

**6.02 BARICITINIB,
Tablet 2 mg,
Tablet 4 mg,
Olumiant[®],
Eli Lilly Australia Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 2 submission requested Authority Required (In Writing) and Authority Required (Streamlined) PBS listing of baricitinib (BARI) 2 mg and 4 mg tablets for initial and continuing treatment of adults with severe atopic dermatitis (AD).
- 1.2 Listing was requested on the basis of a comparison with dupilumab (DUPI), which is a subcutaneously (SC) administered interleukin-4 (IL-4) inhibitor currently listed on the PBS for severe AD. The PBAC noted that BARI is a novel medicine, as no other Janus Kinase (JAK) inhibitor is available on the PBS for AD and is an oral treatment alternative for patients currently eligible for treatment with DUPI. Safety concerns limit the long-term use of other oral treatments (such as ciclosporin A (CsA)) in severe AD. The PBAC also considered the PBS listing of upadacitinib, which is another JAK inhibitor and oral treatment, for severe AD at the July 2021 meeting. Prior to the PBS listing of DUPI, the PBAC had acknowledged the high-unmet need for treatments in moderate-to-severe AD (paragraph 6.50, DUPI PDS, July 2019). Since PBS listing of DUPI for severe AD, there may be higher unmet need for patients with moderate AD.

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

Component	Description
Population	Adults with severe AD in whom an adequate response has not been achieved with TCS.
Intervention	Baricitinib 2 mg or 4 mg tablet, orally once daily
Comparator	Dupilumab 600 mg subcutaneously as an initial dose, followed by 300 mg subcutaneously every two weeks.
Outcomes	Primary outcomes: Proportion of patients achieving IGA of 0 or 1 with a ≥ 2-point improvement at Week 16, proportion of patients achieving EASI75 at Week 16, proportion of patients achieving EASI50 at Week 16. Secondary outcomes: Change in physician and patient reported AD severity scores, including EASI, SCORAD, DLQI, POEM, itch NRS. PBS response criteria (post-hoc outcome): Composite measure of response EASI-50 and improvement in DLQI≥4 (at Week 16).
Clinical claim	Baricitinib is inferior to dupilumab in terms of efficacy, and non-inferior in terms of safety, in patients with severe AD for whom an adequate response has not been achieved with TCS.

Source: Table 1.1-1, p34 of the submission.

Abbreviations: AD=atopic dermatitis; TCS=topical corticosteroids; IGA=investigator's global assessment of the patient's overall severity of their AD; EASI=Eczema Area and Severity Index; SCORAD=Scoring Atopic Dermatitis; DLQI=Dermatology Life Quality Index; POEM=Patient Oriented Eczema Measure; NRS=Numerical Rating Scale; EASI50/75=50/75% improvement in EASI score.

2 Background

Registration status

- 2.1 BARI was approved by the TGA on 11th February 2021 for the following indication:
 “Olumiant® is indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy.”

The TGA indication is broader than the proposed PBS listing, given treatment is approved for moderate-to-severe disease but the requested PBS criteria would restrict treatment to patients with severe disease (see definition below).

Previous PBAC consideration

- 2.2 This is the first submission to the PBAC for BARI for the requested indication. BARI is currently PBS listed for rheumatoid arthritis (recommended March 2018).

For more detail on PBAC’s view, see Section 7 PBAC Outcome.

3 Requested listing

- 3.1 The sponsor’s requested restrictions are presented below.

Name, Restriction, Manner of administration and form	Maximum quantity (packs)	Maximum quantity (units)	No. of Rpts	Dispensed price for maximum quantity (DPMQ)	Proprietary Name and Manufacturer
BARICITINIB					
Initial 1					
2mg tablet, 28	1	28	4		
Initial 2 – balance of supply					
4mg tablet, 28	1	28	3		
Continuing 1					
2mg tablet, 28	1	28	5	\$ [REDACTED] (published price*)	Olumiant® Eli Lilly Australia Pty Limited
4mg tablet, 28	1	28	5		
Continuing 2 – balance of supply					
2mg tablet, 28	1	28	4		
4mg tablet, 28	1	28	4		

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
PBS Indication:	Chronic severe atopic dermatitis
Treatment criteria:	Must be treated by a dermatologist; OR Must be treated by a physician with expertise in treating atopic dermatitis
Treatment phase:	Initial 1
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing
Clinical criteria:	Patient must have severe atopic dermatitis with a PGA score of 4 and an EASI score \geq 20; OR Patient must have severe atopic dermatitis of the face or palm of hand; AND Patient must have failed to achieve an adequate response to topical therapies (topical corticosteroids and/or topical calcineurin inhibitors); AND Treatment must be as systemic monotherapy (other than oral corticosteroids);

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AND Patient must not receive more than 20 weeks of treatment under this restriction.	
Population criteria: Patient must be aged 18 years or older	
Treatment phase:	Initial 2 – balance of supply
Restriction:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria: Patient must have insufficient therapy with this drug under the Initial restriction to complete up to 20 weeks of treatment.	
Prescribing instructions: Patient must not have achieved sustained control of disease activity with baricitinib 2 mg once daily.	
Treatment phase:	Continuing 1
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing
Clinical criteria: Patient must have received this drug as their most recent course of PBS subsidised treatment for this condition (with the exception of topical corticosteroids, topical calcineurin inhibitors and oral corticosteroids); AND Patient must have demonstrated an adequate response to their most recent course of PBS-subsidised treatment with this drug; AND Treatment must be as systemic monotherapy (other than oral corticosteroids); AND Patient must not receive more than 24 weeks of treatment per continuing treatment course under this restriction.	
Prescriber Instructions: An adequate response to treatment (whole body) is defined as both: <ol style="list-style-type: none"> 1. An improvement of the EASI score of $\geq 50\%$, or sustained at that level compared to the pre-treatment baseline value; 2. An improvement of the DLQI score of ≥ 4, or sustained at that level compared to the pre-treatment baseline value. An adequate response to treatment (face and palm of hand) is defined as either: <ol style="list-style-type: none"> 1. An improvement of the EASI score of at least 3 of the 4 subscores for erythema, oedema/papulation, excoriation and lichenification to mild or better, or sustained at this level, as compared to the pre-treatment baseline values; OR 2. A reduction by 75% or more of the skin area affected, or sustained at this level, as compared to the pre-treatment baseline value. 	
Treatment phase:	Continuing 2 – balance of supply
Restriction:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria: Patient must have received insufficient therapy with this drug for this condition under the continuing treatment restriction to complete 24 weeks of treatment; AND Treatment must be as systemic monotherapy (other than oral corticosteroids); AND The treatment must provide no more than the balance of up to 24 weeks of therapy	
Prescribing instructions: A dose of 4 mg once daily may be considered for patients who have not achieved sustained control of disease activity with 2 mg once daily. Dose tapering to 2 mg once daily should be considered once the patient has achieved sustained control of disease with 4 mg once daily.	
Treatment phase:	Grandfather
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing
Clinical criteria:	

Patient must have a documented history of severe atopic dermatitis with an Eczema Area and Severity Index (EASI) score of ≥ 20 and a Physician's Global Assessment (PGA) score of ≥ 4 ; Patient must have severe atopic dermatitis of the face or palm of hand;

AND

Patient must have failed to achieve an adequate response to topical therapies (topical corticosteroids and/or topical calcineurin inhibitors) prior to commencing non-PBS subsidised therapy with this drug for this condition;

AND

Patient must have received treatment with this drug for this condition prior to <PBS listing date>;

AND

Patient must have demonstrated an adequate response following at least 16 weeks of non-PBS-subsidised treatment with this drug;

AND

Treatment must be as systemic monotherapy (other than oral corticosteroids);

AND

Patient must not receive more than 24 weeks of treatment under this restriction

Prescribing instructions:

An adequate response to treatment (whole body) is defined as both:

1. An improvement of the EASI score of $\geq 50\%$, or sustained at that level compared to the pre-treatment baseline value;
2. An improvement of the DLQI score of ≥ 4 , or sustained at that level compared to the pre-treatment baseline value.

An adequate response to treatment (face and palm of hand) is defined as either:

1. An improvement of the EASI score of at least 3 of the 4 subscores for erythema, oedema/papulation, excoriation and lichenification to mild or better, or sustained at this level, as compared to the pre-treatment baseline values; OR
2. A reduction by 75% or more of the skin area affected, or sustained at this level, as compared to the pre-treatment baseline value.

* The submission requested a special pricing arrangement to be negotiated with the Department of Health. The requested published price was derived from the published price for dupilumab less ████% to account for the inferior effectiveness of baricitinib.

Source: Table 1.4-1, pp50-51 of the submission & Tables 1.4-2 to 1.4-6, pp 53-61 of the submission.

- 3.2 The sponsor requested Authority Required (In Writing) and Authority Required (Streamlined) listing of BARI 2 mg and 4 mg tablets for initial and continuing treatment of adults with severe AD, including transitioning ('Grandfather') arrangements. The requested listing requires patients to initiate treatment on BARI 2 mg, and allows for up titration to BARI 4 mg during the initial treatment period at the doctor's discretion (after the first 4 weeks of treatment) via a streamlined (initial) balance of supply restriction. Continuing treatment on BARI 2 mg or 4 mg is conditional on meeting the clinical response criteria within the first 16 weeks of treatment, and a streamlined (continuing) balance of supply restriction allows for dose tapering from BARI 4 mg to BARI 2 mg at the doctor's discretion.
- 3.3 The submission stated a transitioning ('Grandfather') arrangements would be necessary to provide continuing treatment for an estimated 500 patients enrolled in an early access program. The pre-PBAC response stated there are currently 106 patients receiving treatment with BARI through a special access program and all are expected to meet the PBS eligibility criteria in the initial listing.
- 3.4 The requested quantities would provide for 20 weeks of initial treatment (5 packs) and 24 weeks of continuing treatment (6 packs), in line with the wording of the restrictions. The requested 20 week duration for initial treatment allows for sufficient time for clinicians to up titrate from BARI 2 mg to BARI 4 mg if a patient does not

achieve an adequate response. The requested listing would provide clinicians with maximum flexibility in how doses are up titrated and tapered through the balance of supply restriction; however, the requested number of repeats may (unintentionally) provide more than 20 weeks for initial treatment and 24 weeks of continuing treatment in patients who require dose adjustment. It may also be appropriate to limit the number of repeats for the initial balance of supply restriction for BARI 4 mg (down from 16 weeks) given treatment discontinuation is recommended after 8 weeks in patients who fail to respond (and presumably patients would be monitored more closely).

- 3.5 The sponsor requested a flat pricing structure for the 2 mg and 4 mg formulations, and a special pricing arrangement (SPA) that would maintain the current published DPMQs as for rheumatoid arthritis (\$1,271.34). The submission stated that without knowledge of the current effective price for DUPI, the sponsor is unable to calculate an effective price for BARI. In Section 3, the submission proposed a [REDACTED] % relative price reduction for BARI compared to DUPI to reflect the inferior efficacy of BARI. The submission stated that the size of the discount reflects the risk difference across the efficacy outcomes. The sponsor proposed a relative [REDACTED] % discount based on the [REDACTED] reduction in the number of treatment responders, which was less than the approximate [REDACTED] % [REDACTED] reduction in the number of responders with BARI versus DUPI. In the pre-PBAC response the sponsor proposed a further reduced price for BARI (AEMP \$ [REDACTED], [REDACTED] % reduction), to reflect the [REDACTED] % [REDACTED] reduction in response compared to DUPI.
- 3.6 The submission stated that the requested restrictions for BARI were based on the ‘proposed’ restrictions for DUPI (taking into consideration PBAC feedback from July 2019). Aside from differences in the population criteria owing to the TGA indications (adolescents and adults for DUPI compared to only adults for BARI), there are notable differences compared to the approved PBS listing of DUPI (listed on 1 March 2021), including:
- For DUPI, there are separate restrictions for the treatment of patients with severe AD affecting the i) whole body, or ii) face/hands. In contrast, the criteria for whole body and face/hands are considered within the same restriction for BARI.
 - For DUPI, the continuing treatment criteria allow for patients to resume treatment if patients have temporarily ceased treatment for reasons other than lack of response, but there is no such allowance in the requested listing for BARI.
 - For patients with severe AD affecting the face/hands, there are no disease specific criteria for initial treatment with BARI, whereas eligible patients for initial treatment with DUPI must have at least 2 of the Eczema Area and Severity Index (EASI) symptom sub-scores rated as severe or ≥30% surface area of the face/hands affected.
 - For patients with severe AD affecting the face/hands, the proposed response criteria for BARI is slightly different to the approved response criteria for DUPI.

