5.02 CALCIPOTRIOL WITH BETAMETHASONE, Cream containing calcipotriol 50 micrograms with betamethasone 500 micrograms (as dipropionate) per g, 60g, Wynzora®, Actor Pharmaceuticals Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule (Restricted Benefit) listing for calcipotriol 0.005% with betamethasone (as dipropionate) 0.05% (hereafter CAL/BDP) cream, 60 g, for the treatment of chronic stable plaque type psoriasis vulgaris in adult patients who have not adequately responded to potent topical corticosteroid (TCS) monotherapy.

1.2 Listing was requested on the basis of a cost-minimisation approach versus CAL/BDP foam and ointment.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Topical treatment of chronic stable plaque type psoriasis of the scalp and body in adults.
Intervention	Calcipotriol 50 microgram/g and betamethasone (as dipropionate) 500 microgram/g cream, 60 g.
Comparator	Primary: calcipotriol 50 microgram/g and betamethasone (as dipropionate) 500 microgram/g foam, 60 g Secondary: calcipotriol 50 microgram/g and betamethasone (as dipropionate) 500 microgram/g ointment, 30 g.
Outcomes	Efficacy outcomes include PGA and mPASI Quality of life outcomes include PTCS, SGA, DLQI, EQ-5D and EQ-VAS, itch by NRS.
Clinical claim	In patients with chronic stable plaque-type psoriasis, CAL/BDP cream is superior in terms of efficacy and non-inferior in terms of safety when compared with CAL/BDP ointment and non-inferior in terms of safety and efficacy when compared with CAL/BDP foam.

Source: Table 1-2, p16 of the submission.
CAL/BDP = calcipotriol 50 microgram/g and betamethasone 500 microgram/g; DLQI = Dermatology Life Quality Index; EQ-5D = European Quality-of-life Five Dimensions questionnaire; EQ-VAS = EQ-5D Visual Analogue Scale; mPASI = Modified Psoriasis Area and Severity Index; NRS = numerical rating scale; PGA = Physician's Global Assessment; PTCS = Psoriasis Treatment Convenience Scale; SGA = Subjects' Global Assessment of disease severity.

2 Background

Registration status

2.1 CAL/BDP cream was Therapeutic Goods Administration (TGA) registered on 25 November 2024 for:

- topical treatment of scalp psoriasis

- topical treatment of mild to moderate plaque psoriasis on the body in adults.

Based on the Product Information (PI), the cream should be applied to affected areas once daily for up to 8 weeks, and treatment should be discontinued when control is achieved. Due to the content of calcipotriol, the maximum daily dose should not exceed 15 g, the maximum weekly dose should not exceed 100 g, and the treated body surface area (BSA) should not exceed 30% (Wynzora® PI).

2.2 The approved TGA indication for CAL/BDP cream is consistent with those of the ointment and foam, the relevant comparators in the submission, except that the indications for the CAL/BDP foam and ointment do not specify use on the scalp or body. Specifically, the approved indication for the foam is "topical treatment of psoriasis vulgaris in adults" and for ointment "indicated for the once daily topical treatment of plaque-type psoriasis vulgaris amenable to topical therapy". Furthermore, disease severity is not specified in the approved indications for CAL/BDP foam and ointment.

Previous PBAC consideration

2.3 This is the first consideration of CAL/BDP cream by the Pharmaceutical Benefits Advisory Committee (PBAC).

- The PBAC recommended listing a 30 g CAL/BDP ointment in July 2009, as a Restricted Benefit on a cost-minimisation basis compared with the individual components for use in the treatment of chronic stable plaque psoriasis in a patient not adequately controlled with either calcipotriol or potent TCS monotherapy (Section 12, calcipotriol with betamethasone dipropionate, Public Summary Document (PSD), July 2009 PBAC meeting).
- The PBAC recommended listing a 30 g and 60 g CAL/BDP gel in November 2015, on a cost-minimisation basis to the ointment formulation (paragraph 6.27, calcipotriol with betamethasone dipropionate, PSD, Nov 2015 PBAC meeting).
- In November 2016, the PBAC recommended listing a 60 g CAL/BDP foam formulation, on a cost-utility basis against the ointment (paragraph 7.1, calcipotriol with betamethasone dipropionate, PSD, Nov 2016).

2.4 Currently, only the CAL/BDP 30 g ointment and 60 g foam are listed on the Pharmaceutical Benefits Scheme (PBS) for the treatment of chronic stable plaque type psoriasis that is inadequately controlled by potent TCS monotherapy. The gel (60 g) was delisted from the PBS in November 2022 after becoming Supply Only in November 2021, and the 30 g gel was delisted from the PBS in August 2018.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 The submission requested a Section 85 (General Schedule) Restricted Benefit listing for CAL/BDP cream consistent with the indication in the TGA-approved PI, and with the current PBS listings for CAL/BDP ointment (30 g) and foam (60 g) formulations.

3.2 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack		**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
CALCIPOTRIOL + BETAMETHASONE						
calcipotriol 0.005% + betamethasone (as dipropionate) 0.05% cream, 60 g		NEW (GE)	1	1	1	Wynzora
Restriction Summary [NEW] / Treatment of Concept: [NEW]						
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)					
	Prescriber type: ☒Medical Practitioners ☒Nurse Practitioners					
	Restriction type: ☒ Restricted benefit					
	Administrative Advice: **Continuing Therapy Only:** For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.					
	Indication: Chronic stable plaque type psoriasis vulgaris					
	Clinical criteria:					
	The condition must be inadequately controlled by potent topical corticosteroid monotherapy.					
	~~**Population criteria:**~~					
	~~Patient must be 18 years or older~~					
MEDICINAL PRODUCT medicinal product pack		**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
CALCIPOTRIOL + BETAMETHASONE						
calcipotriol 0.005% + betamethasone (as dipropionate) 0.05% cream, 60 g		NEW (GE)	2	2	1	Wynzora
Restriction Summary [NEW] / Treatment of Concept: [NEW]						
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)					
	Prescriber type: ☒Medical Practitioners ☒Nurse Practitioners					
	Restriction type: ☒ Restricted benefit					
	Administrative Advice: **Continuing Therapy Only:** For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.					
	Indication: Chronic stable plaque type psoriasis vulgaris					

	Clinical criteria:
	The condition must be stable for the prescriber to consider the listed maximum quantity of this medicine suitable for this patient,
	AND
	Clinical criteria:
	The condition must be inadequately controlled by potent topical corticosteroid monotherapy.
	~~**Population criteria:**~~
	~~Patient must be 18 years or older~~

3.3 The submission requested listing with a maximum quantity of 1 pack (60 g) and maximum of 1 repeat, and a corresponding 60-day maximum dispensed quantity listing of 2 packs with 1 repeat, consistent with the current PBS listings for CAL/BDP foam and ointment.

3.4 The submission requested that medical practitioners and nurse practitioners be included as eligible prescribers for the CAL/BDP cream listings, consistent with the current PBS listings for CAL/BDP foam and ointment.

3.5 The listing requested in the submission included the population criterion: 'Patient must be 18 years or older'. This is consistent with the CAL/BDP cream PI. The PIs for CAL/BDP foam and ointment also state that treatment is not recommended for patients below the age of 18 years, however the current PBS listings for CAL/BDP foam and ointment do not include this population criterion.

3.6 The requested restriction for CAL/BDP cream did not include a stopping criterion. This is consistent with the current PBS listings for CAL/BDP foam and ointment which do not include a stopping criterion. According to the PI, the recommended duration of treatment with CAL/BDP cream is up to 8 weeks, and treatment should be discontinued when disease control is achieved.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Psoriasis is a chronic inflammatory skin condition associated with several comorbidities and has a significant impact on patients' quality-of-life (QoL). Systemic manifestations of psoriasis may include arthritis, cardiovascular disease, depression, diabetes, anxiety, and obesity. Australia has one of the highest prevalence rates for psoriasis, at 1.88% overall and 2.38% in adults.[1,2] Plaque psoriasis (psoriasis vulgaris)

[1] Parisi R., Iskandar I.Y.K, Kontopantelis E, et al, (2020), 'National, regional, and worldwide epidemiology of psoriasis: systematic analysis and modelling study', BMJ 369:m1590.
[2] Global Psoriasis Atlas, (2024), 'Prevalence Data Australia', available at www.globalpsoriasisatlas.org/en/

is the most common type of psoriasis accounting for approximately 90% of psoriasis cases.[3,4] Plaque psoriasis is characterised by erythematous scaly patches or plaques that can occur on any region of the skin, with the scalp being the most common initial location.

4.2 Based on the Therapeutic Guidelines (2025)5, topical therapies, such as keratolytics, TCS, vitamin D analogues, coal tar extracts, and combinations of these agents, are recommended for the treatment of mild to moderate plaque psoriasis. Patients who have demonstrated an inadequate response to TCS monotherapy may be considered for treatment with a combination of TCS and calcipotriol. Currently, as outlined in paragraph 2.3, the only combination products containing calcipotriol available in Australia are those with betamethasone (as dipropionate), which is listed on the PBS in both foam and ointment formulations.

4.3 Calcipotriol is a vitamin D analogue and betamethasone dipropionate is a synthetic fluorinated corticosteroid. In combination, CAL/BDP products promote greater anti-inflammatory and anti-proliferative effects than either component alone.6 CAL/BDP cream is a topical aqueous formulation, which the submission claimed provides greater improvements in quality of life, along with superior treatment satisfaction and adherence, when compared to other available CAL/BDP products.

4.4 The submission proposed that CAL/BDP cream would be positioned in the same place in the treatment pathway as the currently listed CAL/BDP foam and ointment products. This was reasonable, given the CAL/BDP foam and ointment contain the same active ingredients at the same strength as CAL/BDP cream, with differences only in formulation.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated CAL/BDP foam as the main comparator and CAL/BDP ointment as the secondary comparator. This was appropriate. CAL/BDP foam accounts

[3] Armstrong A.W., Read C., (2020), 'Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review,' JAMA 323(19) pp. 1945-1960.
[4] Rendon A., Schäkel K, (2019), 'Psoriasis Pathogenesis and Treatment', Int J Mol Sci 20(6):1475.
[5] Therapeutic Guidelines, 'Advice for managing psoriasis in primary care', published August 2022 (amended February 2025), accessed on April 2025, available at https://app.tg.org.au/2ae0edf6-8508-4da1-a9d9-4012cb89c705
[6] Lebwohl M., Tyring S., Bukhalo M., et al, (2016), 'Fixed Combination Aerosol Foam Calcipotriene 0.005% (Cal) Plus Betamethasone Dipropionate 0.064% (BD) is More Efficacious than Cal or BD Aerosol Foam Alone for Psoriasis Vulgaris: A Randomized, Double-blind, Multicenter, Three-arm, Phase 2 Study', J Clin Aesthet Dermatol 9(2): 34-41.

for the majority of the market share within the proposed PBS population, based on data from the PBS Item Statistics, and was therefore nominated as a primary comparator.

5.2 While several topical TCS monotherapies are available as first-line treatments for plaque psoriasis on the PBS, they were not considered comparators, as the proposed restriction requires prior inadequate response to potent TCS monotherapy. Furthermore, systemic and biologic treatments are indicated for severe psoriasis and later line of therapy and thus were not considered comparators in this submission. This was reasonable.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission conducted a literature review to identify relevant randomised controlled trials (RCTs) comparing the safety and efficacy of CAL/BDP cream versus each of CAL/BDP foam and CAL/BDP ointment.

