National Institute for Health and Care Excellence

Health Technology Evaluation

Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]
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	Incyte Biosciences UK Ltd	Incyte agrees that the proposed evaluation is appropriate. Given the lack of licensed treatment options available to patients with non-segmental vitiligo, there is a clear need to evaluate a licensed therapy for these patients. Thus, Incyte welcomes an evaluation of its technology (ruxolitinib 1.5% cream (Opzelura)) and considers the proposed evaluation route (i.e., single technology appraisal) appropriate.	Thank you for your comment. This topic has been routed to the technology appraisal programme.
	British Association of Dermatologists	Vitiligo affects 1% of the population worldwide. Around 50% of patients develop vitiligo before the age of 20 and around 80% before the age of 30. A recent systematic review into the psychological burden of vitiligo on its patients revealed that vitiligo on the face, or affecting other visible areas, and vitiligo in people under 30 are major risk factors for severe anxiety, depression, low self-esteem and even suicidal ideation. The risk of this can be higher amongst people of colour, as the condition is more noticeable in people with darker skin tones. Many people with vitiligo require	Thank you for your comment. No action needed.

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		antidepressants to help them cope with this skin condition (Ezzedine *et al.* 2021 10.1007/s40257-021-00631-6). There is no licensed treatment for vitiligo and currently available (off license) treatment options for vitiligo are often unsatisfactory. The frequency of disease, social and mental health impact warrant further NICE appraisals to evaluate treatments for this underserved patient group.	
Wording	Incyte Biosciences UK Ltd	Incyte considers the wording of the remit to be appropriate.	Thank you for your comment. No action needed.
	British Association of Dermatologists	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.* Yes	Thank you for your comment. No action needed.
Timing issues	Incyte Biosciences UK Ltd	Incyte believes that timely NICE guidance for ruxolitinib 1.5% cream would be valuable to the NHS and to patients who currently have to manage their disease without licensed treatments. In 2019, 85.0% of the prevalent population in the UK were not receiving any vitiligo-related treatment (1). Vitiligo carries a high psychosocial burden on patients. An estimated 58.7% of patients with vitiligo internationally report having been diagnosed with a mental health disease, most commonly anxiety and depression disorders (2). In the UK, the most common mental health comorbidities are anxiety/depression (24.6%), depression (18.5%) and anxiety (16.0%) (1). In the first five years following diagnosis with vitiligo, over a quarter of patients (26.6%) use antidepressants and/or anxiolytics. In particular, children and adolescents report regular stigmatisation (93.2%) and bullying (21.7%) due to	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.

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		their vitiligo, resulting in low self-esteem, restricted activity and school attendance and social isolation (3). Additionally, those with darker skin tones, where vitiligo is more noticeable, are thought to report worse quality of life (QoL) (4). The NHS Long Term Plan states that mental health is a clinical priority, thus highlighting the urgent need to address the psychosocial burden resulting from vitiligo (5)	
	British Association of Dermatologists	Vitiligo has a profound, negative psychological impact on people affected by it (see above). The current referral pathway suggests that patients with vitiligo on visible areas (such as the face) or patients with significant psychological impact (irrespective of the affected body surface area), should be referred to secondary care for further management (British Association of Dermatologists Dermatology Referral Guidelines - Vitiligo. https://www.bad.org.uk/referrals/vitiligo/). This further management usually involves phototherapy. Unfortunately, in the current climate of NHS crisis, dermatology waiting lists vary between 12-24 months for general dermatology clinics. In addition, once seen in secondary care, many patients with vitiligo are unable to start phototherapy either due to long NHS waiting lists (over 1 year at some centres, following first assessment by a dermatologist) for this treatment option, and/or personal time constrains (i.e. the need to attend 3 times a week for 9-12 months). Furthermore, many dermatology departments offer phototherapy to a small cohort of patients with vitiligo due to the prolonged course of treatment. As such, patients with other dermatological diseases (such as eczema or psoriasis) who usually require shorter courses are prioritised instead. In addition, recently updated guidelines for vitiligo by the British Association of Dermatologists (Eleftheriadou *et al.* 2022 10.1111/bjd.20596) suggests that early treatment of vitiligo seems to be more efficacious compared to treatment of long-standing disease; therefore, there is an urgent need for an efficacious, topical treatment for vitiligo, which would not require hospital	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.

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		visits for prolonged time and could be prescribed to both children and adults as soon as they are diagnosed with vitiligo by a dermatologist.	
	The Vitiligo Society	There is an urgent need for effective treatment pathways for the vitiligo community. Historically and currently there is no cure and no reliable treatment option for those living with vitiligo - this is the number one priority for the vast majority of those with the condition and their families who our charity supports.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.

Comment 2: the draft scope

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Background information	Incyte Biosciences UK Ltd	Overall, the data presented in the background information is broadly accurate. However, Incyte believes the prevalence of vitiligo is overestimated based on historical sources. A recent UK-based analysis using Clinical Practice Research Datalink (CPRD) that is representative of UK population estimated the prevalence of vitiligo as 0.30% (0.21%−0.38%), and the overall mean (range) incidence rate as 0.164 (0.096-0.188) per 1,000 person-years between 2010 and 2021 (1, 6).	Thank you for your comment. The statistics used in the scope are based on 1 in 100 people prevalence in England. The number of people affected has been updated to reflect the latest population statistics in England.