For DUPI, response is defined as:

(a) (i) A rating of either mild (1) to none (0) on at least 3 of the assessments of erythema, oedema/papulation, excoriation and lichenification mentioned in the EASI; OR (ii) At least a 75% reduction in the skin area affected by this condition compared to baseline; AND

(b) An improvement in Dermatology Life Quality Index (DLQI) score of at least 4 points compared to baseline.

- For DUPI, prescribing is restricted to dermatologists and clinical immunologists, but the requested 'treatment criteria' for BARI allows prescribing by any physician with expertise in treating AD. The submission stated that the rationale for broadening this criterion was that clinical immunologists may not be accessible in rural and remote settings; however, access to dermatologists was not considered in this argument.

3.7 The Pre-Sub-Committee Response (PSCR) stated that the sponsor was amenable to revising the restriction (in alignment with the DUPI restrictions). The PBAC considered that it would be appropriate for the listing to align with that for DUPI in terms of allowed prescribers, and initial and continuing assessment criteria.

3.8 Based on the requested restriction, patients who fail to respond to treatment with DUPI would be eligible for BARI and vice versa. The sequential use of these two treatments (or potentially three treatments including the near-market comparator upadacitinib, see paragraph 1.2) is consistent with the proposed clinical management algorithm presented in the submission (but inconsistent with the financial estimates, see paragraph 6.53). The PSCR stated that BARI has a different mechanism of action to DUPI and, as such, non-response to one medicine does not preclude a patient responding to the other medicine. The PSCR also stated that sequential treatment is in the best interest of patients, despite the potential for increased market growth. The ESC noted that it may be reasonable for patients who fail DUPI to be treated with BARI based on the different mechanism of action, however given the lower efficacy for BARI, the ESC considered that it is unclear whether BARI is likely to be of benefit in these patients.

For more detail on PBAC's view, see Section 7 PBAC Outcome.

4 Population and disease

4.1 AD is a chronic, systemic, inflammatory disease that affects skin and is characterised by persistent itch and marked redness. Altered immune responses render AD patients at increased risk of bacterial, viral, and fungal skin infections. AD is also associated with comorbid conditions affecting sleep, pain, psychologic domains, and physical and social functioning.

4.2 The requested listing would place BARI as an alternative orally administered treatment option to DUPI SC injections, for adult patients with severe AD who have failed to

achieve an adequate response to topical therapy. The proposed clinical management algorithm lists other orally administered therapies (including CsA, azathioprine, methotrexate and mycophenolate mofetil) at the same line of treatment, however, safety concerns limit their use in clinical practice.

- 4.3 BARI is an oral selective inhibitor of JAK1 and JAK2, which are important in transmitting inflammatory cytokine signals in AD. The approved product information (PI) for BARI states the recommended dose for severe AD is 2 mg orally, once daily. A dose of 4 mg orally, once daily may also be considered for patients who do not achieve sustained control of disease activity with 2 mg daily. Dose tapering to 2 mg once daily is recommended and should be considered once the patient has achieved sustained control of disease with 4 mg once daily. Treatment should be discontinued in patients who do not demonstrate evidence of benefit after 8 weeks of treatment with 4 mg. The recommended BARI 2 mg commencement dose in Australia differs from other jurisdictions such as in Europe where BARI 4 mg is recommended. In making this recommendation, the TGA adopted a ‘quality use of medicines’ approach supporting the use of the lowest effective commencement dose. The PBAC noted there was no clear evidence that up-titration from 2 mg to 4 mg for patients with inadequate response to 2 mg, improved outcomes (see also paragraphs 6.30 and 6.31).
- 4.4 The PI states monitoring of effects on laboratory tests including ANC, ALC, Hb and hepatic enzymes, should occur before treatment initiation and then according to routine patient management. Lipid monitoring is recommended at Week 0 and Week 12, then according to local hyperlipidaemia guidelines thereafter.

For more detail on PBAC’s view, see Section 7 PBAC Outcome.

5 Comparator

- 5.1 The submission nominated DUPI 600 mg SC as an initial dose, then 300 mg SC every two weeks as the appropriate comparator. DUPI is the only biologic treatment currently PBS listed for severe AD in patients who have failed to achieve a response with topical therapies. The main argument provided in support of this nomination was that DUPI is the treatment most likely to be replaced by BARI.
- 5.2 The submission also nominated CsA, a calcineurin inhibitor, as a potentially relevant comparator, given it is PBS listed for severe AD in patients who have failed to respond to other systemic therapies or when their use is inappropriate. When considering PBS listing of DUPI, the PBAC considered “CsA to be an additional relevant comparator given the broader proposed patient population, but acknowledged the toxicity of CsA limited its use in clinical practice, and the paucity of clinical evidence prevented a reliable indirect comparison of the efficacy of DUPI versus CsA... [and] hence was not considered informative” (paragraph 7.5, DUPI Public Summary Document (PSD), July 2019). The submission stated the same conclusion can be drawn with regard to a comparison between BARI and CsA and was therefore not considered in this submission. The PBAC considered this was reasonable, and a similar argument could

be made for other systemic treatments, which have unrestricted listings on the PBS at recommended doses (such as methotrexate, azathioprine and mycophenolate mofetil).

- 5.3 The submission also identified two other JAK inhibitors as near-market comparators, upadacitinib and abrocitinib, but neither were considered due to limited publicly available clinical evidence at the time of writing the submission. At the time of the evaluation, there was one published trial (NCT02925117) comparing upadacitinib versus placebo (PBO), which could inform an indirect comparison versus BARI. As noted above, the PBAC will also consider PBS listing of upadacitinib for the treatment of severe AD at the July 2021 meeting.

For more detail on PBAC’s view, see Section 7 PBAC Outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item and provided a written statement from two clinicians. The clinicians discussed the burden of disease in terms of itch, sleep disturbance, skin pain, and reduced quality of life; the impact of which can extend to family members, and affect education attainment, employment engagement, and the health care system in general. The clinicians emphasised the importance of availability of multiple, safe, and effective therapeutic options for these patients.
- 6.2 The clinicians stated that one of the key features of the phase 3 trials for BARI is that it demonstrates an ability to rapidly improve symptoms, and that this is a distinguishing characteristic for the JAK inhibitors over DUPI, which supports the inclusion of JAK inhibitors like BARI on the PBS.
- 6.3 One of the clinicians noted their personal clinical experience that has involved treating over 100 patients with JAK inhibitors (BARI/upadacitinib/abrocitinib) and IL-4/IL-13 inhibitors (DUPI/tralokinumab/lebrikizumab) in Australia and the United States for severe atopic dermatitis. The clinician stated they observed more rapid remission of severe disease, and less administration burden and adverse effects (e.g. “red face” secondary to *Malassezia* yeast sensitisation) with BARI than DUPI.

Consumer comments

- 6.4 The PBAC noted and welcomed the input from individuals (13) and organisations (2) via the Consumer Comments facility on the PBS website.
- 6.5 The PBAC noted the advice received from AD support groups: Eczema Support Australia and Allergy & Anaphylaxis Australia (A&AA). The organisations noted that patients with AD vary in response to treatments as well as contraindications and side effects from treatments and, therefore, access to alternatives to DUPI are highly valued by patients and clinicians.
- 6.6 Eczema Support Australia noted that disease management is complex, and currently

patients with AD classified as moderate do not qualify for treatment with DUPI despite fluctuating disease severity/flares. Some patients with AD classified as moderate may remain on CsA (which has a poor AE profile) or would need to cease treatment, allowing their AD to worsen, in order to qualify for treatment with DUPI. Both Eczema Support Australia and A&AA requested that the PBAC consider the issues involved in living with AD and consider including patients with moderate to severe AD, noting the disease burden and unmet need for patients with moderate AD. The PBAC noted that advice from both groups was supportive of the evidence provided in the submission.

- 6.7 Comments from consumers noted the impact of AD on their quality of life. Consumers reported having inadequate response to DUPI, not being eligible for DUPI via the PBS, or experiencing side effects from treatment with DUPI, and were therefore keen to trial a JAK inhibitor such as BARI. One individual described an improvement in their appearance and condition after recently starting treatment with BARI.

Clinical trials

- 6.8 The submission was based on six head-to-head randomised trials comparing BARI to PBO and six trials comparing DUPI to PBO, which informed an indirect treatment comparison between BARI vs DUPI:

- BARI vs PBO, as monotherapy: BREEZE-AD1, BREEZE-AD2, BREEZE-AD5.
- BARI vs PBO, in combination with TCS: BREEZE-AD4, BREEZE-AD7, JAHG.
- DUPI vs PBO, as monotherapy: Study 1021, SOLO 1, SOLO 2
- DUPI vs PBO, in combination with TCS: CAFÉ, CHRONOS, JADE-COMPARE

The PBAC has previously considered evidence from five of the six DUPI trials included in this submission (SOLO 1, SOLO 2, CAFÉ, CHRONOS and Study 1021 (referred to as 'Phase IIb' in previous submissions)) during consideration of DUPI in July 2018, July 2019 and March 2020. JADE Compare provides new evidence for DUPI not previously considered by the PBAC, however results for this trial are not yet published (interim results available via clinicaltrials.gov).

- 6.9 In addition, the submission also presented available results from an on-going long-term extension study of BARI (BREEZE-AD3) as supportive evidence to inform the maintenance of response over time and the up-titration from BARI 2 mg to 4 mg, for BARI vs PBO. The main evidence presented in the submission was for patients who commenced and remained on either BARI 2 mg or BARI 4 mg, rather than the recommended titrating and tapering of doses.
- 6.10 Table 2 provides citation details of the trials presented in the submission.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Baricitinib trials		
BREEZE-AD1 NCT03334396 (I4V-MC-JAHL)	A multicenter, randomised, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of baricitinib in adult patients with moderate to severe atopic dermatitis (BREEZE-AD1).	CSR, September 2019
& BREEZE-AD2 NCT03334422 (I4V-MC-JAHM)	A multicenter, randomised, double blind, placebo controlled, Phase 3 study to evaluate the efficacy and safety of baricitinib in patients with moderate to severe atopic dermatitis (BREEZE-AD2).	CSR, October 2019
	Simpson EL, Lacour JP, Spelman L et al. Baricitinib in patients with moderate to severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomised monotherapy phase III trials.	Br J Dermatol 2020; 183: 242-255
BREEZE-AD5 NCT03435081 (I4V-MC-JAIW)	A multicenter, randomised, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of baricitinib in adult patients with moderate to severe atopic dermatitis.	CSR, May 2020
	Simpson EL, Forman S, Silverberg JI et al. Baricitinib in patients with moderate-to-severe atopic dermatitis: Results from a randomized monotherapy Phase 3 trial in the United States and Canada (BREEZE-AD5).	J Amer Acad Dermatol. Online ahead of print: https://doi.org/10.1016/j.jaad.2021.02.028
BREEZE-AD4 NCT03428100 (I4V-MC-JAIN)	A Phase 3, multicenter, double blind, randomized, placebo-controlled study evaluating the safety and efficacy of baricitinib in combination with topical corticosteroids in adult patients with moderate to severe atopic dermatitis who have experienced failure to cyclosporine or are intolerant to, or have contraindication to, cyclosporine.	CSR, April 2020
BREEZE-AD7 NCT03733301 (I4V-MC-JAIY)	A multicenter, randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of baricitinib in combination with topical corticosteroids in adult patients with moderate to severe atopic dermatitis.	CSR, October 2019
JAHG NCT02576938 (I4V-MC-JAHG)	A randomized, double-blind, placebo-controlled, Phase 2 study to evaluate the safety and efficacy of baricitinib in patients with moderate-to-severe atopic dermatitis.	CSR, October 2017
	Guttman-Yassky E, Silverberg JI, Nemoto O et al. Baricitinib in adult patients with moderate to severe atopic dermatitis: A phase 2 parallel, double-blinded, randomised placebo-controlled multiple-dose study.	J Am Acad Dermatol 2019; 80 (4): 913-921.e9.
BREEZE-AD3 NCT03334435 (I4V-MC-JAHN)	A Phase 3 multicenter, double-blind study to evaluate the long-term safety and efficacy of baricitinib in adult patients with atopic dermatitis.	CSR, April 2020
Dupilumab trials		
Study 1021 NCT01859988 (R668-AD-1021)	Thaçi D, Simpson EL, Beck LA et al. Efficacy and safety of dupilumab in adults with moderate to severe atopic dermatitis inadequately controlled by topical treatments: A randomised, placebo-controlled, dose-ranging phase 2b trial. Lancet 2016; 387 (10013): 40-52.	Lancet 2016; 387 (10013): 40-52.
SOLO 1 NCT02277743 (R668-AD-1334) & SOLO 2 NCT02277769 (R668-AD-1416)	Simpson EL, Bieber T, Guttman-Yassky E et al. Two Phase 3 Trials of dupilumab versus placebo in atopic dermatitis.	New Engl J Med 2016; 375 (24): 2335-2348.
CHRONOS NCT02260986 (R668-AD-1224)	Blauvelt A, de Bruin-Weller M, Gooderman M et al. Long-term management of moderate to severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial.	Lancet 2017; 389 (10086): 2287-2303