CAL/BDP cream versus ointment

6.4 The submission was based on three RCTs; one phase 2 trial comparing CAL/BDP cream to ointment (MC2-01-C3) and two phase 3 trials comparing CAL/BDP cream with gel (MC2-01-C2 and MC2-01-C7). The CAL/BDP gel was used as a proxy for the ointment, based on the assumption of equivalent efficacy and safety between the gel and ointment formulations. The submission claimed the PBAC had previously considered CAL/BDP gel and ointment to have equivalent efficacy and safety, with an equi-effective dose defined as 1 g of gel to 1 g of ointment. In the November 2015 submission, the claim of equivalent efficacy and safety between CAL/BDP gel and ointment was based on direct and indirect evidence provided. The trial and study presented were not designed to show non-inferiority, the trial had a small sample size and short treatment duration, and the study was not designed as a comparative effectiveness study. Limited safety data was presented in the direct evidence provided. The trials included in the indirect comparison had limited exchangeability and there were differences in the trial populations' baseline disease state (patients using gel may have had a milder disease state). Overall, the PBAC considered that CAL/BDP gel was most likely to have similar efficacy and safety to CAL/BDP ointment

(paragraphs 6.16-6.18, calcipotriol and betamethasone dipropionate gel, PSD, November 2015 PBAC Meeting).

CAL/BDP cream versus foam

6.5 In the absence of direct head-to-head trials comparing CAL/BDP cream with foam, the submission relied on four published indirect treatment comparison (ITC) studies (Bewly et al. 2022, Reich et al. 2022, Papp et al. 2022, and Jalili et al. 2024). These studies conducted anchored and/or unanchored matching-adjusted indirect comparisons (MAICs) of CAL/BDP cream with CAL/BDP foam, using CAL/BDP gel as the common comparator.

6.6 These ITCs included data from the two CAL/BDP cream (MC2-01-C2 and MC2-01-C7) and up to five CAL/BDP foam trials (PSO-ABLE, PSO-INSIGHTFUL, PSO-LONG, PSO-FAST, LEO90100-07, and LEO90100-35). Papp et al. 2022 included data from five of these trials. The remaining ITCs included data from four trials (Jalili et al. 2022) or two trials (Bewley et al. 2022 and Reich et al. 2022), depending on the comparison. Of these, data from the LEO90100-35 has been previously considered in the submission for both CAL/BDP gel in November 2015 and CAL/BDP foam in November 2016.

6.7 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
CAL/BDP cream versus CAL/BDP ointment		
MC2-01-C3 (NCT03462927)	A Randomised, Multicentre, Open-label, Parallel-group Maximal Use Trial, Evaluating the Pharmacokinetic Profile of the Active Ingredients and their Metabolites after application of MC2-01 Cream compared with Active Comparator in Subjects with Extensive Psoriasis Vulgaris.	July 2019
CAL/BDP cream versus CAL/BDP gel		
MC2-01-C2 (NCT03308799)	A Randomised, Multicentre, Investigator-Blind, Parallel-Group Trial to Evaluate the Efficacy and Safety of MC2-01 Cream Compared to MC2-01 Cream Vehicle and Active Comparator in Subjects with Mild-to-Moderate Psoriasis Vulgaris.	April 2019
	Selmer J, Vestbjerg B, Praestegaard M, et al. MC2-01 cream has improved overall psoriasis treatment efficacy compared to calcipotriene plus betamethasone dipropionate topical suspension [Abstract].	J Psoriasis Psoriatic Arthritis 2019;4(3)166-7.
	Stein Gold L, Green LJ, Dhawan S, et al. Calcipotriene and betamethasone dipropionate cream combines high efficacy, favourable safety, and treatment preference in a single product for topical treatment of psoriasis.	Journal of Dermatology for Physician Assistants 2021;15(4):67-8.
	Stein Gold L, Green LJ, Dhawan S, et al. A Phase 3, Randomized Trial Demonstrating the Improved Efficacy and Patient Acceptability of Fixed Dose Calcipotriene and Betamethasone Dipropionate Cream.	J Drugs Dermatol 2021;20(4):420-5.
	Armstrong A, Praestegaard M, Selmer J, et al. Combined analysis of two head-to-head Phase 3 trials demonstrating superior improvement of patient reported outcomes for calcipotriene and betamethasone dipropionate cream compared to gel/topical suspension in treatment of plaque psoriasis.	J Clin Aesthet Dermatol 2022;15(4 SUPPL 1):S25.
	Armstrong A, Pinter A, Selmer J, et al. Pooled Analysis Demonstrating Superior Patient-Reported Psoriasis Treatment Outcomes for Calcipotriene/ Betamethasone Dipropionate Cream Versus Suspension/Gel.	J Drugs Dermatol 2022;21(3):242-8.
	Pinter A, Green LJ, Selmer J, et al. A pooled analysis of randomized, controlled, phase 3 trials investigating the efficacy and safety of a novel, fixed dose calcipotriene and betamethasone dipropionate cream for the topical treatment of plaque psoriasis.	J Eur Acad Dermatol Venereol 2022 Feb;36(2):228-36.
	Kontzias CL, Curcio A, Gorodokin B, et al. Efficacy, Convenience, and Safety of Calcipotriene-Betamethasone Dipropionate Cream in Skin of Colour Patients With Plaque Psoriasis.	J Drugs Dermatol 2023;22(7):668-72.
	Pinter A, Stein Gold L, Reich A, et al. A novel, fixed-dose calcipotriol and betamethasone dipropionate cream for the topical treatment of plaque psoriasis: Direct and indirect evidence from phase 3 trials discussed at the 30th EADV Congress 2021.	J Eur Acad Dermatol Venereol 2023;37(suppl.1):14-9.
MC2-01-C7 (NCT03802344, EUCTR2018-001970-66-CZ)	A Randomised, Multicentre, Investigator-Blind, Parallel-Group Trial to Evaluate the Efficacy and Safety of MC2-01 Cream Compared to Vehicle and Active Comparator in Subjects with Mild-to-Moderate Psoriasis Vulgaris.	April 2020
	Pinter A, Reich A, Arenberger P, et al. Randomized Phase 3 trial demonstrating high efficacy, favourable safety and convenience of a novel calcipotriol and betamethasone dipropionate cream for the treatment of psoriasis.	J Eur Acad Dermatol Venereol 2023 Nov;37(11):2327-35.

Trial ID	Protocol title/ Publication title	Publication citation
	Halioua B, Caillet G, Taieb C, et al. A novel calcipotriol and betamethasone dipropionate (CAL/BDP) PAD-cream demonstrates greater improvements in daily activities and personal relationships than CAL/BDP gel/TS: A post-hoc analysis of DLQI outcomes from two phase 3 placebo-controlled randomized clinical trials in mild-to-moderate psoriasis.	J Eur Acad Dermatol Venereol 2024 Apr;38(4):e326-8.
CAL/BDP cream versus CAL/BDP foam		
Anchored MAIC	Bewley A, Barker E, Baker H, et al. An anchored matching-adjusted indirect comparison of fixed-dose combination calcipotriol and betamethasone dipropionate (Cal/BDP) cream versus Cal/BDP foam for the treatment of psoriasis.	J Dermatolog Treat 2022 Dec;33(8):3191-8.
Anchored and unanchored MAIC	Papp KA, Thoning H, Gerdes S, et al. Matching-adjusted indirect comparison of efficacy outcomes in trials of calcipotriol plus betamethasone dipropionate foam and cream formulations for the treatment of plaque psoriasis.	J Dermatolog Treat 2022 Nov;33(7):3005-13.
Indirect comparison	Reich A, Selmer J, Galván J, et al. Efficacy, quality of life, and treatment satisfaction: an indirect comparison of calcipotriol/betamethasone dipropionate cream versus foam for treatment of psoriasis.	Curr Med Res Opin 2022 Sep;38(9):1521-9.
Anchored and unanchored MAIC	Jalili A, Thoning H, Jablonski Bernasconi MY, et al. Matching-adjusted Indirect Comparison of Dermatology Life Quality Index 0/1 Response in Trials of Calcipotriol Plus Betamethasone Dipropionate Foam and Cream Formulations in Patients with Psoriasis.	Acta Derm Venereol 2024 Feb 8;104:adv12623.
Narrative review	Torres T, Galván J, Crutchley N, et al. Calcipotriol and Betamethasone Dipropionate Cream Based on PAD Technology for the Treatment of Plaque Psoriasis: A Narrative Review.	Dermatol Ther (Heidelb) 2023 Oct;13(10):2153-69.
Critical appraisal	Fargnoli MC, De Simone C, Gisondi P, et al. Topical Treatment for the Management of Mild-to-Moderate Psoriasis: A Critical Appraisal of the Current Literature.	Dermatol Ther (Heidelb). 2023 Nov;13(11):2527-47.

Source: Table 2-3, pp44-46 of the submission.
CAL/BDP = calcipotriol with betamethasone dipropionate; MAIC = matching-adjusted indirect comparison

6.8 The key features of the direct randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias*	Patient population	Outcome(s)
CAL/BDP cream versus CAL/BDP ointment					
MC2-01-C3	63 (CAL/BDP cream: 32 CAL/BDP ointment: 31)	R, OL, PG, MC, Phase II CAL/BDP cream: 8 weeks CAL/BDP ointment: 4 weeks	High	Patients with extensive psoriasis vulgaris on trunk, limbs or scalp	Primary: PK profile; Secondary: effect on HPA axis and calcium metabolism; other outcomes: PGA, PTCS, safety
CAL/BDP cream versus CAL/BDP gel					
MC2-01-C2	796 (CAL/BDP cream: 343 CAL/BDP gel: 338 Vehicle: 115)	R, OL, IB, PG, MC, Phase III 8 weeks	High	Patients with mild to moderate psoriasis vulgaris on trunk or limbs	Primary: PGA; Secondary: mPASI; SGA; DLQI; EQ-5D, itch by NRS; safety
MC2-01-C7	490 (CAL/BDP cream: 213 CAL/BDP gel: 209 Vehicle: 68)	R, OL, IB, PG, MC, Phase III 8 weeks	High	Patients with psoriasis vulgaris on trunk, limbs and scalp	Primary: mPASI; Secondary: PGA; PTCS; SGA; DLQI; EQ-5D; EQ-VAS; safety

Source: Section 2.3, pp49-58 of the submission.
CAL/BDP = calcipotriol with betamethasone dipropionate; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQoL five dimensions; EQ-VAS = European Quality-Visual Analogue Scale; HPA = hypothalamic pituitary adrenal; IB = investigator-blinded; MC = multi-centre; mPASI = Modified Psoriasis Area and Severity Index; N = total participants in group; NRS = numerical rating scale; OL = open label; PG = parallel group; PGA = Physician's Global Assessment; PK = pharmacokinetics; PTCS = Psoriasis Treatment Convenience Scale; R = randomised; SGA = Subject's Global Assessment of disease severity.
*added during evaluation.

6.9 MC2-01-C3 was designed to assess the pharmacokinetic profile of the active ingredients in CAL/BDP cream and ointment in patients with extensive psoriasis vulgaris, with the hypothalamic pituitary adrenal (HPA) axis and calcium metabolism as secondary outcomes, and Physician's Global Assessment (PGA), Psoriasis Treatment Convenience Scale (PTCS) and adverse events (AEs) as other outcomes. Patients randomised to CAL/BDP cream received treatment for 8 weeks, compared to 4 weeks for those randomised to CAL/BDP ointment. This was consistent with the respective PIs.

6.10 MC2-01-C2 and MC2-01-C7 were designed to demonstrate superiority of CAL/BDP cream to cream vehicle and non-inferiority of CAL/BDP cream to gel (topical suspension in the MC2-01-C2 in the United States and gel in the MC2-01-C7). The trials reported outcomes such as PGA (primary outcome in MC2-01-C2), modified Psoriasis Area Severity Index (mPASI; primary outcome in MC2-01-C7), PTCS, Subject's Global Assessment (SGA), Dermatology Life Quality Index (DLQI), QoL, and safety. However, only results for PGA, mPASI, and PTCS were presented in the submission. In both trials, patients were randomised to receive CAL/BDP cream, CAL/BDP gel, or a cream vehicle for 8 weeks. This was consistent with the respective PIs.