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	British Association of Dermatologists	The background section of the draft scope does not reflect the profound psychological effects of vitiligo on people affected by it (see above, as well as Thompson *et al*. 2022 10.1192/bjo.2022.591, Grimes & Miller 2018 10.1016/j.ijwd.2017.11.005 and Elbuluk *et al.* 2017 10.1016/j.det.2016.11.002). In addition, the British Association of Dermatologists guidelines for the management of people with vitiligo have recently been updated (Eleftheriadou *et al.* 2022 10.1111/bjd.20596). With regards to the last paragraph of the background section, please see below: There are currently no licensed treatments for vitiligo. All patients with vitiligo require advice on sun protection, in order to avoid sunburn with minimal sun exposure, and psychological evaluation to identify level of psychological distress (mild, moderate or severe). If moderate or severe psychological distress is identified, patients should be offered referral to psychological services for further psychological evaluation and treatment. Also, vitamin D levels should be checked in patients who are avoiding the sun. Current off-label pharmacological treatments include corticosteroids and calcineurin inhibitors (mainly topical tacrolimus). Other treatments include whole body or localised phototherapy (as monotherapy or combined with topical corticosteroids or tacrolimus), which is only available in secondary care and requires thrice weekly hospital visits for 9-12 months. Other treatments such as excimer laser and surgery are not currently available on the NHS. Depigmentation (permanent removal of the remaining pigment) is only suitable for a small number of patients with universal vitiligo (i.e. vitiligo which covers over 80% of the total body surface area) and following careful psychological evaluation. This intervention is only available in a handful of NHS hospitals.	Thank you for your comment. The background section is intended to provide a brief summary of the condition. The suggested changes on the psychological impact have been added to the scope.

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		In addition, vitiligo has been shown to be associated with other autoimmune diseases such as thyroid disorders, pernicious anemia, Addison's. Autoimmunity is considered a contributor to the pathogenesis of vitiligo. Incidence of thyroid disease in patients with vitiligo is up to 52% and patients with vitiligo are at increased risk of Graves disease and even thyroid cancer; therefore, patients with vitiligo should be routinely screened for thyroid function and antithyroid antibodies.	
	The Vitiligo Society	'Vitiligo affects males and females, and all ethnicities equally but it is more noticeable in people with darker skin tones.' This is not strictly true and depends on the % and location of skin affected. It should also be noted that the 'noticeability' of vitiligo does not necessarily correspond to the psychological and social impact that is felt by each individual.	Thank you for your comment. The scope has been updated to include this comment on noticeability
Population	Incyte Biosciences UK Ltd	The anticipated license wording for ruxolitinib 1.5% cream (Opzelura) is "non-segmental vitiligo with facial involvement in adults and adolescents from 12 years of age" (7, 8). Incyte considers the population stated in the draft scope to be appropriate but suggests restricting to non-segmental vitiligo with facial involvement as per the anticipated license wording.	Thank you for your comment. The population has been updated
	British Association of Dermatologists	*Is the population defined appropriately?* Yes	The population has been updated to align with the anticipated marketing authorisation.
	The Vitiligo Society	We understand the population that is being defined here, however we also understand that this treatment has the potential to be effective for those with segmental vitiligo and would be keen to understand if/when these members of our community could be considered.	Thank you for your comment. The population described is intended for the indicated marketing

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			authorisation population. No action needed.
Subgroups	Incyte Biosciences UK Ltd	Ruxolitinib 1.5% cream (Opzelura) is not anticipated to demonstrate differential clinical efficacy in any specific subgroups.	Thank you for your comment. No action needed.
	British Association of Dermatologists	*Are there groups within the population that should be considered separately? For example, are there subgroups in which the technology is expected to be more clinically or cost effective? If subgroups have been suggested in the scope, are these appropriate?* No	Thank you for your comment. No action needed.
Comparators	Incyte Biosciences UK Ltd	There are currently no approved treatments for vitiligo. Patients with vitiligo who receive treatment use off-label products which consist of topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), phototherapy, laser therapy, topical vitamin D analogues and a combination of phototherapy with TCI/TCS (9-12). UK-based data highlight that 85% of patients do not receive any vitiligo-related treatment (1), indicating that the relevant comparator for ruxolitinib 1.5% topical cream is best supportive care (BSC). BSC is captured in the control arm of the company-sponsored TRuE-V studies, which compared the efficacy of ruxolitinib 1.5% cream (Opzelura) to vehicle cream (13, 14). Thus, current established clinical management consists of best supportive care – which includes camouflage makeup and over-the-counter preparations, as adopted in the TRuE-V studies – TCS, TCI and phototherapy. However, given the low use of these off-label treatments that have not been well evaluated in clinical trials , they should not be considered relevant comparators (1).	Thank you for your comment. The comparator has been kept broad to allow consideration of what is established clinical management during the appraisal

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	British Association of Dermatologists	Your stated comparator is “established clinical management without ruxolitinib” (p.2) Current clinical management of vitiligo often includes either no treatment (due to variability of currently available treatments results and accessibility issues) or topical treatments as first line. Ruxolitinib cream is a topical preparation, which is marketed for application to a maximum of 10% of total body surface area. This means that its comparators could also be topical treatments such as topical corticosteroids or topical calcineurin inhibitors. However, neither topical corticosteroids (TCS) nor topical calcineurin inhibitors (TCI) are licenced for vitiligo and different strengths (of TSC and TCI), and frequencies (e.g. once a day, twice a day) are currently being used across the UK. Comparing ruxolitinib cream to treatments with systemic effect, such as oral corticosteroids or phototherapy would not be appropriate.	Thank you for your comment. The comparators listed are intended to be broad and include all established clinical management. No action needed.
Outcomes	Incyte Biosciences UK Ltd	Incyte agrees that the suggested outcomes are appropriate but note that stabilisation of vitiligo was not captured in the TRuE-V studies. However, Incyte deems that the endpoint of time to relapse (< F-VASI75) in the long-term treatment extension study (TRuE-V LTE) adequately captures maintenance of response to treatment. The TRuE-V studies did not collect EQ-5D responses from patients, therefore direct generation of utility scores was not feasible. Incyte intends to generate EQ-5D data utilising appropriate mapping algorithms. However, it is worth noting that EQ-5D may not fully capture the health-related quality of life impairment of patients living with vitiligo. This lack of content validity of EQ-5D instrument was substantiated by a large ceiling effect observed in the EQ-5D data at baseline from the Hi-Light trial, whereby many patients at baseline reported almost “perfect health” on the EQ-5D instrument and therefore be unable to report an improvement from treatment in a responder analysis. The	Thank you for your comment. No action needed.

