	5 (3 to 10)
Size of target lesion (cm^2)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	28 (16 to 100)	28 (16 to 100)	32 (16 to 100)	25 (16 to 98)
Signs				
Erythema (target lesion)				
2 = mild	4 (6.8%)	5 (7.9%)	5 (8.5%)	2 (6.5%)
3 = moderate	53 (89.8%)	53 (84.1%)	48 (81.4%)	27 (87.1%)
4 = severe	2 (3.4%)	5 (7.9%)	6 (10.2%)	2 (6.5%)
Plaque elevation (target lesion)				
2 = mild	9 (15.3%)	11 (17.5%)	6 (10.2%)	4 (12.9%)
3 = moderate	47 (79.7%)	46 (73.0%)	50 (84.7%)	22 (71.0%)
4 = severe	3 (5.1%)	6 (9.5%)	3 (5.1%)	5 (16.1%)
Scaling (target lesion)				
2 = mild	10 (16.9%)	10 (15.9%)	16 (27.1%)	5 (16.1%)
3 = moderate	45 (76.3%)	46 (73.0%)	37 (62.7%)	21 (67.7%)
4 = severe	4 (6.8%)	7 (11.1%)	6 (10.2%)	5 (16.1%)

BSA = body surface area; HP/TAZ = halobetasol propionate and tazarotene; IGA = Investigator's Global Assessment; ITT = intention to treat; SD = standard deviation.

Source: Clinical Study Reports for Study 201.[41]

Interventions

Patients were randomized 2:2:2:1 to receive HP/TAZ lotion, HP monad (0.01%) lotion, TAZ monad (0.045%) lotion, or vehicle lotion, respectively. The assigned study drug was applied topically to the affected area, once daily for eight weeks. Patients were followed up four weeks post-treatment cessation, at week 12.

Outcomes

None of the efficacy end points were designated as primary. Efficacy analysis included: the percentage of patients with treatment success defined as at least a two-grade improvement from baseline in the IGA score and an IGA score equating to clear or almost clear measured at weeks 2, 4, 6, 8, and week 12; the percentage of patients with treatment success or failure at all time points; the percentage of patients with a two-grade improvement from baseline in the IGA score at all time points; and the proportion of patients with a two-grade improvement from baseline in the score for each of the signs of psoriasis (erythema, plaque elevation, and scaling), and changes in disease severity from baseline at each time point.

Statistical Analysis

The efficacy analyses were performed using the ITT population which included all patients who were randomized and dispensed HP/TAZ lotion. Missing efficacy data up to week 8 was imputed with the LOCF method; no imputations were made for missing week 12 efficacy data and for missing safety data. The sample size for this study was based on clinical considerations only as no formal sample size calculation was performed. Treatment effect size for the difference between HP/TAZ and HP monad, TAZ monad, or vehicle was also calculated to determine sample size for the phase III pivotal trials.

Formal statistical tests were performed on the data pertaining to the study objectives outlined above. A Cochran-Mantel-Haenszel test was performed, comparing HP/TAZ lotion to vehicle and to each monad. For patients to be included in the statistical analysis of the psoriasis signs of the selected target lesion, the lesion had to have a baseline grade of 2. No adjustments for multiplicity were performed.

Data pertaining to safety were presented with the safety analysis set. This population included patients which were randomized, received at least one dose of HP/TAZ lotion, and had at least one post-baseline safety assessment.

Patient Disposition

The patient disposition for Study 201 has been summarized in Table 35. The proportion of patients who discontinued from the study was higher in the monad TAZ group (20.3%), and lower in the monad HP group (1.6%) when compared to the other treatment groups. Within the monad TAZ group, the most common reasons for study discontinuation were AEs (25%) and patient request (25%). The other treatment groups were well distributed in terms of proportion of patients which were discontinued from the study.

Table 35: Patient Disposition (All Randomized Patients)

	HP/TAZ	Monad HP	Monad TAZ	Vehicle
Screened, N	Not reported			
Randomized, n (%)	59	63	59	31
Discontinued from study, n (%)	4 (6.8%)	1 (1.6%)	12 (20.3%)	2 (6.5%)
Reason for discontinuation, n (%)				
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Protocol violation	[redacted]	[redacted]	[redacted]	[redacted]
Patient request	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]
Worsening condition	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
ITT, n	59	63	59	31
PP, n	55	58	51	28
Safety, n	59	62	58	31

HP/TAZ = halobetasol propionate and tazarotene; ITT = intention to treat; PP = per protocol.

Source: Clinical Study Reports for Study 201.[41]

Exposure to Study Treatments

The duration of exposure to study drug was summarized in Table 36. [redacted]

The amount of study drug used and the number of applications [redacted]

Table 36: Exposure to Study Drug (Safety Set)

	HP/TAZ N = 59	Monad HP N = 62	Monad TAZ N = 58	Vehicle N = 31
Amount of study drug used (g)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Number of applications				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]

HP/TAZ = halobetasol propionate and tazarotene; SD = standard deviation.

Source: Clinical Study Reports for Study 201.[41]

Efficacy

Treatment Success in IGA

The treatment success in IGA is summarized in Table 37. At week 8, 52.5% of patients in the HP/TAZ group achieved treatment success based on the IGA compared with 33.3% of patients in the monad HP group, 18.6 % of patients in the monad TAZ group, and 9.7% of patients in the vehicle group.

Table 37: Treatment Success in IGA (ITT Set)

	HP/TAZ N = 59	Monad HP N = 63	Monad TAZ N = 59	Vehicle N = 31
Treatment success at week 8				
Treatment success[a] (% of patients)	31 (52.5%)	21 (33.3%)	11 (18.6%)	3 (9.7%)
Treatment failure (% of patients)	28 (47.5%)	42 (66.7%)	48 (81.4%)	28 (90.3%)
P value[b]		0.033	< 0.001	< 0.001
Treatment success[a] at week 12				
Treatment success (% of patients)	21 (38.2%)	13 (21.0%)	6 (12.8%)	2 (6.9%)
Treatment failure (% of patients)	34 (61.8%)	49 (79%)	41 (87.2%)	27 (93.1%)
P value[b]		0.042	0.004	0.002
Treatment success[a] at week 6				
Treatment success (% of patients)	19 (32.2%)	16 (25.4%)	9 (15.3%)	1 (3.2%)
Treatment failure (% of patients)	40 (67.8%)	47 (74.6%)	50 (84.7%)	30 (96.8%)
P value[b]		[redacted]	[redacted]	[redacted]
Treatment success[a] at week 4				
Treatment success (% of patients)	15 (25.4%)	11 (7.5%)	1 (1.7%)	2 (6.5%)
Treatment failure (% of patients)	44 (74.6%)	52 (82.5%)	58 (98.3%)	29 (93.5%)
P value[b]		[redacted]	[redacted]	[redacted]
Treatment success[a] at week 2				
Treatment success (% of patients)	7 (11.9%)	3 (4.8%)	1 (1.7%)	0
Treatment failure (% of patients)	52 (88.1%)	60 (95.2%)	58 (98.3%)	31 (100%)
P value[b]		[redacted]	0.029	0.047

HP/TAZ = halobetasol propionate and tazarotene; IGA = Investigator's Global Assessment; ITT = intention to treat.

[a] *Success* was defined as at least a two-grade improvement from baseline in the IGA score and an IGA score equating to clear or almost clear.

[b] P value from a Cochran-Mantel-Haenszel test. Pairwise tests were conducted comparing HP/TAZ to vehicle and HP/TAZ to each monad.

Source: Clinical Study Reports for Study 201.[41]

Treatment Success for Psoriasis Signs (Erythema, Plaque Elevation, and Scaling)

A summary of the proportion of patients who achieved at least a two-grade improvement from baseline for the signs of psoriasis, erythema, plaque elevation, and scaling is summarized in Table 38, Table 39, and Table 40, respectively.

For erythema, at week 8, 54.2% of patients in the HP/TAZ group achieved treatment success based on the psoriasis signs scale compared with [redacted] of patients in the monad HP

group, [redacted] of patients in the monad TAZ group, and [redacted] of patients in the vehicle group (Table 38).

For plaque elevation, at week 8, 67.8% of patients in the HP/TAZ group achieved treatment success based on the psoriasis signs scale compared with [redacted] of patients in the monad HP group, [redacted] of patients in the monad TAZ group, and [redacted] of patients in the vehicle group (Table 39).

For scaling, at week 8, 64.4% of patients in the HP/TAZ group achieved treatment success based on the psoriasis signs scale compared with [redacted] of patients in the monad HP group, [redacted] of patients in the monad TAZ group, and [redacted] of patients in the vehicle group (Table 40).

Table 38: Treatment Success for Erythema Psoriasis Sign at the Target Lesion (ITT Set)

	HP/TAZ N = 59	Monad HP N = 63	Monad TAZ N = 59	Vehicle N = 31
Week 8				
Success[a] (% of patients)	32 (54.2%)	[redacted]	[redacted]	[redacted]
Failure (% of patients)	27 (45.8%)	[redacted]	[redacted]	[redacted]
P value[b]		[redacted]	[redacted]	[redacted]
Week 12				
Success[a] (% of patients)	27 (49.1%)	24 (38.7%)	14 (29.8%)	4 (13.8%)
Failure (% of patients)	28 (50.9%)	38 (61.3%)	33 (70.2%)	25 (86.2%)
P value[b]		0.26	0.049	0.002
Week 6				
Success[a] (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
Failure (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]		[redacted]	[redacted]	[redacted]
Week 4				
Success[a] (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
Failure (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]		[redacted]	[redacted]	[redacted]
Week 2				
Success[a] (% of patients)	13 (22%)	10 (15.9%)	2 (3.4%)	2 (6.5%)
Failure (% of patients)	46 (78%)	53 (84.1%)	57 (96.6%)	29 (93.5%)
P value[b]		0.387	0.002	0.061

HP/TAZ = halobetasol propionate and tazarotene; ITT = intention to treat.

[a] *Success* was defined as at least a two-grade improvement from baseline. Patients with at least a baseline grade of 2 in the sign qualified for summaries.

[b] P value from a Cochran-Mantel-Haenszel test. Pairwise tests were conducted comparing HP/TAZ to vehicle and HP/TAZ to each monad.

Source: Clinical Study Report for Study 201.[41]

Table 39: Treatment Success for Plaque Elevation Psoriasis Sign at the Target Lesion (ITT Set)

	HP/TAZ N = 59	Monad HP N = 63	Monad TAZ N = 59	Vehicle N = 31
Week 8				
Success[a] (% of patients)	40 (67.8%)	[redacted]	[redacted]	[redacted]
Failure (% of patients)	19 (32.2%)	[redacted]	[redacted]	[redacted]
P value[b]		[redacted]	[redacted]	[redacted]
Week 12				
Success[a] (% of patients)	30 (54.5%)	30 (48.4%)	15 (31.9%)	6 (20.7%)
Failure (% of patients)	25 (45.5%)	32 (51.6%)	32 (68.1%)	23 (79.3%)
P value[b]		0.508	0.022	0.003
Week 6				
Success[a] (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
Failure (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]		[redacted]	[redacted]	[redacted]
Week 4				
Success[a] (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
Failure (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]		[redacted]	[redacted]	[redacted]
Week 2				
Success[a] (% of patients)	27 (45.8%)	12 (19%)	8 (13.6%)	3 (9.7%)
Failure (% of patients)	32 (54.2%)	51 (81%)	51 (86.4%)	28 (90.3%)
P value[b]		0.002	< 0.001	0.001

HP/TAZ = halobetasol propionate and tazarotene; ITT = intention to treat.