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Trial ID	Protocol title/ Publication title	Publication citation
CAFÉ NCT02755649 (R668-AD-1424)	de Bruin-Weller M, Thaçi D, Smith CH et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ).	Br J Dermatol 2018; 178 (5): 1083-1101.
JADE Compare NCT03720470 (B7451029)	Study Evaluating Efficacy and Safety of PF-04965842 and Dupilumab in Adult Subjects With Moderate to Severe Atopic Dermatitis on Background Topical Therapy (JADE Compare).	No publication, results available from ClinicalTrials.gov: NCT03720470

Source: Table 2.2-1, pp78-81 of the submission.

6.11 Table 3 presents the key features of the included randomised trials. The submission presented data only for the treatment arms at the relevant/approved doses (excluding data for BARI 1 mg daily, DUPI 300 mg weekly/200 mg every 2 weeks/100 mg every 4 weeks).

Table 3: Key features of the included evidence

Trial	N	Design/duration	Bias	Relevant comparison	Patient population	Primary outcome(s)
BARI trials						
BREEZE-AD1	497*	P3, R, MC, DB, PC 16wk, rescue therapy allowed [^]	Low	BARI 2 mg D	Moderate to severe AD	IGA of 0 or 1 at Wk16 ^a
BREEZE-AD2	490*		Low	BARI 4 mg D PBO		
BREEZE-AD5	293*	P3, R, MC, DB 104wk, PC 16wk, rescue therapy allowed [^] up until wk16	Low	BARI 2 mg D PBO	Moderate to severe AD	EASI75 at wk16 ^b
BREEZE-AD4	370*	P3, R, MC, DB 52wk, PC 16wk, rescue therapy allowed [^]	Low	BARI 2 mg D +TCS BARI 4 mg D +TCS PBO +TCS	Moderate to severe AD	EASI75 at wk16 ^b
BREEZE-AD7	329	P3, R, MC, DB, PC 16wk, rescue therapy allowed [^]	Low	BARI 2 mg D +TCS BARI 4 mg D +TCS PBO +TCS	Moderate to severe AD	IGA of 0 or 1 at Wk16 ^a
JAHG	124	P2, R, MC, DB, PC 16wk, use of rescue therapy not specified in protocol	Low	BARI 2 mg D +TCS BARI 4 mg D +TCS PBO +TCS	Moderate to severe AD	EASI50 at wk16 ^b
DUPI trials						
Study 1021	125*	P2b, R, MC, DB, PC 16wk, rescue therapy allowed [^]	Low	DUPI 300 mg Q2W [†] PBO	Moderate to severe AD	% change in investigator reported EASI at wk16
SOLO 1	448*	P3, R, MC, DB, PC 16wk, rescue therapy allowed [^]	Low	DUPI 300 mg Q2W [†]	Moderate to severe AD	IGA of 0 or 1 ^a and EASI75 ^s at wk16 ^b
SOLO 2	469*		Low	PBO		
CAFÉ	215	P3, R, MC, DB, PC 16wk, rescue therapy allowed [^]	Low	DUPI 300 mg Q2W [†] +TCS PBO +TCS	Moderate to severe AD	EASI75 at wk16 ^b
CHRONOS	421	P3, R, MC, DB, PC 52wk, rescue therapy allowed > wk 2 [#]	Low	DUPI 300 mg Q2W [†] +TCS PBO +TCS	Moderate to severe AD	IGA of 0 or 1 ^a and EASI75 at wk16 ^b
JADE Compare	373*	P3, R, MC, DB, DD, PC, AC 16wk, use of rescue therapy not specified in protocol	Low	DUPI 300 mg Q2W [†] +TCS PBO +TCS	Moderate to severe AD	IGA of 0 or 1 ^a and EASI75 at wk12 ^b

Source: Tables 2.2-2, 2.2-3 & 2.2-4, pp83-87 & 90-92, text on pp81, 85, 88-89 of the submission and related publications/CSRs/protocols. Abbreviations: P2/3=phase 2 or 3; DB=double blind; DD=double dummy; MC=multi-centre; R=randomised; PC=placebo-controlled; AC=active control; SOC=standard-of-care; TCS=topical corticosteroids; wk=week; BARI=baricitinib; DUPI=dupilumab; TCS=topical corticosteroids; PBO=placebo; D=once daily; Q2W=once every 2 weeks; IGA =Investigator's Global Assessment; EASI=Eczema Area and Severity Index; EASI50/75 = improvement of at least 50/75% from baseline in Eczema Area and Severity Index.

^a Proportion of patients achieving IGA of 0 or 1 with a ≥ 2 -point improvement (i.e.: from a baseline of 3 or 4 on the 5-point IGA scale)

^b At least 50/75% improvement/reduction from baseline in EASI score.

* Excluding patients randomised to the following treatment arms: BARI 1mg, DUPI 300 mg weekly/200 mg every 2 weeks/100 mg every 4 weeks or abrocitinib 100 or 200 mg daily.

† DUPI dosing comprised 600 mg loading, then 300 mg every 2 weeks thereafter.

^ Protocols allowed investigators to rescue patients who were experiencing unacceptable or worsening of symptoms at any time (time frames from study start not specified). Patients who received rescue therapy were discontinued from study treatment and considered non-responders.

§ EASI 75 was a coprimary outcome in EU and Japan and a key secondary outcome elsewhere.

Rescue medication was imputed using a multiple imputation model with ANCOVA. Data after rescue treatment were set to missing and then imputed with treatment, randomisation strata, and the corresponding baseline value of the endpoint included in the model.

- 6.12 All trials were phase 2/2b or 3, multicentre, randomised, PBO and/or active controlled (JADE Compare only), parallel group with a double-blind phase of at least 16 weeks. Patients had moderate-to-severe AD and were required to have experienced an inadequate response to TCS (at least 6 months). Concomitant use of daily emollients was allowed and encouraged in all trials, but concomitant use of TCS was allowed in the three BARI trials (BREEZE-AD4, BREEZE-AD7 and JAHG) and three DUPI trials (CAFÉ, CHRONOS and JADE Compare). Rescue therapy was allowed prior to the primary endpoint in most trials, but patients who received rescue therapy were considered non-responders for categorical endpoints. There was some variability in selection criteria across trials with respect to the definitions of moderate-to-severe AD, but baseline characteristics of enrolled patients were generally similar across the trials. The ESC recalled that the PBAC previously considered standard of care includes concomitant TCS, (para 5.1, DUPI PSD, July 2018 PBAC meeting) and considered that the trials that allowed ongoing use of TCS were the most relevant to Australian clinical practice, where TCS would be expected to be continued in combination with BARI.
- 6.13 Patients who completed the 16-week treatment period of BREEZE-AD1, BREEZE-AD2 or BREEZE-AD7 were eligible to enrol in the long-term extension trial BREEZE-AD3. In an open-label addendum to the trial protocol, patients who did not complete the treatment period of an originating trial were also eligible to receive open-label BARI 2 mg for 52 weeks. Responders or partial responders (defined by Investigator's Global Assessment, IGA) in the originating trials continued the same BARI dose, and non-responders were re-randomised to BARI 2 mg or 4 mg. At the time of the submission, the extension trial was still on-going with results at Week 52 available for patients enrolled from BREEZE-AD1 and BREEZE-AD2, and results at Week 16 for patients from BREEZE-AD7 and open-label patients.
- 6.14 Under the current PBS listing for DUPI, patients face different eligibility and response criteria depending on the affected area.
- For patients with severe AD affecting the whole body, initial treatment requires a PGA score of 4 and an EASI score ≥ 20 , and continuing treatment requires a $\geq 50\%$

improvement from baseline in EASI (i.e. EASI50) and an improvement from baseline in DLQI ≥ 4 points.

- For patients with severe AD affecting the face/palm of hands, initial treatment requires ≥ 2 of the EASI symptom sub-scores rated as severe or $\geq 30\%$ surface area of the face/hands affected, and continuing treatment requires ≥ 3 of the EASI symptom sub-scores rated as mild or none or $\geq 75\%$ reduction in the skin area affected compared to baseline, and an improvement from baseline in DLQI ≥ 4 points.

6.15 The PBAC has previously considered EASI (marker of lesions) and DLQI outcomes (patient impact) as being key patient relevant outcomes for the treatment of AD; and accepted that [for patients with AD affecting the whole body] an EASI 50 response combined with a DLQI improvement of ≥ 4 points are likely to be clinically reasonable and able to capture patients with a meaningful response to treatment (para 7.4, DUPI PSD March 2020 PBAC meeting). The PBAC also considered that it would be clinically appropriate for a separate listing in patients with AD affecting the face and hands, who would not be eligible under the whole body criteria due to the relatively small body surface area involved. The PBAC considered that listing for these patients should include improvement in DLQI as a criterion for continuing treatment (para 7.5, DUPI PSD March 2020 PBAC meeting).

6.16 Table 4 summarises the primary and key secondary/exploratory endpoints measured across trials, which included EASI50 response and DLQI ≥ 4 at 16 weeks.

Table 4: Primary (1°), key secondary (2°) and other secondary/exploratory/post-hoc (✓) outcomes reported at Week 16 (unless otherwise indicated) across BARI and DUPI trials

Trials	EASI 50 ^a	EASI 75 ^a	EASI 90 ^a	% change EASI ^b	IGA of 0 or 1 ^c	DLQI ≥ 4 ^d	DLQI 0/1 ^e	Change DLQI ^f
Baricitinib trials								
BREEZE-AD1	✓	2°	2°	2°	1°	✓	✓	✓
BREEZE-AD2	✓	2°	2°	2°	1°	✓	✓	✓
BREEZE-AD5	✓	1°	2°	2°	2°	✓	✓	✓
BREEZE-AD4	✓	1°	2°	2°	2°	✓	✓	✓
BREEZE-AD7	✓	2°	2°	2°	1°	✓	✓	✓
JAHG	1°			2°	2°	2°	2°	2°
Dupilumab trials								
Study 1021	2°	2°	2°	1°	2°	2°		✓
SOLO 1	✓	1° / 2° ^g	✓	✓	1° / 2° ^g	✓		✓
SOLO 2	✓	1° / 2° ^g	✓	✓	1° / 2° ^g	✓		✓
CAFÉ	2°	1°	2°	2°	2°	✓		2°
CHRONOS	✓	1°	✓	✓	1°	✓		
JADE Compare	✓	1° (Wk12) 2° (Wk16)	✓		1° (Wk12) 2° (Wk16)			✓

Source: Compiled during evaluation with reference to Table 2.4-8 of the submission and related CSRs/protocols.