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		utility estimates derived from disease-specific outcome measures from the TRuE-V studies to EQ-5D is likely to be affected in the same manner (15).	
	British Association of Dermatologists	Internationally agreed consensus on core outcomes set for vitiligo clinical trials include the following outcomes as essential: repigmentation, side effects and maintenance of gained repigmentation. Four items were further recommended for inclusion: cosmetic acceptability of results (measured by the Vitiligo Noticeability Scale), quality of life, cessation of spreading and tolerability or burden of treatment (Eleftheriadou et al. 2015 10.1111/pcmr.12354). Therefore the choice of outcomes is appropriate.	Thank you for your comment. No action needed.
	The Vitiligo Society	We were unclear about the 'health related quality of life measure' - we are assuming that this is related to the psychological and social impacts of vitiligo - which are hugely significant within our community. We would appreciate this outcome clarified a little more as it's a key outcome for the community we represent.	Thank you for your comment. It is anticipated that psychological distress will fall under health related quality of life.
Equality	Incyte Biosciences UK Ltd	Although vitiligo is more noticeable in people with dark skin tones, as noted in the draft scope, Incyte aim to make ruxolitinib 1.5% cream (Opzelura) available for all patients. Therefore, no equality issues are foreseen in terms of providing ruxolitinib 1.5% cream (Opzelura) to eligible patients.	Thank you for your comment.
	British Association of Dermatologists	As vitiligo develops before the age of 20 in about 50% of patients, including children in the draft remit was particularly important. Although more noticeable in people with darker skin tones, vitiligo affects people with all skin tones and can be psychologically devastating, regardless of the patient's skin colour. Also, vitiliginous patches burn easily in the sun regardless of patient's "normal" skin tone.	Thank you for your comment.

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		Finally, some quality of life measures may not adequately capture the impact of living with skin condition such as vitiligo, as skin in patients with vitiligo is not usually sore or painful (unless sunburned). Also these measures may not capture anxiety and depression, hence patients with vitiligo often "score" lower compared to patients with other skin conditions. Additionally, they may discriminate against those who are non-native English speakers.	
Other considerations	Incyte Biosciences UK Ltd	Ruxolitinib 1.5% cream (Opzelura) will be the first treatment to be licensed specifically for non-segmental vitiligo. Incyte note the lack of specific standardised outcomes for vitiligo prior to the design of the TRuE-V clinical development programme, as well as challenges in stratifying the severity of vitiligo.	Thank you for your comment.
	British Association of Dermatologists	None	Thank you for your comment.
Questions for consultation	Incyte Biosciences UK Ltd	**Have all relevant comparators for ruxolitinib been included in the scope? Which treatments are considered to be established clinical practice in the NHS for segmental and non-segmental vitiligo?** Incyte considers that this question has already been covered in the above sections and have no further comments. **Are the outcomes listed appropriate?** Incyte considers that this question has already been covered in the above sections and have no further comments.	Thank you for your comments. These are noted.

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		Are there any subgroups of people in whom ruxolitinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? Incyte considers that this question has already been covered in the above sections and have no further comments **Where do you consider ruxolitinib will fit into the existing care pathway for non-segmental vitiligo?** As stated above in the comparators section, although there is an established clinical management for vitiligo, the majority of UK patients do not use any treatments for their condition. Ruxolitinib 1.5% cream (Opzelura) is anticipated to be positioned as a treatment option in the existing care pathway for non-segmental vitiligo. **Do you consider ruxolitinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Yes, ruxolitinib 1.5% cream (Opzelura) is an innovative treatment with a positive CHMP opinion specifically for non-segmental vitiligo. [redacted] (16). Ruxolitinib 1.5% cream (Opzelura) is an innovative topical formulation containing a small molecule, selective JAK1/2 inhibitor, RUX cream directly targets vitiligo pathogenesis to address the 3 vitiligo treatment goals for early and long-term disease control, reflected by a sustained response with continuous use. Introducing a licensed topical JAK inhibitor, with demonstrated long-term efficacy and tolerability in two robust multicentre	

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		Phase III double-blind randomised clinical trials, as well as a definitive mechanism of action, represents a step-change in the management of vitiligo. **Do you consider that the use of ruxolitinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** Yes. As stated above in the 'timing issues' section, vitiligo carries a high psychosocial burden on patients, including depression and anxiety. Patients living with vitiligo suffer stigmatisation as a result of the misconceptions associated with the disease, resulting in low self-esteem, restricted activity and school attendance, social isolation and discrimination in employment. Several patient-reported outcome (PRO) instruments have been used in vitiligo to measure several aspects of the disease, including the vitiligo noticeability scale (VNS), vitiligo-specific quality-of-life instrument (VitiQoL) and dermatology life quality index (DLQI). As described above in the 'outcomes' section, health-related benefits associated with repigmentation in responders will not be fully captured by the EQ-5D data mapped from disease-specific outcome measures from the TRuE-V studies due to its lack of content validity and the observed ceiling effects in vitiligo patients. The European Academy of Dermatology and Venerology (EADV) Task Force evaluated the use of HRQoL instruments in vitiligo, noting the DLQI as the most frequently used instrument. However, the EADV also noted that some items in the DLQI are irrelevant for most patients with vitiligo (e.g., itching) (17).	

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		Although DLQI can provide a general picture of impaired quality of life, it is not sufficiently specific to capture nuances on how patients with vitiligo handle their overall disease burden (18). For instance, the DLQI captures outcomes in the previous 7 days, which is not adapted to vitiligo given the slow repigmentation process. Furthermore, the DLQI questionnaire allocates a portion of their items to ask about symptoms which are relatively less problematic in vitiligo (19). VitiQoL is a disease-specific HRQoL tool that emphasises three primary factors (behaviour, participation limitation and stigma) (20). It was used as an exploratory outcome in the TruE-V trials, however, it was not validated for the assessment of responsiveness over time. Further, as noted in the draft scope, vitiligo appears before 20 years of age in more than half of patients. As patients have had to manage with the disease in the absence of approved therapies, even disease-specific instruments for measuring patient-reported outcomes might not fully capture treatment benefit due to repigmentation as derived through the QALY calculation.	
	British Association of Dermatologists	**Have all relevant comparators for ruxolitinib been included in the scope? Which treatments are considered to be established clinical practice in the NHS for segmental and non-segmental vitiligo?** In addition to the information already provided in the relevant section about comparator, first line treatment for the management of vitiligo includes topical corticosteroids and topical calcineurin inhibitors. Second line treatment mainly for widespread vitiligo, included phototherapy (either as monotherapy or combined with topical treatments) or for rapidly progressive vitiligo-combination of oral corticosteroids and phototherapy. Finally, third line treatments, which are mostly not available on the NHS and/or are only suitable/appropriate for a small sub-population of vitiligo patients, include excimer laser, depigmentation and surgical treatments.	Thank you for your comments. The background section has been updated to take into account treatments available in the NHS.