[a] *Success* was defined as at least a two-grade improvement from baseline. Patients with at least a baseline grade of 2 in the sign qualified for summaries.

[b] P value from a Cochran-Mantel-Haenszel test. Pairwise tests were conducted comparing HP/TAZ to vehicle and HP/TAZ to each monad.

Source: Clinical Study Report for Study 201.[41]

Table 40: Treatment Success for Scaling Psoriasis Sign at the Target Lesion (ITT Set)

	HP/TAZ N = 59	Monad HP N = 63	Monad TAZ N = 59	Vehicle N = 31
Week 8				
Success[a] (% of patients)	38 (64.4%)	[redacted]	[redacted]	[redacted]
Failure (% of patients)	21 (35.6%)	[redacted]	[redacted]	[redacted]
P value[b]		[redacted]	[redacted]	[redacted]
Week 12				
Success[a] (% of patients)	30 (54.5%)	30 (48.4%)	11 (23.4%)	6 (20.7%)
Failure (% of patients)	25 (45.5%)	32 (51.6%)	36 (76.6%)	23 (79.3%)
P value[b]		0.508	0.001	0.003
Week 6				
Success[a] (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
Failure (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]		[redacted]	[redacted]	[redacted]

	HP/TAZ N = 59	Monad HP N = 63	Monad TAZ N = 59	Vehicle N = 31
Week 4				
Success[a] (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
Failure (% of patients)	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]		[redacted]	[redacted]	[redacted]
Week 2				
Success[a] (% of patients)	24 (40.7%)	14 (22.2%)	7 (11.9%)	2 (6.5%)
Failure (% of patients)	35 (59.3%)	49 (77.8%)	52 (88.1%)	29 (93.5%)
P value[b]		0.028	< 0.001	0.001

HP/TAZ = halobetasol propionate and tazarotene; ITT = intention to treat.

[a] *Success* was defined as at least a two-grade improvement from baseline. Patients with at least a baseline grade of 2 in the sign qualified for summaries.

[b] P value from a Cochran-Mantel-Haenszel test. Pairwise tests were conducted comparing HP/TAZ to vehicle and HP/TAZ to each monad.

Source: Clinical Study Report for Study 201.[41]

Harms

A summary of the harms reported for Study 201 has been provided in Table 41. The most common AEs were reported in the HP/TAZ group (33.9%) and the monad TAZ group (46.6%). The most common AEs were application site reactions which also most commonly occurred in the HP/TAZ and monad TAZ groups. Five patients reported a serious AE; no particular SAE occurred in more than one patient.

WDAEs, deaths, and notable harms are also reported in Table 41. A lower percentage of patients discontinued the study drug and/or withdrew from the study prematurely due to AEs in the HP/TAZ group (3.4%), monad HP (0%), and vehicle (3.2%) groups compared with the monad TAZ group (12.1%). Non-serious treatment-emergent AEs that led to premature discontinuation in the HP/TAZ group including application site reactions such as erythema, pruritus, and cellulitis were reported, and in the monad TAZ group application site reactions such as pruritus, discoloration, swelling, erythema, pain, dermatitis, and an increase in BSA of psoriasis was reported. In addition, one death occurred in the vehicle group, due to severe congestive heart failure. Regarding the notable harms, two patients in the HP/TAZ groups experienced folliculitis and one patient in the HP/TAZ and monad HP each experienced hyperglycemia. Only patients in the HP/TAZ and monad TAZ groups experienced skin reactions such as burning or stinging (1.7% and 1.7%), pruritus (3.4% and 6.9%), and atrophy (1.7% and 0%), respectively.

Table 41: Summary of Harms (Safety Set)

	HP/TAZ N = 59	Monad HP N = 62	Monad TAZ N = 58	Vehicle N = 31
Patients with ≥ 1 AE				
n (%)	20 (33.9%)	13 (21%)	27 (46.6%)	7 (22.6%)
Most common events,[a] n (%)				
Application site dermatitis	0	0	2 (3.4%)	0
Application site erythema	1 (1.7%)	0	3 (5.2%)	0
Application site pain	2 (3.4%)	0	5 (8.6%)	1 (3.2%)
Application site pruritus	2 (3.4%)	0	4 (6.9%)	0

	HP/TAZ N = 59	Monad HP N = 62	Monad TAZ N = 58	Vehicle N = 31
Application site folliculitis	2 (3.4%)	0	0	0
Muscle strain	0	2 (3.2%)	0	0
Arthralgia	0	2 (3.2%)	0	0
Musculoskeletal pain	0	1 (1.6%)	2 (3.4%)	0
Headache	3 (5.1%)	0	1 (1.7%)	1 (3.2%)
Syncope	2 (3.4%)	0	0	0
Dermatitis contact	0	0	2 (3.4%)	0
Psoriasis	2 (3.4%)	0	1 (1.7%)	0
Sinusitis	1 (1.7%)	0	1 (1.7%)	0
Hyperglycemia	1 (1.7%)	1 (1.6%)	0	0
Patients with ≥ 1 SAE				
n (%)	0	1 (1.6%)	1 (1.7%)	2 (6.5%)
SAEs by preferred term, n (%)				
Acute myocardial infarction	0	1 (1.6%)	0	0
Cardiac failure congestive	0	0	0	1 (3.2%)
Coronary artery disease	0	1 (1.6%)	0	0
Hernia obstructive	0	0	0	1 (3.2%)
Infection	0	0	0	1 (3.2%)
Patients who stopped treatment due to AEs[b]				
n (%)	2 (3.4%)	0	7 (12.1%)	1 (3.2%)
Deaths				
n (%)	0	0	0	1 (3.2%)
Notable harms				
AEs of interest, n (%)				
Folliculitis	2 (3.4%)	0	0	0
HPA axis suppression (secondary glucocorticoid insufficiency, adrenal hypercorticism [Cushing syndrome, hyperglycemia, glycosuria])	1 (1.7%)	1 (1.6%)	0	0
Hypersensitivity events	0	0	0	0
Skin burning or stinging	1 (1.7%)	0	1 (1.7%)	0
Skin itching (pruritis)	2 (3.4%)	0	4 (6.9%)	0
Severe skin dryness	0	0	0	0
Thinning of skin (skin atrophy)	1 (1.7%)	0	0	0

AE = adverse event; HPA = hypothalamic pituitary adrenal; HP/TAZ = halobetasol propionate and tazarotene; SAE = serious adverse event.

[a] Frequency of more than one patient in any active treatment group.

[b] Includes patients with a treatment-emergent AE leading to permanent withdrawal of study drug and/or early study discontinuation.

Source: Clinical Study Report for Study 201.[41]

Critical Appraisal

Internal Validity

Study 201 used acceptable methods of randomization and concealment of treatment allocation, and thus blinding was not identified as an issue within this study. Baseline demographics and disease characteristics were mostly balanced, with a slightly higher proportion of males in the monad TAZ group, and a slightly higher proportion of patients with severe disease in the monad HP group. Moreover, there was a disproportionately higher percentage of patients which discontinued from the study in the monad TAZ group. Further, this study may also be limited by inclusion of participants who only had a three-month washout period for immunomodulatory therapy (biologics), which may be too short of a washout period for some of the biologics. Last, the efficacy results presented within Study 201 may be limited by a lack of adjustment for multiplicity, increasing the risk for type I error of the psoriasis signs scale outcomes and the treatment success in IGA.

External Validity

The generalizability of this study to a Canadian patient population is questionable given that the study did not include any patients in Canada and the demographics of the population included in this study may not reflect the diversity of patients within Canada. Further, the generalizability is compromised by the inclusion of participants that may be representative of patients with mild-to-moderate rather than moderate-to-severe plaque psoriasis population. According to the Canadian Guidelines for the Management of Plaque Psoriasis, moderate-to-severe plaque psoriasis is defined with a lower limit of 10% BSA affected by psoriasis.[4] Within Study 201, at baseline, patients presented with a mean range of 5.1% to 6% BSA affected by psoriasis, which appears to be a milder form of the disease than is to be expected in patients presenting with moderate-to-severe psoriasis in clinical practice in Canada. CADTH acknowledges that the definitions for disease severity vary across international guidelines, for example, the American Academy of Dermatology and the National Psoriasis Foundation define disease severity by BSA involvement with less than 3% BSA considered mild, 3% to 10% BSA considered moderate, and greater than 10% BSA considered severe disease.[13,14] However, the clinical expert consulted by CADTH for this review viewed the patient population in Study 201 as milder than what would be expected in a population of Canadian patients with moderate-to-severe psoriasis.

Summary

Although the results of Study 201 suggest that a higher proportion of patients in the HP/TAZ group achieved treatment success at week 8 based on the IGA, and that a higher proportion of patients in the HP/TAZ group achieved treatment success when compared to the monad TAZ and vehicle groups in each of the psoriasis signs, these results must be considered with an increased risk of type I error since none of these end points were adjusted for multiplicity. In terms of safety, there were a high proportion of patients which experienced AEs in the HP/TAZ and monad TAZ groups. Notably, a higher proportion of patients discontinued study drug due to AEs in the monad TAZ group. Limitations to note are the minor imbalances in demographics and disease characteristics, imbalanced discontinuation rates within the treatment groups, and the inclusion of participants with a three-month washout period for biologics. Furthermore, the patient population appears to be representative of Canadian patients with mild-to-moderate rather than moderate-to-severe plaque psoriasis. Thus, the evidence provided by Study 201 is limited by concerns

with the internal validity and applicability to a Canadian population with moderate-to-severe plaque psoriasis.

Discussion

Summary of Available Evidence

Two multi-centre, double-blind RCTs met the inclusion criteria for the systematic review: Study 301 (N = 203) and Study 302 (N = 215). These trials were designed to evaluate the efficacy and safety of HP/TAZ compared to vehicle in adults with moderate-to-severe plaque psoriasis. Patients were randomized 2:1 to receive HP/TAZ or vehicle once daily for eight weeks. The primary outcome in both trials was treatment success at week 8, where treatment success was defined as having at least a two-grade improvement from baseline in the IGA score and an IGA score of clear or almost clear (0 or 1). Improvement in the signs and symptoms of psoriasis, percentage BSA affected by psoriasis, and HRQoL assessed using the DLQI were also included in the evaluation of efficacy in the two studies. The pooled analysis of Study 301 and Study 302 supports the CADTH pharmacoeconomic model submitted by the sponsor and is summarized in Appendix 4.

In addition, one sponsor-submitted NMA was included in this report, which compared HP/TAZ and other topical therapies available in Canada to vehicle in patients with moderate-to-severe plaque psoriasis. Two other studies submitted by the sponsor of adult patients with moderate-to-severe plaque psoriasis were summarized for this review. The first was an open-label, single-arm study that provided an assessment of safety for the use of HP/TAZ in four-week treatment cycles as needed over 52 weeks (Study 303). The second was a phase II RCT (Study 201) that compared HP/TAZ with each of its monads and vehicle.