Abbreviations: EASI=Eczema Area and Severity Index; IGA=Investigator's Global Assessment; DLQI=Dermatology Life Quality Index.

^a At least 50/75/90% improvement/reduction from baseline in EASI score.

^b % change from baseline in EASI score.

^c Proportion of patients achieving IGA of 0 or 1 with a ≥2-point improvement (i.e.: from a baseline of 3 or 4 on the 5-point IGA scale).

^d Proportion of patients achieving an improvement (reduction) in DLQI ≥ 4.

^e Proportion of patients achieving DLQI score of 0/1 for patients with a DLQI score > 1 at baseline.

^f Mean change or absolute and percentage change from baseline in the DLQI total scores.

^g EASI 75 was a coprimary outcome in Europe and Japan and a key secondary outcome elsewhere.

6.17 The trials provide clinical evidence for patients with AD affecting the whole body (as none of the trials enrolled patients with AD exclusively affecting the face and hands), but neither the PBS response criteria (i.e. EASI 50 **and** DLQI ≥4) nor the PBS population (i.e. severe AD, defined as EASI score ≥20 **and** PGA score = 4) were pre-specified analyses in any of the trials.

6.18 The submission did not provide any evidence to support listing of BARI in patients with severe AD affecting the face and hands. For DUPI, the decision to extend listing to patients with disease affecting the face and hands was based on a post-hoc analysis indicating similar and statistically significant improvements in EASI score for all body areas assessed, including head & neck, trunk, upper limbs, lower limbs (para 3.4, DUPI PSD March 2020 PBAC meeting). The PSCR provided a post-hoc analysis for the head and neck region EASI 50 and EASI 74 scores in the BARI trials (BREEZE-AD1 and BREEZE-AD2). In the pooled BREEZE-AD1 and BREEZE-AD2 trials, there were 1,239 patients of whom 1,215 (98.1%) had head and neck involvement. The PSCR claimed that the response to BARI in the head and neck region is consistent with the response to BARI in the whole body. The ESC considered this was in line with the evidence presented for DUPI to justify the additional restriction.

Comparative effectiveness

Treatment response at Week 16

- 6.19 The submission presented a series of indirect treatment comparisons between BARI 2 mg and BARI 4 mg versus DUPI 300 mg, using PBO as a common comparator, for different outcomes at Week 16 in the PBS subgroup (i.e. severe AD) and the ITT population (i.e. moderate and severe AD). For the PBS subgroup, severe AD was defined as EASI score ≥ 20 and IGA score = 4 at baseline.
- 6.20 For the PBS response outcome in the PBS subgroup, the submission presented post-hoc results from the BARI trials and relied on limited data reported in the DUPI PSD (March 2020, Table 10). For the DUPI trials, however, data was only available for CsA-naïve and CsA-experienced patients pooled across monotherapy and combination therapy trials, rather than the outcomes in each trial. Hence, it was not possible to assess or control for the heterogeneity of treatment effect across the different DUPI trials (i.e. monotherapy versus combination therapy trials). Given these limitations and the post-hoc nature of the PBS response outcome, the submission also presented indirect comparisons for other efficacy outcomes in the ITT populations, to have a more complete view of the comparative efficacy between BARI and DUPI.
- 6.21 Table 5 presents results of the PBS response outcome in the PBS subgroup across the trials.

Table 5: Trial results and indirect treatment comparison for PBS response outcome (EASI-50 AND DLQI ≥4) at Week 16, in PBS population (severe AD, defined as: IGA=4 AND EASI ≥20 at baseline)

Trial	Drug n/N (%)	Control n/N (%)	RR# (95%CI)	RD# (95%CI)	NNT* (95%CI)
Monotherapy					
BARI 2 mg v PBO					
BREEZE-AD1	8/48 (16.7)	9/100 (9.0)	1.85 (0.76,4.50)	0.08 (-0.04,0.20)	-
BREEZE-AD2	13/58 (22.4)	6/116 (5.2)	4.33 (1.74,10.81)	0.17 (0.06,0.29)	6 (4,17)
BREEZE-AD5	10/49 (20.4)	3/55 (5.5)	3.74 (1.09,12.82)	0.15 (0.02,0.28)	7 (4,50)
MA	31/155 (20.0)	18/271 (6.6)	2.97 (1.69,5.24)	0.13 (0.06,0.20)	8 (5,17)
BARI 4 mg v PBO					
BREEZE-AD1	15/51 (29.4)	9/100 (9.0)	3.27 (1.54,6.95)	0.20 (0.07,0.34)	5 (3,15)
BREEZE-AD2	10/60 (16.7)	6/116 (5.2)	3.22 (1.23,8.44)	0.11 (0.01,0.22)	10 (5,100)
MA	25/111 (22.5)	15/216 (6.9)	3.25 (1.79,5.89)	0.15 (0.06,0.23)	7 (5,17)
BARI 4 mg v BARI 2 mg					
BREEZE-AD1	15/51 (29.4)	8/48 (16.7)	1.76 (0.82,3.78)	0.13 (-0.04,0.29)	-
BREEZE-AD2	10/60 (16.7)	13/58 (22.4)	0.74 (0.35,1.56)	-0.06 (-0.20,0.09)	-
MA	25/111 (22.5)	21/106 (19.8)	1.14 (0.49,2.66)	0.03 (-0.15,0.21)	-
Combination therapy					
BARI 2 mg +TCS v PBO +TCS					
BREEZE-AD4	29/83 (34.9)	13/49 (26.5)	1.32 (0.76,2.28)	0.08 (-0.08,0.24)	-
BREEZE-AD7	22/49 (44.9)	16/44 (36.4)	1.23 (0.75,2.03)	0.09 (-0.11,0.28)	-
JAHG	8/16 (50.0)	3/16 (18.8)	2.67 (0.86,8.27)	0.31 (0.00,0.62)	-
MA	59/148 (39.9)	32/109 (29.4)	1.37 (0.96,1.94)	0.12 (0.00,0.23)	-
BARI 4 mg + TCS v PBO + TCS					
BREEZE-AD4	17/44 (38.6)	13/49 (26.5)	1.46 (0.80,2.64)	0.12 (-0.07,0.31)	-
BREEZE-AD7	30/49 (61.2)	16/44 (36.4)	1.68 (1.07,2.64)	0.25 (0.05,0.45)	4 (3,20)
JAHG	4/9 (44.4)	3/16 (18.8)	2.37 (0.68,8.31)	0.26 (-0.12,0.63)	-
MA	51/102 (50.0)	32/109 (29.4)	1.65 (1.17,2.32)	0.19 (0.06,0.32)	6 (4,17)
BARI 4 mg v BARI 2 mg					
BREEZE-AD4	17/44 (38.6)	29/83 (34.9)	1.11 (0.68,1.75)	0.04 (-0.13,0.22)	-
BREEZE-AD7	30/49 (61.2)	22/49 (44.9)	1.36 (0.94,2.03)	0.16 (-0.04,0.35)	-
JAHG	4/9 (44.4)	8/16 (50.0)	0.89 (0.34,1.99)	-0.06 (-0.42,0.33)	-
MA	51/102 (50.0)	59/148 (39.9)	1.25 (0.95,1.65)	0.10 (-0.02,0.22)	-
Monotherapy + combination therapy					
BARI 2 mg ± TCS v PBO ± TCS					
BREEZE-AD1, BREEZE-AD2, BREEZE-AD5, BREEZE-AD4, BREEZE-AD7, JAHG	90/303 (29.7)	50/380 (13.2)	1.92 (1.25,2.95)	0.13 (0.07,0.19)	8 (6,15)
BARI 4 mg ± TCS v PBO ± TCS					
BREEZE-AD1, BREEZE-AD2, BREEZE-AD4, BREEZE-AD7, JAHG	76/213 (35.7)	47/325 (14.5)	1.98 (1.44,2.72)	0.16 (0.09,0.23)	7 (5,12)
DUPI 300 mg† ± TCS v PBO ± TCS#					
1021, SOLO 1, SOLO 2, CHRONOS	190/318 (59.7)	74/424 (17.5)	3.42 (2.73,4.29)	0.42 (0.36,0.49)	3 (3,3)
Indirect comparisons					
Monotherapy + combination therapy					
BARI 2 mg ± TCS v DUPI 300 mg ± TCS			0.56 (0.35,0.91)	-0.29(-0.38,-0.20)	-
BARI 4 mg ± TCS v DUPI 300 mg ± TCS			0.58 (0.39,0.86)	-0.26(-0.36,-0.16)	-

Source: Table 2.6.1, pp237-240 of the submission; Table 2.6.4, pp251-252 of the submission

Abbreviations: BARI=baricitinib; DUPI=dupilumab; PBO=placebo; TCS=topical corticosteroids; RR=risk ratio; RD=risk difference; NNT=number needed to treat; CI=confidence interval; n=number of participants with event; N=total participants in group; MA=meta-analysis; EASI= Eczema Area and Severity Index; IGA=Investigator's Global Assessment. **Bold**=statistically significant results.

† DUPI dosing comprised 600 mg loading, then 300 mg every 2 weeks thereafter.

Individual results were not available for monotherapy or combination therapy for DUPI trials, therefore the combined MA result only is provided.

- 6.22 The results demonstrated that a significantly larger proportion of patients in the PBS subgroup achieved the PBS response outcome at Week 16 with active treatment (BARI 4 mg or DUPI) compared to PBO, either as monotherapy or in combination with TCS. The ESC noted that for the 2 mg BARI dose, compared with PBO, a significantly larger proportion of patients achieved the PBS response outcome in the monotherapy trials but for the combination trials for 2 mg BARI the result was not statistically significant in any individual trials or the meta-analysis. Overall, the magnitude of the treatment effect was similar for both doses of BARI, but considerably larger with DUPI. The results of indirect treatment comparisons showed statistically significant differences in favour of DUPI compared to BARI 2 mg (RD: -0.29, 95% CI: -0.38, -0.20) and BARI 4 mg (RD: -0.26, 95% CI: -0.36, -0.16).
- 6.23 The ESC noted that the benefit for BARI appeared to be somewhat attenuated in the trials that allowed concomitant TCS. The risk ratio (RR) for BARI 2 mg monotherapy compared to PBO was RR: 2.97 (95% CI: 1.69, 5.24) versus RR: 1.37 (95% CI: 0.96, 1.94) for combination therapy (which was not statistically significant). The ESC considered these results indicate that BARI 2 mg may be no more effective than PBO when concomitant TCS are used. The pre-PBAC response stated that most patients are expected to receive treatment with BARI 4 mg + TCS in Australian clinical practice and hence the BARI 2 mg results are less relevant.
- 6.24 Table 6 presents a summary of results for the indirect treatment comparisons between BARI and DUPI in the ITT population.

