National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Baricitinib for treating moderate to severe atopic dermatitis ID1622
Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	National Eczema Society	Yes, it would be appropriate to refer this topic to NICE for appraisal.	Thank you for your comment. No changes needed.
	GlaxoSmithKline	Yes.	Thank you for your comment.
	Eli Lilly and Company Limited	Yes, this is an appropriate topic to defer to NICE for appraisal.	Thank you for your comment. No changes needed.
Wording	National Eczema Society	Yes, the wording of the remit reflects the issue(s) of clinical and cost effectiveness about this technology.	Thank you for your comment. No changes needed.
	GlaxoSmithKline	Yes.	Thank you for your comment.

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	Eli Lilly and Company Limited	Agree.	Thank you for your comment. No changes needed.
Timing Issues	National Eczema Society	N/A	-
	Eli Lilly and Company Limited	Advice to the NHS should be as close to marketing authorisation as is feasible within the NICE appraisal programme.	Thank you for your comments. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.
Any additional comments on the draft remit	National Eczema Society	N/A	-
	Eli Lilly and Company Limited	No further comments.	Thank you.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	National Eczema Society	The background information appears to be accurate and complete.	Thank you for your comments. The background has been updated.
	GlaxoSmithKline	We request the removal of the word “possible” in the last sentence of paragraph 3 in the Background section to reflect the language used in TA177. Alitretinoin is the most strongly recommended treatment for refractory severe chronic hand dermatitis by the international ESCD guidelines on hand eczema and NICE appraisal Evidence Review Group conducted a cost effectiveness evaluation which showed Alitretinoin to dominate other alternative (unlicensed) treatments.	Thank you for your comments. The word “possible” was removed.
	Eli Lilly and Company Limited	This section provides comprehensive background information, although the following points should be considered with respect to current understanding of atopic dermatitis: Atopic dermatitis (AD) causes pruritus attacks, which is the primary source of morbidity in this disorder (Simpson 2012). Pruritus often leads to an “itch–scratch” cycle. Despite topical and/or conventional therapies, persistent and severe itch is experienced in 85.8% of moderate to severe AD patients resulting in a decrease in QoL (Simpson et al. 2016). Pruritus from AD can worsen at night, resulting in sleep disturbances, with approximately 27% of adult patients with AD experiencing sleep disturbance as a result of itching (Langenbruch et al. 2014). In adult patients with moderate to severe AD, sleep quality and latency were significantly associated with poor QoL (Yano et al. 2013).	Thank you for your comments. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. The nature of the condition and care required will be considered in any appraisal of baricitinib. Scope unchanged.

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		References 1. Simpson EL. Comorbidity in atopic dermatitis. *Curr Dermatol Rep*. 2012;1(1):29-38. 2. Simpson EL, et al. Patient burden of moderate to severe atopic dermatitis (AD): Insights from a phase 2b clinical trial of dupilumab in adults. *J AM Acad Dermatol.* 2016;74(3):491-498 3. Langenbruch A, Radtke M, Franzke N, Ring J, Foelster-Holst R, Augustin M. Quality of health care of atopic eczema in Germany: results of the national health care study AtopicHealth. *J Eur Acad Dermatol Venereol*. 2014;28(6):719-726. 4. Yano C, Saeki H, Ishiji T, Ishiuji Y, Sato J, Tofuku Y, Nakagawa H. Impact of disease severity on sleep quality in Japanese patients with atopic dermatitis. *J Dermatol Sci*. 2013;72(2):195-197.	
The technology/ intervention	National Eczema Society	Yes, as far as we are aware.	Thank you for your comment. No changes needed.
	GlaxoSmithKline	Yes	Thank you for your comment.
	Eli Lilly and Company Limited	This section provides a comprehensive description of the technology, although the following points should be considered: Baricitinib (Olumiant®) is a reversible highly selective Janus kinase inhibitor for JAK1 and JAK2 that blocks the JAK-signal transducer and activator of transcription (STAT) pathway and inflammatory response in AD pathogenesis. Baricitinib is administered orally.	Thank you for your comments. This section aims to provide a brief description of the technology, it is not designed to be exhaustive in its detail. Scope unchanged.