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		Where do you consider ruxolitinib will fit into the existing care pathway for non-segmental vitiligo? Due to the lack of licensed treatments for vitiligo, and the fact that usually first line treatment for vitiligo includes topical preparations (TCS or TCI), ruxolitinib would fit into the first line treatment category alongside TCS and TCI. **Do you consider ruxolitinib to be innovative in its potential to make a significant and substantial impact on health- related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Current clinical recommendations for the management of vitiligo are based on trials of poor to moderate quality. The majority of studies had fewer than 50 participants and very few studies specifically included children with the exception of one UK multicentred RCT, which included over 500 patients with vitiligo (Thomas *et al.* 2021 10.1111/bjd.19592). This national RCT investigated the effectiveness of targeted phototherapy (hand-held NB UVB) in combination with topical corticosteroid (TCS) compared to TCS alone and hand-held NB-UVB alone, for localized vitiligo. The results showed that the proportions with target patch treatment success were 17% (TCS), 22% (targeted phototherapy) and 27% (for combination treatment). As previously mentioned, there is no licensed treatment for vitiligo in the UK and results of currently available treatments can often be unsatisfactory. Vitiligo is a debilitating and psychologically devastating skin disease, which usually appears in the young population. Vitiligo is of autoimmune nature and is often associated with other autoimmune diseases, and requires its bearers to avoid the sun and/or risk sun burns with minimal sun exposure; therefore, there is an urgent need for an effective and licensed treatment for vitiligo patients in the UK.	

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		Do you consider that the use of ruxolitinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Repigmentation (return of the colour) of vitiligo patches is one of the essential outcomes recommended by patients and clinicians to be measured in all clinical trials. Furthermore, three large international workshops with patients with vitiligo and their parents or caregivers were conducted in order to define successful repigmentation from the patients' point of view and to propose how and when repigmentation should be evaluated in clinical trials in vitiligo. Results revealed that both an objective and a subjective scale to measure repigmentation should be used. In particular, alongside percentage of repigmentation (objective scale), a subjective, patient reported scale such as Vitiligo Noticeability Scale, should be used (Eleftheriadou *et al.* 2019 10.1111/bjd.17544). A recently conducted, retrospective, observational study, using UK general practice data (2004–2020) revealed that people with vitiligo have a higher incidence of recurrent depressive disorder (RDD) and anxiety disorder than controls, and this risk increase may be greatest in Black and minority ethnic populations. In addition, people with vitiligo and psychological comorbidity had more primary care encounters, more time off from work and higher unemployment (Thompson *et al*. 2022 10.1192/bjo.2022.591). **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** 1) As above, inclusion of patient reported outcome measure to measure repigmentation: Vitiligo Noticeability Score.	

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		2) Burden of vitiligo on its patients and on UK healthcare system was captured in a large UK population-based cohort study (Thompson *et al*. 2022 10.1192/bjo.2022.591) and revealed that people newly diagnosed with vitiligo have an increased risk of subsequently being diagnosed with new-onset depression (25%) and anxiety (23%) compared with the general population, and that this risk increase may be greatest in Black and minority ethnic populations (up to 72% risk increase for RDD;). This is important as there is some evidence for vitiligo being associated with stigmatisation in people of British South Asian heritage. Finally, people with both vitiligo and a mental health comorbidity have increased use of primary care services, and are twice as likely to have recorded time off work requests and unemployment. 3) Therefore, levels of psychological distress should be evaluated in patients with vitiligo as recommended by the BAD guidelines for vitiligo (Eleftheriadou *et al.* 2022 10.1111/bjd.20596). Examples of widely used tools for capturing psychological distress is PHQ4 or 7 and GAD-9. Also, examples of vitiligo specific quality of life/burden of disease tools include Vitiligo Impact Patient Scale (VIPs) (Salzes *et al.* 2016 10.1038/JID.2015.398).	
	The Vitiligo Society	1. Is this a practical treatment pathway for patients with universal vitiligo? i.e. those who want to apply to their whole body, or is the advice to apply to face/extremities only for those patients?	Thank you for your comments. This technology will be evaluated according to

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		2. Could the efficacy of ruxolitinib be increased or decreased when used in concert with existing conventional vitiligo treatments e.g. phototherapy?	its marketing authorisation.
Additional comments on the draft scope	Incyte Biosciences UK Ltd	Incyte would like to propose the following stakeholders for this appraisal: - Healthcare professional groups: British Psychological Society - Relevant research groups: Centre for Evidence Based Dermatology (CEBD), The University of Nottingham	Thank you for your comment.
	British Association of Dermatologists	We would recommend adding Vitiligo Support UK to the list of patient support groups.	Thank you for your comment.
	Vitiligo Support UK	Introduction: We are a charity supporting patients with vitiligo in England and Wales. Our remit is to provide support, advocacy and information about the disease to patients, their families and friends. In this capacity, our Chair of trustees has been involved as patient representative in: The production of the British Association of Dermatologists Guidelines for Managing People with Vitiligo (Eleftheriadou et al.; 2021; British Journal of Dermatology, Volume 186, Issue 1, 1 January 2022, Pages 18–29). The production of the British Association of Dermatologists and British Photodermatology Group Guidelines for Narrowband Ultraviolet B Phototherapy 2022 (Goulden et al.; 2022; British Journal of Dermatology, Volume 187, Issue 3, 1 September 2022, Pages 295–308). The production and editing of the British Association of Dermatologists/British Photodermatology Group/NICE kitemarked Phototherapy Clinical Standards. The Outpatient Recovery and Transformation Dermatology Working Group (NHS)	Thank you for your comments. These have been noted and the relevant sections of the scope have been updated.