6.11 The description of the key outcomes presented in the submission are summarised below.

Table 4: Key outcomes presented in the submission

Outcome	Description	Scale
PGA	The physician's impression of the psoriatic plaque thickening, scaling and erythema, at a single point. PGA is measured separately for the body (trunk or limbs) and scalp.	0 (clear) to 4 (severe psoriasis)
mPASI	The extent and severity of three clinical signs (redness, thickness and scaliness) on the arms, trunk and legs, excluding the scalp.	0 (no psoriatic involvement) to 64.8 (very severe and extensive area with psoriasis)
PTCS	Treatment convenience and overall satisfaction using five core items, and each item is scored by patients on a scale of 1 (low satisfaction) to 10 (high satisfaction).	5 (low satisfaction) to 50 (high satisfaction)

Source: Section 1.1.2.2, pp18-19; Section 1.1.2.3, pp19-20 of the submission and MC2-01-C2 CSR.
CSR = clinical study report; mPASI = Modified Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; PTCS = Psoriasis Treatment Convenience Scale.

6.12 According to the Australian College of Dermatologists (ACD) consensus adaption7, PGA is a validated objective score, with adequate response to treatment defined as 0 (clear) or 1 (almost clear). However, the definition of treatment success using PGA varied in the trials presented in the submission. The MC2-01-C3 trial defined PGA success as a minimum two-point decrease from baseline (on a scale of 0 to 4, with higher score indicating severe condition), whereas MC2-01-C2 and MC2-01-C7 defined PGA success as both a minimum two-point reduction from baseline and achieving a PGA score of 0 or 1.

6.13 All three trials reported changes in mPASI score from baseline, to assess the extent and severity of three clinical signs (redness, thickness and scaliness) on the arms, trunk and legs. The mPASI score ranges from 0 to 64.8, with higher scores indicating more severe and extensive disease. However, the ACD consensus adaptation does not explicitly define an adequate treatment response based on changes in mPASI from baseline.

6.14 The use of both PGA and mPASI to assess efficacy in both the pivotal efficacy studies (MC2-01-C2 and MC2-01-C7) was considered appropriate by the TGA, based on the Clinical Evaluation Report for CAL/BDP cream, which was presented as an attachment to the submission.

6.15 PTCS is a patient-rated treatment convenience measure which was developed by MC2 Therapeutics and implemented in a clinical trial assessing CAL/BDP cream. The submission states that the PTCS was validated in Feldman et al. (2021). The evaluation considered the use of PTCS to inform treatment efficacy to be uncertain due to several limitations identified in its development and validation. These limitations include:

- the study by Feldman et al. (2021) was industry-funded;

[7] The Australian College of Dermatologist (ACD), (2024), 'ACD consensus adaptation – Treatment goals for moderate-to-severe psoriasis in paediatric and adult Australian patients', accessed on March 2025, available at www.dermcoll.edu.au/wp-content/uploads/2024/05/ACD-Consensus-Adaptation-Psoriasis-May-2024.pdf

- lack of generalisability as PTCS was only used in RCTs with CAL/BDP cream;
- low internal consistency reliability (Cronbach's alpha = 0.61, below the predefined threshold of 0.7);
- absence of test-retest reliability data (intersubject variation of more than 60% of total variation);
- lack of criterion validity due to absence of gold standard comparator;
- no reported exploratory or confirmatory factor analysis to assess the structure;
- no evaluation of correlation of PTCS scores and other patient-reported outcomes, such as treatment adherence or QoL.

6.16 All three trials were assessed as having a high risk of bias (Table 4). MC2-01-C3 was an open-label study, with both patients and investigators unblinded, leading to a high risk of detection bias. MC2-01-C2 and MC2-01-C7 were investigator-blinded only, but the differences in formulation and packaging may have unblinded patients, potentially affecting the reliability of reported outcomes.

6.17 The submission stated that there was no established minimally clinically important difference (MCID) for PGA and mPASI in psoriasis for the comparative efficacy of two products. No information was presented regarding the MCID for PTCS.

Comparative effectiveness

CAL/BDP cream versus ointment

6.18 At Week 4 of the MC2-01-C3 study, the PGA treatment success rates were comparable in both CAL/BDP cream and ointment groups (29.6% versus 26.7%). However, only 25.9% of the patients treated with CAL/BDP cream achieved a PGA 0 or 1 at Week 4, indicating that most patients failed to achieve an adequate treatment response based on the ACD consensus adaptation. Similarly, only 26.7% of the patients treated with CAL/BDP ointment achieved PGA 0 or 1 at Week 4.

6.19 The submission stated that CAL/BDP cream had a statistically significant better treatment convenience compared to ointment, based on the PTCS least square means (LSM) difference of 4.7 (95% CI: 1.3, 8.2), and higher mean scores for preferences regarding the greasiness of the two topical products. The mean scores were similar on the attributes related to ease of use, moisturising effect, and overall satisfaction. The PTCS results may be confounded by the lack of reporting on the site of psoriasis in the trials, as the site of psoriasis may impact the patient's preference for either cream or ointment. In addition, it was uncertain if the difference in the PTCS results between the CAL/BDP cream and ointment group was clinically meaningful, and there are several limitations of the PTCS measure as discussed in paragraph 6.15.

CAL/BDP cream versus gel

6.20 In both MC2-01-C2 and MC2-01-C7, the intention-to-treat (ITT) population, all randomised subjects, was the primary analysis set for efficacy outcomes for the analysis of superiority of CAL/BDP cream and gel versus the vehicle. The per-protocol (PP) population, patients in the ITT population who completed the trial without any major protocol violations, was the primary analysis for the analysis of non-inferiority of CAL/BDP cream versus gel in MC2-01-C2. Using PP population for analysis may introduce selection bias and compromise randomisation, potentially overestimating treatment efficacy.

6.21 In both trials, a variety of methods were used to handle missing efficacy data for the ITT population, with multiple imputation as the primary imputation method. No imputations were made for missing data in the PP population, except for PTCS, where the last-observation-carried forward (LOCF) method was applied. The submission did not report the percentage of missing data, and as a result, the impact of the potential bias remains unclear. Inconsistency in handling missing data was inappropriate and undermined comparability. Furthermore, LOCF assumes stability after dropout which may not reflect actual disease progression and subsequently bias the results.

Physician's Global Assessment (PGA) of Psoriasis Severity

6.22 The results on PGA success rate in MC2-01-C2 are presented in Table 5.

Table 5: PGA treatment success at Week 8 in MC2-01-C2

	CAL/BDP cream	CAL/BDP gel	Vehicle
ITT Population (Multiple Imputation)			
PGA Treatment Success Rate[a]			
N	342	337	115
Percentage of patients with PGA treatment success (%)	37.4	22.8	3.7
Superiority Analysis, Logistic Regression[b]			
Odds Ratio, CAL/BDP cream or gel vs. vehicle	**17.1**	**8.0**	-
Odds Ratio 95% CI	**6.1, 47.8**	**2.8, 22.4**	-
Per-protocol Population (Observed Cases)			
PGA Treatment Success Rate[a]			
n/N (%)	121/302 (40.1)	67/279 (24.0)	4/88 (4.5)
95% CI[c]	34.5, 45.6	19.0, 29.0	-
Non-inferiority Analysis[d]			
Success Rate Difference, CAL/BDP cream versus gel	16.1		-
Success Rate Difference 95% CI	8.6, 23.5		-

Source: Table 2-37, pp83-84 of the submission

CAL/BDP = calcipotriol with betamethasone dipropionate; CI = confidence interval; n = number of participants with event; N = total participants in group; PGA = Physician's Global Assessment; ITT = intent to treat; vs = versus.

[a] PGA success is defined as a minimum 2-point decrease from Baseline to Week 8 on the PGA of disease severity on the trunk and limbs.

[b] Logistic model includes treatment and baseline value of PGA (mild/moderate) as independent variables. Analysis site is not included in the model due to partial data separation.

[c] 95% confidence interval estimated using normal approximation.

[d] Non-inferiority margin used is 10% points.

Bold indicates statistically significant results.

6.23 At Week 8, the proportions of patients achieving PGA treatment success were 37.4%

for the CAL/BDP cream group, 22.8% in the CAL/BDP gel group, and 3.7% in the vehicle group. Both CAL/BDP cream and CAL/BDP gel were statistically significantly more effective than the vehicle, with an odds ratio (OR) of 17.1 (95% CI: 6.1, 47.8) and OR of 8.0 (95% CI: 2.8, 22.4), respectively.

6.24 As superiority to vehicle was achieved for both CAL/BDP cream and CAL/BDP gel, the non-inferiority analysis comparing CAL/BDP cream to CAL/BDP gel was conducted using a non-inferiority margin of -10% points. Based on the PP population, the PGA treatment success was higher in the CAL/BDP cream group (40.1%) compared to CAL/BDP gel group (24.0%), with the difference in PGA treatment success rate between CAL/BDP cream and gel of 16.1 (95% CI: 8.6, 23.5), and non-inferiority was achieved.

6.25 As the lower bound of the 95% CI was >0, a statistically significantly higher efficacy of CAL/BDP cream compared with gel was assumed. The approach of inferring superiority based on the lower bound of the 95% confidence interval being greater than zero was not appropriate, as superiority should be pre-specified and formally tested.

6.26 The results on PGA success rate in MC2-01-C7 are presented Table 6.

Table 6: PGA treatment success on the body at Week 8 in MC2-01-C7

	CAL/BDP cream	CAL/BDP gel	Vehicle
Full analysis set Population (Multiple Imputation)			
PGA Treatment Success Rate[a]			
N	213	209	68
Percentage of patients with PGA treatment success (%)	50.7	42.7	6.1
95% CI	0.44, 0.58	0.36, 0.50	-0.002, 0.12
Unadjusted Rate Difference vs. vehicle	**0.45**	**0.37**	-
95% CI of Unadjusted Rate Difference	**0.35, 0.54**	**0.27, 0.46**	-
Non-inferiority Analysis[b]			
Unadjusted Rate Difference, CAL/BDP cream vs. gel	0.079	-	-
95% CI of Unadjusted Rate Difference	-0.017, 0.18	-	-
Superiority Analyses by Logistic Regression[c]			
Log Odds Ratio vs. Vehicle	**3.44**	**3.00**	-
95% CI of Log Odds Ratio	**2.13, 4.75**	**1.68, 4.33**	-
Log Odds Ratio vs. CAL/BDP gel	**0.45**		-
95% CI of Log Odds Ratio	**0.01, 0.90**		-

Source: Table 2-42, p92 of the submission.

CAL/BDP = calcipotriol with betamethasone dipropionate; CI = confidence interval; n = number of participants with event; N = total participants in group; PGA = Physician's Global Assessment; vs = versus.

[a] PGA success is defined as a minimum 2-point decrease from Baseline to a severity of clear or almost clear. Confidence interval of rate difference computed using normal approximation.

[b] Non-inferiority margin is 10% points.

[c] Logistic regression model includes randomised treatment, analysis site and Baseline PGA on the body as independent variables. P-values are for test of difference

Bold indicates statistically significant results.

6.27 At Week 8, the proportion of patients achieving PGA treatment success were 50.7% for the CAL/BDP cream group, 42.7% in the CAL/BDP gel group, and 6.1% in the vehicle group. CAL/BDP cream and CAL/BDP gel were statistically significantly more effective

than the vehicle, with an unadjusted rate difference of 0.4 (95% CI: 0.4, 0.5) and 0.4 (95% CI: 0.3, 0.5), respectively.

6.28 As both CAL/BDP cream and CAL/BDP gel demonstrated superiority over vehicle, a non-inferiority analysis comparing CAL/BDP cream to gel was conducted using a non-inferiority margin of -10% points. The unadjusted rate difference in PGA treatment success was 0.1 (95% CI: -0.02, 0.2). The submission concluded that non-inferiority was achieved, as the lower bound of the 2-sided 95% CI was ≥-10%.