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		References **1.** Brunner PM, Guttman-Yassky E, Leung, DYM. The immunology of atopic dermatitis and its reversibility with broad spectrum and targeted therapies. *J Allergy Clin Immunol*. 2017; 139(4Suppl):S65-S76. **2.** Nomura T, Kabashima K. Advances in atopic dermatitis in 2015. *J Allergy Clin Immunol.* 2016;138(6):1548-1555.	
Population	National Eczema Society	Yes, the population is defined appropriately. We don't think there are groups within this population that should be considered separately.	Thank you for your comment. No changes needed.
	GlaxoSmithKline	Yes	Thank you for your comment.
	Eli Lilly and Company Limited	The population has been defined appropriately.	Thank you for your comment. No changes needed.
Comparators	National Eczema Society	Yes, these are the standard treatments for moderate to severe atopic eczema currently used in the NHS with which the technology should be compared. We are unable to describe any one of these as 'best alternative care' – which would be 'best alternative care' would depend on the individual.	Thank you for your comments. No changes needed.
	GlaxoSmithKline	Yes	Thank you for your comment.
	Eli Lilly and Company Limited	The comparators listed provide a comprehensive reference of standard treatment currently used in the NHS. The use of baricitinib within the UK clinical practice is predicted to be following failure (or contraindication) of topical therapies, phototherapy and	Thank you for your comments. As baricitinib is primarily being studied in adults with moderate to severe

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		systemic immunosuppressant agents. Currently only dupilumab and BSC are the only relevant comparators beyond this point. Additionally, alitretinoin is not a relevant comparator, in line with the dupilumab TA534 appraisal: - Alitretinoin is also not a valid comparator based on its licenced indication and place in therapy in treatment of severe chronic hand eczema.	atopic dermatitis that have had an inadequate response or intolerance to existing topical treatments, phototherapy and systemic immunosuppressive therapies are considered relevant comparators. Alitretinoin cannot be conclusively excluded as a comparator at this stage. If evidence allows the company can propose a narrower positioning in their submission for the committee to consider.
Outcomes	National Eczema Society	Yes, these outcome measures will capture the most important health-related benefits (and harms) of baricitinib.	Thank you for your comments. No changes needed.
	GlaxoSmithKline	Yes	Thank you for your comments.
	Eli Lilly and Company Limited	The outcomes measures presented capture the most important health-related benefits of baricitinib.	Thank you for your comments. No changes needed.

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		In addition to improvements in skin lesions and symptoms of AD, baricitinib achieved improvements in symptoms of anxiety and depression using the Hospital Anxiety Depression Scale (HADS) and work productivity scores using the Work Productivity and Activity Impairment Questionnaire (WPAI-AD).	
Economic analysis	National Eczema Society	N/A	-
	GlaxoSmithKline	Yes	Thank you for your comments.
	Eli Lilly and Company Limited	An economic analysis that addresses the requirements of the NICE reference case will be submitted. A lifetime time horizon will be implemented and the NHS and PSSRU perspective will be chosen.	Thank you for your comments. No changes needed.
Equality and Diversity	National Eczema Society	We do not think the proposed remit and scope require changing.	Thank you for your comments. No changes needed.
	GlaxoSmithKline	N/A	-
	Eli Lilly and Company Limited	None identified.	Thank you for your comments. No changes needed.
Other considerations	National Eczema Society	N/A	-