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		Patient lead, the British Association of Dermatologists Patient Engagement Workstream and lay member of the Education Board. Lay member, the British Association of Dermatologists Research Sub-committee. Participation and support in the establishment of the St John's Institute National Vitiligo Service and Registry. We represent patients' views and so our response to the consultation comes from the patients' perspective. We trust that you will consider our response despite any errors that may be contained herein. Questions: Where do you consider ruxolitinib will fit into the existing care pathway for non-segmental vitiligo? First of all, we would like to quote Bergqvist and Ezzedine [1] "Vitiligo should not be dismissed as a cosmetic or insignificant disease, as its effects can be psychologically devastating, often with a considerable burden on daily life". It is this patient experience that we wish to represent in this process. In relation to the concept of an existing care pathway for non-segmental vitiligo we would like to make the following comments. 1. Existing comparable treatments: In our extensive experience with our own and our members' patient pathway with vitiligo, we agree with the contention of the authors of [1], that "The treatment of vitiligo is still one of the most difficult dermatological challenges. An important step in the management of vitiligo is to first acknowledge that it is not merely a cosmetic disease and that there are safe and effective treatments available."	

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		However, there are a number of issues relating to the current treatment pathway. The first is that there appears to be variation in the available guidance relating to the first line treatment for the face and body, including the use of calcineurin inhibitors and the importance of testing for co-morbid auto-immune conditions, specifically thyroid disease. This variation is not helpful for patients as it places a considerable burden on them to ensure that the correct treatment is offered for the correct part of the body and also to ensure that ancillary tests are carried out, as appropriate. To have one treatment as the first-line approach would ensure that time was saved both for the NHS and for patients in their individual lives and the individual economic and social contributions that they make. This variation also appears in patients' experience of the wide and inconsistent range of responses from doctors in different parts of the country/different practices (see Access to First- or Second-Line Treatments below). The lack of standard allows for personal opinion to be delivered as clinical advice to the considerable disadvantage of patients. As an example of that variation, if one was seeking guidance as a clinician for a patient in an appointment about the prescription of a topical calcineurin inhibitor for vitiligo, the Primary Care Dermatology Society [2] provides clear guidance that in relation to "Topical treatments for thin areas of skin - face, flexures, and genitalia Tacrolimus (Protopic ®) 0.1% ointment BD should be considered first-line, which appears to be more effective than other topical calcineurin inhibitors (ie pimecrolimus cream)". However, in the British Association of Dermatologists' Guidelines for Managing People with Vitiligo [3] the use of calcineurin inhibitors is graded as a "Consider" option rather than "Offer", "Consider topical tacrolimus 0.1% ointment twice daily in people with facial vitiligo as an alternative to potent or	

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		very potent topical corticosteroids" (see Table 1 of [3] for further definitions of "Consider" and "Offer"). In the NICE section covering Vitiligo [4], this is downgraded further to "may be an alternative" and "may be useful", "Topical calcineurin inhibitor monotherapy may be an alternative to corticosteroid therapy owing to their better short-term safety profile, especially concerning risks of skin atrophy [Gawkrodger, 2008; Taieb, 2013; de Menezes, 2016]. They may be useful for the treatment of face and neck lesions, particularly in children, and for new actively spreading lesions on thin skin [Taieb, 2013; Bergqvist, 2020]". There is also the important issue for vitiligo patients of common co-morbidities with other autoimmune diseases, making vitiligo a common gateway to further clinical impairment. Dismissal of the condition as cosmetic risks missing preliminary symptoms of common comorbid diseases; for example, the authors of [5] relate that vitiligo "patients had a statistically significant higher prevalence of hypothyroidism, multiple sclerosis, rheumatoid arthritis, idiopathic thrombocytopenic purpura, seronegative arthritis, pernicious anemia, myasthenia gravis, inflammatory bowel disease, lymphoma, and systemic lupus erythematosus" and the authors of [6] conducted research that revealed that "Of 1098 patients with vitiligo, nearly 20% had at least 1 comorbid autoimmune disease. Compared with the general US population, we found a higher prevalence of thyroid disease (12.9%, P < .001), alopecia areata (3.8%, P < .001), inflammatory bowel disease (0.9%, P = .046), pernicious anemia (0.5%, P = .007), systemic lupus erythematosus (0.3%, P = .048), Guillain-Barre syndrome (0.3%, P < .001), discoid lupus (0.2%, P = .003), linear morphea (0.2%, P < .001), myasthenia gravis (0.2%, P = .002), and Sjögren syndrome (0.2%, P = .011)". The most important correlation is that of thyroid disease (hypo- and hyperthyroidism) and vitiligo. The British Association of Dermatologists	

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		Guidelines for the diagnosis and treatment of vitiligo [7] reported that "Patients with vitiligo often develop autoimmune thyroid disease or other autoimmune diseases and a history of auto-immune disease in a family member is obtained in 32% of patients. In one series of 41 adults, a history of autoimmune thyroid disease was found in 14 (34%), suggesting that screening for abnormal thyroid function or the presence of autoantibodies to thyroid antigens may be helpful in the management of adults with vitiligo". However, the relevance of this particular disease for vitiligo patients and the importance of advice to patients of risk and ongoing monitoring/testing also receives slightly varying responses from the three information sources we examined. The first was the website for the Primary Care Dermatology Society [2] which advises clinicians that "Patients require a TFT and thyroid autoantibody screen, and must be educated about symptoms of thyroid disorders" (author's highlights). The British Association of Dermatologists' Guidelines for managing people with vitiligo in [3] render the question of thyroid disease as a "GPP", meaning a "Good practice point (GPP)" which are "recommendations (R)…derived from informal consensus", and advises, "Screen for antithyroid antibodies and thyroid function in people with vitiligo (including children) to identify those at high risk of developing autoimmune thyroid disease". Meanwhile, [4] states "Consider arranging blood tests for co-morbid autoimmune disease if a diagnosis of non-segmental vitiligo is suspected, such as: Thyroid function tests and thyroid autoantibodies. Note: checking autoantibodies for other autoimmune conditions is only recommended if the person's history, family history, and/or other test results are suggestive" (author's highlight).	

