National Institute for Health and Care Excellence

Health Technology Evaluation

Remibrutinib for treating chronic spontaneous urticaria inadequately controlled by H1-antihistamines ID6356
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Novartis Pharmaceuticals UK Ltd	We consider this topic appropriate for evaluation, and the proposed evaluation route (STA) is also appropriate.	Thank you for your comment. No action needed.
	The Royal College of Pathologists	The evaluation and proposed evaluation route are appropriate.	Thank you for your comment. No action needed.
	British Society for Immunology Clinical Immunology Professional Network	In light of the published research evidence in CSU and unmet need for treatment for some patients with CSU, Remibrutinib does merit evaluation as an additional agent.	Thank you for your comment. No action needed.

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	British Association of Dermatologists	We agree this evaluation and that its route is appropriate and reasonable.	Thank you for your comment. No action needed.
Wording	Novartis Pharmaceuticals UK Ltd	The current wording is appropriate.	Thank you for your comment. No action needed.
	The Royal College of Pathologists	The wording is appropriate	Thank you for your comment. No action needed.
	British Society for Immunology Clinical Immunology Professional Network	The economic analysis documented appears appropriate.	Thank you for your comment. No action needed.
	British Association of Dermatologists	We agree with the wording of the remit.	Thank you for your comment. No action needed.
Additional comments on the draft remit: Timing	Novartis Pharmaceuticals UK Ltd	We are anticipating obtaining a UK marketing authorisation in [redacted] (best case). The timing of this evaluation is therefore appropriate.	Thank you for your comment. No action needed.
	The Royal College of Pathologists	Would be good if evaluation could be undertaken soon as there remains an unmet need for the treatment of chronic spontaneous urticaria in some patients where currently available treatments are ineffective. There is also a	Thank you for your comment. No action needed.

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		limited number of licensed evidence-based treatments for chronic spontaneous urticaria.	
	British Society for Immunology Clinical Immunology Professional Network	This evaluation would be welcome as soon as possible to increase access to licensed medications for CSU. For many patients there is an unmet need for treatment.	Thank you for your comment. No action needed.
	British Association of Dermatologists	This evaluation is urgent and timely. Interventions for people with chronic spontaneous urticaria (CSU) are primarily prescribed to reduce symptoms, and patients still experience poor quality of life (QoL) with high unmet needs. Currently, people with CSU inadequately controlled with second-generation H_1-antihistamines at the standard dose, may be treated with up to fourfold the approved dose with some success. However, the addition of montelukast (a leukotriene receptor antagonist which has currently been subject to a warning from the MHRA about potential neuro-psychiatric side-effects https://www.gov.uk/drug-safety-update/montelukast-reminder-of-the-risk-of-neuropsychiatric-reactions) and/or subsequent generation H_2-antihistamines (e.g. famotidine) usually add little clinical benefit, At the point where up to fourfold standard dosing of H_1-antihistamines is ineffective, clinicians are advised in guidelines (https://doi.org/10.1111/bjd.20892) to consider omalizumab (OMA) (TA339; https://www.nice.org.uk/guidance/ta339/chapter/1-Recommendations). Other less commonly used drugs include conventional systemic immunosuppressants such as methotrexate and ciclosporin. The success of OMA is not comprehensive (primary and secondary failure exist); the success of methotrexate and ciclosporin is variable and/or temporary (ciclosporin is not used long-term due to its nephrotoxicity). The availability of remibrutinib would increase the treatment options for these patients, especially those who do not respond adequately or are intolerant of	Thank you for your comment. No action needed.

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		second- or third-line therapies, including OMA. Oral dosing of remibrutinib would benefit needle-phobic patients who would otherwise require treatment with OMA. Currently, there are no other Bruton kinase inhibitors available for people with CSU.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Novartis Pharmaceuticals UK Ltd	The background information describes omalizumab as a 'second line treatment option for previously treated chronic spontaneous urticaria that has not responded to standard H1-antihistamines and LTRAs'. We would point out that given two prior treatments are necessary, omazliumab would be better described as a third-line treatment. Furthermore, NICE TA339 recommends it only in patients in severe CSU, which should be reflected in the description. With reference to the list of treatments used in CSU, we note that updated editions of European (EACCI; Zuberbier et al. 2022) and British (BAD; Sabroe et al. 2022) guidelines now state that there is insufficient evidence to recommend use of H2-antagonists.	Thank you for your comment. The background information for omalizumab has been updated to reflect the recommendation in NICE technology appraisal guidance 339. The comparators are kept inclusive at this stage to allow the committee to consider any comparator technologies for which evidence might be identified, so, H2-antagonists will remain as a comparator.
	The Royal College of Pathologists	Background information is accurate. It should be noted that the only licensed treatments for chronic spontaneous urticaria are standard dose	Thank you for your comment. The scope is intended to be a broad