6.29 The log OR of CAL/BDP cream and gel was 0.5 (95% CI: 0.01, 0.90), which the submission stated showed a statistically significantly difference in treatment success in favour of CAL/BDP cream. However, as stated above in paragraph 6.25, superiority should be pre-specified and formally tested.

Modified Psoriasis Area and Severity Index (mPASI)

6.30 The results on mPASI in MC2-01-C2 are presented in Table 7.

Table 7: Percentage reduction from baseline in mPASI score at Week 8 in MC2-01-C2

	CAL/BDP cream	CAL/BDP gel	Vehicle
ITT Population (Multiple Imputation)			
N	342	337	115
Mean percentage change in mPASI from baseline (%)	62.9	51.3	22.9
Superiority Analysis, ANCOVA[a]			
LSM (SE)	63.2 (1.8)	51.1 (1.8)	22.8 (3.5)
LSM Difference [CAL/BDP cream or gel vs. vehicle] (SE)	**40.4 (3.9)**	**28.4 (3.9)**	-
Per-protocol Population (Observed Cases)			
N	302	279	88
Mean (SD)	64.8 (28.7)	52.3 (33.3)	25.7 (35.3)
Non-inferiority Analysis, ANCOVA[a]			
LSM (SE)	65.1 (1.7)	52.0 (1.8)	25.4 (3.2)
LSM Difference (CAL/BDP cream vs. gel) (SE)	13.1 (2.5)	-	-
96.7% CI	7.8, 18.4	-	-

Source: Table 2-38, p85 of the submission
ANCOVA = analysis of covariance; CAL/BDP = calcipotriol with betamethasone dipropionate; CI = confidence interval; ITT = intent-to-treat; LSM = least square means; mPASI = Modified Psoriasis Area and Severity Index; N = total participants in group; SE = standard error; SD = standard deviation; vs = versus.
Percentage reduction from Baseline in the mPASI score at Week 8 is defined as Baseline score minus Week 8 score divided by Baseline score.
[a] ANCOVA model includes treatment, baseline PGA severity (mild/moderate), baseline mPASI, and analysis site as independent variables. Non-inferiority margin used is 10% points.
Bold indicates statistically significant results.

6.31 At Week 8, the mean percentage reduction from baseline in mPASI score was larger for CAL/BDP cream (-62.9%) than for CAL/BDP gel (-51.3%) or vehicle (-22.9%). The difference was statistically significant for both treatment groups versus vehicle.

6.32 In the PP population, the mean percentage reduction from baseline in mPASI score at Week 8 was higher in the CAL/BDP cream group (64.8%) compared to the CAL/BDP gel group (52.3%) and the vehicle group (25.7%). The LSM difference between CAL/BDP

cream and gel was 13.1 (96.7% CI: 7.8, 18.4).

6.33 The submission concluded that non-inferiority was achieved, as the lower bound of the 2-sided 96.7% CI was ≥-10%. The submission further stated that CAL/BDP cream was statistically significantly more efficacious than CAL/BDP gel as the lower bound of the 96.7% CI was >0. The approach of inferring superiority based on the lower bound of the 96.7% confidence interval being greater than zero was not appropriate, and superiority should be pre-specified and formally tested.

6.34 The results on mPASI in MC2-01-C7 are presented Table 8.

Table 8: Percentage change in mPASI at baseline at Week 8 in MC2-01-C7

	CAL/BDP cream	CAL/BDP gel	Vehicle
FAS Population (Multiple Imputation)			
N	213	209	68
Mean percentage change in mPASI from baseline[a] (%)	-67.5	-63.5	-11.7
Superiority Analysis, ANCOVA[b]			
LSM (SE)	-73.1 (20.8)	-	-16.4 (20.7)
LSM Difference [(CAL/BDP cream vs. vehicle] (SE)	**-56.7 (4.9)**	-	-
Superiority Analysis, ANCOVA[b]			
LSM (SE)	-	-61.2 (22.2)	-9.1 (21.9)
LSM Difference [CAL/BDP gel vs. vehicle] (SE)	-	**-52.0 (5.0)**	-
Non-inferiority and Superiority Analyses of CAL/BDP cream versus CAL/BDP gel[c]			
LSM (SE)	-78.8 (9.7)	-74.6 (9.8)	-
LSM Difference (SE)	-4.2 (2.8)	-	-
95% CI of LSM difference	-9.6, 1.2	-	-

Source: Table 2-41, p90 of the submission.
ANCOVA = analysis of covariance; CAL/BDP = calcipotriol with betamethasone dipropionate; CI = confidence interval; FAS = full analysis set; LSM = least square means; mPASI = Modified Psoriasis Area and Severity Index; N = total participants in group; SE = standard error; vs = versus.
[a] A negative percentage change from Baseline indicates a decrease of mPASI score, i.e. an improvement of symptoms.
[b] The analysis of covariance model includes randomised treatment, analysis site, Baseline PGA severity on the body; and Baseline mPASI as independent variables. P-values are for test of difference.
[c] Non-inferiority margin is 12% points, P-values are for test of difference.
Bold indicates statistically significant.

6.35 At Week 8, the mean percentage reduction from baseline in mPASI score at Week 8 was larger for CAL/BDP cream (-67.5%) than for CAL/BDP gel (-63.5%) or vehicle (- 11.7%). The difference was statistically significant for both treatment groups versus vehicle. The LSM difference between CAL/BDP cream and gel was -4.2 (95% CI: -9.6, 1.2).

6.36 The submission concluded that non-inferiority was achieved, as the upper bound of the 2-sided 95% CI was ≤12%. This was appropriate. The submission stated that the no-difference hypothesis of CAL/BDP cream versus gel could not be rejected (p=0.1), and although the LSM difference in treatment effect favoured CAL/BDP cream, superiority was not achieved.

Psoriasis Treatment Convenience Scale (PTCS)

6.37 The results on PTCS in MC2-01-C2 and MC2-01-C7 are presented below.

Table 9: PTCS total score at Week 8 in MC2-01-C2 and MC2-01-C7.

	CAL/BDP cream	CAL/BDP gel	Vehicle
MC2-01-C2 (ITT population using LOCF)			
N	338	334	110
Mean PTCS score (SD)	41.5 (6.5)	37.5 (7.7)	36.7 (7.2)
Range	22, 50	9, 50	17, 50
Superiority Analysis, ANCOVA[a]			
LSM (SE)	41.5 (0.4)	37.5 (0.4)	36.7 (0.7)
LSM Difference (CAL/BDP cream vs. CAL/BDP gel) (SE)	**4.0 (0.6)**	-	-
98.3% CI	**2.7, 5.3**	-	-
MC2-01-C7 (FAS population using LOCF)			
N	213	209	68
Mean PTCS score (SD)	38.6 (6.2)	36.1 (7.0)	36.2 (7.6)
Range	22, 50	17, 50	5, 50
ANCOVA[a]			
LSM (SE)	43.0 (2.3)	40.5 (2.3)	-
Superiority Analyses by Logistic Regression			
LSM Difference (SE)	**2.5 (0.6)**	-	-
95% CI of LSM difference	**1.2, 3.8**	-	-

Source: Table 2-39, pp87-88; Table 2-43, pp93-94 of the submission.
ANCOVA = analysis of covariance; CAL/BDP = calcipotriol with betamethasone dipropionate; CI = confidence interval; FAS = full analysis set; ITT = intent to treat; LOCF = Last-observation-carried forward; LSM = least square means; N = total participants in group; PTCS = Psoriasis Treatment Convenience Scale; SD = standard deviation; SE = standard error, vs = versus.
A PTCS score is considered valid if subjects have used the study medication at some point within 7 days prior to the day of the assessment. PTCS total score is calculated as the sum of questions 1-5.
[a] ANCOVA model includes treatment, baseline PGA severity (mild/moderate), and analysis site as independent variables.
Non-inferiority margin used is 10% points.
Bold indicates statistically significant results.

6.38 At Week 8 in MC2-01-C2, the mean PTCS score was greater for CAL/BDP cream (41.5) than for CAL/BDP gel (37.5) or vehicle (36.7), with a LSM difference of 4.0 (98.3% CI: 2.7, 5.3). The submission concluded that CAL/BDP cream was superior in terms of treatment convenience compared to CAL/BDP gel. This conclusion was uncertain given the uncertainty in the clinical significance of the PTCS score as discussed in paragraph 6.15.

6.39 At Week 8 in MC2-01-C7, the mean PTCS score was 38.6 for CAL/BDP cream, 36.1 for CAL/BDP gel, and 36.2 for vehicle, with a LSM difference of 2.5 (95% CI: 1.2, 3.8). The submission concluded that CAL/BDP cream was superior in terms of treatment convenience compared to CAL/BDP gel. As described in the previous paragraph, this conclusion was uncertain given the limitations of the PTCS as discussed in paragraph 6.15.

6.40 The LSM difference between CAL/BDP cream versus CAL/BDP gel at Week 4 in both MC2-01-C2 and MC2-01-C7 trials were consistently in favour of CAL/BDP cream; however, it was uncertain if PTCS at Week 4 and Week 8 was sufficient to capture the outcome on treatment convenience for a chronic condition.

CAL/BDP cream versus foam

6.41 As stated in paragraph 6.5, no head-to-head trials comparing CAL/BDP cream with foam were available. Instead, the submission relied on four published ITC studies. Table 10 summarises the key results and conclusions, at the recommended treatment durations (8 weeks for CAL/BDP cream and 4 weeks for CAL/BDP foam), from these studies.

Table 10: A summary of the key results and conclusions presented in the ITCs between CAL/BDP cream and CAL/BDP foam via CAL/BDP gel

Author	Method	Included studies	Results	Conclusion
Bewley et al., 2022	Anchored matching-adjusted indirect comparison was made using IPD from two CAL/BDP cream trials and published aggregated data from two CAL/BDP foam trials	**CAL/BDP cream** MC2-01-C2 MC2-01-C7 **CAL/BDP foam** PSO-ABLE PSO-INSIGHTFUL	Equivalent efficacy (PGA, mPASI, PTCS) Equivalent HRQoL (DLQI)	• CAL/BDP cream and CAL/BDP foam had equivalent efficacy and HRQoL outcomes • CAL/BDP cream was more convenient than foam
Reich et al., 2022	Anchored indirect comparison was made using data from two CAL/BDP cream trials and two CAL/BDP foam trials	**CAL/BDP cream** MC2-01-C2 MC2-01-C7 **CAL/BDP foam** PSO-ABLE PSO-INSIGHTFUL	Equivalent efficacy (PGA, mPASI, PTCS) QoL (DLQI) favoured cream	• CAL/BDP cream and CAL/BDP foam had equivalent efficacy outcomes • CAL/BDP cream significantly improved treatment satisfaction and tended to improve QoL versus CAL/BDP foam
Papp et al., 2022	Anchored and unanchored MAIC analyses were conducted using individual patient data from five CAL/BDP foam trials and two CAL/BDP cream trials	**CAL/BDP cream** MC2-01-C2 MC2-01-C7 **CAL/BDP foam** PSO-ABLE PSO-LONG PSO-FAST LEO90100-07 LEO90100-35	<u>Anchored</u> Equivalent efficacy (PGA, mPASI) <u>Unanchored</u> Efficacy (PGA) favours foam for PSO-FAST, LEO90100-35; efficacy equivalent for LEO90100-7 Efficacy (mPASI) favours foam Efficacy (PGA, mPASI) favours foam for PSO-LONG	CAL/BDP foam had significantly improved efficacy outcomes compared with CAL/BDP cream
Jalili et al., 2024	Anchored and unanchored MAIC analyses were conducted using individual patient data from four CAL/BDP foam trials and two CAL/BDP cream trials (follow-up study to Papp et al., 2022)	**CAL/BDP cream** MC2-01-C2 MC2-01-C7 **CAL/BDP foam** PSO-ABLE PSO-LONG PSO-FAST LEO90100-07	Equivalent QoL (DLQI)	CAL/BDP cream and CAL/BDP foam had equivalent QoL outcomes

Source: Table 2-49, p100; Table 2-50, p100; Table 2-55, p107; Table 2-63, p114; Table 2-65, pp122-123; Table 2-66, p127 of the submission.
CAL/BDP = calcipotriol with betamethasone dipropionate; DLQI = dermatology life quality index; HRQoL = health related quality of life; IPD = individual patient data; ITC = indirect treatment comparison; QoL = quality of life; mPASI = Modified Psoriasis Area and Severity Index; MAIC = matching-adjusted indirect comparison; PGA = Physician's Global Assessment; PTCS = Psoriasis Treatment Convenience Scale.