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		Leaving aside these inconsistencies, the next issue that arises for patients in terms of the information given to them is the role of topical corticosteroids. This topical treatment, rather than calcineurin inhibitors, is definitively the first line experience of treatment that most vitiligo patients appear to receive for all areas of the body. There is guidance on the timing of beginning and ceasing treatment, but there is no clear identification of the extent or nature of improvement that patients will receive. The Health Technology Evaluation provides for assessment of "re-pigmentation; maintenance of response; cessation of spread of stabilisation of vitiligo", however it would be useful to see the data that supports these elements for current first-line treatments as there appears to be very variable results and different inclusion/exclusion criteria for studies, making a comparison difficult, in our opinion. This lack of identification of clear outcomes is also present in the information provided for clinicians to disseminate to patients. For example, see [4] "If a topical corticosteroid is prescribed, arrange regular review to assess treatment response and to monitor for adverse effects. After 1 month, consider discontinuing treatment if there is a good response or there are suspected adverse effects. After 2 months, discontinue treatment if there is a good response". In this extract, and elsewhere, there is no definition of what that "good response" might entail given in relation to an index (e.g., VASI/VETF), and we believe that this allows a small, perifollicular response to potentially be dismissed by clinicians and the patient being taken off the treatment. In addition, to stop treatment in the presence of a "good response", whatever that might mean, is not an adequate length of time, in our opinion, to maintain any anti-inflammatory effects or reduction in autoimmune response without the cream after the eight week period is over. In [2], reference is made to "Once daily applications of a potent topical steroid, eg mometasone 0.1% cream, may be as effective as a super-potent	

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		topical steroid and should be considered first-line for an initial period of three-six months; response to treatment can be slow. If there is limited response, then consider a super-potent topical steroid (eg Dermovate ®)"). However, again, there is no definition given of "effective" or what a slow treatment response is, in terms of the improvement in pigmentation or otherwise. From a patient's perspective of the efficacy of these topical treatments (recent survey of members; 95% of respondents to that question indicated that steroid cream had not worked for them), it appears that there is a two stage process in gaining repigmentation. The first is the anti-inflammatory action of either topical steroids or calcineurin inhibitors slowing or stopping depigmentation and the second is the use of phototherapy (or, rarely, laser therapy) to stimulate melanocytes to gain repigmentation. No advice appears to be given in primary care in terms of that two stage requirement for i) reducing the inflammatory action (through the use of a cream) and ii) the need for stimulating repigmentation with uvb/uva light. This is supported by the fact that, due to limited access to phototherapy, people often observe perifollicular repigmentation due to sun exposure in the summer months. Indeed, on examining the evidence in [8], it appears that combined treatments with phototherapy or laser, or a combination of a topical corticosteroid with another cream had better repigmentation results (>75%) than monotherapy. The results, however, appear very mixed, and the risk of adverse effects reported appear high (e.g., "Sixteen of the 17 studies examining the effect of topical corticosteroids reported adverse effects in some of the participants receiving them. For combination therapies it was not always possible to ascertain which of these adverse effects were attributable to the topical steroids" [8]). In addition, it is now recognised that with all treatments, the effect of CD8+ resident memory T cells means that all treatments need to be repeated, with	

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		attendant risk to the patient's skin of the long-term use of topical steroids or the doses of narrowband uvb, see [9], "Clinical observations uncovered the importance of autoimmune memory in vitiligo because cessation of treatment frequently led to relapse of disease at the site of previous lesions. A subset of memory T cells known as CD8+ resident memory T cells (TRM) are long-lived, nonmigratory memory cells that persist in most nonlymphoid tissues, including the skin. Recent reports describe the presence of CD8+ TRM in lesional vitiligo patient skin and suggest their role as active players in disease maintenance". In relation to ruxolitinib, the trial results [10] refer to the use of a monotherapy compared to a vehicle control, without the need for attendant uva/uvb stimulation, which is a very important step forward in treatment for vitiligo patients. To compare these results, taking the results of the "Interventions for vitiligo" Cochrane Review, there were eight studies in total of those reviewed that involved the comparison of monotherapies with topical interventions alone. The participants in one study were children aged under twelve years, in one study the participants had segmental vitiligo and in four the data were not sufficient to allow for appropriate analyses to be conducted so, in relation to the participants and inclusions/exclusions of the TRuE-V1 and TRuE-V2 trials, we felt these results were not comparable. The studies quoted comparing dual topical therapies did not report significant results in relation to the benchmark of >75% repigmentation [8; Section 1.1.(b)]. The Cochrane Review concludes "There is moderate evidence for the use of topical corticosteroids, although long-term use is likely to lead to adverse effects" but added, "When used as monotherapy, it may be preferable to use superpotent preparations to give a better chance of therapeutic response, but close monitoring for adverse effects will be necessary".	