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		antihistamines and omalizumab. All other treatments, including dose escalation of antihistamines are used off-license. Additionally, the evidence quality for most of the interventions, apart from antihistamines, omalizumab, and ciclosporin is limited. On the basis of the evidence, the EAACI/ GA²LEN/ EuroGuiDerm/ APAAACI guidelines makes recommendations only on antihistamines, omalizumab and ciclosporin. It does not make recommendations on other therapies (including leukotriene receptor antagonists) due to the lack of evidence, although does state that their usage can be considered.	overview of the topic. No action needed.
	British Society for Immunology Clinical Immunology Professional Network	This is a good representation of current UK practice which is a mix of licensed and unlicensed medications. It would also be useful to include background information on BTK inhibitors in the current scope for available medications. This is relevant as different BTK inhibitors have different side effect profiles when it comes to inhibition or lack of inhibition of components of the immune system. This ties into the safety and monitoring considerations.	Thank you for your comment. The comments have not been included as NICE aim to keep the background section of the scope brief. No action needed.
	British Association of Dermatologists	Urticaria is characterised by recurrent, itchy weals and flares together with angioedema (30%) which lasts for less than 24 hours. Episodes of urticaria vary from several times per day or more intermittently, and chronic urticaria means that the patient has intermittent episodes of urticaria lasting for longer than 6 weeks. Chronic urticaria may be associated with systemic symptoms when it is severe and uncontrolled. CSU is a variably understood condition, where the urticaria occurs spontaneously (i.e. without an underling, inducible cause) and is not driven via a true allergic response. It is considered largely an auto-immune condition. CSU commonly causes anxiety, depression,	Thank you for your comment. The comments have not been included as NICE aim to keep the background section of the scope brief. No action needed.

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		sleeplessness, suicidal ideation and other psychosocial co-morbidities. Patients who live with urticaria indicate that, for them, living with CSU is at least as difficult as living with cancer, epilepsy or heart disease. The reported lifetime prevalence rate for CSU is about 1–2%. (https://pubmed.ncbi.nlm.nih.gov/27838325/ https://pubmed.ncbi.nlm.nih.gov/20456386/ https://pubmed.ncbi.nlm.nih.gov/28983950/) The point prevalence of chronic CSU varies from 0.1% in North America to 1.4% in Asia. (https://pubmed.ncbi.nlm.nih.gov/31494963/) CSU is more common in females, except in young children. A more recent publication on the lifetime annual incidence trends in Korea has been published. (https://pubmed.ncbi.nlm.nih.gov/40676759/). The impact of chronic urticaria and its negative effects on work, study and quality of life is well recognised and accepted (https://pubmed.ncbi.nlm.nih.gov/32956489/).	
Population	Novartis Pharmaceuticals UK Ltd	The population proposed is in-line with our anticipated marketing authorisation. Of note, the randomised clinical trials on which our submission will be based had as inclusion criteria Urticaria Activity Score (UAS) ≥16. This defines a population of patients with 'moderate or severe CSU' (Mathias et al. 2012)	Thank you for your comment. The population is kept broad until marketing authorisation is granted. No action required.
	The Royal College of Pathologists	Yes, the population is defined appropriately	Thank you for your comment. No action needed.

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	British Society for Immunology Clinical Immunology Professional Network	The population is defined appropriately.	Thank you for your comment. No action needed.
	British Association of Dermatologists	Yes.	Thank you for your comment. No action needed.
Subgroups	Novartis Pharmaceuticals UK Ltd	We will present clinical and cost-effectiveness data separately for the moderate CSU and severe CSU cohorts. This is because treatment patterns in the UK are different between moderate CSU and severe CSU. Most notably, omalizumab is recommended by NICE in severe CSU but not moderate CSU (NICE TA339). Furthermore, in severe CSU, we will distinguish between omalizumab-naïve and omalizumab-exposed subpopulation with regards to clinical and cost effectiveness results.	Thank you for your comment. The consideration of severity of chronic spontaneous urticaria in subgroup analysis has been added.
	British Society for Immunology Clinical Immunology Professional Network	As BTK is a modulator of a number of components of the immune system, some understanding of whether this drug would be safe or appropriate to use in patients with immunodeficiency, malignancy or autoimmunity, or who are on some kind of immunomodulatory therapy would be useful. Also, CSU does occur in children where there is potentially an even larger unmet need for tolerable medications.	Thank you for your comment. Subgroups may be considered where the clinical effectiveness or value for money of the technology may differ from the overall population. If evidence allows, results for relevant subgroups will