Table 6: Summary of results for indirect treatment comparisons for BARI vs DUPI via PBO, in the ITT population

Outcome & population	RR (95%CI)	RD (95%CI)
EASI-75 response at Week 16		
Monotherapy		
BARI 2 mg v DUPI 300 mg [†]	0.79 (0.53, 1.18)	-0.20 (-0.27, -0.13)
BARI 4 mg v DUPI 300 mg [†]	0.83 (0.53, 1.29)	-0.20 (-0.28, -0.12)
Combination therapy		
BARI 2 mg +TCS v DUPI 300 mg [†] +TCS	0.59 (0.40, 0.89)	-0.29 (-0.40, -0.18)
BARI 4 mg +TCS v DUPI 300 mg [†] +TCS	0.77 (0.56, 1.07)	-0.20 (-0.30, -0.10)
EASI-50 response at Week 16		
Monotherapy		
BARI 2 mg v DUPI 300 mg [†]	0.80 (0.59, 1.07)	-0.27 (-0.35, -0.19)
BARI 4 mg v DUPI 300 mg [†]	0.91 (0.66, 1.26)	-0.23 (-0.34, -0.12)
Combination therapy		
BARI 2 mg +TCS v DUPI 300 mg [†] +TCS	0.79 (0.64, 0.97)	-0.21 (-0.30, -0.11)
BARI 4 mg +TCS v DUPI 300 mg [†] +TCS	0.84 (0.68, 1.04)	-0.16 (-0.26, -0.06)
IGA score of 0 or 1 and ≥2-point improvement at Week 16		
Monotherapy		
BARI 2 mg v DUPI 300 mg [†]	0.77 (0.46, 1.28)	-0.17 (-0.23, -0.11)
BARI 4 mg v DUPI 300 mg [†]	0.77 (0.43, 1.37)	-0.18 (-0.25, -0.12)
Combination therapy		
BARI 2 mg +TCS v DUPI 300 mg [†] +TCS	0.56 (0.35, 0.90)	-0.18 (-0.26, -0.10)
BARI 4 mg +TCS v DUPI 300 mg [†] +TCS	0.77 (0.48, 1.23)	-0.11 (-0.19, -0.02)
DLQI≥4-point improvement at Week 16		
Monotherapy		
BARI 2 mg v DUPI 300 mg [†]	0.87 (0.64, 1.19)	-0.25 (-0.33, -0.17)
BARI 4 mg v DUPI 300 mg [†]	1.17 (0.85, 1.60)	-0.15 (-0.26, -0.04)
Combination therapy		
BARI 2 mg +TCS v DUPI 300 mg [†] +TCS	0.57 (0.46, 0.70)	-0.36 (-0.48, -0.24)
BARI 4 mg +TCS v DUPI 300 mg [†] +TCS	0.66 (0.54, 0.82)	-0.27 (-0.40, -0.14)

Source: Table 2.6.4 (pp251-252), Table 2.6-8 (pp266-267), Table 2.6.9 (pp270-272), Table 2.6-7 (pp262-263) & Table 2.6-3 (pp246-248) of the submission.

Abbreviations: BARI=baricitinib; DUPI=dupilumab; PBO=placebo; TCS=topical corticosteroids; RR=relative risk; RD=risk difference; CI=confidence interval; EASI=Eczema Area and Severity Index; IGA=Investigator's Global Assessment; DLQI=Dermatology Life Quality Index.

Definitions: EASI50/75 = 50/75% improvement/reduction in the EASI score from baseline; IGA score of 0 or 1 and ≥2-point improvement=achievement of a score of 0 or 1 from a baseline of 3 or 4 on the 5-point IGA scale; DLQI≥4=at least 4-point improvement in DLQI from baseline.

Bold=statistically significant results.

[†] DUPI dosing comprised 600 mg loading, then 300 mg every 2 weeks thereafter.

6.25 Results in the ITT population, like the PBS subgroup, showed more patients achieved an adequate response (across all outcomes) with an active treatment versus PBO, and that the magnitude of the treatment effect was significantly larger for DUPI versus BARI 2 mg or 4 mg. Depending on the response outcome assumed, the results suggested for every 100 patients treated compared to DUPI:

- 17 to 27 fewer patients would respond with BARI 2 mg, as monotherapy.
- 15 to 23 fewer patients would respond with BARI 4 mg, as monotherapy.
- 18 to 36 fewer patients would respond with BARI 2 mg, in combination with TCS

- 11 to 27 fewer patients would respond with BARI 4 mg, in combination with TCS

6.26 The ESC considered these results indicate that different conclusions regarding the magnitude of effect can potentially be drawn when assessing the monotherapy or combination therapy trials, depending on the outcome measure. The pre-PBAC response claimed that when considering the comparison of BARI 4 mg + TCS versus DUPI + TCS (which the sponsor considered to be the most relevant) the variability in the reduction in response is markedly reduced; except for the outcome of DLQI \geq 4-point improvement, the RD estimates are reasonably consistent across the outcomes.

Maintenance of response

6.27 Table 7 presents available outcomes reported in BREEZE-AD3, for patients who were responders or partial responders in the originator trials and continued on the same dosing regimen in the extension trial.

Table 7: BREEZE-AD3 results in (i) IGA responders and partial responders at Week 16 of originating trials (continuing treatment on BARI 2 mg or BARI 4 mg), and (ii) patients who met PBS eligibility criteria and PBS response criteria at Week 16 of originating trials (continuing treatment with PBO, BARI 2 mg or BARI 4 mg)

Overall treatment week	IGA responders and IGA partial responders (Wk16)								PBS responders (Wk16)		
	Monotherapy subgroup (BREEZE-AD1, -AD2)				Combination TCS subgroup (BREEZE-AD7)				PBS subgroup (BREEZE-AD1, -AD2, -AD7)		
	IGA 0 or 1		EASI 75		IGA 0 or 1		EASI 75		PBS response		
	BARI 2 mg	BARI 4 mg	BARI 2 mg	BARI 4 mg	BARI 2 mg	BARI 4 mg	BARI 2 mg	BARI 4 mg	PBO	BARI 2 mg	BARI 4 mg
Wk 16 [^]	25/54 (46.3)	32/70 (45.7)	40/57 (74.1)	49/70 (70.0)	21/53 (39.6)	31/63 (49.2)	41/53 (77.4)	45/63 (71.4)	17/17 (100)	28/28 (100)	37/37 (100)
Wk 32	32/54 (59.3)	34/70 (48.6)	38/54 (70.4)	45/70 (64.3)	24/53 (45.3)	20/63 (31.7)	36/53 (67.9)	35/63 (55.6)	9/17 (52.9)	23/28 (82.1)	28/37 (75.7)
Wk 52	34/54 (63.0)	26/70 (37.1)	40/54 (74.1)	36/70 (51.4)	NR	NR	NR	NR	7/17 (41.2)	20/28 (71.4)	23/37 (62.2)
Wk 68	27/54 (50.0)	28/70 (40.0)	35/54 (64.8)	36/70 (51.4)	NR	NR	NR	NR	NR	NR	NR

Source: Tables 2.5-20 to 2.5-21, pp175-176 of the submission; Table 1 in 'A2.24_Post hoc analysis_BREEZE-AD3.doc'

Abbreviations: BARI=baricitinib; EASI=Eczema Area and Severity Index; IGA=Investigator's Global Assessment; NR=not reported; PBO=placebo; TCS=topical corticosteroids; wk=week

[^] Baseline in BREEZE-AD3

6.28 The submission stated that the results showed treatment response generally declined over time. However, interpretation of these results is problematic given the complicated design of BREEZE-AD3, response and eligibility being assessed differently, and the small patient numbers. For BARI 2 mg, the results indicated that IGA and EASI 75 response were mostly maintained over time but declined for BARI 4 mg.

Up-titration from BARI 2 mg to BARI 4 mg

6.29 Table 8 presents available outcomes reported in BREEZE-AD3, for patients who were non-responders (including rescued patients) to BARI 2 mg in the originator trials and re-randomised to BARI 2 mg or BARI 4 mg in the extension trial.

Table 8: BREEZE-AD3 results in IGA non-responders at Week 16 of originating trials for the subgroup of patients initially treated with BARI 2 mg (i.e. BARI 2 mg, then re-randomised to continue BARI 2 mg or up-titrate to BARI 4 mg)

Overall treatment week	Monotherapy (BREEZE-AD1 and BREEZE-AD2)				Combination therapy with TCS (BREEZE-AD7)			
	IGA 0 or 1		EASI 75		IGA 0 or 1		EASI 75	
	BARI 2 mg	BARI 4 mg	BARI 2 mg	BARI 4 mg	BARI 2 mg	BARI 4 mg	BARI 2 mg	BARI 4 mg
Wk 16 [^]	8/84 (9.5)	10/78 (12.8)	22/84 (26.2)	21/78 (26.8)	2/20 (10.0)	1/21 (4.8)	3/20 (15.0)	4/21 (19.0)
Wk 32	13/84 (15.5)	14/78 (17.9)	32/84 (38.1)	30/78 (38.5)	2/20 (10.0)	6/21 (28.6)	4/20 (20.0)	12/21 (57.1)
Wk 52	9/84 (10.7)	13/78 (16.7)	26/84 (31.0)	35/78 (44.9)	NR	NR	NR	NR
Wk 68	16/84 (19.0)	12/78 (15.4)	29/84 (34.5)	27/78 (34.6)	NR	NR	NR	NR

Source: Tables 2.5-22 to 2.5-23, pp178-179 of the submission.

Abbreviations: BARI=baricitinib; EASI=Eczema Area and Severity Index; IGA=Investigator's Global Assessment; NR=not reported; PBO=placebo; TCS=topical corticosteroids; wk=week

[^] Baseline in BREEZE-AD3

6.30 The results show that IGA and EASI 75 response slightly improved over time in both treatment arms, but there was no statistically significant difference between BARI 2 mg and BARI 4 mg. However, the submission argued that interpretation of the results should take account of TCS. Non-responders from the monotherapy trials may include patients with or without TCS at baseline, where TCS was given as a rescue medication. In contrast, non-responders from the combination therapy trial had an inadequate response to treatment despite TCS. Thus, initiation of TCS during the monotherapy trials may have mitigated the impact of an increase in dose, whereas background treatment was unchanged in the combination therapy trial and so the benefit of increasing the dose could be observed.

6.31 Overall, the PBAC considered that the evidence presented in the submission did not clearly demonstrate a benefit for the up-titration from BARI 2 mg to BARI 4 mg in patients with an inadequate response to BARI 2 mg. An improvement in treatment response over time in patients who were non-responders at baseline despite no change in treatment is likely explained by the regression to the mean phenomenon. In addition, any potential mitigating effects of TCS noted by the submission highlights the importance of optimising topical treatments in practice, and would imply that the treatment effects observed in the monotherapy trials may not be realised in practice.

Comparative harms

6.32 The submission presented a summary of adverse events (AEs) and treatment emergent infections over 16 weeks for BARI and DUPI trials. Safety outcomes were analysed in the safety population (all randomised patients who received at least one

dose of a study drug). The most commonly reported adverse events for BARI in the PBO-controlled periods of the trials included nasopharyngitis, headache and increased blood creatinine phosphokinase. The most common adverse event leading to discontinuation decreased white blood cell count. Known common AEs (>5% occurrence) in the BARI PI include: nasopharyngitis, headache, upper respiratory tract infections, herpes simplex infection and LDL cholesterol ≥ 130 mg/dL.

- 6.33 The submission presented pooled safety results of BARI and DUPI trials and conducted indirect safety comparisons for BARI vs DUPI via PBO for three broad categories: any AEs, serious treatment emergent adverse event (TEAEs) and discontinuation due to AEs at Week 16 (Table 9). Overall, there were no statistically significant differences between BARI and DUPI for these safety outcomes.

Table 9: Pooled safety results and indirect safety comparisons of BARI vs DUPI via PBO to Week 16

Safety outcome	BARI trials			DUPI trials		Indirect comparison, RD (95% CI)	
	BARI 2 mg	BARI 4 mg	PBO	DUPI 300 mg	PBO	BARI 2 mg vs DUPI	BARI 4 mg vs DUPI
Any AEs	421/721 (58.4)	300/489 (61.3)	457/889 (51.4)	545/746 (73.1)	706/940 (75.1)	0.06 (-0.02, 0.13)	0.11 (-0.01, 0.22)
Serious TEAEs	12/721 (1.7)	14/489 (2.9)	24/889 (2.7)	19/746 (2.5)	46/940 (4.9)	0.01 (-0.01, 0.03)	0.02 (-0.01, 0.05)
Discontinuation due to AEs	12/721 (1.7)	14/489 (2.9)	17/889 (1.9)	12/746 (1.6)	35/940 (3.7)	0.01 (-0.01, 0.03)	0.02 (-0.01, 0.04)

Source: compiled during evaluation using information from: Table 2.6-12, 2.6-13, 2.6-14, pp282-283, 285-286, 288-289 of the submission. Abbreviations: CI=confidence interval; RD=risk difference; AE=adverse events; TEAE=treatment emergent adverse events; DUPI=dupilumab; PBO=placebo.