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		In relation to ruxolitinib, the summary of the trial report states that in “TRuE-V1, the percentage of patients with an F-VASI75 response at week 24 was 29.8% in the ruxolitinib-cream group and 7.4% in the vehicle group (relative risk, 4.0; 95% confidence interval [CI], 1.9 to 8.4; P<0.001). In TRuE-V2, the percentages were 30.9% and 11.4%, respectively (relative risk, 2.7; 95% CI, 1.5 to 4.9; P<0.001). The results for key secondary end points showed superiority of ruxolitinib cream over vehicle control” [10]. As with other trials, adverse effects were reported, “Among patients who applied ruxolitinib cream throughout 52 weeks, adverse events occurred in 54.8% in TRuE-V1 and 62.3% in TRuE-V2; the most common adverse events were application-site acne (6.3% and 6.6%, respectively), nasopharyngitis (5.4% and 6.1%), and application-site pruritus (5.4% and 5.3%)”. We would also like to comment on the inclusion in the “other treatments” on page 1 of the Health and Technology Evaluation of “excimer laser treatment”. It is our experience that this is not routinely (never) offered in the NHS and so should not, in our opinion, be considered as a treatment that is part of the package offered to vitiligo patients. If this is incorrect, we would be interested to receive a list of the dermatology departments that offer excimer laser as a treatment to vitiligo patients so we can advise our members accordingly. Licensing In terms of the fact that there are currently no licensed treatments for vitiligo in England and Wales (“Many treatments used for vitiligo are unlicensed. "Unlicensed" means the medicine's manufacturer has not applied for a licence for it to be used to treat your condition” [11]), the net effect of this for patients is that the treatments deliver a generalised anti-inflammatory effect but are not specific to the complex processes underlying the destruction of the melanocytes. Ruxolitinib offers a completely different treatment effect to the current unlicensed treatments on offer (see below).	

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		2. Access to first- or second-line treatment within the NHS This is a significant issue for patients and should be considered. It is our recommendation that ruxolitinib should be available to patients in the primary care setting and subject to co-ordinated guidelines for its use across common sites of information for clinicians. The first aspect of the difficulties in accessing treatment is that there appears to be an unfortunate trend of personal opinion influencing that access or referral to secondary care. These are some of the comments from our members about their experience of trying to access the “existing care pathway” (comments deidentified and provided with members’ consent; produced verbatim): “I’ve found the whole process long and distressing. I’ve had to push every step of the way for treatment options, and often felt like I knew more than the doctor a lot of time. I have been asked ‘what do you want us to do?’ several times, which made me feel like no one actually wants to help, and was told that because I’m fair skinned they recommend I learn to live with it.” “My GP told me there’s no treatment, I asked about tacrolimus and he said “but that would mean a referral to derm, I can’t prescribe it”. I’ve since acquired tacrolimus privately.” “Fast forward 3 years, I ask my GP about narrow UVB treatment - he says it’s takes too many appointments to be worth it. I acquire a narrow UVB for use at home, google studies for the protocol and use it at home unsupervised. Both of these treatments work well, they reduce the psychological impact I have from permanently looking grumpy (vit either side of my mouth and chin) but my GP seemed to consider himself a one man NICE authority!” “On first seeing a GP she said, I’ve never seen it that bad, GP said the wait was. Year in the nhs so I paid to go to a private dermatologist”	

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		This issue of access drives patients to try alternative sources of treatment, for example supplementation, or use of at-home handheld phototherapy units. These are all performed without medical supervision, at possible risk to patients. As a member commented ""if the impact of vitiligo is making people source their own different options for treatment/concealing, then there's an inherent risk that something would go wrong. So not providing access to suitable, proven treatments actually puts patient care at risk" If referral is made to secondary care, waiting lists for dermatology are variable across England and Wales and range from, for example, 29 weeks in the University Hospitals of Derby and Burton NHS Foundation Trust, the Royal Devon University Healthcare Trust is currently 23 weeks; the Guys' and St Thomas's Trust in London waiting list is 15 weeks and at the United Lincolnshire Hospitals' Trust it is 28 weeks [12–15]. In some trusts, waiting lists are lower, but there is anecdotal evidence from patients of an informal triaging of patients being refused access to secondary care due to the misapprehension that treatments do not work, and that this is a purely cosmetic condition, and in this respect we refer again to [1], "An important step in the management of vitiligo is to first acknowledge that it is not merely a cosmetic disease and that there are safe and effective treatments available". 3. Conclusion From the perspective of patients, the results of [10] and the ruxolitinib cream, have two very important features, which is first that repigmentation takes place effectively with application of ruxolitinib alone (a feature controlled by the key exclusion criteria in the trial of "use of the following therapies for vitiligo before baseline: any biologic or experimental therapy within 12 weeks (or 5 half-lives), phototherapy within 8 weeks, immunomodulating treatments within 4 weeks, or topical treatments within 1 week"). This means that with	

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		the use of this drug, patients' requirements for phototherapy would significantly reduce, decreasing both costs and demand in this area. Second, this is the first cream that acts not merely as a tool for the reduction in autoimmune inflammation in the cells generally but by targeting the specific pathway that leads to depigmentation, i.e., the cytokine pathway using JAK and STAT pathways to achieve the deleterious effect [p. 576; 1]. We believe therefore that this drug represents an extraordinary step forward in patient treatment. It is the first drug brought to the market that targets the specific cellular process of destruction of a patient's melanocytes, the disease's aetiology, and works on the basis of previous, extensive research into JAK inhibitors in relation to inflammatory diseases manifested systemically [e.g., 16]. Therefore, as a patient organisation we believe that ruxolitinib should be made available in primary care in England and Wales for the following reasons: • It would avoid the necessity for referral into secondary care thereby reducing the considerable volume currently present on waiting lists; • It is a drug that has been the subject of considerable, very recent research focused on the vitiligo population, the aetiology of vitiligo and the disease pathway, and not on general dermatology issues, as with steroid creams and calcineurin inhibitors (the majority of prescriptions for which relate to tacrolimus); • Topical treatments require frequent reviews (as evidenced above in relation to topical steroids) and this is better conducted in primary care than secondary care; • The issue also relates importantly to patient convenience as hospital visits can significantly disadvantage people, for example in terms of cost for	

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		those without access to transport or impact on economic contribution for those who are working; • The model of dermatology provision is being reviewed (we are members of the Outpatient Recovery and Transformation Dermatology Working Group and also the British Association of Dermatologists Education Board) and the focus should, we believe, be on the appropriate triage of patients into secondary care who require hospital-based treatment (e.g., narrowband uvb or other phototherapy interventions or complex drug interventions of biologics or immunomodulators). Do you consider ruxolitinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? As mentioned in our response to the question "Where do you consider ruxolitinib will fit into the existing care pathway for non-segmental vitiligo?" we believe that this is an enormous step change in treatment options for vitiligo due in part to the fact that the treatment target of the cream is in the aetiology of the disease. Whilst it is a long-term treatment (due to the erratic onset of the disease and also the role of CD8+ resident memory T cells mentioned above) it reduces the need for phototherapy as it is a standalone treatment. A cream prescribed in primary care for use at home represents a significant time saving on phototherapy ("…it is suggested that phototherapy should be continued for at least 12 months to achieve a maximal response" [1]; "Treatment frequency should be 2-3x/wk. In two separate studies comparing 2x/wk vs. 3x/wk for vitiligo (Excimer laser) (3) and psoriasis (nbUVB) (4), 3x/weekly produced faster results than 2x/weekly, however eventually the two	