Interpretation of Results

Efficacy

HRQoL was identified as an outcome that is important to patients as noted in the patient input submission for this review, by the clinical expert consulted for this review, and in the clinical practice guidelines[4,7] which noted that improved HRQoL is an important outcome for patients that is also a priority in the treatment decision-making process from the clinician perspective. In the two pivotal trials for HP/TAZ, HRQoL was included as an exploratory outcome and measured using the DLQI, which is a well-validated and disease-specific tool. Descriptive analyses were provided, and between-group comparisons were not conducted. After eight weeks of treatment, a reduction in DLQI score was observed in both HP/TAZ and vehicle groups in both studies, which may suggest an improvement in HRQoL. However, in the absence of formal statistical testing, no conclusions can be made as to whether DLQI was actually reduced in either group, or whether there were any differences in DLQI between the two treatment groups.

The primary and secondary outcomes (treatment success based on IGA), and exploratory outcome of BSA affected by psoriasis, in addition to the IGA score by study visit, were reported as outcomes related to skin clearance. In both trials, a statistically significant difference between HP/TAZ and vehicle in terms of the proportion of patients who achieved treatment success based on the IGA was reported at week 8. Similar results were observed at week 12, 6, and 4. Whether the definition used for treatment success is clinically

meaningful is unknown as a MID was not identified for the change in IGA score over time, but a score of clear or almost clear is generally accepted as a clinically meaningful score.[12] Of note, this was based on the six-point PGA rather than the five-point IGA. A formal assessment of the five-point IGA specifically was not identified during this review. When considering these results, it is important to note the limitations of these analyses, which include the subjective nature and poor inter-rater reliability of the IGA scale,[12] and the lack of an active comparator, which introduce uncertainty to the results. The IGA is also not an outcome typically used to assess patients in clinical practice.

A descriptive subgroup analysis of treatment success based on the IGA at week 8, by baseline disease severity, was reported in both trials. None of the patients in the vehicle treatment groups with severe disease based on the IGA at baseline achieved treatment success. The proportion of patients with treatment success at week 8 was numerically greater for the HP/TAZ groups than vehicle for both patients with moderate and severe disease at baseline. The latter is consistent with the primary analysis; however, no firm conclusions can be drawn about any of the subgroups in the absence of formal pre-specified testing. The subgroup analyses are also limited by their sample size, as less than 20% of the overall population in each of the two trials were included in the subgroup analysis of patients with severe disease at baseline.

The percentage of BSA affected by psoriasis was an exploratory outcome reported descriptively as a change from baseline. Similar to the DLQI, no between-group comparisons were made, and data were not imputed, limiting the conclusions that can be drawn from this outcome. Nonetheless, the magnitude of the treatment difference was large and the data suggest that the mean (SD) change from baseline in percentage BSA affected was greater in the HP/TAZ groups than vehicle at week 8 in both trials. According to the clinical expert on this review, this outcome is not clinically relevant to Canadian clinical practice.

Improvement in the signs of psoriasis (treatment success, defined as a two-grade improvement in each of erythema, plaque elevation, and scaling) was reported as an exploratory outcome in the two trials. Like the other efficacy outcomes that have been discussed, the proportion of patients that achieved treatment success at week 8 was greater among the HP/TAZ group than the vehicle group. Between-group statistical comparisons were reported for this outcome, which need to be interpreted with increased risk for type I error as the outcome was not adjusted for multiplicity. Evidence of validity, reliability, and responsiveness of the five-point scales used to assess the signs of psoriasis or a MID was not identified for this review. This outcome may be useful for comparison to other clinical trials but lacks clinical relevance. According to the clinical expert consulted for this review, a patient is typically not assessed based on the individual signs of psoriasis in clinical practice. As previously mentioned, signs and symptoms are assessed informally with a focus on how they impact a patient's HRQoL.

Productivity and treatment adherence were included in the CADTH review protocol; however, these outcomes were not assessed in any of the trials for HP/TAZ. Treatment compliance was reported as a safety outcome, defined by a patient using between 80% and 120% of the expected applications of study drug. By this definition, treatment compliance was high, ranging from [redacted] in the two trials, which is not consistent with what is observed in clinical practice. The high rate of adherence observed in the clinical trials likely contributed to an overestimation of treatment effect compared to what would be observed in clinical practice. Nonadherence is a prominent issue in general practice that may impact

treatment efficacy, to the point where identifying a treatment that patients are willing to work with is considered alongside identifying a safe and effective option when selecting an appropriate therapy.[4,7] The clinical expert consulted for this review noted that in practice patients often discontinue treatment for various reasons, ranging from cost or a lost tube to the fact that the treatment is messy or has an odour. They also noted that the HP/TAZ is a water-based lotion that maybe preferable to patients; however, these types of topical agents are usually more expensive and therefore may not be accessible to many patients.

At the time of this review, there was no direct comparative evidence for HP/TAZ versus other topical treatments for psoriasis. The sponsor submitted an NMA with the purpose of evaluating the relative efficacy of topical therapies approved for the treatment of moderate-to-severe plaque psoriasis in Canada. The investigated topical therapies included HP/TAZ, high potency corticosteroid/vitamin D analogue combination (BD/VDA), very high potency corticosteroids, retinoids (TAZ), VDAs, and high potency corticosteroids. The results of the NMA suggest that after eight weeks of treatment, both combination therapies (HP/TAZ and BD/VDA) were superior to vehicle in achieving treatment success; however, the NMA was performed to examine the relative treatment effect between active topical therapies to vehicle, rather than between active therapies. In addition, the analyses have a number of limitations that impact the internal and external validity creating substantial uncertainty around the results. Therefore, the comparative efficacy and safety of HP/TAZ to other active topical therapies, such as BD/VDA, was inconclusive for the study population due to the limitations in the analyses and substantial uncertainty.

Harms

Overall, AEs were more frequent among patients randomized to HP/TAZ than vehicle. The most commonly reported AE was contact dermatitis, which occurred only in patients randomized to HP/TAZ, and none of the patients who received vehicle in either Study 301 or Study 302. The other AEs reported occurred in no more than five patients per treatment group. Severe adverse events were infrequent and only occurred in the HP/TAZ group of Study 301. No SAE was observed in more than one patient. No deaths were reported, and WDAEs did not appear to be the result of any particular event. A list of notable harms was included in the CADTH systematic review protocol. Of these, pruritus, skin atrophy, folliculitis, burning sensation, skin irritation, and hypersensitivity events were reported. The most frequently reported notable harm was pruritus, which was reported for 2.9% to 5.5% of patients in each treatment group except vehicle of Study 301 (0%). The remaining AEs were reported in five or fewer patients in total. In summary, there are few to no concerns regarding the safety of HP/TAZ based on treatment for eight weeks.

A long-term assessment of safety was conducted in Study 303 and demonstrated safety and tolerability of HP/TAZ intermittent treatment up to one year. During this study, patients discontinued treatment if they achieved treatment success, then reinitiated treatment for a four-week period if disease worsened. Patients were evaluated in four-week cycles for 52 weeks. More than half (57.1%) of patients experienced an AE and 18 (3.3%) patients experienced a SAE. Of the patients who stopped treatment due to AEs (7.5%), most did so due to application site reactions within the first three months. Overall, intermittent treatment with HP/TAZ once daily therapy seemed to be well-tolerated up to 52 weeks. There were no alarming safety signals observed.

The FDA's review of HP/TAZ was the only regulatory report available at the time of this review. The FDA concluded that a sufficient assessment of safety had been conducted in the target population.[42] It is important to note that the indication approved by the FDA is for

"for the topical treatment of plaque psoriasis," which includes a broader patient population than the Health Canada indication. Similar to the discussion of efficacy results, the available safety information for HP/TAZ is limited in its applicability to patients with moderate-to-severe plaque psoriasis, specifically. Moreover, there is a lack of comparative safety data and therefore, safety of HP/TAZ compared to other treatments available for plaque psoriasis is unknown. An assessment of safety was also not included in the sponsor-submitted NMA.

Other Considerations

A topic deserving consideration is that the evidence provided for this review does not align with the anticipated use of HP/TAZ in clinical practice. The clinical expert consulted by CADTH anticipated that HP/TAZ would not be used as a monotherapy in patients with moderate-to-severe psoriasis, and was more likely to be used as an adjunct to phototherapy or systemic therapy (either conventional systemic treatment of biologics). In both Study 301 and Study 302, HP/TAZ was administered as monotherapy and there were no patients in either study who received concomitant treatment with conventional systemic treatment or biologics. This is aligned with the criteria that patients were ineligible for participation in the study if they had used phototherapy, photochemotherapy, or non-biologic systemic psoriasis therapy within four weeks prior to baseline or had used biologics known to affect psoriasis within three months of baseline visit.

According to the clinical expert consulted by CADTH for this review, HP/TAZ is anticipated to be used in patients with mild disease severity, as these patients may be adequately managed on topical therapy. This is aligned with the indication of HP/TAZ approved by the FDA for "the topical treatment of plaque psoriasis," which is not restricted to patients with moderate-to-severe psoriasis.

Conclusions

Based on the available evidence, HP/TAZ demonstrated efficacy in adult patients with plaque psoriasis in terms of skin clearance based on the IGA. In the two trials included in the CADTH review, the difference between HP/TAZ and vehicle in the proportion of patients achieving treatment success (defined by at least a two-grade improvement from baseline in the IGA score in addition to an IGA score of clear or almost clear) at week 8 was statistically significant in favour of HP/TAZ ($P < 0.001$). HRQoL was identified as an outcome that is important to patients and was measured using the DLQI in both studies; however, no conclusions can be made regarding the effect of HP/TAZ on HRQoL due to the exploratory nature of the outcome and lack of statistical testing. In addition, HP/TAZ does not appear to be associated with any safety signals. Key limitations are the lack of comparative evidence, lack of long-term data, and generalizability of the patient population; of note, the patients included in Study 301 and Study 302 may not be representative of Canadian patients with moderate-to-severe plaque psoriasis.

In the absence of direct evidence, the sponsor submitted an NMA with the purpose of evaluating the relative efficacy of topical therapies approved for the treatment of moderate-to-severe plaque psoriasis in Canada. The results of the NMA suggest that after eight weeks of treatment, both combination therapies (HP/TAZ and BD/VDA) were superior to vehicle in achieving treatment success; however, the NMA was performed to examine the relative treatment effect between active topical therapies to vehicle, rather than between active therapies.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	February 12, 2020
Alerts:	Bi-weekly search updates until project completion
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a 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
MeSH	Medical Subject Heading
exp	Explode a subject heading
.ti	Title
.ab	Abstract
.dq	Candidate term word (Embase)
.ot	Original title
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(Duobrii* or IDP 118 or IDP118).ti,ab,kf,ot,hw.
2	((HP adj10 psoriasis) or halobetasol* or ulobetasol* or ultravate* or miracorten* or bryhali* or jemdel* or tabitral* or IDP122 or IDP 122 or BMY30056 or BMY-30056 or CGP14458 or CGP-14,458 or CGP-14458 or 91A0K1TY3Z or 9P6159HM7T).ti,ab,kf,ot,hw,rn,nm.
3	((TAZ adj10 psoriasis) or tazaroten* or avage* or fabior* or tazorac* or zorac* or tazoral* or AGN190168 or AGN-190168 or 81BDR9Y8PS).ti,ab,kf,ot,hw,rn,nm.
4	2 and 3
5	1 or 4
6	5 use medall
7	(Duobrii* or IDP 118 or IDP118).ti,ab,kw,dq.
8	*ulobetasol propionate/
9	((HP adj10 psoriasis) or halobetasol* or ulobetasol* or ultravate* or miracorten* or bryhali* or jemdel* or tabitral* or IDP122 or IDP 122 or BMY30056 or BMY-30056 or CGP14458 or CGP-14,458 or CGP-14458).ti,ab,kw,dq.
10	8 or 9
11	*tazarotene/
12	((TAZ adj10 psoriasis) or tazarotene* or avage* or fabior* or tazorac* or tazoral* or zorac* or AGN190168 or AGN-190168).ti,ab,kw,dq.
13	11 or 12
14	10 and 13
15	7 or 14
16	(conference abstract or conference review).pt.
17	15 not 16
18	17 use oemezd
19	6 or 18
20	remove duplicates from 19

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search terms: Duobrii or (halobetasol propionate and tazarotene) AND plaque psoriasis
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms: Duobrii or (halobetasol propionate and tazarotene)

OTHER DATABASES	
PubMed	Searched 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:	February 25, 2020
Keywords:	Duobrii or (halobetasol propionate and tazarotene) / plaque psoriasis
Limits:	None

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Health Statistics.