- 6.34 In the TGA Delegate’s Overview, it was concluded “that the safety data showed a safety profile consistent with the known adverse effects of baricitinib and did not raise any new major safety concerns.” However, the clinical evaluator did raise some concern regarding recent reports of venous thromboembolism (VTE) and numerical imbalances of AEs between BARI 4 mg and 2 mg doses over time (Delegate’s Summary and Request for ACM advice: Baricitinib). Long-term safety data has also raised concerns regarding thrombosis risk with JAK inhibitors. In 2018, the U.S. Food and Drug Administration (FDA) only approved the BARI 2 mg once daily (BARI 4 mg was not approved) with a black box warning that included a caution related to deep venous thrombosis (DVT), pulmonary embolism (PE) and arterial thrombosis. In July 2019, the FDA also instated a black box warning for tofacitinib 10 mg due to an increased risk of thrombosis and mortality seen in the post-marketing study (paragraph 6.12, upadacitinib PSD in Rheumatoid Arthritis, November 2019 PBAC meeting). Overall, there were limited cases of VTE reported across AD studies examined by the TGA, but there were serious and fatal cases, and a thrombosis/VTE risk not seen in other development programs for AD. The PSCR stated that there were no fatal cases of thrombosis/VTE across 8 randomised controlled trials of BARI in patients with AD, which comprised of data from 2,531 patients treated with BARI for 2,247 patient-years (Bieber et al, 2021).

- 6.35 A possible underlying mechanism of BARI induced platelet elevation has been noted. The TGA Delegate’s Overview discussed that “from the efficacy side for baricitinib, for some patients under some circumstances the 4 mg dose may provide some benefit over the 2 mg dose. From the safety side for baricitinib, based on numerical imbalance between the two doses and recent increase reporting of VTE, it is likely that 4 mg dose would carry a higher risk of harm compared to the 2 mg dose.” As a result, the Delegate’s Overview recommended: “the proposed dosage regimen for the treatment of AD be to start with baricitinib 2 mg and increasing to baricitinib 4 mg only if there is no evidence of efficacy for short duration.”
- 6.36 The ESC noted that the majority of safety outcomes were only reported up to 16 weeks, and comparisons with DUPI were only presented in broad categories. The ESC also noted there is an increased risk of infection (herpes zoster and serious and opportunistic infections) and malignancy associated with JAK inhibitors versus IL-4 inhibitors as a result of immunosuppression, and an increased risk of thrombosis. The PBAC noted that the pre-PBAC response referred to a publication of a safety analysis of BARI in the treatment of rheumatoid arthritis with up to 8.4 years of treatment exposure¹. The pre-PBAC response stated the incidence of serious infections was (2.7 per 100 patient-years), herpes zoster (3.0 per 100 patient-years), malignancy excluding non-melanoma skin cancer (NMSC) (0.9 per 100 patient-years), NMSC (0.3 per 100 patient-years), major cardiovascular events (0.3 per 100 patient-years) and DVT/PE (0.5 per 100 patient-years). The sponsor stated that these rates were consistent with earlier analyses and the safety profile remains stable over time.

Clinical claim

- 6.37 The submission described BARI as inferior in terms of efficacy and similar in terms of safety compared with DUPI, based on pairwise indirect treatment comparisons using PBO as the common comparator.
- 6.38 The ESC agreed with the evaluation that the submission’s claim of inferior efficacy of BARI compared to DUPI was reasonable, however the magnitude of the reduction in response is uncertain and varied depending on the statistic considered and whether monotherapy trials were included, affecting the economic analysis. To better reflect PBS use (where TCS will be used), the ESC considered it would be preferable that the comparisons are based on BARI + TCS versus DUPI + TCS, noting that it was not possible to present these analyses as the data for PBS responders for DUPI was only available for the pooled monotherapy and combination therapy trials.
- 6.39 The ESC considered that the submission’s claim of similar safety for BARI compared to DUPI was potentially supported, but that more detailed assessment of the AEs in the

¹ Genovese et al 2020a. “Safety Profile of Baricitinib for the Treatment of Rheumatoid Arthritis up to 8.4 Years: An Updated Integrated Safety Analysis” EULAR 3rd June 2020.

trials would be helpful, as well as considering whether longer-term data from other indications could be used to better understand the BARI safety profile.

- 6.40 The PBAC considered that the claim of inferior comparative effectiveness was reasonable, though the magnitude of difference in response was uncertain.
- 6.41 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

- 6.42 The submission presented a comparison of BARI to DUPI, using the doses recommended for AD (BARI 2 mg/4 mg once daily and DUPI 600 mg as an initial dose, then 300 mg every two weeks, thereafter). The analysis was based on an equivalent cost over a 2-year period to capture differences in dosing regimens and medicine-specific monitoring (additional routine monitoring costs are required with BARI treatment), less a [REDACTED] % discount on the total costs to account for inferiority of BARI. Given the clinical conclusion was inferior effectiveness versus DUPI, a more appropriate approach would have been a cost effectiveness analysis (see PBAC Guidelines v5 p60). The submission's cost comparison is unlikely to capture the full cost and consequences of BARI listing on the PBS.
- 6.43 The submission stated that the effective price for DUPI was not available to the Sponsor, therefore the proposed price for BARI was a [REDACTED] % relative price reduction compared to the published price of DUPI and costs were totalled over 2 years of treatment. The price reduction was based on the estimated [REDACTED] % [REDACTED] reduction in PBS responders at Week 16 with BARI 2 mg compared to DUPI. However, the submission's approach was inconsistent with the clinical findings where [REDACTED] % is the estimated [REDACTED] reduction in PBS initial responders for BARI 2 mg versus DUPI. Given the submission had applied a relative cost reduction to reflect BARI's inferior efficacy, the more appropriate statistic to use would be the [REDACTED] reduction in response, which is [REDACTED] % (i.e.: [REDACTED] for BARI 2 mg versus DUPI, see Table 5). Based on this statistic, the estimated price of BARI 2 mg would be \$ [REDACTED] AEMP (versus \$ [REDACTED] estimated by the submission). This is summarised in Table 10.

Table 10: Results of the economic analysis

Component	BARI 2 mg		DUPI 300 mg
	█% relative reduction	█% relative reduction	
Price reduction versus DUPI			-
PBS item, max quantity	1 pack, 28 tablets		1 pack, 2 pre-filled syringes
DPMQ	\$ █	\$ █ #	\$1,754.22
AEMP	\$ █	\$ █	\$1,609.86
Total units required over 2 years	26		26.5
Monitoring costs	Lipid & liver function tests: \$58.25 (5 tests) Hb, ALC, ANC: \$84.75 (5 tests) Total monitoring costs: \$143.00		NA
Cost per 2 years	\$ █*	\$ █^	\$42,661.29

Source: Table 3.4-3, p318 of the submission.

Abbreviations: BARI=baricitinib; DUPI=dupilumab; NA=not applicable; ANC=absolute neutrophil count; ALC=absolute lymphocyte count; Hb=haemoglobin.

* Calculated using a █% relative reduction on cost of treatment versus DUPI over 2 years.

^ Calculated assuming a █% relative reduction on cost of treatment versus DUPI over 2 years.

Estimated during the evaluation using DPMQ effective Jan 2021 based on 7th Community Pharmacy Agreement (\$54.14 wholesale mark-up, \$59.49 pharmacy mark-up, \$7.74 dispensing fee).

§ Back calculated from cost over 2 years by subtracting monitoring costs then dividing by total units required over 2 years.

6.44 The ESC noted that the █% reduction in response does not consider:

- any differences in continued response between DUPI and BARI beyond 16 weeks, which is inconsistent with assumptions used in Section 4, where fewer BARI patients-maintained response over time versus DUPI; and
- other sequelae of inferior effectiveness such as a resultant reduction in quality of life or increase in cost of alternative treatments to manage the condition.

The ESC considered that it may be appropriate for the economic analysis to include the costs of the additional alternative treatments required to maintain the (negative) incremental response between BARI and DUPI, which would further reduce the BARI price.

6.45 An indicative non-comparative cost per responder analysis over 2 years was conducted during the evaluation using the same continued response rates for DUPI and BARI as was applied in Section 4 of the submission, this is summarised in Table 11.

Table 11: Response and costs in the first 2 years of the financial estimates model, based on published DPMQ

	DUPI	BARI 2 mg	BARI 4 mg
Proportion on treatment			
Wk 0 to 16	1.00	1.00	1.00
Wk 16 to 40	0.60	0.30	0.36
Wk 40 to 52	0.57	0.21	0.22
Wk 52 to 104	0.50	0.18	0.19
Weeks of response[^]			
Wk 0 to 16	0	0	0
Wk 16 to 52	21.15	9.67	11.20
Wk 52 to 104	25.79	9.59	10.01
Total	46.93	19.27	21.21
Scripts			
Wk 0 to 16	4.50	4.00	4.00
Wk 16 to 52	5.29	2.42	2.80
Wk 52 to 104	6.45	2.40	2.50
Total	16.23	8.82	9.30
Costs[#], total			
Wk 0 to 16	\$7,893.99	\$ [REDACTED]	\$ [REDACTED]
Wk 16 to 52	\$9,274.76	\$ [REDACTED]	\$ [REDACTED]
Wk 52 to 104	\$11,308.29	\$ [REDACTED]	\$ [REDACTED]
Total	\$28,477.05	\$ [REDACTED]	\$ [REDACTED]
Cost per responder, Wk16	\$13,244.95	\$ [REDACTED]	\$ [REDACTED]
Cost per week of response			
Wk 0 to 52	\$811.82	\$ [REDACTED]	\$ [REDACTED]
Wk 52 to 104	\$438.56	\$ [REDACTED]	\$ [REDACTED]
Total	\$606.75	\$ [REDACTED]	\$ [REDACTED]

Source: constructed during the evaluation from the financial estimates model presented in the submission

Abbreviations: BARI=baricitinib; DPMQ=dispensed price for maximum quantity; DUPI=dupilumab; wk=week

[^] Response assumed for those on treatment after Week 16.

[#] Published DPMQs (\$1,754.22 per DUPI script; \$ [REDACTED] per BARI script) plus MBS cost of \$23.73 per script of BARI at 80% benefit

6.46 The cost per responder at 16 weeks suggested a higher cost per responder for BARI versus DUPI. A cost per week of response analysis at 2 years indicated a lower number of response weeks over the 2 years and lower cost per week of response for BARI versus DUPI; noting that the analysis is limited in that it is not incremental, and does not take into account the differences for funding treatments that are less effective and less costly (i.e. with an ICER in the south west quadrant of the cost effectiveness plane). The PSCR argued based on the cost per week of response that the [REDACTED]% price reduction meets the requirements of a cost-minimisation analysis as the cost per outcome (i.e., week of response) is the same between alternatives (i.e., BARI and DUPI) after explicitly accounting for differences in response rates at and beyond week 16. The ESC considered that the cost per responder at 16 weeks for BARI should not be more than that for DUPI, particularly given the relative (loss of) efficacy and therefore an additional reduction in price would be appropriate. The pre-PBAC response agreed to a price reduction of [REDACTED]%, resulting in an AEMP of \$ [REDACTED] for both BARI 2 mg and BARI 4 mg (see Table 10).