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			be considered by the committee during the evaluation. No action needed.
	British Association of Dermatologists	None that we are aware of, currently.	Thank you for your comment. No action needed.
Comparators	Novartis Pharmaceuticals UK Ltd	The list of comparators does not reflect standard practise in the UK. Although the population in this appraisal is 'patients with CSU inadequately controlled by H1-antihistamines, patients will still be receiving H1- antihistamines, and subsequent therapies are considered 'add-ons'. As such, H1- antihistamines (as 'background' therapy) are a key comparator. Updated editions of European (EACCI; Zuberbier et al. 2022) and British (BAD; Sabroe et al. 2022) guidelines now state that there is insufficient evidence to recommend use of H2-antagonists, despite being recommended in previous guideline versions. As such, we do not believe H2-antagonists are an appropriate comparator for remibrutinib. Oral corticosteroids are confined to short, infrequent courses over a few days as rescue treatment for severe exacerbations of CSU. They may also be used if a patient has an upcoming event for which they prioritise being symptom-free, e.g. a wedding. These are distinct use cases as compared to H1-antihistamines, remibrutinib and omalizumab, which are long-term treatments. Consistent with this, the remibrutinib REMIX trials allowed use of corticosteroids as a rescue medication (Metz et al. 2025). As such, we do not believe oral corticosteroids are an appropriate comparator for remibrutinib. We do not believe that immunosuppressants are a suitable comparator. Of these drugs, only ciclosporin is regularly used, and only in patients with severe disease refractory to H1-antihistmines and omalizumab. European guidelines (EACCI; Zuberbier et al. 2022) state that ciclosporin cannot be	NICE keeps the comparators list inclusive. The most appropriate comparators will be discussed by the committee. In its evidence submission, the company should provide a clear rationale for excluding any comparators listed in the final scope. The scope has been updated to include H1 antihistamines as a comparator. Corticosteroids have been removed as a comparator based on

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		recommended as a standard treatment due to the higher incidence of adverse effects. Furthermore, the evidence base for all immunosuppressant drugs (ciclosporin included) is very limited, making formal clinical or cost-effectiveness comparisons challenging. We would reiterate that NICE guidance TA339 recommends omalizumab only for severe CSU, and that this should be reflected in omalizumab's listing as a comparator. We therefore suggest the following list of comparators for this appraisal: · H1-antihistamines · Omalizumab (in severe CSU) · Leukotriene receptor antagonists We would also point out that leukotriene receptor antagonists (LTRAs) are listed for 'consideration' in British guidelines (BAD; Sabroe et al. 2022); and European guidelines (EACCI; Zuberbier et al. 2022) describe the level of evidence for their use as 'low'. As such, we would consider LTRAs a minor comparator for remibrutinib in this appraisal.	responses to the scoping consultation. The British (BAD; Sabroe et al. 2022) guidelines say that H2-antagonists may be considered if urticaria is associated with dyspepsia, although dyspepsia should be investigated appropriately. The guidelines also say that ciclosporin may be offered in addition to a second-generation H1 - antihistamine, to people whose symptoms are inadequately controlled by first-line options. So, these will remain as a comparators
	The Royal College of Pathologists	Comparators are generally representative of treatments used in the NHS. Long-term oral corticosteroids are not appropriate as a comparator as this is actively discouraged in guidelines due to the side effect profile, although can be used in short courses for severe exacerbations.	Thank you for your comment. Corticosteroids have been removed as a

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			comparator based on responses to the scoping consultation.
	British Society for Immunology Clinical Immunology Professional Network	Yes, there is a mix of licensed and unlicensed medications used for CSU and it is important to consider both as comparators as all in common use in UK NHS practice.	Thank you for your comment. No action needed.
	British Association of Dermatologists	Oral corticosteroids are not an appropriate comparator as they are only prescribed in an emergency for short, infrequent courses of a few days as rescue treatment to control severe exacerbations in UK clinical practice. (https://doi.org/10.1111/bjd.20892) H_2-antihistamines and montelukast should only be used as add-on treatments to H_1-antihistamines. Please also note comments above. Mycophenolate mofetil and oral tacrolimus might not be appropriate comparators as these are third-line treatment options for people with CSU. Methotrexate and ciclosporin are part of guidelines for patients with CSU, but the former is variably effective and requires considerable monitoring and the latter is not used long-term. (https://doi.org/10.1111/bjd.20892)	Corticosteroids have been removed as a comparator based on responses to the scoping consultation. NICE keeps the comparators list inclusive. The most appropriate comparators will be discussed by the committee. So, mycophenolate mofetil, oral tacrolimus, methotrexate and ciclosporin will remain as comparators.