Appendix 2: Excluded Studies

Table 42: Excluded Studies

Reference	Reason for exclusion
Anonymous. Halobetasol 0.01%/Tazarotene 0.045% Lotion in the Treatment of Moderate-to-Severe Plaque Psoriasis: Maintenance of Therapeutic Effect After Cessation of Therapy. Journal of Drugs in Dermatology: JDD. 2019;18(8):815-820.	Pooled analysis
Del Rosso JQ, Kircik L, Lin T, Pillai R. Halobetasol 0.01%/Tazarotene 0.045% Fixed-combination Lotion in the Treatment of Plaque Psoriasis: Sensitization and Irritation Potential. The Journal of Clinical & Aesthetic Dermatology. 2019;12(1):11-15.	Study population (healthy volunteers)
Lebwohl MG, Sugarman JL, Gold LS, et al. Long-Term Safety Results From A Phase 3 Open-Label Study Of A Fixed Combination Halobetasol Propionate 0.01% And Tazarotene 0.045% Lotion In Moderate-To-Severe Plaque Psoriasis. J Am Acad Dermatol. 2019;80(1):282-285.	Letter to the Editor
Bhatia ND, Pariser DM, Kircik L, et al. Safety and Efficacy of a Halobetasol 0.01%/Tazarotene 0.045% Fixed Combination Lotion in the Treatment of Moderate-to-severe Plaque Psoriasis: A Comparison with Halobetasol Propionate 0.05% Cream. The Journal of Clinical & Aesthetic Dermatology. 2018;11(11):15-19.	Phase II study
Gold LS, Lebwohl MG, Sugarman JL, et al. Safety and efficacy of a fixed combination of halobetasol and tazarotene in the treatment of moderate-to-severe plaque psoriasis: Results of 2 phase 3 randomized controlled trials. J Am Acad Dermatol. 2018;79(2):287-293.	Pooled analysis
Stein Gold L, Bagel J, Lebwohl M, Lin T, Martin G, Pillai R. Halobetasol and Tazarotene: Further Defining the Role of a Unique Fixed Combination Topical Lotion in Moderate-to-Severe Plaque Psoriasis. Journal of Drugs in Dermatology: JDD. 2018;17(12):1290-1296.	Post hoc analysis
Stein Gold L, Kircik LH, Pariser D, et al. Rapid Onset of Action in Patients With Moderate-to-Severe Plaque Psoriasis With Halobetasol 0.01%/Tazarotene 0.045% Fixed Combination. Journal of Drugs in Dermatology: JDD. 2018;17(8):863-868.	Phase II study
Sugarman JL, Weiss J, Tanghetti EA, et al. Safety and Efficacy of a Fixed Combination Halobetasol and Tazarotene Lotion in the Treatment of Moderate-to-Severe Plaque Psoriasis: A Pooled Analysis of Two Phase 3 Studies. Journal of Drugs in Dermatology: JDD. 2018;17(8):855-861.	Pooled analysis
Rivera AM, Hsu S. Topical halobetasol propionate in the treatment of plaque psoriasis: a review. Am J Clin Dermatol. 2005;6(5):311-316.	Review article

Appendix 3: Detailed Outcome Data

Health-Related Quality of Life

Table 43: Change From Baseline in DLQI Score (ITT Set)

	Total N	Baseline	Week 4		4 weeks following end of treatment (week 12)	
		Mean (SD)	Mean (SD)	Mean change from baseline (SD)	Mean (SD)	Mean change from baseline (SD)
DLQI						
Study 301						
HP/TAZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vehicle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study 302						
HP/TAZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vehicle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DLQI = Dermatology Life Quality Index; HP/TAZ = halobetasol propionate and tazarotene; ITT = intention to treat; SD = standard deviation.

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

Skin Clearance

Table 44: Change From Baseline of Affected BSA (ITT Set)

		BSA affected by psoriasis					
		Baseline	Week 2	Week 4	Week 6	Week 8	Week 12
Study 301							
HP/TAZ N = 135	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vehicle N = 68	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study 302							
HP/TAZ N = 141	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vehicle N = 74	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSA = body surface area; HP/TAZ = halobetasol propionate and tazarotene; ITT = intention to treat; SD = standard deviation.

[a] Assessment of BSA affected by psoriasis did not include areas of the face, scalp, palms, soles, axillae, and other intertriginous areas.

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

Signs and Symptoms of Psoriasis

Table 45: Summary of the Signs of Psoriasis (Scaling) by Visit for the Target Lesion (ITT Set)

			% of patients					
		N at baseline	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12
Scaling (target lesion)								
Study 301								
HP/TAZ N = 135	0 – None	[redacted]						
	1 – Minimum							
	2 – Mild							
	3 – Moderate							
	4 – Severe							
Vehicle N = 68	0 – None							
	1 – Minimum							
	2 – Mild							
	3 – Moderate							
	4 – Severe							
Study 302								
HP/TAZ N = 141	0 – None							
	1 – Minimum							
	2 – Mild							
	3 – Moderate							
	4 – Severe							
Vehicle N = 74	0 – None							
	1 – Minimum							
	2 – Mild							
	3 – Moderate							
	4 – Severe							

HP/TAZ = halobetasol propionate and tazarotene; ITT = intention to treat.

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

Table 46: Summary of the Signs of Psoriasis (Plaque Elevation) by Visit for the Target Lesion (ITT Set)

			% of patients					
		N at baseline	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12
Plaque Elevation (Target Lesion)								
Study 301								
HP/TAZ N = 135	0 – None	[redacted]						
	1 – Minimum							
	2 – Mild							
	3 – Moderate							
	4 – Severe							

			% of patients					
		N at baseline	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12
Vehicle N = 68	0 – None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1 – Minimum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2 – Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3 – Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4 – Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study 302								
HP/TAZ N = 141	0 – None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1 – Minimum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2 – Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3 – Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4 – Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vehicle N = 74	0 – None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1 – Minimum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2 – Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3 – Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4 – Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HP/TAZ = halobetasol propionate and tazarotene; ITT = intention to treat.

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

Table 47: Summary of the Signs of Psoriasis (Erythema) by Visit for the Target Lesion (ITT Set)

			% of patients					
		N at baseline	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12
Erythema (target lesion)								
Study 301								
HP/TAZ N = 135	0 – None	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1 – Minimum	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2 – Mild	15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3 – Moderate	109	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4 – Severe	11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vehicle N = 68	0 – None	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1 – Minimum	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2 – Mild	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3 – Moderate	55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4 – Severe	8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study 302								
HP/TAZ N = 141	0 - None	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1 - Minimum	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2 – Mild	10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3 – Moderate	112	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4 – Severe	19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

			% of patients					
		N at baseline	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12
Vehicle N = 74	0 – None	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1 – Minimum	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2 – Mild	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3 – Moderate	55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4 – Severe	13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HP/TAZ = halobetasol propionate and tazarotene; ITT = intention to treat.

Source: Clinical Study Reports for Study 301[10] and Study 302.[11]

Appendix 4: Summary of Pooled Analysis

Objective

To summarize the results of a pooled analysis of the two phase III pivotal trials, Study 301 and Study 302, for HP/TAZ (Duobrii).

Methods

All the patients who were randomized to Study 301 (N = 203) and Study 302 (N = 215) were included in the pooled analysis, for a total of 418 patients included in the ITT population used for efficacy analyses. The safety population consisted of 410 patients, which were used for the assessment of safety. The discrepancy between the two was due to a lack of post-baseline safety evaluation of eight patients.

The pooled analysis used the same primary efficacy end point as the individual pivotal trials: the percentage of patients with treatment success, defined by at least a two-grade improvement from baseline in the IGA and an IGA score of clear or almost clear at week 8. The secondary end points used the same definition of treatment success, but were reported at week 12, 6, 4, and 2. The percentage of patients with at least a two-grade improvement from baseline in the score of each of the three signs of psoriasis (erythema, plaque elevation, and scaling) were reported as exploratory end points at week 8, 12, 6, 4, and 2. A two-grade improvement of IGA scores and change from baseline in BSA were also summarized.

All pooled analyses of efficacy data were descriptive and no hypothesis testing was conducted. The MCMC multiple imputation method was used to handle missing efficacy data, as per the method used in Study 301 and Study 302. As previously described, the ITT set was used for all efficacy analyses, but the week 8 and week 12 per-protocol populations were also used.

Results

Patient Disposition

Table 48: Patient Disposition (All Randomized Patients)

	Pooled analysis (Study 301 + Study 302)	
	HP/TAZ	Vehicle
Screened, N	Not reported	
Randomized, N (%)	276	142
Discontinued from study, n (%)	44 (15.9)	24 (16.9)
Reason for discontinuation, n (%)		
Adverse event	11 (4.0)	4 (2.8)
Patient request	17 (6.2)	12 (8.5)
Protocol violation	3 (1.1)	0
Lost to follow-up	9 (3.3)	6 (4.2)
Worsening condition	3 (1.1)	2 (1.4)
Other	1 (0.4)	0
ITT, N	276 (100.0)	142 (100.0)

	Pooled analysis (Study 301 + Study 302)	
PP,[a] n	229 (83.0)	120 (84.5)
Safety, n	270 (97.8)	140 (98.6)

HP/TAZ = halobetasol propionate and tazarotene; ITT = intention to treat; PP = per protocol.

[a] Data are for the week 8 PP population. Data for the week 12 PP population is also available (HP/TAZ = 220, vehicle = 113).