6.47 The PBAC noted that the evaluation provided results of sensitivity analyses for BARI using the PBAC accepted DUPI economic model from November 2020. The analyses followed all assumptions used in the DUPI model, the DUPI model had reported results

separately for the CsA naïve and experienced populations (using different utility assumptions). For simplicity, the evaluation followed the utilities for the CsA naïve population, which the PBAC had considered to be more representative of the PBS population. The only values that were changed by the evaluator were: drug costs and response rates for DUPI or BARI. Given the BARI submission only provided results for a pooled CsA naïve and experienced population, results for DUPI vs PBO were also re-estimated for the pooled population using the CsA naïve utility assumptions.

- 6.48 The ESC noted that gains are not valued the same as losses and the literature suggests much higher willingness to accept (WTA) for south west quadrant ICERs compared to willingness to pay (WTP) for north east quadrant ICERs (where treatments are more costly but more effective), indicating potential further price reductions are required to achieve an acceptable cost effectiveness in the south west quadrant for BARI versus DUPI.
- 6.49 Similarly, the ESC noted that there is reduced willingness to accept uncertainty regarding ICERs in the south west quadrant. The ESC noted that there was a high degree of uncertainty in the clinical data informing the economic analysis in that the incremental reduction in responders was based on indirect comparisons and varied depending on the trials included in the analysis (e.g. monotherapy/combination therapy trials).

Drug cost/patient/2-years

- 6.50 Assuming a DPMQ of \$ [REDACTED] (i.e. requested published price) and 26 scripts plus \$143 for routine monitoring costs over a 2-year period, the cost of BARI 2 mg or 4 mg per patient over 2-years is \$ [REDACTED].

Estimated PBS usage & financial implications

- 6.51 This submission was not considered by DUSC. The submission estimated the financial impact of the proposed listing of BARI using an epidemiological approach, plus treatment of an anticipated 500 to < 5000 grandfathered patients enrolled in an early access program at the time of PBS listing. The analysis presented in the submission used published DPMQs because the sponsor was not aware of the confidential effective price for DUPI.
- 6.52 The epidemiological approach was based on the following assumptions:
- The total eligible population was informed by the proportion of patients who have severe AD (PGA=4 and EASI ≥20), uncontrolled despite TCS therapy as estimated in the DUPI PSD (March 2020 PBAC meeting).
 - The number of patients eligible for treatment with DUPI was estimated by applying the DUPI uptake rate (assumed from DUPI PSD March 2020) to the prevalent patients with severe AD uncontrolled on TCS therapy and who had not been treated with DUPI before.

- The number of patients initiating BARI was estimated by applying the BARI uptake rate to the prevalent pool of new and prevalent patients who had not been treated with DUPI before and instead would be treated with BARI.
 - The number of continuing patients was estimated by applying the initial and continuing response rates to the patients initiating with DUPI or BARI.
 - The number of scripts was estimated by applying the scripts by treatment period i.e. initial (Weeks 0 to 16) and continuing (Weeks 16 to 40 and Weeks 40 to 52) or annual (Year 2 to Year 6) to the number of patients treated with DUPI or BARI.
 - The submission estimated the annual change in DUPI scripts as a difference between dispensed scripts for DUPI and BARI.
 - For the requested grandfathering restriction, the submission assumed 500 eligible patients will be treated with BARI in Year 1, commencing as continuing patients.
 - The submission also assumed patients initiating with BARI would have two lipid and hepatic transaminase tests and one test for neutrophil count, lymphocyte count and haemoglobin. Patients continuing treatment would have each of the aforementioned tests every six months.
- 6.53 The overall estimates assumed that patients would not be treated with sequential treatments or re-trial biologic therapies including DUPI and BARI following treatment failure. However, as discussed in Section 3, the requested listing did not preclude sequential use and the PSCR stated that sequential treatment is in the best interest of patients, despite the potential for increased market growth.
- 6.54 Table 12 summarises the key inputs in the financial estimates.

Table 12: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comment
Eligible population			
Australian population aged ≥18 years	Yr 1: 20,429,953 Yr 2: 20,757,917 Yr 3: 21,082,471 Yr 4: 21,411,852 Yr 5: 21,744,502 Yr 6: 22,073,220	ABS 3222.0 Population Projection	Reasonable.
Prevalence of severe AD	45 per 10,000	Assumed 9% of Australian adults have AD and 5% have severe AD (Table 19, Dupilumab PSD March 2020 PBAC meeting)	Consistent with estimate used for dupilumab PBAC submission.
Proportion of severe AD patients with EASI≥20	95%	Table 19, Dupilumab PSD March 2020 PBAC meeting	Consistent with estimate used for dupilumab PBAC submission. The eligible PBS adult population initiating treatment must have severe disease defined by PGA=4 and EASI≥20.
Proportion of patients on TCS therapy with uncontrolled AD	68%	Table 19, Dupilumab PSD March 2020 PBAC meeting	Consistent with estimate used for dupilumab PBAC submission.
Treatment utilisation			
DUPI uptake rate	Yr 1: 5% Yr 2: 5.5% Yr 3: 6% Yr 4: 6.5% Yr 5: 7% Yr 6: 7.5%	Table 19, Dupilumab PSD March 2020 PBAC meeting	It is uncertain whether the assumed uptake rate derived from the Dupilumab PSD March 2020 is reasonable for the current financial model given the current model structure assumed uptake rate would increase in each year, accounting for new and prevalent patients from the prevalent pool who had not been treated with DUPI before. In the March 2020 assessment of DUPI financial model, the PBAC considered it was not reasonable that the uptake rate of new patients from the prevalent pool would increase each year, and instead the increasing uptake rate should be applied to reflect the proportion of continuing patients (para 6.56, Dupilumab PSD March 2020). -
BARI uptake rate	Yr 1: % Yr 2: % Yr 3: % Yr 4: % Yr 5: % Yr 6: %	Assumption	The submission did not provide any data to support this assumption. The submission assumed the uptake of BARI would increase each year because BARI is administered orally (versus SC injection of DUPI) despite inferior efficacy. The PBAC considered that safety was also a factor that would moderate uptake of BARI.
DUPI response rate	Initial: 59.6% Wk 40: 95.7% Yr 2: 83.2% Yr 3: 79.9% Yr 4: 77.2% Yr 5: 74.8% Yr 6: 74.8%	Table 19, Dupilumab PSD March 2020 PBAC meeting	Reasonably based on Dupilumab PSD March 2020, although the submission assumed DUPI response at Week 42 was Week 40 in the model. As was considered by the PBAC for DUPI submissions, estimates for continuing response were derived from very small number of patients and considered highly uncertain (para 6.42, 7.8, dupilumab, PSD, March 2020 PBAC meeting).

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Data	Value	Source	Comment		
BARI response rate	%	2 mg	4 mg	BREEZE-AD3 pooled analysis including post-hoc analysis at Wk 44. Response rate for Yr 2 to Yr 6 estimated relative to DUPI response (Table 19, Dupilumab PSD March 2020 PBAC meeting) e.g. Yr 2 BARI response = Wk 44 BARI response x (Yr 2 / Wk 42 DUPI response),	The submission assumed in the base case the response rate for BARI 2 mg for all patients including those initiating or continuing with BARI 4 mg, which may be an overestimate of the treatment effect. Under the requested listing patients could up titrate from BARI 2 mg to BARI 4 mg if they do not achieve adequate response. The submission also assumed BARI response at Week 44 from BREEZE-AD3 was Week 40 in the model. The continuing response rates for BARI were based on limited data from a very small number of patients at Week 44 and extrapolated to Year 6 based on assumptions, they are considered highly uncertain.
	Initial	29.7	35.7		
	Wk 40	71.4	62.2		
	Yr 2	62.1	54.1		
	Yr 3	59.6	51.9		
	Yr 4	57.6	50.1		
	Yr 5	55.8	48.6		
	Yr 6	55.8	48.6		
Total scripts / patient / year	Wk	DUPI	BARI	Current and proposed PBS listing	
	0-16	4.5	4		
	16-40	6	6		
	40-52	3	3		
	Yr 2	13	13		
BARI scripts by strength	2 mg: 30% 4 mg: 70%	Assumption		The assumed script proportions by strength could not be verified. However, the financial impact is not sensitive to this parameter given both strengths have the same price.	
Costs					
BARI 28 x 2 mg / 4 mg	\$ [REDACTED]	Calculated based on the requested AEMP		Correctly calculated.	
DUPI 2 x 300 mg/ 2 mL	\$1754.22	PBS item 12292Y		Appropriate. Concurs with the current published DPMQ for DUPI.	
% PBS/RPBS	PBS: 96.5% RPBS: 3.5%	PBS/RPBS scripts for triamcinolone (item 2117K, 2118L) and hydrocortisone (item 2881P, 2882Q).		The submission assumed the scripts by beneficiary type and average co-payment per script based on PBS services data for triamcinolone and hydrocortisone as a proxy for BARI and DUPI, which may not reasonably represent the utilisation of biologics in AD given the price of triamcinolone and hydrocortisone are below the general patient co-pay and would not be collected in the PBS service data. This is likely to lead to an overestimate of the cost of each script to the PBS.	
Patient co-pay	PBS: \$5.34 RPBS: \$4.46	Weighted average across general and concessional PBS/RPBS services of triamcinolone and hydrocortisone			
MBS costs	Lipids, hepatic transaminases: \$11.65 Haemoglobin and absolute neutrophil & lymphocyte: \$16.95	MBS items 66503, 65070		Reasonable.	

Abbreviations: AD=atopic dermatitis; BARI=baricitinib; DUPI=dupilumab; EASI=Eczema Area and Severity Index; TCS=topical corticosteroids; DLQI=Dermatology Life Quality Index; PGA=Physician's Global Assessment; SA=sensitivity analysis; VTE=venous thromboembolism

Source: Table 4.1-1, pp320-322 of the submission.

6.55 Table 13 summarises the estimated net financial implications for the proposed listing of BARI on the PBS/RPBS for AD.

Table 13: Estimation of number of treated patients and prescriptions

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated number of prevalent patients						
Prevalent population with severe AD	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Eligible population	█ ²	█ ³	█ ³	█ ³	█ ³	█ ³
Patients initiating PBS/RPBS treatment, DUPI or BARI	█ ⁴	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Patients initiating PBS/RPBS treatment, BARI						
New patients	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Grandfathered	█ ⁴	-	-	-	-	-
Estimated use of BARI[^]						
Patients treated with BARI						
Initiating patients	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Continuing patients (include grandfathered)	█ ⁴	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
BARI scripts						
BARI 2 mg initial	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
BARI 2 mg continuing	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
BARI 4 mg initial	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
BARI 4 mg continuing	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
BARI PBS/RPBS cost	\$ █ ⁸	\$ █ ⁸	\$ █ ⁸	\$ █ ⁸	\$ █ ⁸	\$ █ ⁸
BARI net PBS/RPBS cost	\$ █ ⁸	\$ █ ⁸	\$ █ ⁸	\$ █ ⁸	\$ █ ⁸	\$ █ ⁸
Estimated changes of use of the proposed listing						
Patients substituting DUPI for BARI						
Initiating patients	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Continuing patients	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
DUPI scripts						
DUPI initial	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁷
DUPI continuing	█ ⁴	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
DUPI PBS/RPBS cost	-\$ █ ⁸	-\$ █ ⁹	-\$ █ ⁹	-\$ █ ⁹	-\$ █ ⁹	-\$ █ ⁹
DUPI net PBS/RPBS cost	-\$ █ ⁸	-\$ █ ⁹	-\$ █ ⁹	-\$ █ ⁹	-\$ █ ⁹	-\$ █ ⁹
Net financial implications to the government						
Net cost to PBS/RPBS	-\$ █ ⁸	-\$ █ ⁸	-\$ █ ⁸	-\$ █ ⁸	-\$ █ ⁸	-\$ █ ⁹
Net cost to MBS	\$ █ ⁸	\$ █ ⁸	\$ █ ⁸	\$ █ ⁸	\$ █ ⁸	\$ █ ⁸
Net cost to PBS/RPBS/MBS	-\$ █ ⁸	-\$ █ ⁸	-\$ █ ⁸	-\$ █ ⁸	-\$ █ ⁸	-\$ █ ⁹

Source: Tables 4.2-1 to 4.5-3, pp330-341 of the submission.