6.42 Based on Bewley at al. (2022), an anchored MAIC between CAL/BDP cream and foam using CAL/BDP gel as the common anchor, showed no statistically significant differences in efficacy outcomes, including PGA success (OR=0.7, 95% CI: 0.4, 1.2), 75% reduction in psoriasis area and severity index (mPASI75) (OR=0.7, 95% CI: 0.4, 1.2), and improvement of DLQI from baseline (mean difference [MD]=0.9, 95% CI: -0.3, 2.1) in the matched population at the recommended treatment duration. The overall patient-rated treatment satisfaction at Week 1 was in favour of CAL/BDP cream over foam (MD=0.3, 95% CI: 0.02, 0.5). While the differences were not statistically significant, point estimates suggested greater improvements in PGA success and mPASI75 with the CAL/BDP foam, whereas the CAL/BDP cream showed a greater improvement in DLQI from baseline.

6.43 Reich et al. (2022) conducted an ITC between CAL/BDP cream and foam, using gel as the common comparator. At the recommended treatment duration, no statistically significant differences were observed in the PGA success (RR=0.8, 95% CI: 0.6, 1.1), PASI75 response (RR=0.9, 95% CI: 0.6, 1.1), and DLQI improvement (MD= - 1.0, 95% CI= -2.2, 0.2). Similar to Bewley et al. (2022), the point estimates for PGA success rate and mPASI75 favoured CAL/BDP foam, while improvement in DLQI from baseline favoured CAL/BDP cream. Furthermore, treatment with CAL/BDP foam was associated with statistically significant PGA success (RR=0.7; 95% CI: 0.5, 1.0) and PASI75 (RR=0.8; 95% CI: 0.6, 1.0) compared to CAL/BDP cream at Week 8. The overall patient-rated treatment satisfaction at Week 1 was in favour of CAL/BDP cream over foam (MD on PTCS for CAL/BDP cream versus foam: 0.6, 95% CI: 0.1, 1.1).

6.44 The results from Bewley et al. (2022) and Reich et al. (2022) and their comparison may be uncertain due to several limitations: (i) study population heterogeneity; (ii) treatment satisfaction was assessed at Week 1, despite the trial duration ranging from 4 to 8 weeks; (iii) different instruments were matched to assess treatment satisfaction across arms—PTCS in the CAL/BDP cream group and the Topical Product Usability Questionnaire (TPUQ) in the CAL/BDP foam group; (iv) limitation associated with using PTCS as a measure of treatment satisfaction, as outlined in paragraph 6.15; (v) lack of inpatient level data for CAL/BDP foam studies; and (vi) exclusion of four CAL/BDP foam RCTs (PSO-FAST, PSO-LONG, LEO90100-07, and LEO90100-35) from the MAIC due to the absence of a common comparator.

6.45 Papp et al. (2022) conducted both anchored and unanchored MAICs using published aggregate data from the CAL/BDP cream and individual patient data from the CAL/BDP foam trials. The analyses were stratified by trial population (United States [US], European Union [EU], and pooled). Based on the anchored MAIC, at the

recommended treatment duration, patients treated with CAL/BDP foam were more likely to achieve PGA success and showed greater mean improvements in mPASI compared to those treated with CAL/BDP cream; however, these differences were not statistically significant except for the mPASI analysis in the EU population. In the unanchored MAICs, CAL/BDP foam was statistically significantly more effective in achieving PGA success in five of the six analyses. Additionally, mean reductions in mPASI were consistently and statistically significantly greater with CAL/BDP foam compared to CAL/BDP cream.

6.46 Papp et al. (2022) identified several study limitations which increased the risk of bias to the results: (i) heterogeneity in the study populations, (ii) only one comparative evidence in anchored analysis, (iii) rounding of patient numbers and small sample sizes, and (iv) uncertainty surrounding the validity of the patient reported outcomes, specifically the PTCS and TPUQ measures.

6.47 Jalili at al. (2024) was designed as a follow-up study to Papp et al. (2022) and compared QoL (in terms of DLQI) using both anchored and unanchored MAIC. Based on the anchored MAIC (via CAL/BDP gel), no statistically significant differences were observed in the DLQI 0/1 response between CAL/BDP cream and foam at the recommended treatment duration (OR=0.7, 95% CI: 0.4, 1.2), although the point estimate favoured the cream. Similarly, the unanchored MAICs also showed no statistically significant differences in the DLQI 0/1 response (OR=1.0, 95% CI: 0.8, 1.3). The submission highlighted several limitations of the study, including the potential for bias due to unobserved differences across trials and the small sample size in the CAL/BDP foam (LEO900100-07) study.

6.48 Overall, the ITCs showed that CAL/BDP cream and CAL/BDP foam had equivalent efficacy and health related QoL, except for the unanchored comparisons in Papp et al. (2022) which showed efficacy in favour of CAL/BDP foam. In addition, the results from Bewley et al. (2022) and Reich et al. (2022) suggested that treatment convenience and satisfaction was greater with CAL/BDP cream, compared to CAL/BDP ointment. However, the conclusion from the ITCs were uncertain given the limitations noted above (for further details refer paragraphs 6.44, 6.46 and 6.47).

Comparative harms

CAL/BDP cream versus ointment

6.49 Table 11 and Table 12 summarise the key safety outcomes, based on the safety population in all three CAL/BDP foam trials.

Table 11: Summary of key adverse events in the MC2-01-C3 trial

Trial ID	CAL/BDP cream n/N (%)	CAL/BDP ointment n/N (%)	RR (95% CI)*	RD (95% CI)*
Day 0 – week 4[a]				
TEAE, n (%)	2 / 32 (6.3%)	5 / 31 (16.1%)	0.4 (0.1,1.9)	-0.1 (-0.3,0.1)
Treatment-related TEAE, n (%)	1 / 32 (3.1%)	3 / 31 (9.7%)	0.3 (0.04,2.9)	-0.1 (-0.2,0.1)
Serious AE, n (%)	0	1 / 31 (3.2%)	NA	-0.03 (-0.1,0.03)
Serious TEAE, n (%)	0	1 / 31 (3.2%)	NA	-0.03 (-0.1,0.03)
AEs leading to study discontinuation, n (%)	1 / 32 (3.1%)	0	NA	0.03 (-0.03,0.1)

Source: Table 2-44, p95 of the submission.

AE = adverse event; CAL/BDP = calcipotriol with betamethasone dipropionate; CI = confidence interval; n = number of participants reporting data; N = total participants in group; NA = not available; RD = risk difference; RR = relative risk; TEAE = treatment emergent adverse event.

[a] Includes TEAEs with an onset date on or before Week 4 visit for CAL/BDP cream subjects, and all TEAEs for CAL/BDP gel subjects.

*added during evaluation

6.50 By Week 4 of the MC2-01-C3 trial, only one incident of treatment-related treatment emergent adverse event (TEAE) was reported in the CAL/BDP cream group, due to application site folliculitis, and three events of treatment-related TEAEs in the CAL/BDP ointment group, due to cortisol deficiency, application site folliculitis and frequent urination. No serious TEAEs were reported in the CAL/BDP cream group during the trial, as opposed to one serious TEAE in the CAL/BDP ointment group (the nature of the serious TEAE was not specified in the MC2-01-C3 CSR). After Week 4, the most common treatment-related TEAEs associated with CAL/BDP cream were HPA axis suppression (n=5), hypercorticoidism (n=1), application site rash (n=1), and application site pruritus (n=1). A total of six patients (18.8%) had CAL/BDP cream discontinued due to AEs such as HPA suppression (n=5) and steroid-induced folliculitis and pruritis (n=1), post Week 4.

CAL/BDP cream versus gel

Table 12: Summary of key adverse events in the randomised trials

	CAL/BDP cream n/N (%)	CAL/BDP gel n/N (%)	Vehicle n/N (%)	RR (95% CI) CAL/BDP cream vs. gel*	RD (95% CI) CAL/BDP cream vs. gel*
MC2-01-C2					
TEAE[a], n (%)	90 / 342 (26.3%)	76 / 337 (22.6%)	32 / 115 (27.8%)	1.2 (0.9,1.5)	0.04 (-0.03,0.1)
Treatment-related TEAE[a], n (%)	12 / 342 (3.5%)	11 / 337 (3.3%)	5 / 115 (4.3%)	1.1 (0.5,2.4)	0.0 (-0.03,0.03)
Serious AE[a], n (%)	8 / 342 (2.3%)	9 / 337 (2.7%)	4 / 115 (3.5%)	0.9 (0.3,2.2)	-0.0 (-0.03,0.02)
Serious TEAE[a], n (%)	8 / 342 (2.3%)	9 / 337 (2.7%)	4 / 115 (3.5%)	0.9 (0.3,2.2)	-0.0 (-0.03,0.02)
AEs leading to study discontinuation[a], n (%)	2 / 342 (0.6%)	3 / 337 (0.9%)	4 / 115 (3.5%)	0.7 (0.1,3.9)	-0.0 (-0.02,0.01)
MC2-01-C7					
TEAE[b], n (%)	58 / 213 (27.2%)	46 / 209 (22.0%)	17 / 67 (25.4%)	1.2 (0.9,1.7)	0.05 (-0.03,0.1)
Treatment-related TEAE[b], n (%)	11 / 213 (5.2%)	3 / 209 (1.4%)	7 / 67 (10.4%)	**3.6 (1.0,12.7)**	**0.04 (0.003,0.07)**
Serious AE, n (%)	1 / 213 (0.5%)	3 / 209 (1.4%)	1 / 67 (1.5%)	0.3 (0.03,3.1)	-0.01 (-0.03,0.01)
Serious TEAE[b], n (%)	1 / 213 (0.5%)	3 / 209 (1.4%)	1 / 67 (1.5%)	0.3 (0.03,3.1)	-0.01 (-0.03,0.01)
TEAEs leading to treatment discontinuation, n (%)	1 / 213 (0.5%)	2 / 209 (1.0%)	4[c] / 67 (6.0%)	0.5 (0.04,5.4)	-0.005 (-0.02,0.01)

Source: Table 2-45, p96; Table 2-46, p97 of the submission.
AE = adverse event; CAL/BDP = calcipotriol with betamethasone dipropionate; CI = confidence interval; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk; TEAE = treatment emergent adverse event; vs = versus.
[a] For each treatment, a subject will be counted once only within each AE category. TEAEs include all AEs starting or worsening after the first dose of study drug.
[b] TEAE was defined as AEs starting or worsening after the first application.
[c] One AE led to discontinuation of investigational medicinal product (vehicle) and trial. As the "action taken for investigational medicinal product" for this AE falsely was documented with "no change" this AE is not counted in the Table. Number was added based on information in subjects data listings.
*added during evaluation
Bold indicates statistically significant results

6.51 Based on the MC2-01-C2 CSR, the most common serious TEAEs associated with CAL/BDP cream were application site issues (n=6) and application site folliculitis (n=2). In the CAL/BDP gel arm, nine patients had serious TEAEs (infection [n=3]; atrial fibrillation [n=1]; chest pain [n=1]; fever [n=1]; dehydration [n=1]; cervix carcinoma [n=1]; nephrolithiasis [n=1]; and chronic obstructive pulmonary disease [n=1]). None of the serious TEAEs were related to the treatment. Two patients discontinued CAL/BDP cream due to non-cutaneous AEs unrelated to the treatment, and three patients discontinued CAL/BDP gel due to application site folliculitis, dermatitis, and dizziness with headache.