Source: Clinical Study Report for Pooled Analysis of Study 301 and Study 302.[43]

Table 49: Summary of Baseline Characteristics (ITT Set)

	Pooled analysis (Study 301 + Study 302)	
Characteristic	**HP/TAZ N = 276**	**Vehicle N = 142**
Demographic characteristics		
Age, mean (SD)	50.0 (14.2)	51.0 (13.2)
Sex (% male), n (%)	175 (63.4)	97 (68.3)
Ethnicity		
Hispanic or Latino	78 (28.3)	37 (26.1)
Not Hispanic or Latino	198 (71.7)	105 (73.9)
Race		
White	232 (84.1)	126 (88.7)
Black or African American	18 (16.5)	9 (6.3)
Asian	16 (5.8)	5 (3.5)
Other	10 (3.6)	2 (1.4)
Baseline disease characteristics		
IGA score, n (%)		
3 = moderate	237 (85.9)	119 (83.8)
4 = severe	39 (14.1)	23 (16.2)
Percentage BSA affected by psoriasis		
Mean (SD)	6.0 (2.86)	5.7 (2.54)
Median (range)	5.0 (3 to 12)	5.0 (3 to 12)
Size of target lesion (cm^2)		
Mean (SD)	36.4 (22.5)	39.7 (23.6)
Median (range)	26.5 (16 to 100)	30.0 (16 to 100)
Signs		
Erythema (target lesion)		
2 = mild	25 (9.1)	11 (7.7)
3 = moderate	221 (80.1)	110 (77.5)
4 = severe	30 (10.9)	21 (14.8)
Plaque elevation (target lesion)		
2 = mild	30 (10.9)	14 (9.9)
3 = moderate	212 (76.8)	108 (76.1)
4 = severe	34 (12.3)	20 (14.1)
Scaling (target lesion)		
2 = mild	36 (13.0)	22 (15.5)

Characteristic	Pooled analysis (Study 301 + Study 302)	
	HP/TAZ N = 276	Vehicle N = 142
3 = moderate	203 (73.6)	100 (70.4)
4 = severe	37 (13.4)	20 (14.1)

BSA = body surface area; HP/TAZ = halobetasol propionate and tazarotene; IGA = Investigator's Global Assessment; ITT = intention to treat; SD = standard deviation.

Source: Clinical Study Report for Pooled Analysis of Study 301 and Study 302.[43]

Exposure

Table 50: Exposure to Study Drug (ITT Set)

	Pooled analysis (Study 301 + Study 302)	
	HP/TAZ N = 276	Vehicle N = 142
Amount of study drug used (g)		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Number of days exposed		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Number of applications		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

HP/TAZ = halobetasol propionate and tazarotene; SD = standard deviation.

Source: Clinical Study Report for Pooled Analysis of Study 301 and Study 302.[43]

Efficacy

Health-Related Quality of Life

HRQoL was not reported in the pooled analysis of Study 301 and Study 302.

Skin Clearance

Table 51: Treatment Success in IGA (ITT Set)

Pooled analysis (Study 301 + Study 302)			
Time point	Treatment outcome (% patients)	HP/TAZ N = 276	Vehicle N = 142
Week 2	Success[a]	[redacted]	[redacted]
	Failure	[redacted]	[redacted]
Week 4	Success[a]	[redacted]	[redacted]
	Failure	[redacted]	[redacted]
Week 6	Success[a]	[redacted]	[redacted]
	Failure	[redacted]	[redacted]
Week 8	Success[a]	[redacted]	[redacted]
	Failure	[redacted]	[redacted]

Pooled analysis (Study 301 + Study 302)			
Time point	**Treatment outcome (% patients)**	**HP/TAZ N = 276**	**Vehicle N = 142**
Week 12	Success[a]	[redacted]	[redacted]
	Failure	[redacted]	[redacted]

HP/TAZ = halobetasol propionate and tazarotene; IGA = Investigator's Global Assessment; ITT = intention to treat; MCMC = Markov chain Monte Carlo.

Note: Missing data were handled using multiple imputation (MCMC).

[a] *Treatment success* was defined as at least a two-grade improvement from baseline in the IGA score and an IGA score equal to clear or almost clear.

Source: Clinical Study Report for Pooled Analysis of Study 301 and Study 302.[43]

Table 52: Change From Baseline of Affected BSA (ITT Set)

Pooled analysis (Study 301 + Study 302)				
	Total N	**Baseline**	**End-of-treatment time point (week 8)**	
		Mean (SD)	**Mean (SD)**	**Percentage change from baseline, mean (SD)**
Percentage BSA[a] affected by psoriasis				
HP/TAZ	276	6.0 (2.9)	3.6 (2.9)	–37.6 (39.5)
Vehicle	142	5.7 (2.5)	5.3 (3.4)	–3.1 (61.1)

BSA = body surface area; HP/TAZ = halobetasol propionate and tazarotene; ITT = intention to treat; SD = standard deviation.

[a] Assessment of BSA affected by psoriasis did not include areas of the face, scalp, palms, soles, axillae, and other intertriginous areas.

Source: Clinical Study Report for Pooled Analysis of Study 301 and Study 302.[43]

Psoriasis-Related Signs and Symptoms

Table 53: Improvement From Baseline for Each Sign of Psoriasis (ITT Set)

Pooled Analysis (Study 301 + Study 302)			
Time point	**Treatment outcome (% patients)**	**HP/TAZ N = 276**	**Vehicle N = 142**
Week 2	Success[a]	[redacted]	[redacted]
	Failure	[redacted]	[redacted]
Week 4	Success[a]	[redacted]	[redacted]
	Failure	[redacted]	[redacted]
Week 6	Success[a]	[redacted]	[redacted]
	Failure	[redacted]	[redacted]
Week 8	Success[a]	[redacted]	[redacted]
	Failure	[redacted]	[redacted]
Week 12	Success[a]	[redacted]	[redacted]
	Failure	[redacted]	[redacted]

HP/TAZ = halobetasol propionate and tazarotene; ITT = intention to treat; MCMC = Markov chain Monte Carlo.

Note: For all end points, Cochran-Mantel-Haenszel test was stratified by analysis centre. Values were adjusted for multiple imputation (MCMC).

[a] *Treatment success* was defined as at least a two-grade improvement from baseline for each of the signs of psoriasis (erythema, plaque elevation, and scaling).

Source: Clinical Study Report for Pooled Analysis of Study 301 and Study 302.[43]

Treatment Adherence

Similar to the individual pivotal trials, the pooled analysis of Study 301 and Study 302 did not directly assess treatment adherence as an efficacy outcome, but compliance was reported. A patient who was compliant was defined as a patient who applied between 80% and 120% of the expected applications while enrolled in the respective study. Of the patients treated with HP/TAZ, [redacted] were compliant. For patients receiving vehicle, [redacted] were compliant.

Safety

Harms

Table 54: Summary of Harms, up to Week 8 Study Visit (Safety Set)

	Pooled analysis (Study 301 + Study 302)	
	HP/TAZ N = 270	Vehicle N = 140
Patients with ≥ 1 AE		
n (%)	97 (35.9)	30 (21.4)
Most common AEs,[a] n (%)		
Contact dermatitis	20 (7.4)	0
Pruritus	8 (3.0)	4 (2.9)
Skin atrophy	5 (1.9)	0
Patients with ≥ 1 SAE		
n (%)	3 (1.1)	0
SAEs by preferred term, n (%)		
Cellulitis staphylococcal, asthma exacerbation[b]	1 (0.4)	0
Pneumonia	1 (0.4)	0
Anemia	1 (0.4)	0
Patients who stopped treatment due to AEs[c]		
n (%)	17 (6.3)	5 (3.6)
AEs by preferred term, n (%)		
Deaths		
n (%)	0	0
Notable harms		
AE of interest, n (%)		
Pruritus	8 (3.0)	4 (2.9)
Thinning of skin (skin atrophy)	5 (1.9)	4 (2.9)
Folliculitis	5 (1.9)	0
Skin irritation	2	1 (0.7)
Burning sensation	2 (0.7)	2 (1.4)
Hypersensitivity events	1 (0.4)	1 (0.7)

	Pooled analysis (Study 301 + Study 302)	
	HP/TAZ N = 270	Vehicle N = 140
HPA axis suppression[d]	0	0
Severe dryness	0	0

AE = adverse event; HP/TAZ = halobetasol propionate and tazarotene; HPA = hypothalamic pituitary adrenal; SAE = serious adverse event.

[a] Frequency of two or more patients in any treatment group.

[b] One patient reported two SAEs: cellulitis staphylococcal (1) and asthma (1).

[c] Includes patients with a treatment-emergent AE leading to permanent withdrawal of study drug and/or early study discontinuation.

[d] Includes: secondary glucocorticoid insufficiency, adrenal hypercorticism (Cushing syndrome, hyperglycemia, glycosuria).

Source: Clinical Study Report for Pooled Analysis of Study 301 and Study 302.[43]

Appendix 5: Description and Appraisal of Outcome Measures

Aim

To describe the outcome measures summarized in Table 55, and review their measurement properties including validity, reliability, responsiveness to change, and MID.

Of the four outcome measures, the IGA was described in greater detail as this was the primary end point under review in Study 301 and Study 302. Validation of BSA and the generic tool, DLQI, was included. Of note, limited information was available for the psoriasis signs evaluation tool.

Findings

The validity, reliability, and responsiveness of each outcome measure were summarized and evaluated. Interpretation of the reliability and validity metrics were based on the following criteria:

- Inter-rater reliability, kappa statistics (level of agreement):[44]
  - less than 0 = poor agreement
  - 0.00 to 0.21 = slight agreement
  - 0.21 to 0.40 = fair agreement
  - 0.41 to 0.60 = moderate agreement
  - 0.61 to 0.8 = substantial
  - 0.81 to 1.00 = almost perfect agreement.
- Internal consistency (Cronbach's alpha) and test-retest reliability: 0.7 or greater is considered acceptable[45]
- Validity (i.e., between-scale comparison [correlation coefficient, r]):[46]
  - 0.3 or less = weak
  - 0.3 to 0.5 or more = moderate
  - greater than 0.5 = strong.

Table 55: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
DLQI	10-item, dermatology-specific quality of life questionnaire to assess limitations related to the impact of skin disease. The response options range from 0 (not affected at all) to 3 (very much affected) and DLQI scores range from 0 to 30, with lower scores indicating better quality of life.	**Validity:** Construct validity of the DLQI in the psoriasis population was based on correlation of the instrument with either generic, dermatologic, or disease-specific instruments over 37 separate studies;[38] the DLQI corelated the greatest with the bodily pain (r = 0.61) and	The MID of the DLQI in patients with psoriasis was estimated using 3 anchor-based methods. Estimates ranged from 2.2 to 6.9.[34] Another study in patients with psoriasis treated with adalimumab reported an MID of 3.2.[47]

Outcome measure	Type	Conclusions about measurement properties	MID
		social functioning domains (r = 0.68) of the SF-36, as well as the overall EQ-5D index score (r = 0.71).[34] **Reliability:** Reliability was assessed in the original validation study of the DLQI by Finlay and Khan in a population of various skin diseases;[33] the test-retest reliability correlation coefficients were high for both the overall score (Spearman rank correlation = 0.99) and for individual questions (0.95 to 0.98).[33] Slightly lower correlation coefficients (ranging from 0.56 to 0.99) were reported in a later systematic review by Basra et al.[38] **Responsiveness:** Responsiveness to change was measured by comparing DLQI data with PASI and PGA scores.[34] The DLQI demonstrated equal responsiveness to the PASI and PGA scores with correlation coefficients of r = 0.69 and r = 0.71, which was not achieved by the general tools, the EQ-5D (r = 0.44) and SF-36 (r = 0.44).[34]	In the most recent systematic review of RCTs in psoriasis, the DLQI MID was reported to be a score change of 5.[48]
IGA	5-point scale used to measure the severity of disease at a single point in time (static IGA); IGA scores range from 0 (clear) to 4 (severe).	There are no studies evaluating the validity, reliability, or responsiveness of the 5-point IGA scale.	The MID has not been identified at this time.
Psoriasis signs	5-point scale used to measure the severity of the signs of psoriasis (erythema, plaque elevation, and scaling); scores for each scale can range from 0 (none) to 4 (severe).	There is no information regarding the validity, reliability, or responsiveness to change of this scale.	There is no scientific literature regarding the MID of this scale. The clinical expert consulted in this review noted that a 2-grade improvement within this scale for any of the signs of psoriasis (erythema, plaque elevation, and scaling) is a clinically meaningful difference.