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		schedules resulted in equivalent efficacy. Therefore, if the patient's schedule allows, I recommend starting at 3x/weekly for the first 3 months, and then decreasing to 2x/weekly thereafter" [17]) There is also a cost that should be calculated of patients' time engaged in ineffective treatments, attendance at secondary care clinical appointments or phototherapy sessions based in hospitals of varying distances from the patient, the management of adverse effects of prolonged steroid treatment, the management of erythema from phototherapy and its impact on the treatment course and the economic impact of time away from work, education or voluntary contributions to the community. We consider that one of the important health-related benefits will be to people's psychological health as this is a disease with a profound psychosocial impact. It prevents people from engaging fully in social activities including sports, education at all levels, social engagement, work opportunities and intimate relationships. We have both people in the public eye now treating the disease positively and yet also a large group of patients who are still neglected by the healthcare system, who struggle with the impact of their disease, and who restrict their daily activities as a result. We have long been aware that the disease may well be dismissed by healthcare professionals as something that "only" affects one's appearance, something that is reflected in [1]. However, this neglects to consider three things. First, in general terms, the "skin plays an important role in our interaction with the world and visible skin disorders can limit healthy psychosocial development owing to the stigma these disorders create" [p. 584; 1]. Secondly, on top of that general impact, this skin disease now occurs in a context where our society has been transformed in the last ten years, in terms	

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		of the daily psychosocial transactions, by the advent of social media that has increased focus on external appearance in a way that has never been encountered before, particularly for young people and as a result may not have been encountered or taken into account by the current generation of healthcare leaders/professionals. It increases the impact of any differences in appearance, in particular ones caused by an unpredictable and chronic disease. Third, psychological health appears to be still given a lower priority than physical health, despite increases in funding. This has meant, in our opinion, that funding for mental healthcare has lagged behind that for physical diseases and that, due to a concatenation of circumstances including the COVID-19 pandemic, we now face a mental health crisis in this country in general terms, let alone in terms of specialised provision for those with a dermatological condition affecting their appearance. Unfortunately, there are also still very limited specialised Psychodermatology services available in England and Wales to meet this need. Figures obtained in [18] reported that "[The] results showed that less than a quarter of the respondents (24%) have access to a nearby dedicated psychodermatology service. Additionally, the psychodermatology units do not have a unified configuration and clinical provision model differs nationally. Only around 5% of the clinicians have access to a clinic that provides psychology–dermatology–oncology service, and even fewer have access to a paediatric psychodermatology (4.8%). Engagement in psychodermatology research was reported by around 12% of the participants." It is our contention that if a disease such as vitiligo, that causes profound psychological 'dis-ease', continues to be dismissed on the grounds that it only affects patients mentally and is cosmetic only this represents a failure of the healthcare system in this country.	

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		In addition, where the provision of existing psychodermatology services is so sparse, any attempt to treat vitiligo by offering specialist counselling provision or psychological support in lieu of a pharmacological intervention would be both expensive, as it would require building a service from the ground up, and also non-condition-specific as vitiligo would be one of many dermatology diseases requiring access to such a service. As examples of the impact, we share with you some of our members' comments about their condition (comments deidentified and provided with members' consent; produced verbatim): "I am very aware of it and it stops me relaxing outside as I'm so aware of sun damage or enjoying holidays, etc." "I am so desperately waiting on this breakthrough treatment , it effects my life daily, I dread summer and without sounding dramatic I just want to be normal, nothing special just normal" "After several trips to the doctors over the course of 18 months they finally referred me to the dermatologist to get confirmation that it was vitiligo. After a long wait for an appointment I was told that there was no cure but if I had skin like him (he was Indian) he'd understand my insecurities more. I came away from this appointment feeling as though I had just wasted his time." "I have my honeymoon coming up in September and feel more dread about being in the sun and it making my patches more noticeable and it's really upsetting that I can't be more excited about this special occasion" "My daughter has it and its affecting her mentally and she does not look in the mirror at all" "Losing my father thirteen years ago had a big impact on me but I can honestly say my vitiligo has had a far greater impact on me as with grieving time is a healer, with this disease there is no definitive treatment/cure and as such you cannot heal and cannot get my head around the fact I will possibly	

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		have to be like this the rest of my life leading me into a state of depression and often with suicidal thoughts." "I lack any confidence at all- it has stopped me living my life to the fullest!!" "I was given 10 sessions phototherapy and then was told it wasn't working and end of treatment. It has certainly changed my life and not for the good" This is a treatable disease. It causes incredible damage to the individual in their families, their communities, their cultural identity and their occupations. There are no treatments currently that work in the long term or target the specific mechanisms of the disease. Ruxolitinib brings hope to us as patients with this condition but more importantly it brings tangible results. We ask you to please consider carefully the benefits it can bring to a suffering community. Do you consider that the use of ruxolitinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please see above in relation to our contention that improved psychological health is one of the key outcomes for improved pigmentation in patients. In terms of the measurement of this psychosocial burden, we are also concerned, along with the patient support charities before us in relation to other dermatology conditions, that the EQ-5D may not capture data relevant to the assessment of health-related benefits of this treatment and any improvements that it may bring. There are strong arguments to be made to employ adjunctive instruments that test specifically for the impact of this disease. To that end, instruments such as the Vitiligo Impact Patient Scale (VIPs)10 or the vitiligo-specific quality-of-life instrument (VitiQoL) [3] might be employed alongside EQ-5D.	

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