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	GlaxoSmithKline	For “skin colour subgroups”, should this be Fitzpatrick skin type I-VI? Should a subgroup also include ‘Severity of Dermatitis i.e.moderate vs severe?	Thank you for your comments. If evidence allows the company can present sub-groups in their submission for the committee to consider. No changes needed.
	Eli Lilly and Company Limited	No additional issues.	Thank you for your comments. No changes needed.
Innovation	National Eczema Society	Yes, we consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and improve the way that current need is met. The introduction of baricitinib wouldn’t necessarily lead to a ‘step-change’ in the management of eczema. Nevertheless, its availability would broaden patient choice, which is vital given the limited treatment options for the condition at present, and increase the likelihood that people with moderate to severe eczema would find a treatment that is effective for them. People with moderate to severe eczema are currently faced with the choice of managing the best they can with topical treatments, in great pain and discomfort, or starting phototherapy (which is not universally available) or immunosuppressant drugs of uncertain efficacy with the potential for significant long-term harm through severe adverse side effects. The biologic drug dupilumab has fewer potential side effects than broader immunosuppressant drugs, but it is only available to people who have tried and failed on at least one oral immunosuppressant drug, and those who would not be eligible to take them.	Thank you for your comments. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No action needed.

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		Even if baricitinib is only made available under the same circumstances as dupilumab, it will constitute an additional treatment option for people with severe eczema, increasing the likelihood that they will find a treatment that works effectively for them. It also has the potential to reduce the need for topical steroid treatment, which people with severe eczema desperately want and deserve. Baricitinib is taken orally, whereas dupilumab is administered by subcutaneous injection. The BREEZE trial data results are impressive in terms of symptom improvement and the rapidity with which symptoms improved. 'Efficacy And Safety of Baricitinib in Moderate to Severe Atopic Dermatitis: Results Of Two Phase 3 Monotherapy Randomized, Double-Blind, Placebo controlled 16-Week Trials (Breeze-Ad1 and Breeze-Ad2)' (2019) by Eric L. Simpson et al shows baricitinib's rapid onset of action. Significant improvement in itch was achieved as early as Week 1 for 4-mg and Week 2 for 2-mg. Improvements in night-time awakenings, skin pain, dermatology life quality index, and Patient-Oriented Eczema Measure were observed by Week 1 for both 4-mg and 2-mg. 'Efficacy and Safety of Baricitinib in Combination with Topical Corticosteroids in Moderate to Severe Atopic Dermatitis: Results of a Phase 3 Randomized, Double-Blind, Placebo-Controlled 16-week Trial (BREEZE-AD7)' (2019) by Kristian Reich et al also showed rapid clinically meaningful improvements in the patient-reported outcomes of itch, skin pain and sleep disturbance. Adverse events in these trials were mainly mild and moderate, and the safety profile was consistent with earlier findings. We don't consider that the use of the technology would result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation.	

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	GlaxoSmithKline	N/A	-
	Eli Lilly and Company Limited	Baricitinib has a novel targeted mode of action involving the reversible inhibition of JAK1 and JAK2 enzymes and will potentially be first in class treatment for moderate to severe AD. The results of the pivotal phase III studies have demonstrated significant and substantial improvements on health-related benefits in patients reported outcomes (PROs) including pain, sleep disturbance, itch, quality of life, anxiety and depression – important factors for patients with AD. In addition, baricitinib provides rapid onset of efficacy which is seen as early as week 1 and maintained throughout the trial period. For the patients whose only other treatment is a biologic, baricitinib will provide an alternative and easier treatment option for patients with moderate to severe AD. Given the once daily oral formulation and results of the pivotal phase III studies, baricitinib has the potential to be considered an innovative step-change in the AD treatment paradigm. **Do you consider that the use of baricitinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** Improvement on sleep disturbance due to itch and skin pain, two symptoms that are important to patients, were evaluated in the pivotal phase III studies using novel scales developed by Lilly. These health outcomes represent important factors for patients with AD but may not be entirely captured with the QALY calculation. These represent important potentially additional benefits of baricitinib therapy, particularly given the rapid onset of action, and	Thank you for your comments. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No action needed.