6.52 In MC2-01-C7, a total of 4 serious TEAEs due to non-cutaneous reasons were reported in the CAL/BDP cream (testicular seminoma [n=1]) and gel groups (herpes zoster

meningitis [n=1]; fracture [n=1]; and pulmonary tuberculosis [n=1]), and none were related to the assigned treatment. Only one patient discontinued CAL/BDP cream due to moderate urticaria. Two patients discontinued CAL/BDP gel due to non-cutaneous reasons: gastrointestinal symptoms and pulmonary tuberculosis.

CAL/BDP cream versus foam

6.53 The submission did not present any comparative safety data between CAL/BDP cream and foam. Moreover, none of the published ITC included safety outcomes.

Benefits/harms

6.54 A benefits and harms table is not presented as the submission made a claim of non-inferiority against CAL/BDP foam.

6.55 The submission made a claim of superiority against CAL/BDP ointment; however, a benefits/harms table is not presented as the benefits of CAL/BDP cream versus ointment were based on a pharmacokinetics study (MC2-01-C3) which showed comparable PGA treatment success rates. Although that study showed statistically significant better PTCS scores with CAL/BDP cream compared to ointment, there were several limitations with the PTCS as discussed in paragraph 6.15. The harms were presented in Table 11.

Clinical claim

6.56 The submission described CAL/BDP cream as superior in terms of efficacy and non-inferior in terms of safety compared to CAL/BDP ointment. The claim of superiority in efficacy was not adequately supported by the evidence because:

- The evidence was based on a head-to-head pharmacokinetic trial comparing CAL/BDP cream with ointment (MC2-01-C3), and two non-inferiority trials between CAL/BDP cream and gel (MC2-01-C2 and MC2-01-C7), assuming gel as a proxy for ointment. The Pre-Sub-Committee Response (PSCR) maintained that CAL/BDP gel was a relevant proxy for CAL/BDP ointment, due to the PBAC previously considering the equi-effective dose is 1 gram gel to 1 gram ointment.
- The MC2-01-C3 trial demonstrated similar efficacy between the treatment arms in terms of PGA success rate (29.6% vs. 26.7%). The PSCR stated that the MC2-01-C3 trial was a small study and was designed to demonstrate equivalent safety outcomes between CAL/BDP cream and ointment. It claimed that the small sample size was not large enough to evaluate superior efficacy between treatments, and that superior efficacy of CAL/BDP cream is demonstrated in the MC2-01-C2 and MC2-01-C7 trials.
- While CAL/BDP cream showed statistically significant greater treatment convenience in MC2-01-C3 using the PTCS, the PTCS was developed by the sponsor (MC2 Therapeutics) and this instrument has several limitations, including low internal consistency and lack of external validity, as outlined in paragraph 6.15.

The PSCR claimed a literature review was undertaken, which reported that patients often find use of ointment to be messy, and there were concerns about its impact on adherence. Compliance studies found that poor adherence to topical treatments for psoriasis can contribute to poor treatment outcomes,[8] and patients generally prefer light, moisturising and quickly absorbing forms over ointment for ease of use and cosmetic acceptability. The PSCR stated that a literature review found an absence of a validated patient questionnaire specific for evaluating psoriasis treatment convenience, and the PTCS was therefore developed. The PSCR claimed that developing the PTCS followed Food and Drug Administration (FDA) guidance on patient-reported outcome (PRO) validation and the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) on good practice. The PSCR claimed that analysis of the validity of the instrument showed a modest to good relative effect size and high sensitivity to detect treatment differences.

- MC2-01-C2 and MC2-01-C7 trials were designed to demonstrate non-inferiority rather than superiority. Therefore, the approach of inferring superiority based on the lower bound of the 95% confidence interval being greater than zero was not appropriate, as superiority should be pre-specified and formally tested. The PSCR acknowledged that in MC2-01-C7 superiority was not achieved and that the difference in treatment success rate for PGA showing statistical significance to the advantage of CAL/BDP cream was outside the confirmatory testing hierarchy. The PSCR and pre-PBAC response maintained that in MC2-01-C2 the difference in PGA treatment success rate between cream and gel demonstrated statistical significance at the 0.05 level, and argued that the cream was superior to gel across the range of plausible true treatment differences. The PSCR and pre-PBAC response maintained that superiority of CAL/BDP cream compared to CAL/BDP gel has been demonstrated.
- The proportion of missing data was not reported, and the methods used to handle missing data were inconsistent; thereby, the impact of potential bias remains unclear in MC2-01-C2 and MC2-01-C7 trials.
- The findings in these trials may have been confounded by a higher mean amount of drug used in the CAL/BDP cream groups compared to the comparator arms. The PSCR claimed that additional analyses for MC2-01-C2 and MC2-01-C7 trials were conducted to evaluate efficacy by amount of drug used, and that efficacy of CAL/BDP cream was higher than CAL/BDP gel efficacy regardless of the amount used. The pre-PBAC response referred to post-hoc analyses undertaken to compare the percentage change in BSA psoriatic involvement from baseline to

[8] Zivkovich AH, Feldman SR, (2009), 'Are ointments better than other vehicles for corticosteroid treatment of psoriasis?' J Drugs Dermatol 8(6):570-2.

week 8 for cream and active comparator in the MC2-01-C2 and MC2-01-C7 trials, based on the amount of drug used, to support its claim.

6.57 Considering the results of non-inferiority in efficacy and safety outcomes between CAL/BDP cream and CAL/BDP gel in MC2-01-C2 and MC2-01-C7 trials, and assuming CAL/BDP gel and CAL/BDP ointment have similar safety and efficacy, the efficacy and safety of CAL/BDP cream and CAL/BDP ointment are likely comparable.

6.58 The ESC considered there was a high risk of bias in the MC2-01-C3, MC2-01-C2 and MC2-01-C7 trials, and noted that MC2-01-C3 was a small study where the primary outcomes was the pharmacokinetic profile. The ESC considered the findings for MC2-01-C2 and MC2-01-C7 trials demonstrated non-inferiority between the cream and the gel and considered the inference that the cream has superior efficacy compared to the gel may not be statistically appropriate.

6.59 The ESC noted that the PTCS was developed by the sponsor and was focused on the ease of use of the product and feeling of the treatment (e.g. greasiness). The ESC considered that while convenience is an important part of patient experience, it does not directly indicate adherence. The ESC considered that the claim that CAL/BDP cream was superior in terms of treatment convenience compared to CAL/BDP gel was uncertain, given uncertainty in the clinical significance of the PTCS score.

6.60 The ESC considered there was insufficient evidence to support the claim that CAL/BDP cream had superior efficacy compared to CAL/BDP ointment.

6.61 The submission described CAL/BDP cream as non-inferior in terms of effectiveness and safety compared with CAL/BDP foam. The claim for non-inferior effectiveness was probably reasonable but is uncertain, and for non-inferior safety was uncertain because:

- No head-to-head trials comparing CAL/BDP cream with foam were available; instead, the submission relied on four published unanchored and anchored ITC studies.
- Several limitations were identified across these studies, including heterogeneity among studies, the exclusion of CAL/BDP foam trials from the anchored ITCs due to the absence of a common comparator, and the use of different instruments to assess treatment satisfaction across treatment arms: PTCS in the CAL/BDP cream group and the TPUQ in the CAL/BDP foam group.

6.62 The ESC considered there were limitations in the studies provided comparing CAL/BDP cream and CAL/BDP foam, and there was a lack of safety data comparing CAL/BDP cream with the foam.

6.63 The PSCR acknowledged that ITC studies present a measure of uncertainty due to a lack of head-to-head studies, but argued that the submission presented a robust analysis of all available peer-reviewed, published ITCs in the absence of head-to-head trials. The PSCR claimed that anchored matching ITCs provide the most robust analysis

of comparative efficacy in the absence of head-to-head trials, and that when analysed using an anchored MAIC methodology, CAL/BDP cream was shown to have equivalent efficacy to CAL/BDP foam, and the cream had higher treatment satisfaction. The PSCR maintained that the evidence presented supports the claim that CAL/BDP cream has non-inferior efficacy and safety compared with CAL/BDP foam.

6.64 Overall, the ESC considered that CAL/BDP cream demonstrated non-inferior efficacy to both CAL/BDP ointment and foam.

6.65 The PBAC considered that the claim of superior comparative effectiveness compared to CAL/BDP ointment was not adequately supported by the data. The PBAC considered that the claim of non-inferior comparative safety compared to CAL/BDP ointment was reasonable.

6.66 The PBAC considered that the claim of non-inferior comparative effectiveness and safety compared to CAL/BDP foam was reasonable.

Economic analysis

6.67 The submission presented a cost-minimisation approach. The key components are shown in Table 13.

Table 13: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in Section 2, effectiveness is assumed to be non-inferior to CAL/BDP foam and superior to CAL/BDP ointment.
Therapeutic claim: safety	Based on evidence presented in Section 2, safety is assumed to be non-inferior to both CAL/BDP foam and CAL/BDP ointment.
Evidence base	A direct randomised trial versus CAL/BDP ointment Direct randomised trials versus CAL/BDP gel, as a proxy to ointment* Indirect treatment comparison of randomised trials versus CAL/BDP foam.
Equi-effective doses	Cost-minimisation for the proposed medicine was conducted on a gram-for-gram basis as a 50/50 split between CAL/BDP foam and CAL/BDP ointment.
Direct medicine costs	CAL/BDP, 0.05% foam 60 g, 1 pack: AEMP of $67.19 CAL/BDP, 0.05% ointment 30 g, 1 pack: AEMP of $23.83 CAL/BDP, 0.05% cream 60 g, 1 pack: Cost-minimised AEMP of $57.43
Other costs or cost offsets	None

Source: Table 3-3, p135; Table 3-5, p137 of the submission.
AEMP = approved ex-manufacturer price; CAL/BDP = calcipotriol with betamethasone dipropionate; g = gram.
*added during evaluation

6.68 The submission stated that CAL/BDP cream will uptake a market share from both the CAL/BDP products (foam and ointment) listed on the PBS. As a result, the submission proposed a 50/50 cost-minimisation split between CAL/BDP foam and ointment on a gram-for-gram basis. This was informed by the dispensed units from the PBS Item Statistics over six years, which indicated that CAL/BDP foam (11091R and 13520N (60-day maximum dispensed quantity listing)) accounted for approximately 56% of the PBS market share while CAL/BDP ointment (9494Q and 13577N (60-day maximum dispensed quantity listing)) comprised the remaining 44%. Although the market share is based on PBS Item Statistics data, it remains uncertain whether CAL/BDP cream will

capture market share from foam or ointment, or what the proportions of market share from the foam or ointment would be. The utilisation may be influenced by various factors such as patient preferences, clinician recommendation, product availability, and the site and size of psoriasis.

6.69 The equi-effective doses were estimated by the submission as CAL/BDP cream 1 gram to CAL/BDP foam 1 gram or CAL/BDP ointment 1 gram.

6.70 Based on their respective PIs, the dosing regimen for CAL/BDP cream is once daily with a recommended treatment period of up to 8 weeks, whereas for CAL/BDP foam and CAL/BDP ointment, the dosing regimen is also once daily but with a recommended treatment period of up to 4 weeks. While the submission acknowledged that the recommended treatment duration varied between the CAL/BDP products, it did not account for the difference in duration of therapy when estimating the equi-effective doses.