Outcome measure	Type	Conclusions about measurement properties	MID
BSA	Percentage BSA affected by psoriasis is estimated through the 1% rule, where the subject's flat palm represents 1% of total BSA.	**Validity:** This is not relevant to the evaluation of BSA. **Reliability:** Inter-rater reliability was evaluated in two studies which determined an ICC of 0.91[49] and 0.96[50] when dermatologists used the 1% rule in BSA determination. Inter-rater variability was determined to be high in 2 separate studies: • a systematic review conducted by Puzenat et al. determined CV > 30%[51] • Bozek et al. found a CV = 57.1 when 10 dermatologists evaluated 9 patients.[52] Test-retest reliability was evaluated in 2 separate studies; high test-retest reliability was found in both studies with an ICC of 0.98[49] and 0.96.[52] **Responsiveness:** Currently, there is no evidence regarding the responsiveness to change of the use of the 1% rule in BSA determination.	There is no scientific literature regarding the MID of BSA affected by psoriasis. The clinical expert consulted in this review noted that a 1/3 reduction in BSA affected by psoriasis is a clinically meaningful difference.

BSA = body surface area; CV = coefficient of variation; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimensions; ICC = intraclass correlation coefficient; IGA = Investigator's Global Assessment; MID = minimal important difference; PASI = Psoriasis Area Severity Index; PGA = Physician's Global Assessment; RCT = randomized controlled trial; SF-36 = Short Form (36) Health Survey.

Source: Reolid et al.,[49] Chandran et al.,[50] Puzenat et al.,[51] Bozek et al.,[52] Basra et al.,[38] Shikiar et al.,[34] Finlay et al.,[33] Melilli et al.,[47] Ali et al.[48]

Dermatology Life Quality Index

The DLQI is a widely used dermatology-specific HRQoL instrument which assesses the impact of skin disease.[33] It is a 10-item questionnaire that covers six domains over a one-week recall period: symptoms and feeling, daily activities, leisure, work and school, personal relationships, and treatment. Each item is scored on a four-point Likert scale: 0, (not at all affected/not relevant), 1 (a little affected), 2 (a lot affected), and 3 (very much affected). The overall DLQI score is a numeric score between 0 to 30, with lower scores indicating better HRQoL. At least 80% of the questions must be answered for a score to be reported.[33,34] The final numeric score translates to the effect of the patient's disease on their quality of life where 0 to 1 equals no effect, 2 to 5 equals small effect, 6 to 10 equals moderate effect, 11 to 20 equals very large effect, and 21 to 30 equals extremely large effect. The DLQI can be completed within a few minutes, making it a very time-efficient scoring system for use in clinical settings,[53] although the clinical expert consulted by CADTH for this review stated that in clinical practice, HRQoL is assessed through a discussion with the patient.

Validity

The DLQI was developed in 1994, and since has been validated in many studies.[33,34,38,53-55] Construct validity of the DLQI was based on the correlation of the instrument with either generic, dermatologic, or disease-specific instruments in more than 37 separate studies.[38] Shikiar et al. reported a good correlation (correlation coefficient [r] > 0.61) with three different itch measures in a study combining results from trials in moderate-to-severe plaque psoriasis (N = 1,095).[54] A later study by Shikiar et al. demonstrated excellent correlation between the DLQI and generic HRQoL instruments in a population of 147 patients with moderate-to-severe plaque psoriasis randomized to adalimumab versus placebo; the DLQI correlated the greatest with the bodily pain (r = 0.61) and social functioning domains (r = 0.68) of the Short Form (36) Health Survey, as well as the overall EuroQol 5-Dimensions questionnaire index score (r = 0.71).[34]

Reliability

In the original validation study by Finlay and Khan, the reliability of the DLQI was assessed with 53 patients with a variety of skin diseases by completing the questionnaire twice, 7 to 10 days apart.[33] The test-retest reliability correlation coefficients were obtained using the Spearman rank correlation test, which were high for both the overall score (0.99) and individual questions (0.95 to 0.98).[33] The good test-retest reliability of the DLQI was also confirmed in a systematic review by Basra et al., with eight of 12 international studies reporting correlation coefficients greater than 0.56 and up to 0.99.[38] The same review reported good internal consistency reliability of the DLQI which is based on 22 international studies with Cronbach alpha coefficients ranging from 0.75 to 0.92.[38]

Responsiveness

Responsiveness to change in the clinical status of a patient was measured by comparing DLQI data with PASI and PGA scores.[34] The correlations between the DLQI and the two disease severity scores were r = 0.69 and r = 0.71, respectively. The DLQI demonstrated equal responsiveness to the PASI and PGA scores with correlation coefficients of r = 0.69 and r = 0.71, which was not achieved by the general tools, the EuroQol 5-Dimensions questionnaire (r = 0.44) and Short Form (36) Health Survey (r = 0.44).[34] In a second study assessing responsiveness, Shikiar et al. contrasted change in DLQI scores in patients who were defined as clinical responders (achievement of PASI 75 response by week 12) with those characterized as nonresponders (< PASI 50). DLQI scores in responders improved by 12.17 points, compared with 1.77 points in the nonresponders subgroup. The difference was statistically significant (t = 9.0, effect size = 0.40, P < 0.0001).[34] Additional studies demonstrating the responsiveness of the DLQI were also identified in the systematic review by Basra et al.[38,55]

MID

Shikiar et al. estimated the MID of the DLQI in patients with moderate-to-severe plaque psoriasis (N = 147) using three anchor-based methods; MID-1 was based on scores from near-responders (PASI improvement of 25% to 49%), MID-2 was based on partial responders (PASI improvement 50% to 74%), and MID-3 corresponded to the difference between nonresponders and minimal responders for the PGA score. The authors also estimated the MID using one-half of the SD of baseline scores.[34] Estimates ranged from 2.2 to 6.9.[34] It should be noted that these approaches lack patient-based anchors and therefore do not necessarily identify the minimal difference that a patient would consider important. Another study in patients with moderate-to-severe plaque psoriasis (N = 147) treated with

adalimumab reported an MID of 3.2.[47] In the most recent systematic review of RCTs in patients with chronic psoriasis, the DLQI MID was reported to be a score change of five.[48]

Limitations

The DLQI was the first dermatology-specific tool to evaluate skin-related HRQoL and was originally developed for use in routine practice.[33] While the tool focuses on the patient's daily functioning, it has been criticized for not fully capturing emotional and mental states.[56] Therefore, the DLQI may lack conceptual validity in the psychological consequences of living with psoriasis.

Investigator's Global Assessment

The IGA is a subjective measurement of the clinical signs of psoriasis, where psoriatic lesions are graded for erythema, induration, and scaling. Various IGAs have been used in psoriasis with different descriptions and scores, with the most common IGA versions using five- to six-point scales.[57,58] There are two types of IGAs, a static form which measures the investigator's measurement of the disease at a given point in time, and a dynamic form in which the investigator evaluates the level of improvement or deterioration from a baseline.[57,59] The static form of the IGA is preferred over the dynamic form given that it does not rely on the investigator's recall of the patient's disease severity observed at baseline or a previous visit. In the two studies under review, a five-point, static version of the IGA was used.[10,11] To generate the IGA score, psoriatic lesions are graded for erythema, induration, and scaling based on a scale of 0 to 4 (Table 56) that is then averaged across all lesions to obtain a single estimate of the patient's overall severity of disease at a given point in time. The three items are given equal weighting. The sum of the three scales is determined and then divided by three for a final IGA score from 0 to 4 (Table 56).

Table 56: Investigator's Global Assessment Scale

Grade	Score	Erythema	Induration	Scaling
Clear	**0**	No evidence of erythema	No evidence of plaque elevation above normal skin level	No evidence of scaling
Almost clear	**1**	Faint pink or light red erythema on most plaques	Slight or barely perceptible elevation of plaques above normal skin level	Some plaques with fine scales
Mild	**2**	Most to all plaques are pink/light red in colour	Some plaques have definite elevation above normal skin level, typically with edges that are indistinct and sloped on some of the plaques	Most to all plaques have some fine scales but are not fully covered; some plaques are completely covered with fine scale
Moderate	**3**	Most to all plaques are bright red, some plaques may be dark red in colour	Definite elevation of most to all plaques, rounded or sloped edges on most of the plaques	Some plaques are at least partially covered with a coarse scale, most to all plaques are nearly covered with fine or coarse scale
Severe	**4**	Most or all plaques are bright, dark, or dusky red	Almost all plaques are raised and well-demarcated; sharp edges on virtually all plaques	Most to all plaques are covered with coarse, thick scales

Source: Clinical Study Reports for Study 201,[41] Study 301,[10] Study 302,[11] and Study 303.[40]

Although the five-point static IGA scale was used in the pivotal trials to evaluate treatment efficacy, there are no studies evaluating validity, reliability, or responsiveness of this five-point scale. However, the six-point IGA scale has been evaluated in terms of its validity, reliability, responsiveness to change, and MID. Because this scale is used to determine treatment efficacy, a primary outcome of the pivotal trials, we have summarized the literature in the following pertaining to this six-point scale. However, it should be noted that any conclusions about validity of outcomes are limited due to the use of a different scale.

The only difference between the five-point and the six-point IGA scale is the inclusion of a *very severe* category in the six-point IGA scale. In this category, the patient is given a score of 5 and is described as having "very severe thickening with hard edges; dark deep red coloration; very severe/very coarse scaling covering all lesions."[60] However, there are very few patients which fall into the highest category of very severe in previous studies that used the six-point IGA scale.[60]

The PGA denotes scales used by clinicians, whereas the IGA is used by investigators in clinical trials.[60] The IGA and the PGA scales are the same scales, with the only difference being the use of IGA by investigators in clinical trials specifically, and the more commonplace use of PGA by clinicians.[60] Oftentimes the IGA and PGA scales are used interchangeably in the literature validating the scales.[60] There is an abundance of evidence validating the six-point PGA scale, and limited high-quality evidence validating the six-point IGA scale. Since use of the five-point IGA scale is important in determining the primary outcomes of the pivotal trials, CADTH has summarized the data available for the six-point scale PGA scale which was gathered in a clinical trial setting.