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Outcomes	Novartis Pharmaceuticals UK Ltd	Long-term corticosteroid use is explicitly not recommended for patients with CSU in EACCI (Zuberbier et al. 2022) and BAD (Sabroe et al. 2022) guidelines. As such, we do not believe that reducing or discontinuing corticosteroid use is an appropriate outcome, as patients with CSU should not receive corticosteroids as long-term treatment.	Thank you for your comment. The outcomes are kept broad at this stage. No action required.
	The Royal College of Pathologists	Outcome measures are appropriate. Use of patient reported outcomes measures (e.g. UAS7, UCT etc) should be included as a means for determining some of these outcome measures.	Thank you for your comment. NICE does not specify particular scales or instruments in scopes to avoid giving the impression that some measures are more acceptable than others and to discourage the exclusion of clinical trials that used measurement scales/instruments not specified in the scope No action needed.
	British Society for Immunology Clinical Immunology Professional Network	The outcomes listed are appropriate.	Thank you for your comment. No action needed.

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	British Association of Dermatologists	Improvement in CSU symptoms is usually measured by the reduction in the Urticaria Activity Score over 7 days (UAS7) tool. A UAS7 score of ≥28 representing severe urticaria is stipulated as the entry criterion for people with CSU requiring OMA. (https://www.nice.org.uk/guidance/ta339/chapter/1-Recommendations). A lower threshold of urticaria severity of 16/42 is accepted in some centres for restarting treatment with OMA for patients who relapse after completing a 6 month course. QoL measures such as the Dermatology Life Quality Index (DLQI) may be considered. The impact of CSU on patients' QoL and psychological/psychosocial well-being across all ages is well documented. (https://pubmed.ncbi.nlm.nih.gov/32246853/; https://pubmed.ncbi.nlm.nih.gov/39922285/) Angioedema activity in people with CSU, where applicable, and quality of life scores, are important for patients with predominant histaminergic angioedema The urticaria control test in people with CSU might be a useful overall measure of disease control Reducing or discontinuing oral corticosteroid is no longer an appropriate outcome measure since long-term oral corticosteroids are no longer used for managing severe CSU because of their well-known and predictable adverse effects. They are only prescribed for short, infrequent courses of a few days as rescue treatment to control severe exacerbations in UK clinical practice. (https://doi.org/10.1111/bjd.20892)	Thank you for your comment. Specific scales are not listed as part of the scope. The outcomes are kept broad at this stage. No action needed.

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Equality	Novartis Pharmaceuticals UK Ltd	CSU predominantly affects females. Real-world evidence from the UK found that 78% of patients with H1-antihistamine-refractory CSU were female (Maurer 2020). We have identified no further equality considerations for this appraisal.	Thank you for your comment. The committee will consider all inequalities presented. No action needed.
	British Society for Immunology Clinical Immunology Professional Network	No concerns.	Thank you for your comment. No action needed.
	British Association of Dermatologists	None that we are aware of, but CSU also affects children and young people (particularly those aged 16-18) which might need consideration.	Thank you for your comment. Children and young people are outside of the remit of this appraisal. No action needed.
Other considerations	Novartis Pharmaceuticals UK Ltd	None.	Thank you for your comment. No action needed.
	British Society for Immunology Clinical Immunology	In the adverse effects of treatment review, establish reassurance of the low immune adverse event rate with this specific BTK inhibitor. Also consider post marketing surveillance data to look at immune counts over a prolonged period of time to establish if there is any accumulative effect of this drug seen.	Thank you for your comment. No action needed.

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	Professional Network		
	British Association of Dermatologists	Administration of remibrutinib should only be made in secondary care for people with CSU who also qualify for other systemics and/or biologics (e.g. OMA). The pathway will be the same for those who have failed on maximum doses of H_1-antihistamines.	Thank you for your comment. No action needed.
Questions for consultation	Novartis Pharmaceuticals UK Ltd	Remibrutinib in existing pathway: We anticipate that remibrutinib will be prescribed in secondary care with routine follow-up in primary care (option B). As many patients with moderate CSU are treated in primary care, and remibrutinib is an oral treatment, it would be a good option for prescription in primary care. Omalizumab and immunosuppressant drugs are typically prescribed in secondary care with routine follow-up in secondary care. Managed access: We believe that remibrutinib may be a candidate for managed access if suitable long-term uncertainty is a feature of the appraisal. Health-related benefits outside of QALY calculation: There is evidence that more severe states of CSU can have an increased effect on patient mortality. This may be due to a number of comorbidities, including suicide (Kolhkir et al. 2025). Due to a lack of robust data, we have not captured this health-related benefit of treatment in our economic analysis. Use outside of SmPC: Of the comparators listed in the draft scope, LTRAs, prednisolone, H2-antagonists and the listed immunosuppressants do not have CSU listed as a therapeutic indication in their SmPC. As stated above, we do not believe that immunosuppressants, prednisolone or H2-antagonists are appropriate comparators in this appraisal.	Thank you for your comment. No action needed.