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		baricitinib ability to produce clinically meaningful improvements in skin pain (4 or more point improvement from baseline) and sleep disturbance (increasing the proportion of nights without night time awakenings due to itch). **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** Data that will enable the Appraisal Committee to take account of these non-QALY benefits will all be derived from the pivotal phase III trials.	
Questions for consultation	National Eczema Society	N/A	-
	GlaxoSmithKline	The proposed Single Technology Appraisal process is appropriate.	Thank you for your comments. No action needed.
	Eli Lilly and Company Limited	**Q1. What is established clinical practice in the NHS for patients with moderate to severe dermatitis that have an inadequate response or intolerance to existing topical treatments?** Patients with moderate to severe atopic dermatitis that have an inadequate response or intolerance to existing topical treatments may receive high potency topical corticosteroids (TCS) and/or phototherapy, and then systemic treatments if these options are not adequate to manage the disease. Currently, 2 systemic therapies are approved for patients with moderate to severe AD before BSC: • Ciclosporin to treat severe AD • Dupilumab for moderate to severe AD when systemic treatment has failed and BSC is the only available option	Thank you for your comments. As baricitinib is primarily being studied in adults with moderate to severe atopic dermatitis that have had an inadequate response or intolerance to existing topical treatments, the population and comparators specified in the scope will reflect

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		Ciclosporin although thought to be efficacious can lead to irreversible renal toxicity, hypertension, and hematopoietic adverse events and for this reason is not intended for long-term use. Dupilumab, a recently approved injectable although efficacious for patients with moderate to severe AD it has the following limitations: • Not all patients achieve disease control (Simpson et al. 2016b) • Injection causes anxiety for some patients (Simpson et al. 2016b) • Injection site reactions occur in 13% of dupilumab-treated patients • Conjunctivitis occurs in 7% of patients within 16 weeks of starting treatment and 34% of patients during long-term treatment (Simpson et al. 2016b, Ariens et al. 2019). <u>References:</u> 1. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, Silverberg JI, Deleuran M, Kataoka Y, Lacour JP, Kingo K, Worm M, Poulin Y, Wollenberg A, Soo Y, Graham NM, Pirozzi G, Akinlade B, Staudinger H, Mastey V, Eckert L, Gadkari A, Stahl N, Yancopoulos GD, Ardeleanu M; SOLO 1 and SOLO 2 Investigators. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016b;375(24):2335-2348. 2. Ariëns LFM, van der Schaft J, Bakker DS, Balak D, Romeijn MLE, Kouwenhoven T, Kamsteeg M, Giovannone B, Drylewicz J, van Amerongen CCA, Delemarre EM, Knol EF, van Wijk F, Nierkens S, Thijs JL, Schuttelaar MLA, de Bruin-Weller MS. Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: first clinical and biomarker results from the BioDay registry	this positioning. If evidence allows the company can propose a narrower positioning in their submission for the committee to consider.

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		[published online ahead of print 08 October 2019]. Allergy. 2019. doi: 10.1111/all.14080. **Q2. Have all relevant comparators for baricitinib been included in the scope?** Our comments on comparators have been captured above. **Q3. Should best supportive care be included as a comparator? And if so, how it should be defined?** BSC will be included as a comparator for those patients who are have no response or intolerance to dupilumab or baricitinib. BSC can be defined as a combination of emollients, low to mid potency topical corticosteroids (TCS), phototherapy, psychological support and rescue therapy such as higher potency topical or oral corticosteroids or topical calcineurin inhibitors (TCIs). **Q4. Are the outcomes listed appropriate?** Our comments on outcomes have been captured above. **Q5. Is the subgroup suggested in 'other considerations appropriate? Are there any other subgroups of people in whom baricitinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?** The suggested subgroup of people who are ciclosporin naïve and those who have previously received ciclosporin is appropriate. No others have been identified.	

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		Q6. Where do you consider baricitinib will fit into the existing NICE pathway, Treating eczema in people over 12? We would anticipate that baricitinib will fit in the pathway a as a treatment option for patients aged 18 or over with moderate to severe AD which is uncontrolled with standard therapy; after topical steroids, topical tacrolimus, phototherapy and have failed or intolerant/contraindicated to at least 1 systemic therapy. **Q7. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly** None identified.	
Any additional comments on the draft scope	National Eczema Society	N/A	-
	GlaxoSmithKline	No.	Thank you for your comment.
	Eli Lilly and Company Limited	No further comments	Thank you for your comment.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

None.