6.71 In clinical practice, patients may be treated beyond the recommended course duration of 8 weeks for CAL/BDP cream and 4 weeks for CAL/BDP foam or ointment, or repeat the treatment course multiple times, given that plaque psoriasis is a chronic condition. Additionally, patients who respond earlier to treatment may cease treatment prior to the maximum recommended treatment duration. Different products have different recommendations for ongoing treatment (e.g. Entsilar foam spray PI recommends the foam be used for 4 weeks, and patients who have responded to treatment can use long-term maintenance treatment applying foam twice weekly on two non-consecutive days; Daivobet® ointment PI recommends that treatment 'should be intermittent for up to one year… Treatment should be limited to four week periods with calcipotriol used alone for one month between periods of use of Daivobet 50/500 ointment as needed' (Daivobet Ointment PI)).

6.72 Patients may also adjust their usage according to their response to treatment and frequency of flare ups. The utilisation may also be affected by patients' preferences for certain formulations due to the site of psoriatic plaque, occlusive effect of the formulation, and extent of psoriasis. Therefore, the actual duration of treatment and preference for different CAL/BDP products in clinical practice remains uncertain.

6.73 During the PBAC consideration of CAL/BDP gel in November 2015, the PBAC deemed the approach of assuming a dose of 1 g gel to 1 g ointment appropriate (paragraph 6.30, calcipotriol with betamethasone dipropionate gel, PSD, November 2015 PBAC meeting), despite the difference in the treatment duration between CAL/BDP gel (8 weeks) and ointment (4 weeks).

6.74 However, during the PBAC consideration of CAL/BDP foam in November 2016, an economic model with a time horizon of 48 weeks was presented based on superior efficacy of CAL/BDP foam compared to CAL/BDP gel (paragraph 6.23 and 6.28, calcipotriol with betamethasone dipropionate foam, PSD, November 2016 PBAC meeting), despite the difference in the treatment duration of CAL/BDP foam (4 weeks)

and CAL/BDP gel (8 weeks). The ESC noted that if patients responded earlier to treatment, continuation of use might cease before the standard 4-week treatment period, potentially resulting in cost savings (paragraph 6.29, calcipotriol with betamethasone dipropionate foam, PSD, November 2016 PBAC meeting).

6.75 The PSCR argued that as psoriasis is a chronic condition, in clinical practice duration of use of treatment may not always align with the standard recommended treatment duration. The PSCR claimed that patients using CAL/BDP cream may have improved adherence due to better acceptability and convenience, which will hasten disease resolution and reduce usage overall. Patients may not require 8 weeks of use if disease control is achieved earlier. However, this was not reflected in the MC2-01-C2 and MC2-01-C7 CSRs, where the overall amount of drug used was higher in the CAL/BDP cream group compared to the CAL/BDP gel group.

6.76 The PSCR further maintained that after initial treatment CAL/BDP cream will be used as maintenance treatment, which is consistent with other topical products. The PSCR referred to the PBAC's consideration of CAL/BDP gel in November 2015, where it deemed the approach of assuming 1 g gel to 1 g ointment appropriate, despite the differences in treatment duration (8 weeks for gel and 4 weeks for ointment).

6.77 Based on the clinical evidence presented by the submission, there was insufficient evidence to support a price premium over the least expensive PBS-listed CAL/BDP product (i.e., ointment) for the treatment of chronic plaque type psoriasis in adults.

6.78 The cost-minimisation was presented based on drug acquisition cost only. No differences were assumed in the utilisation of other healthcare resources relating to administration of the drugs or management of AEs. This was reasonable.

6.79 The results of the cost minimisation approach as presented in the submission are shown in Table 14.

Table 14: Results of the cost-minimisation approach

	Component	CAL/BDP foam	CAL/BDP ointment	CAL/BDP cream
a*	DPMQ	$85.70[a] $160.17[b]	$39.08[a] $64.71[b]	$75.21[a] $138.13[b]
b*	AEMP	$67.19	$23.83	$57.43
c*	Pack size (g)	60	30	60
d = b / c*	Cost per gram	$1.12	$0.79	$0.96
	Average cost per gram	$0.96		$0.96

Source: Table 3-4 and Table 3-5, p137 of the submission.
AEMP = approved ex-manufacturer price; CAL/BDP = calcipotriol with betamethasone dipropionate; DPMQ = dispensed price for maximum quantity; g = gram.
[a] DPMQ based on maximum quantity of one pack.
[b] DPMQ based on maximum quantity of two packs (60 Day Maximum Dispensed Quantity).
*added during evaluation

6.80 Based on the cost-minimised approved ex-manufacturer price (AEMP), the dispensed price for maximum quantity (DPMQ) for CAL/BDP cream was estimated to be $75.21 for a maximum quantity of 1 pack, and $138.13 for a maximum quantity of 2 packs.

6.81 Table 15 presents the results of sensitivity analyses conducted during the evaluation to estimate the impact of incorporating treatment duration into equi-effective dosing, as well as to determine the cost-minimised price based on lowest-cost comparator, i.e., CAL/BDP ointment.

Table 15: Results of sensitivity analyses using published AEMP of CAL/BDP

Component	CAL/BDP cream 60 g	Change from base case (%)
Base case		
Cost per pack AEMP	$57.43	-
DPMQ for 1 pack	$75.21	-
DPMQ for 2 packs	$138.13	-
Applying the treatment duration based on the recommended treatment duration in PIs[a]		
Cost per pack AEMP	$28.71	-50.0%
DPMQ for 1 pack	$44.33	-41.1%
DPMQ for 2 packs	$75.21	-45.65%
Cost minimisation based on CAL/BDP ointment alone[b] and similar treatment duration to CAL/BDP ointment		
Cost per pack AEMP	$47.66	-17.0%
DPMQ for 1 pack	$64.70	-14.0%
DPMQ for 2 packs	$116.07	-16.0%
Applying the treatment duration based on the PIs[a] and cost minimisation based on CAL/BDP ointment alone[b]		
Cost per pack AEMP	$23.83	-58.5%
DPMQ for 1 pack	$39.08	-48.0%
DPMQ for 2 packs	$64.71	-53.2%

Source: Calculated during evaluation

AEMP = approved ex-manufacturer price; CAL/BDP = calcipotriol with betamethasone dipropionate; DPMQ = dispensed price for maximum quantity; g = gram; PI = Product Information; RCT = randomised controlled trial.

[a] Based on the respective PIs, the recommended treatment period with CAL/BDP cream is up to 8 weeks, and with CAL/BDP foam or ointment is up to 4 weeks.

[b] Based on the non-inferior effectiveness demonstrated in RCTs (MC2-01-C2 and MC2-01-C7) of CAL/BDP cream versus gel, and assuming an equivalent dose of 1 g gel to 1 g ointment was appropriate (paragraph 6.30, calcipotriol with betamethasone dipropionate gel, PSD, November 2015 PBAC meeting).

6.82 The sensitivity analyses showed that applying the recommended treatment duration for CAL/BDP products, based on their respective PIs, resulted in a 50% reduction in the cost-minimised AEMP of CAL/BDP cream. Additionally, cost-minimisation to CAL/BDP ointment alone, the lowest cost-comparator, resulted in a 17% reduction in the cost-minimised AEMP of CAL/BDP cream. By considering both recommended treatment duration based on PIs and cost-minimisation to CAL/BDP ointment alone, the cost-minimised AEMP for CAL/BDP cream reduced by 58.5%. The ESC noted that estimated costs of CAL/BDP cream is significantly affected based on the recommended treatment duration.

6.83 The PSCR stated that the sponsor is willing to negotiate on the proposed AEMP so that there is an appropriate impact to the health budget, and would like patients to have access to CAL/BDP cream in a timely manner.

Drug cost/patient/course

6.84 The drug cost per patient per course for CAL/BDP cream depends on the area affected and the duration of use. However, using the maximum weekly dose of 100 g over 8 weeks (treatment duration as per the PI), a total of 14 packs of CAL/BDP cream 60 g

will be required, resulting in total drug cost per patient per course of $1,052.94 (DPMQ of $75.21 x 14 packs).

6.85 The drug cost per patient per course for the lowest cost CAL/BDP product currently listed on PBS, that is CAL/BDP ointment 30 g, is $547.12 (DPMQ of $39.08 and a total of 14 packs required), based on the maximum weekly dose of 100 g over 4 weeks (treatment duration as per the PI).

6.86 The drug cost per patient per course for CAL/BDP foam 60 g, is $599.90 (DPMQ for one pack of $85.70 x 7 packs), based on the maximum weekly dose of 100 g over 4 weeks (treatment duration as per the PI).

Estimated PBS usage & financial implications

6.87 This submission was not considered by DUSC.

6.88 The submission applied a market share approach to estimate the utilisation and financial impact of listing CAL/BDP cream for the treatment of plaque psoriasis. Key inputs and sources are presented in Table 16.

Table 16: Key inputs for financial estimates

Parameter	Value applied	Source	Comment
PBS+RPBS units dispensed for CAL/BDP foam	2019: [redacted][1] 2020: [redacted][2] 2021: [redacted][3] 2022: [redacted][3] 2023: [redacted][3] 2024: [redacted][3]	Based on PBS utilisation data for CAL/BDP foam (11091R, 13520N)	This was appropriate.
PBS+RPBS units dispensed for CAL/BDP ointment	2019: [redacted][4] 2020: [redacted][4] 2021: [redacted][2] 2022: [redacted][2] 2023: [redacted][3] 2024: [redacted][3]	Based on PBS utilisation data for CAL/BDP ointment (9494Q, 13577N)	This was appropriate.
Annual growth	CAL/BDP foam: 11.36% CAL/BDP ointment: 5.91%	Based on the 5-year linear trendlines of units of CAL/BDP foam and ointment dispensed in years 2019-2024	The approach was reasonable; however, the annual growth calculated during the evaluation, using the 5-year linear trendlines equation presented in the submission, were 11.75% for CAL/BDP foam and 7.23% for CAL/BDP ointment. Based on the revised Budget Impact Model provided by the sponsor, the annual growth rates were revised to 12.62% and 7.21%.
Market share	[redacted]% of the CAL/BDP foam and ointment each in Year 1, increasing to [redacted]% by Year 4.	Based on the sponsor's assumption using internal forecast and international market share data	This was uncertain as the uptake of CAL/BDP cream could be influenced by various factors such as patient preferences, clinician recommendation, product availability, and the site and size of psoriasis. Furthermore, the uptake rates differed from the IMS data provided by the submission.
CAL/BDP cream 60 g	AEMP: $57.43 DPMQ: $75.21 (max qty=1) $138.13 (max qty=2)	Cost-minimised price as presented in economic analysis	This was proposed by the sponsor based on a CMA using 50/50 split between CAL/BDP foam and ointment on a gram-to-gram basis.
CAL/BDP foam 60 g	Published DPMQ: $85.70 (max qty=1) $160.17 (max qty=2)	PBS item: 11091R 13520N	This was appropriate.
CAL/BDP ointment 30 g	Published DPMQ: $39.08 (max qty=1) $64.71 (max qty=2)	PBS item: 9494Q 13577N	This was appropriate.

Source: Table 4-2, pp141-142; Table 4-3, p142; Table 4-6, p143; Table 4-9, p145; Section 4.2, pp141-143 of the submission.
AEMP = approved ex-manufacturer price; CAL/BDP = calcipotriol with betamethasone dipropionate; CMA = cost-minimisation analysis; DPMQ = Dispensed Price for Maximum Quantity; g =gram; max qty = maximum quantity; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
The redacted values correspond to the following ranges:
[1] *70,000 to < 80,000*
[2] *80,000 to < 90,000*
[3] *100,000 to < 200,000*
[4] *90,000 to < 100,000*

6.89 The submission used utilisation data from the PBS Item Statistics to estimate the market size and growth of CAL/BDP products, and used International Market Share (IMS) data and internal forecasting to estimate the market share for CAL/BDP cream.