Validity

The most recent study assessing the validity of the PGA evaluated data from four phase III clinical studies of tofacitinib in patients with psoriasis (N = 3,641).[61] Confirmatory factor analysis used to test the fit of the PGA measurement model demonstrated that equal weighting of the three items (erythema, induration, and scaling) was appropriate, as indicated by Bentler's Comparative Fit Index values greater than 0.98 (acceptable fit defined as > 0.9) and standardized path coefficients all above the threshold of 0.4. Construct validity was assessed using a known-group approach, measuring the relationship between PGA and PASI through a repeated measures model. A positive relationship between the PGA and PASI scores was observed which was stable and replicable across the four studies, indicating that the PGA could discriminate between different degrees of disease severity.[61]

Simpson et al. evaluated the construct and content validity of the PGA by its association with the DLQI.[62] The correlation between PGA and DLQI was moderately positive (r = 0.29 to 0.43) at post-therapy time points. As with the PASI instrument, the authors found the scaling score to be minimally and inconsistently associated with DLQI score, while erythema and induration were positively correlated with the DLQI score. In contrast to Callis Duffin et al.[61], Simpson and colleagues concluded that the equal weighing of the three items would not accurately capture the varying degrees to which these factors affect the patient's rating of quality of life.[62]

Convergent and divergent validity were assessed by determining the correlation of the PGA with three additional outcome measures: the PASI, patient global assessment, and DLQI.[61] Pearson correlation coefficients between PGA and the three scales ranged from 0.4 to 0.79, with the strongest correlation found with PASI. These findings were consistent with a

previous psychometric validation study of the PGA in a single phase III trial by Cappelleri et al.[63] and in several other studies.[51,58,64,65]

Reliability

Callis Duffin et al. evaluated consistency of PGA measurements between screening and baseline visits, when no change in terms of disease severity was expected.[61] The intraclass correlation coefficient (ICC) value for the pooled data was 0.70, suggesting an acceptable test-retest reliability over a stable period. The same study assessed internal consistency reliability demonstrating that the scoring items (erythema, induration, and scaling) were highly consistent with each other (Cronbach coefficient alpha ≥ 0.90) at the primary assessment points in all four trials. The internal consistency reliability was less convincing (Cronbach coefficient alpha 0.50 to 0.63) for the values observed at baseline, likely a result of the specific inclusion criteria of the trials.[61]

Responsiveness

No evidence regarding the responsiveness of the five-point or six-point IGA or PGA was identified from the literature at this time.

Clinical Relevance

There are no studies evaluating the MID of the PGA at this time. However, it is generally accepted that a clinically meaningful score in the PGA is a score of clear or minimal.[12] Furthermore, some trials define efficacy as a two-point reduction in the total PGA score.[59] The two trials under review, Study 301 and Study 302, have defined a score of clear or almost clear (score of 0 or 1, respectively) with a minimum of a two-point difference as a clinically important threshold.

Strengths and Limitations

The PGA has been shown to be reliable based on test-retest data and internal consistency, however inter-rater reliability due to variability, especially in untrained observers, can be poor.[12] Within a study, however, the PGA correlated well with the PASI and HRQoL measures.[66] Furthermore, a systematic review by Robinson et al. including 30 RCTs of biologic drugs in psoriasis from 2001 to 2010 found that the PGA (scores of 0 or 1) correlated very tightly with the PASI 75 (r = 0.9157).[59] Furthermore, given that the PGA has many different scales and scoring variations, comparisons between studies is made very difficult.[12]

Moreover, the PGA's inability to measure the extent of psoriasis (i.e., amount of BSA affected), inability to discriminate small changes in severity, and lack of consideration for nonskin symptoms are further limitations.[60] In addition, no MID has been established for psoriasis at this time.

Psoriasis Signs

The signs of psoriasis (erythema, plaque elevation, and scaling) were assessed for the selected target lesion using a subjective scale outlined in Table 57. According to the sponsor, the results from the psoriasis signs scale permits detection of changes specific to patient's selected target lesion. The sponsor states that many similar scales are widely used in the therapeutic area of psoriasis as erythema, plaque elevation, and scaling are recognized as being basic characteristics of psoriasis lesions.

Table 57: Assessment of Psoriasis Signs Scale

Score	Grade	Description
Erythema		
0	**None**	No erythema
1	**Minimum**	Pink discoloration, minimal erythema
2	**Mild**	Most or all plaques are light red to red in colour
3	**Moderate**	Most or all plaques are bright red or dark in colour
4	**Severe**	Most plaques are dusky red with purple hue
Plaque elevation		
0	**None**	No evidence elevation above the normal skin level
1	**Minimum**	Slight, just discernible elevation above normal skin level
2	**Mild**	Some plaques show definite elevation with indistinct edges
3	**Moderate**	Most plaques have definite elevation with distinct edges that are rounded or sloped
4	**Severe**	Almost all plaques are raised above normal skin level with sharp edges
Scaling		
0	**None**	No scales on very few plaques
1	**Minimum**	Occasional fine scales hardly noticeable
2	**Mild**	Most plaques have fine scales
3	**Moderate**	Some plaques have coarse scales while most plaques have fine scales
4	**Severe**	Most plaques are covered by thick coarse scales

Source: Clinical Study Reports for Study 201,[41] Study 301,[10] and Study 302.[11]

Currently, there was no information identified in the independent literature search conducted by CADTH pertaining to this scale on the construct of the grading for this assessment, including evidence on its validity, reliability, responsiveness to change, or clinical relevance. Although there was no MID identified in the literature, it should be noted that the clinical expert consulted in this review indicated that a decrease of two points in any of the signs of psoriasis would be considered a clinically important outcome for patients.

Limitations

Limitations for use of this scale are the lack of evidence on its validity, reliability, responsiveness to change, and clinical relevance.

Body Surface Area

BSA affected by psoriasis is used to determine extent of psoriasis coverage within a patient. BSA was calculated in the pivotal trials with the 1% rule. This estimation uses a flat palm in which the subject's palm represents approximately 1% of the total BSA. The subject or investigators then use their flat palm to estimate the percentage BSA affected by psoriasis.[35] The BSA calculation in the pivotal trials did not include areas of the face, scalp, palms, soles, axillae, and other intertriginous areas.[10,11] It is generally accepted that if a patient presents with a BSA affected of 0% to 3% or less is considered low BSA affected, 3% to 10% or less is considered medium BSA affected, and BSA affected of greater than 10% is considered a high amount of BSA involvement.[36]

Validity

Evaluation of validity for BSA as an outcome is not relevant, since BSA is not performed to measure disease severity but instead is used as a quantitative measure of BSA covered by psoriasis.

Reliability

The reliability of evaluating BSA affected by psoriasis has been assessed in several studies.[36,49-52,67] Inter-rater reliability was evaluated in two separate studies. The first was Reolid et al., who found high inter-rater reliability with an ICC of 0.91 when 56 patients' BSA was evaluated by two dermatologists.[49] Moderate agreement in inter-rater reliability was found when percentage BSA affected by psoriasis was evaluated for 20 patients by 19 different doctors, with an ICC of 0.47. When these data were analyzed excluding rheumatologists (which are less trained to determine BSA), the inter-rater reliability ICC for dermatologists only was 0.96.[50]

Test-retest reliability for use of the 1% rule to determine BSA affected by psoriasis was evaluated in two separate studies. In the first, Reolid et al. demonstrated high test-retest reliability for BSA determination when 56 patients were evaluated, two days apart with an ICC of 0.98.[49] Second, Bozek et al. found very good test-retest reliability of BSA with an ICC of 0.96.[52]

A systematic review conducted by Puzenat et al. found that the BSA displayed an acceptable amount of intra-rater variability (coefficient of variation < 10%), however the inter-rater variability was high (coefficient of variation > 30%).[51] High inter-rater variability (coefficient of variation = 57.1) was also found in a study conducted by Bozek et al.[52]

Clinical Relevance

There is no literature pertaining to the MID of BSA affected by psoriasis. The clinical expert consulted in this review indicated that a one-third reduction in BSA affected by psoriasis after treatment is a clinically important difference for patients.

Limitations

Limitations of use of the 1% rule to estimate BSA affected by psoriasis are the high inter-rater variability, data showing that the 1% rule is inaccurate, lack of MID data, and the lack of ability to correlate BSA with disease severity. The high inter-rater variability can be explained by data from a meta-analysis performed by Rhodes et al., which found that the palm estimates 0.9% BSA in adult men and 0.85% BSA in adult women. Moreover, they found that body mass index and ethnic origin influence these values. [68]

The clinical expert consulted by CADTH for this review informed that it is inaccurate to use BSA as the sole way to determine disease severity. This is due to the fact that if the location of psoriasis significantly affects HRQoL (i.e., centre of face, soles of feet so patient cannot walk), a patient may be classified as a more severe psoriasis patient even if total BSA affected is very low. Moreover, if a patient's psoriatic lesions improve by reducing thickness, redness, or scaling this may not necessarily be reflected with a change in BSA.

References

1. CDR submission: duobrii (halobetasol propionate (0.01%) and tazarotene (0.045%) lotion, once daily [CONFIDENTIAL sponsor's submission]. Laval (QC): Bausch Health, Canada Inc.; 2020 Feb 3.
2. Blauvelt A, Ehst B. Pathophysiology of psoriasis. *UpToDate*. Waltham (MA): UpToDate; 2019: www.uptodate.com. Accessed 2019 Oct 15.
3. Papp K, Gulliver W, Lynde C, Poulin Y, Ashkenas J, Canadian Psoriasis Guidelines Committee. Canadian guidelines for the management of plaque psoriasis: overview. *J Cutan Med Surg.* 2011;15(4):210-219.
4. Canadian Psoriasis Guidelines Committee. Canadian guidelines for the management of plaque psoriasis. Ottawa (ON): Canadian Dermatology Association; 2009: https://www.dermatology.ca/wp-content/uploads/2012/01/cdnpsoriasisguidelines.pdf. Accessed 2019 Oct 15.
5. Canadian Dermatology Association. Psoriasis-diagnosing different forms of psoriasis. 2019; https://dermatology.ca/public-patients/skin/psoriasis/. Accessed 2020 Mar 23.
6. Canadian Psoriasis Guidelines Addendum Committee. 2016 Addendum to the Canadian guidelines for the management of plaque psoriasis 2009. *J Cutan Med Surg.* 2016;20(5):375-431.
7. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol.* 2009;60(4):643-659.
8. National Institute for Health Care and Excellence. Psoriasis: assessment and management. *(Clinical guideline CG153)* 2012; https://www.nice.org.uk/guidance/cg153. Accessed 2020 May 26.
9. Duobrii (halobetasol propionate and tazarotene lotion 0.01% w/w halobetasol propionate and 0.045% w/w tazarotene) [product monograph]. Laval (QC): Bausch Health, Canada Inc.; 2020 Jun 8.
10. Clinical Study Report: V01-118A-301. A phase 3, multicenter, double-blind, randomized, vehicle controlled clinical study to assess the safety and efficacy of IDP-118 in the treatment of plaque psoriasis [CONFIDENTIAL internal sponsor's report]. Petaluma (CA): Valeant Pharmaceuticals North America LLC; 2017 Feb 28.
11. Clinical Study Report: V01-118A-302. A phase 3, multicenter, double-blind, randomized, vehicle controlled clinical study to assess the safety and efficacy of IDP-118 in the treatment of plaque psoriasisTitle of report [CONFIDENTIAL internal sponsor's report]. Petaluma (CA): Valeant Pharmaceuticals North America LCC; 2017 Feb 28.
12. Weisman S, Pollack CR, Gottschalk RW. Psoriasis disease severity measures: comparing efficacy of treatments for severe psoriasis. *J Dermatolog Treat.* 2003;14(3):158-165.
13. Elmets CA, Leonardi CL, Davis DMR, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. *J Am Acad Dermatol.* 2019;80(4):1073-1113.
14. Menter A, Gelfand JM, Connor C, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. *J Am Acad Dermatol.* 2020;82(6):1445-1486.
15. Van Voorhees AS, Feldman SR, Lebwohl MG, Mendelin A, Ritchlin C. The psoriasis and psoriatic arthritis pocket guide. Treatment algorithms and management options. Portland (OR): National Psoriasis Foundation; 2018: https://www.psoriasis.org/sites/default/files/npf_pocketguide_2018.pdf. Accessed 2019 Oct 15.
16. Bhole VM, Choi HK, Burns LC, et al. Differences in body mass index among individuals with PsA, psoriasis, RA and the general population. *Rheumatology (Oxford).* 2012;51(3):552-556.
17. Dowlatshahi EA, Wakkee M, Arends LR, Nijsten T. The prevalence and odds of depressive symptoms and clinical depression in psoriasis patients: a systematic review and meta-analysis. *J Invest Dermatol.* 2014;134(6):1542-1551.
18. Eder L, Chandran V, Shen H, et al. Incidence of arthritis in a prospective cohort of psoriasis patients. *Arthritis Care Res (Hoboken).* 2011;63(4):619-622.
19. Kimball AB, Guerin A, Latremouille-Viau D, et al. Coronary heart disease and stroke risk in patients with psoriasis: retrospective analysis. *Am J Med.* 2010;123(4):350-357.
20. Li W, Han J, Hu FB, Curhan GC, Qureshi AA. Psoriasis and risk of type 2 diabetes among women and men in the United States: a population-based cohort study. *J Invest Dermatol.* 2012;132(2):291-298.
21. Samarasekera EJ, Neilson JM, Warren RB, Parnham J, Smith CH. Incidence of cardiovascular disease in individuals with psoriasis: a systematic review and meta-analysis. *J Invest Dermatol.* 2013;133(10):2340-2346.
22. Wan J, Wang S, Haynes K, Denburg MR, Shin DB, Gelfand JM. Risk of moderate to advanced kidney disease in patients with psoriasis: population based cohort study. *BMJ.* 2013;347:f5961.
23. National Psoriasis Foundation. What's tops in, topical steroid treatments? Just looking for the topical steroid potency chart? https://www.psoriasis.org/about-psoriasis/treatments/topicals/steroids/potency-chart. Accessed 2020 May 26.
24. Kragballe K. Topical corticosteroids: mechanisms of action. *Acta Derm Venereol Suppl (Stockh).* 1989;151:7-10; discussion 47-52.
25. Silkis (calcitriol): 3 µg/g ointment [product monograph]. Thornhill (ON): Galderma Canada Inc.; 2017 Oct 17.