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	The Royal College of Pathologists	Remibrutinib may fit into the existing care pathways in one of two possible ways depending on cost-effectiveness analysis and individual clinical decision making. These are: in patients where omalizumab has had an insufficient response or if there is another reason why omalizumab may not be appropriate to use, or at the same place in the treatment pathway where omalizumab is being considered with the choice being made based on individual patient characteristics. Remibrutinib should be prescribed in secondary care with routine follow-up in secondary care. Remibrutinib would be a candidate for managed access. Remibrutinib is unlikely to result in substantial health-related benefits not already included in the QALY calculation. Most comparator treatments are not licensed in the SPC for use in chronic spontaneous urticaria. The only licensed treatments are standard dose antihistamines and omalizumab. Many treatments are used off-license due to lack of available options historically for a potentially debilitating disease.	Thank you for your comment. No action needed.
	British Society for Immunology Clinical Immunology	Remibrutinib could be considered either as: 1) An alternative to omalizumab when antihistamines have failed or; 2) A third line treatment as an alternative to unlicensed immunomodulatory drugs in those unable to have, or not responding to omalizumab.	Thank you for your comment. No action needed.

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	Professional Network	Would repeat courses be appropriate and how would this need be assessed and delivered? Omalizumab, once established in secondary care, is often self-administered at home under secondary care supervision. Has this been considered?	
	British Association of Dermatologists	Where do you consider remibrutinib will fit into the existing care pathway for chronic spontaneous urticaria? We consider remibrutinib should be placed either before or (at least) alongside OMA in the existing UK care pathway. (https://doi.org/10.1111/bjd.20892) Please select from the following, will remibrutinib be: ~~Prescribed in primary care with routine follow-up in primary care~~ ~~Prescribed in secondary care with routine follow-up in primary care~~ Prescribed in secondary care with routine follow-up in secondary care ~~Other (please give details):~~ For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. No. Would remibrutinib be a candidate for managed access? No. Do you consider that the use of remibrutinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Improvement in sleep quality is a key measure of successful treatment of CSU that is not captured by the UAS7 or DLQI. If used in the appraisal, the EQ-5D assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. However, mobility	Thank you for your comment. No action needed.

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		impairment and self-care (such as application of creams) are not directly relevant to patients with CSU and is not life-shortening. Therefore, calculation of QALY in CSU utilising the EQ-5D might indicate a higher cost than might be seen in other conditions that impact all 5 criteria with a reduced life expectancy. The REMIX-1 and REMIX-2 trials assessed change in UAS7 scores from baseline to week 12 as the primary outcome, and UAS7 scores of ≤6 at weeks 2 and 12, UAS7 scores of 0 at week 12, and adverse events as secondary outcomes. UAS7 takes into account both the severity of itch and rash (hives) over a 7-day period. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. Phase III REMIX-1 and REMIX-2 clinical trials A long-term study of remibrutinib over 52 weeks demonstrated a favourable safety profile and sustained efficacy (https://pubmed.ncbi.nlm.nih.gov/37866460/) Please indicate if any of the treatments in the scope are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics. OMA is increasingly being used at different dose intervals and doses to achieve and maintain symptom control outside its licensed indication on the basis of international expert opinion. (https://pubmed.ncbi.nlm.nih.gov/34536239/)	

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Additional comments on the draft scope	Novartis Pharmaceuticals UK Ltd	We would request that the British Skin Foundation are also included as a stakeholder	Thank you for your comment. The stakeholder list has been updated.
	British Society for Immunology Clinical Immunology Professional Network	Comments on the provisional stakeholder list We believe it looks appropriate from an immunology and allergy perspective. With regards to comparator companies – no H2 inhibitor companies are represented, for example Sanofi-Aventis for Fexofenadine hydrochloride.	Thank you for your comment. The stakeholder list has been updated.
	British Association of Dermatologists	Comments on the provisional stakeholder list: British Society for Cutaneous Allergy The British Association of Allergy and Clinical Immunology is an important partner to the British Association of Dermatologists in this technology assessment	Thank you for your comment. The stakeholder list has been updated.

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