6.90 The submission estimated average annual growth rates of 11.36% for CAL/BDP foam

and 5.91% for CAL/BDP ointment, based on 5-year linear trendlines using PBS/RPBS utilisation data from 2019-2024. While this approach was reasonable, the annual growth rates calculated during the evaluation, using the 5-year linear trendlines equations presented in the Budget Impact Model worksheet (Attachment 9 to the submission) were slightly higher, at 11.75% for CAL/BDP foam and 7.23% for CAL/BDP ointment. The sponsor subsequently provided a revised Budget Impact Model correcting an error in the initial Budget Impact Model and reflected PBS Item Statistics, which indicated that the annual growth rates for CAL/BDP foam and ointment were 12.62% and 7.21%, respectively.

6.91 The submission assumed that CAL/BDP cream will capture market share equally from CAL/BDP foam and CAL/BDP ointment, based on their current market share of 56% and 44%, respectively. Furthermore, the submission projected that market share for CAL/BDP cream to be [redacted]% in Year 1, increasing to [redacted]% by Year 4, driven by superior patient adherence and treatment satisfaction outcomes. The assumption of equal substitution and uptake rates of CAL/BDP products was uncertain, as the uptake of CAL/BDP cream could be influenced by various factors such as patient preferences, clinician recommendation, product availability, and the site and size of psoriasis. Furthermore, the uptake rates differed from the IMS data provided by the submission. The uptake rates for CAL/BDP cream ranged from [redacted]% to [redacted]% over 3 years in markets with CAL/BDP cream, gel, foam and ointment, based on the sponsor's international market share data (Attachment 10 to the submission).

6.92 The PSCR agreed that the uptake in market share of the different CAL/BDP products is likely to be influenced by several factors. The PSCR provided an example of the closest equivalent market overseas where the introduction of CAL/BDP cream impacted the market share of both CAL/BDP ointment and foam equally.

6.93 The estimated financial implications of listing CAL/BDP cream are presented in Table 17. Estimated financial implications based on the revised Budget Impact model provided by the sponsor are presented in Table 18.

Table 17: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed for CAL/BDP cream	[redacted][1]	[redacted][2]	[redacted][3]	[redacted][4]	[redacted][5]	[redacted][5]
Estimated change in script volume						
CAL/BDP, 0.05% foam	-[redacted][6]	-[redacted][7]	-[redacted][8]	-[redacted][3]	-[redacted][4]	-[redacted][9]
CAL/BDP, 0.05% ointment	-[redacted][6]	-[redacted][7]	-[redacted][10]	-[redacted][2]	-[redacted][8]	-[redacted][8]
Aggregate volumes of scripts	-[redacted][1]	-[redacted][8]	-[redacted][9]	-[redacted][5]	-[redacted][5]	-[redacted][5]
Estimated patient copayments						
Cost of copayments for CAL/BDP foam and ointment	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]
Cost of copayments for CAL/BDP cream	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]
Estimated financial implications of CAL/BDP cream						
Cost to PBS/RPBS less copayments	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]
Estimated financial implications for CAL/BDP foam and ointment						
Cost to PBS/RPBS less copayments	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]
Net financial implications						
Net cost to PBS/RPBS	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]	-$[redacted][11]

Source: Table 4-7, p144; Table 4-10, p145; Table 4-11, p146; Table 4-12, p147 of the submission; and Attachment 9 – Wynzora BIM.xlsx ('3b. Impact – proposed (pub)').

CAL/BDP = calcipotriol with betamethasone dipropionate; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

[1] *10,000 to < 20,000*
[2] *40,000 to < 50,000*
[3] *70,000 to < 80,000*
[4] *80,000 to < 90,000*
[5] *100,000 to < 200,000*
[6] *5,000 to < 10,000*
[7] *20,000 to < 30,000*
[8] *50,000 to < 60,000*[9] *90,000 to < 100,000*
[10] *30,000 to <40,000*
[11] *$0 to <$10 million*

Table 18: Estimated use and financial implications based on revised Budget Impact Model

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed for CAL/BDP cream	[redacted][1]	[redacted][2]	[redacted][3]	[redacted][4]	[redacted][5]	[redacted][5]
Estimated change in script volume						
CAL/BDP, 0.05% foam	-[redacted][6]	-[redacted][7]	-[redacted][8]	-[redacted][3]	-[redacted][9]	-[redacted][10]
CAL/BDP, 0.05% ointment	-[redacted][6]	-[redacted][12]	-[redacted][7]	-[redacted][8]	-[redacted][8]	-[redacted][8]
Aggregate volumes of scripts	-[redacted][1]	-[redacted][8]	-[redacted][10]	-[redacted][5]	-[redacted][5]	-[redacted][5]
Estimated patient copayments						
Cost of copayments for CAL/BDP foam and ointment	$[redacted][13]	$[redacted][13]	$[redacted][13]	$[redacted][13]	$[redacted][13]	$[redacted][13]
Cost of copayments for CAL/BDP cream	-$[redacted][13]	-$[redacted][13]	-$[redacted][13]	-$[redacted][13]	-$[redacted][13]	-$[redacted][13]
Estimated financial implications of CAL/BDP cream						
Cost to PBS/RPBS less copayments	$[redacted][13]	$[redacted][13]	$[redacted][13]	$[redacted][13]	$[redacted][13]	$[redacted][13]
Estimated financial implications for CAL/BDP foam and ointment						
Cost to PBS/RPBS less copayments	-$[redacted][13]	-$[redacted][13]	-$[redacted][13]	-$[redacted][13]	-$[redacted][13]	-$[redacted][13]
Net financial implications						
Net cost to PBS/RPBS	-$[redacted][13]	-$[redacted][13]	-$[redacted][13]	-$[redacted][13]	-$[redacted][13]	-$[redacted][13]

Source: Updated Budget Impact Model from the sponsor.
CAL/BDP = calcipotriol with betamethasone dipropionate; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
The redacted values correspond to the following ranges:
[1] *10,000 to < 20,000*
[2] *40,000 to < 50,000*
[3] *70,000 to < 80,000*
[4] *100,000 to < 200,000*
[5] *100,000 to < 200,000*
[6] *5,000 to < 10,000*
[7] *30,000 to <40,000*
[8] *50,000 to < 60,000*
[9] *80,000 to < 90,000*
[10] *90,000 to < 100,000*
[12] *20,000 to < 30,000*
[13] *$0 to <$10 million*

6.94 The total cost saving to the PBS/RPBS of listing CAL/BDP cream was estimated to be $0 to < $10 million in Year 6, and a total of $0 to < $10 million in the first 6 years of listing, based on the revised Budget Impact Model provided by the sponsor (Table 18). The submission stated that given the requested price for CAL/BDP cream has been cost-minimised to CAL/BDP foam and CAL/BDP ointment, substitution with CAL/BDP cream is expected to be cost neutral, if not cost saving, to the PBS/RPBS. The net cost impact of listing CAL/BDP cream is uncertain as it depends on the market growth and changes in the uptake rate between CAL/BDP cream, foam, and ointment.

6.95 The ESC considered the estimated financial implications to the PBS/RPBS was uncertain, and will depend on factors that impact the choice and uptake of CAL/BDP cream, as outlined in paragraph 6.91.

6.96 Sensitivity analyses were conducted during the evaluation to assess the impact of updated market growth rates for CAL/BDP foam and ointment, as well as revising the market share based on the IMS data. Increasing the market growth for CAL/BDP foam and ointment to 11.75% from 11.36% and 7.23% from 5.91%, respectively, increased the cost savings by 3.5%. Furthermore, revising the market share for CAL/BDP cream based on the IMS data provided in the submission ([redacted]% in Year 1, [redacted]% in Year 2, [redacted]% in Years 3-6), increased the cost savings by 36.6%. The pre-PBAC response reiterated its claim that CAL/BDP cream at the requested price would result in cost savings to the Government, even when accounting for sensitivity analyses conducted, due to patients switching from the foam, which has a higher price than what is requested for the cream.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the listing of calcipotriol 0.005% with betamethasone (as dipropionate) 0.05% (CAL/BDP) cream, 60 g, as a General Schedule (Restricted Benefit) listing, for the treatment of chronic stable plaque type psoriasis vulgaris in patients who have not adequately responded to potent topical corticosteroid monotherapy, under the same circumstances as CAL/BDP foam and ointment that are listed on the PBS.

7.2 The PBAC considered the nominated comparators, CAL/BDP foam and ointment, to be appropriate, and noted that CAL/BDP cream has the same place in therapy as CAL/BDP foam and ointment. The PBAC noted CAL/BDP cream provides another option for patients requiring topical CAL/BDP, and that the cream may be preferred by some patients due to factors such as being easier to apply than foam, lower risk of staining clothes, less mess, and a better feel on the skin (e.g. less greasiness).

7.3 The PBAC noted the submission claimed CAL/BDP cream had superior efficacy compared to CAL/BDP ointment. The PBAC considered this claim was not adequately supported by the evidence provided because the evidence was based on one head-to-head pharmacokinetic trial comparing the cream with ointment, and two non-inferiority trials between CAL/BDP cream and gel (using gel as a proxy for ointment). The head-to-head trial demonstrated similarly efficacy between the cream and ointment, and the trials comparing the cream with gel were designed to demonstrate non-inferiority (rather than superiority).

7.4 The PBAC considered that CAL/BDP cream had non-inferior comparative efficacy and safety compared to CAL/BDP ointment and CAL/BDP foam.

7.5 The PBAC therefore recommended listing CAL/BDP cream on a cost-minimisation basis to the lowest cost CAL/BDP formulation listed on the PBS (CAL/BDP ointment). The PBAC advised the equi-effective doses are 1 gram CAL/BDP cream to 1 gram CAL/BDP foam and 1 gram CAL/BDP ointment.

7.6 The PBAC recommended listings for CAL/BDP cream consistent with the PBS listings for CAL/BDP foam and ointment, and recommended listing with a maximum quantity of 1 pack (60 g) and maximum of 1 repeat, and a corresponding 60-day maximum dispensed quantity listing of 2 packs with 1 repeat.

7.7 The PBAC advised that CAL/BDP cream is suitable for prescribing by nurse practitioners.

7.8 The PBAC recommended that the Early Supply Rule should apply.

7.9 The PBAC considered the financial estimates to be likely reasonable, however noted there were uncertainties in the uptake of CAL/BDP cream and the market share captured from CAL/BDP foam and ointment. The PBAC noted the uptake of CAL/BDP cream could be influenced by factors such as patient and prescriber preferences, product availability, and the site and size of psoriasis. The PBAC noted that as CAL/BDP cream is recommended on a cost-minimisation basis to the lowest cost comparator, it will at least be cost-neutral to the PBS/RPBS, and there may be a small cost saving if CAL/BDP cream takes market share from CAL/BDP foam, which is listed at a higher price.

7.10 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because CAL/BDP cream is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over CAL/BDP foam and ointment, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were not met.

7.11 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
CALCIPOTRIOL + BETAMETHASONE					
calcipotriol 0.005% + betamethasone (as dipropionate) 0.05% cream, 60 g	NEW (GE)	1	1	1	Wynzora
Restriction Summary [NEW] / Treatment of Concept: [NEW]					
Concept ID	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)				

(for internal Dept. use)	**Prescriber type:** ☒Medical Practitioners ☒Nurse Practitioners
	Restriction type: ☒ Restricted benefit
	Indication: Chronic stable plaque type psoriasis vulgaris
	Clinical criteria:
	The condition must be inadequately controlled by potent topical corticosteroid monotherapy.

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
CALCIPOTRIOL + BETAMETHASONE					
calcipotriol 0.005% + betamethasone (as dipropionate) 0.05% cream, 60 g	NEW (GE)	2	2	1	Wynzora

Restriction Summary [NEW] / Treatment of Concept: [NEW]	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners ☒Nurse Practitioners
	Restriction type: ☒ Restricted benefit
	Indication: Chronic stable plaque type psoriasis vulgaris
	Clinical criteria:
	The condition must be stable for the prescriber to consider the listed maximum quantity of this medicine suitable for this patient,
	AND
	Clinical criteria:
	The condition must be inadequately controlled by potent topical corticosteroid monotherapy.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.