26. Dovonex (calcipotriol): cream and ointment, 50 mcg/g scalp solution, 50 mcg/mL [product monograph]. Thornhill (ON): LEO Pharma Inc.; 2007 Oct 9.

27. Dovobet gel (calcipotriol and betamethasone dipropionate gel): 50 mcg/g calcipotriol (as monohydrate) and 0.5 mg/g betamethasone (as dipropionate) gel [product monograph]. Thornhill (ON): LEO Pharma Inc.; 2020 Feb 25.

28. Dovobet (calcipotriol and betamethasone dipropionate): ointment, 50 mcg/g calcipotriol (as monohydrate) and 0.5 mg/g betamethasone (as dipropionate) [product monograph]. Thornhill (ON): LEO Pharma Inc.; 2016 Apr 4.

29. Enstilar (calcipotriol and betamethasone dipropionate aerosol foam): 50 mcg/g calcipotriol (as monohydrate) and 0.5 mg/g betamethasone (as dipropionate) [product monograph]. Thornhill (ON): LEO Pharma Inc.; 2020 Jan 22.

30. Duobrii (halobetasol propionate and tazarotene lotion): 0.01% w/w halobetasol propionate and 0.045% w/w tazarotene [product monograph]. Laval (QC): Bausch Health, Canada Inc.; 2020 Mar 19. Accessed 2020 May 8.

31. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol.* 2016;75:40-46.

32. Grey matters: a practical tool for searching health-related grey literature. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/grey-matters. Accessed 2020 Mar 6.

33. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol.* 1994;19(3):210-216.

34. Shikiar R, Willian MK, Okun MM, Thompson CS, Revicki DA. The validity and responsiveness of three quality of life measures in the assessment of psoriasis patients: results of a phase II study. *Health Qual Life Outcomes.* 2006;4:71.

35. Long CC. Finlay AY AR. The rule of hand: 4 areas = 2 FTU = 1 g. *Arch Dermatol.* 1992;128(8):1129-1130.

36. Merola JF, Amato DA, See K, et al. Evaluation of sPGA x BSA as an Outcome Measure and Treatment Target for Clinical Practice. *J Invest Dermatol.* 2018;138(9):1955-1961.

37. Smith CH, Jabbar-Lopez ZK, Yiu ZZ, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017 *Br J Dermatol.* 2017;177:628-636.

38. Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol.* 2008;159(5):997-1035.

39. Efficacy of topical therapies for plaque psoriasis: a systematic literature review and network meta-analysis In: CDR submission: duobrii (halobetasol propionate (0.01%) and tazarotene (0.045%) lotion, once daily [CONFIDENTIAL sponsor's submission]. Laval (QC): Bausch Health, Canada Inc.; 2020 Feb 3.

40. Clinical Study Report: V01-118A-303. A phase 3, multicenter, open label study to evaluate the long term safety of IDP-118 lotion in the treatment of plaque psoriasis [CONFIDENTIAL internal sponsor's report]. Petaluma (CA): Valeant Pharmaceuticals North America LCC; 2017 Jul 10.

41. Clinical Study Report: V01-118A-201 A Phase 2, Multicenter, Double-Blind, Randomized, Vehicle Controlled Clinical Study to Assess the Safety and Efficacy of IDP-118 in the Treatment of Plaque Psoriasis [CONFIDENTIAL internal sponsor's report]. 2015.

42. Center for Drug Evaluation and Research. Multi-discipline review. *Duobrii (halobetasol and tazarotene lotion, 0.01%/0.045%). Company: Bausch Health, Canada Inc. Application No.:209354. Approval date: 04/15/2019*. Rockville (MD): U. S. Food and Drug Administration (FDA); 2019 Apr 24: URL. Accessed 2020 May 27.

43. Bausch Health Canada response to February 11 2020 request for additional information regarding duobrii CDR review: CSR for the pooled analysis. [CONFIDENTIAL additional sponsor's information]. Laval (QC): Bausch Health, Canada Inc.; 2020 Feb 19.

44. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics.* 1977;33(1):159-174.

45. Reeve BB, Wyrwich KW, Wu AW, et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. *Qual Life Res.* 2013;22(8):1889-1905.

46. Cohen J. A power primer. *Psychol Bull.* 1992;112(1):155-159.

47. Melilli L, Shikiar R, Thompson C. Minimal clinically important difference in Dermatology Life Quality Index in moderate to severe plaque psoriasis patients treated with adalimumab. *Journal of American Academy of Dermatology.* 2006;54(AB221(P2894)).

48. Ali FM, Salek MS, Finlay AY, Piguet V. Validation of the electronic PASI application: establishing measurement equivalence. *J Am Acad Dermatol.* 2019;19:19.

49. Reolid A, Servitje O, Ginarte M, et al. Validation of an optical pencil method to estimate the affected body surface area in psoriasis. *Actas Dermo Sifiliograficas.* 2019;28:28.

50. Chandran V, Gottlieb A, Cook RJ, et al. International multicenter psoriasis and psoriatic arthritis reliability trial for the assessment of skin, joints, nails, and dactylitis. *Arthritis Rheum.* 2009;61(9):1235-1242.

51. Puzenat E, Bronsard V, Prey S, et al. What are the best outcome measures for assessing plaque psoriasis severity? A systematic review of the literature. *J Eur Acad Dermatol Venereol.* 2010;24 Suppl 2:10-16.

52. Bozek A, Reich A. The reliability of three psoriasis assessment tools: Psoriasis area and severity index, body surface area and physician global assessment. *Adv.* 2017;26(5):851-856.

53. Lewis V, Finlay AY. 10 years experience of the Dermatology Life Quality Index (DLQI). *J Investig Dermatol Symp Proc.* 2004;9(2):169-180.

54. Shikiar R, Bresnahan BW, Stone SP, Thompson C, Koo J, Revicki DA. Validity and reliability of patient reported outcomes used in psoriasis: results from two randomized clinical trials. *Health Qual Life Outcomes.* 2003;1:53.

55. Mazzotti E, Picardi A, Sampogna F, Sera F, Pasquini P, Abeni D. Sensitivity of the Dermatology Life Quality Index to clinical change in patients with psoriasis. *Br J Dermatol.* 2003;149(2):318-322.

56. Both H, Essink-Bot ML, Busschbach J, Nijsten T. Critical review of generic and dermatology-specific health-related quality of life instruments. *J Invest Dermatol.* 2007;127(12):2726-2739.

57. Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. *Ann Rheum Dis.* 2005;64 Suppl 2:ii65-68; discussion ii69-73.

58. Langley RG, Ellis CN. Evaluating psoriasis with Psoriasis Area and Severity Index, Psoriasis Global Assessment, and Lattice System Physician's Global Assessment. *J Am Acad Dermatol.* 2004;51(4):563-569.

59. Robinson A, Kardos M, Kimball AB. Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI): why do both? A systematic analysis of randomized controlled trials of biologic agents for moderate to severe plaque psoriasis. *J Am Acad Dermatol.* 2012;66(3):369-375.

60. Langley RG, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. *J Dermatolog Treat.* 2015;26(1):23-31.

61. Callis Duffin K, Bushmakin AG, Cappelleri JC, Mallbris L, Mamolo C. A multi-item Physician Global Assessment scale to assess psoriasis disease severity: validation based on four phase III tofacitinib studies. *BMC Dermatol.* 2019;19(1):8.

62. Simpson MJ, Chow C, Morgenstern H, Luger TA, Ellis CN. Comparison of three methods for measuring psoriasis severity in clinical studies (Part 2 of 2): use of quality of life to assess construct validity of the Lattice System Physician's Global Assessment, Psoriasis Area and Severity Index and Static Physician's Global Assessment. *J Eur Acad Dermatol Venereol.* 2015;29(7):1415-1420.

63. Cappelleri JC, Bushmakin AG, Harness J, Mamolo C. Psychometric validation of the physician global assessment scale for assessing severity of psoriasis disease activity. *Qual Life Res.* 2013;22(9):2489-2499.

64. Berth-Jones J, Grotzinger K, Rainville C, et al. A Study examining inter- and intrarater reliability of three scales for measuring severity of psoriasis: Psoriasis Area and Severity Index, Physician's Global Assessment and Lattice System Physician's Global Assessment. *Br J Dermatol.* 2006;155(4):707-713.

65. Bozek A, Reich A. The reliability of three psoriasis assessment tools: Psoriasis area and severity index, body surface area and physician global assessment. *Advances in clinical and experimental medicine : official organ Wroclaw Medical University.* 2017;26(5):851-856.

66. Spuls PI, Lecluse LL, Poulsen ML, Bos JD, Stern RS, Nijsten T. How good are clinical severity and outcome measures for psoriasis?: quantitative evaluation in a systematic review. *J Invest Dermatol.* 2010;130(4):933-943.

67. Fleischer AB, Jr., Feldman SR, Dekle CL. The SAPASI is valid and responsive to psoriasis disease severity changes in a multi-center clinical trial. *J Dermatol.* 1999;26(4):210-215.

68. Rhodes J, Clay C, Phillips M. The surface area of the hand and the palm for estimating percentage of total body surface area: results of a meta-analysis. *Br J Dermatol.* 2013;169(1):76-84.