Abbreviations: AD=atopic dermatitis; BARI=baricitinib; DUPI=dupilumab; EASI=Eczema Area and Severity Index; TCS=topical corticosteroids

[^] BARI scripts were estimated during the evaluation using BARI 4 mg response rate for all patients initiating and continuing BARI. The submission assumed in the base case the response rate of BARI 2 mg.

The redacted values correspond to the following ranges:

- ¹ 90,000 to < 100,000
- ² 50,000 to < 60,000
- ³ 60,000 to < 70,000
- ⁴ 500 to < 5,000
- ⁵ < 500
- ⁶ 5,000 to < 10,000
- ⁷ 10,000 to < 20,000
- ⁸ \$0 to < \$10 million
- ⁹ \$10 million to < \$20 million

6.56 At the requested price for BARI, and based on the published price for DUPI, the submission estimated the proposed listing of BARI would result in a net cost saving of \$40 million to < \$50 million to the health budget over the first 6 years. The estimated net cost saving is uncertain and likely overestimated given:

- The potential underestimate of the market uptake. The financial model assumed only a proportion of the population who would initiate DUPI treatment (new and prevalent patients who have not used DUPI before) would initiate BARI, this reduced the estimated number of patients initiating BARI considerably to < 500, < 500, < 500, < 500 and < 500 in the first 6 years of listing. These estimates are implausibly small when the eligible population (fitting PBS initiation criteria) each year is more than 330 times larger (e.g., 60,000 to < 70,000 eligible patients in Year 6 versus < 500 initiating treatment with BARI).
- A sensitivity analysis assuming an additional 20% patients were treated with standard of care who would not use DUPI but would initiate BARI, showed a reduction in the net cost savings to the government. The PSCR acknowledged that the uptake of BARI (in additional patients who would not otherwise be treated with DUPI) may have been underestimated in the submission for the reasons identified during the evaluation, but stated that the sensitivity analysis indicated that a PBS listing for BARI would continue to be associated with cost savings (albeit reduced). The ESC noted that the PSCR did not provide any information to justify the 20%, or any other data to support a different estimate of uptake additional to DUPI treated patients.
- The ESC considered that BARI and other oral treatments (e.g. upadacitinib) may be preferred treatments at an individual patient level, and are potential alternatives for those who have already failed treatment with DUPI, with the potential to grow the market. Given the results for BARI 2 mg do not meet statistical significance versus standard of care (PBO plus TCS) and the potential for longer-term safety issues, the PBAC considered that its place in therapy was unclear.
- The uncertain treatment response rate or continuing treatment persistence. The submission assumed the treatment response for BARI at Week 40 from a post-hoc analysis of BREEZE-AD3 at Week 44 and the response rate for Year 2 to Year 6 was estimated as a ratio relative to the DUPI response rate, which was calculated from time to first rescue treatment or treatment discontinuation analysis (Table 19, dupilumab PSD March 2020 PBAC meeting). These results were based on data from very few patients and then extrapolated using uncertain assumptions, overall, the continued response rates used in the financial estimates are considered uncertain. A lower continued response rate for BARI favoured it in the financial estimates as costs are reduced when non-responders stop treatment. In contrast, the submission's economic analysis did not consider any further price reductions for BARI versus DUPI for a lower continued response rate over time.

Financial Management – Risk Sharing Arrangements

- 6.57 The sponsor did not propose a Risk Sharing Arrangement in the submission. For DUPI, the PBAC had considered that a [REDACTED] % rebate would be required for expenditure exceeding the estimated financial cost for DUPI to address the potential for use outside the intended population, and to address the potential continuing use in patients who do not have adequate response, where use of DUPI is likely to be less cost-effective.

For more detail on PBAC's view, see Section 7 PBAC Outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of baricitinib (BARI) for the treatment of adults with severe atopic dermatitis (AD). Whilst the PBAC accepted that the claim of inferior efficacy of BARI compared to dupilumab (DUPI) was reasonable, the magnitude of difference in response was uncertain. The PBAC also considered that the safety profile for BARI is inferior to DUPI and noted concerns remain regarding the long-term safety of BARI. As such the PBAC considered that the clinical place of BARI was unclear. Given the uncertainty in the clinical data and because the cost comparison presented in the submission did not capture the full cost and consequences of listing BARI on the PBS, the PBAC considered that the economic analysis was not reliable for decision-making.
- 7.2 The PBAC noted that BARI is a novel medicine, as no other Janus Kinase (JAK) inhibitors are available on the PBS for AD. The PBAC acknowledged the clinical need for additional alternative systemic treatments for severe atopic dermatitis, but considered that there was limited additional need, given the availability of DUPI for patients with severe AD. The PBAC noted that the clinical need remained high for patients with moderate AD, who also experience a high level of disease burden, as outlined in the consumer comments.
- 7.3 The PBAC noted that sequential use of BARI following DUPI and vice versa was not excluded in the proposed restrictions. This was consistent with the proposed clinical management algorithm and consumer comments which expressed a desire to access a JAK inhibitor for patients who did not have an adequate response to DUPI. The pre-PBAC response reiterated that sequential treatment with BARI and DUPI should be allowed given the different mechanisms of action, as non-response to one medicine does not preclude a patient from responding to the other medicine. The PBAC considered given the lower efficacy for BARI, it is unclear whether BARI is likely to be of benefit in patients who fail to respond to DUPI. Furthermore, the PBAC noted that the submission did not present any data to assess efficacy in this group of patients.
- 7.4 The submission presented DUPI as the primary comparator. The main argument provided in support of this nomination was that DUPI is the treatment most likely to be replaced by BARI. The PBAC considered that DUPI was an appropriate choice for

the comparator. The PBAC noted that CsA was a potentially relevant secondary comparator but its use in clinical practice is limited due to toxicity and that UPA was a relevant near market comparator.

- 7.5 The submission was based on six head-to-head randomised trials comparing BARI to PBO and six trials comparing DUPI to PBO, which informed an indirect treatment comparison between BARI versus DUPI. The PBAC noted that the submission relied on the indirect treatment comparison to inform the clinical claim and economic analysis.
- 7.6 The PBAC noted that patients in all trials had moderate to severe AD and were required to have experienced an inadequate response to topical corticosteroids (TCS) (for at least 6 months). Concomitant use of daily emollients was allowed and encouraged in all trials, but concomitant use of TCS was only allowed in three BARI trials (BREEZE-AD4, BREEZE-AD7 and JAHG) and three DUPI trials (CAFÉ, CHRONOS and JADE Compare). The PBAC recalled it previously considered standard of care includes concomitant TCS, (para 5.1, DUPI PSD, July 2018 PBAC meeting) and considered that the trials that allowed ongoing use of TCS were most relevant to Australian clinical practice, where TCS would be expected to be continued in combination with BARI.
- 7.7 The risk ratio (RR) for BARI 2 mg monotherapy compared to PBO was 2.97 (95% CI: 1.69, 5.24) and for combination therapy was 1.37 (95% CI: 0.96, 1.94; difference not statistically significant). The PBAC agreed with the ESC that these results indicate that BARI 2 mg may be no more effective than PBO when concomitant TCS are used.
- 7.8 In terms of the PBS response outcome at Week 16 in the PBS subgroup (severe AD), the results of the indirect treatment comparisons showed statistically significant differences in favour of DUPI compared to BARI 2 mg (RD: -0.29, 95% CI: -0.38, -0.20) and BARI 4 mg (RD: -0.26, 95% CI: -0.36, -0.16). The PBAC noted that the benefit for BARI appeared to be somewhat attenuated in the trials that allowed concomitant TCS. The PBAC considered that for the ITT population different conclusions regarding the magnitude of effect can potentially be drawn when assessing the monotherapy or combination therapy trials, and depending on the outcome measure (see paragraph 6.25). The pre-PBAC response argued that the RD values were relatively consistent across outcomes for the comparison of BARI 4 mg versus DUPI in the combination therapy trials.
- 7.9 The pre-PBAC response stated that most patients are expected to receive treatment with BARI 4 mg + TCS in Australian clinical practice and hence the BARI 2 mg results are less relevant. The submission presented supportive evidence to inform the maintenance of response over time and the up-titration from BARI 2 mg to 4 mg. The PBAC considered that the evidence presented did not clearly demonstrate a benefit for the up-titration from BARI 2 mg to BARI 4 mg in patients with an inadequate response to BARI 2 mg (see Table 8), and the efficacy of this approach in practice is unclear. Furthermore, the PBAC noted that treatment response appeared to generally decline over time, though interpretation of these outcomes was difficult due to small patient numbers and the complicated trial design.

- 7.10 Overall, the PBAC considered that the clinical claim of inferior comparative effectiveness for BARI versus DUPI was reasonable, however the magnitude of the reduction in response is uncertain and varied depending on the statistic considered and whether monotherapy trials were included.
- 7.11 In the BARI trials the majority of safety outcomes were only reported up to 16 weeks, and comparisons with DUPI were only presented in broad categories. The ESC noted there is an increased risk of infection (herpes zoster and serious and opportunistic infections) and malignancy associated with JAK inhibitors versus IL-4 inhibitors as a result of immunosuppression, and an increased risk of thrombosis. Although additional safety data in treatment of rheumatoid arthritis up to 8.4 years was provided in the pre-PBAC response, the PBAC considered long-term safety concerns remain regarding the risk of thrombosis from JAK inhibitors and BARI is likely to be inferior to DUPI in terms of safety based on the increased risk of infections.
- 7.12 The submission presented a cost comparison of BARI and DUPI over a two-year period based on the doses recommended for AD: BARI 2 mg/4 mg once daily and DUPI 600 mg as an initial dose, then 300 mg every two weeks thereafter. The cost calculations included a [REDACTED] % discount on the total costs to reflect the inferior efficacy of BARI, based on the estimated [REDACTED] percentage reduction in responders for BARI versus DUPI at Week 16. In the pre-PBAC response the discount was increased to [REDACTED] %, based on the [REDACTED] for BARI 2 mg versus DUPI (see Table 5).
- 7.13 The PBAC noted that the economic evaluation presented in the submission did not capture the full incremental cost and consequences of listing BARI on the PBS. Given the clinical conclusion was inferior effectiveness versus DUPI, the PBAC considered a cost-effectiveness analysis would have been a more appropriate approach in order to capture i) any differences in continued response between DUPI and BARI beyond 16 weeks; and ii) other sequelae of inferior effectiveness such as a reduction in quality of life or increase in the cost of alternative treatments to manage the condition. The PBAC noted that analyses undertaken during the evaluation using the DUPI model were consistent with a larger price discount than the original [REDACTED] %. The PBAC further noted the literature suggests higher willingness to accept (WTA) for south west quadrant ICERs (where treatments are less effective and less costly) compared to willingness to pay (WTP) for north east quadrant ICERs (where treatments are more effective and more costly), indicating potential further price reductions are required to achieve an acceptable cost effectiveness in the south west quadrant for BARI versus DUPI.
- 7.14 The PBAC noted that the submission estimated a net cost saving for the PBS due to the lower price for BARI compared to DUPI. The PBAC considered that the estimated number of patients initiating BARI treatment was low (< 500 - < 500 patients in each year) and may be underestimated. However, the PBAC considered given the inferior efficacy and safety compared with DUPI that it may not be reasonable to assume that BARI would replace DUPI in practice and therefore the cost savings estimated may not be realised.

- 7.15 The PBAC considered that any resubmission should consider the appropriate clinical place for BARI, given its inferior efficacy and safety compared with DUPI. The PBAC also considered that a revised economic evaluation should capture the full incremental cost and consequences of listing BARI on the PBS, as outlined in paragraph 7.13.
- 7.16 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 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.

9 Sponsor's Comment

The sponsor had no comment.