Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Patient and Clinician Group Input

Ruxolitinib (Opzelura)

(Incyte Biosciences Canada Corporation)

Indication:

- Topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older.

October 28, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

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CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Ruxolitinib
Indication: Nonsegmental Vitiligo
Name of Patient Group: Canadian Skin Patient Alliance and Vitiligo Voices Canada
Author of Submission: Sabrina Ribau, Programs Manager (CSPA); Shahnawaz Towheed (VVC); Omar Sharife (VVC)

1. About Your Patient Group

This submission is supported through a collaboration between the Canadian Skin Patient Alliance (CSPA) and Vitiligo Voices Canada. CSPA is a national charity organization that improves the health and well-being of people across Canada affected by skin, hair, and nail conditions through collaboration, advocacy, and education. For more information, please visit: https://canadianskin.ca/en/.

Vitiligo Voices Canada (VVC) is a national patient support organization dedicated to empowering individuals living with vitiligo across Canada. Co-founded by vitiligo patients, VVC provides a safe space for patients to share their experiences, find community, and access vital resources. Through advocacy, education, and peer support, VVC aims to raise awareness about the impact of vitiligo on patients' lives and advocate for improved access to care and treatments, helping individuals with vitiligo feel seen, heard, and supported. For more information, please visit https://www.instagram.com/vitiligovoicescanada/

2. Information Gathering

2.1 Data gathering

Information for this submission was compiled from a patient and caregiver survey shared on CSPA's and Vitiligo Voices Canada's communications channels from September 26 to October 15, 2024, and on CSPA's website, in both English and in French. In this submission we report on combined English and French survey responses. A total of 19 survey responses were received, 17 in English and two in French. Personal experience from people living with vitiligo involved in the project was also gathered and included for this submission. We had no survey respondents with experience with the drug under review.

2.2 Regional data

The patient and caregiver survey contained 19 respondents from Canada, with the largest number being from Ontario (36.84%, n=7). A smaller proportion of respondents also came from Alberta (21.05%, n=4), British Columbia (10.53%, n=2), Newfoundland and Labrador (10.53%, n=2), Yukon (5.26%, n=1), Quebec (5.26%, n=1), Nova Scotia (5.26%, n=1), and New Brunswick (5.26%, n=1). There were no survey respondents from Northwest Territories, Nunavut, Saskatchewan, Manitoba, or Prince Edward Island.

2.3 Survey Demographics

When asked about their age, the respondents (n=13) were all over 25 years old, with more than half of respondents being over 55. Twenty-three percent (n=3) were 25-34 years old, 15% (n=2) were 35-44 years old, 8% (n=1) were 45-54 years old, 38% (n=5) were 55-64, and 15% (n=2) were over 65 years old. There were no individuals under 25 years old surveyed. For those who answered the question (n=12), 33% (n=4) of respondents have had vitiligo for less than five years, 25% (n=3) for five to 10 years and 25% (n=3) for longer than 20 years. Additionally, one participant (n=1) has had vitiligo for 10-15 years, and another participant (n=1) for 15-20 years, respectively. Most respondents reported having moderate (33%, n=4) or severe (33%, n=4) vitiligo, and 17% (n=2) reported their vitiligo as mild. Two respondents reported that they were unsure of the current severity of their vitiligo. The most common comorbidities were autoimmune disease in 50% (n=5) of respondents and mental health conditions (e.g., depression, anxiety) in 30% (n=3) of respondents. Two respondents selected "Other", with one sharing that they took a "thyroid pill," and another reported that

they had Type 1 diabetes, kidney disease, eczema, and a hypothyroid condition. Regarding sex and gender, 10 (n=10) reported being female, and three (n=3) identified as male. Two respondents reported that they were caregivers, however only one filled the subsequent survey questions related to caregivers.

When asked how they best described themselves, 61.54% (n=8) described themselves as white/Caucasian, 15.38% (n=2) described themselves as South Asian, one as southern European, one as southeast Asian, and one as West Asian and/or Middle Eastern, respectively.

3. Disease Experience

Vitiligo is far more than a cosmetic condition; it deeply impacts patients' psychological well-being, social interactions, and day-to-day functioning. While the physical manifestation of vitiligo—visible patches of depigmented skin—may seem to be the primary issue from the outside, the reality is that the disorder can profoundly disrupt the emotional, mental, and social aspects of patients' lives.

From an early age, individuals diagnosed with vitiligo experience a sense of **otherness**. Children with vitiligo are often subject to stares, bullying, and exclusion, which can severely affect their self-esteem and social development. Many patients describe feeling alienated from their peers, struggling with questions of identity and belonging. In particular, 75% of respondents reported that vitiligo impacted their "sense of self or personal identity," while 42% reported that it impacted their "daily activities" and "social life." Twenty-five per cent (25%) of respondents also shared that vitiligo impacted their sense of belonging, their intimate relationships (33%), and their family relationships (25%). This isolation can extend into adulthood, where vitiligo sufferers often grapple with a fractured sense of self.

"Woke up one day in my 30s with vitiligo. Now I wake up wondering where the next spot will be. Try to not let it bother me, but it's hard."

One of the most challenging aspects of vitiligo is its unpredictable progression. Patches may appear suddenly, spread, or remain localized, creating a continuous cycle of uncertainty. This lack of control exacerbates patients' anxiety and can lead to a profound sense of helplessness. Many patients live in constant fear of when the next patch might emerge, or whether the condition will progress to universal vitiligo, where most or all the skin is affected. This unpredictability can discourage people from engaging in social events, forming close relationships, or pursuing careers in visible, public-facing roles. They may also feel pressured to make burdensome lifestyle changes, such as applying camouflage makeup to conceal spots, and wearing long-sleeved clothing during summer months.

"Depressive moods every spring. Shame of my body. Tired of putting on sunscreen so I deprive myself of going out in the sun."

The psychological impact is one of the most significant burdens of the disease. Depression and anxiety are common among vitiligo patients, and in severe cases, suicidal ideation and attempts can occur. The sociocultural standards of beauty further exacerbate the emotional strain faced, especially among individuals with richly pigmented skin tones who experience a more stark contrast from their original complexion. Vitiligo challenges deeply ingrained notions of appearance, leaving patients feeling as though they do not fit into societal norms. At times, particularly for those with darker skin tones, this can lead to outcast and judgment from social and cultural groups, impacting the patient and their family's well-being, exacerbating the burden of vitiligo.

"It's embarrassing. I cover it up with makeup so people don't notice."

For many patients, the challenge of managing social perceptions is as burdensome as managing the disease itself. Vitiligo often invites unwanted attention and questions, with strangers feeling entitled to ask invasive questions or offer unsolicited advice. For some, daily interactions become fraught with anxiety, as they anticipate stares, whispers, and the constant need to explain their condition. This social burden leads to self-isolation, avoidance of public spaces, and, in many cases, the development of social anxiety disorder. The resulting withdrawal symptoms contribute to significant financial burdens on both individual and systemic levels, including lost workplace productivity and increased healthcare costs associated with mental health support. These factors underscore the economic value of investing in accessible treatments like Ruxolitinib, which could help alleviate the broader societal costs of untreated vitiligo.

***"I'm tired of getting my hopes up when treatments aren't guaranteed to work; I'm exhausted from trying treatments that don't yield results."* [*40% of patients surveyed*]**

Another critical aspect of living with vitiligo is the emotional exhaustion of constantly seeking treatment. Patients navigate an overwhelming array of treatment options, from topical corticosteroids and phototherapy to experimental treatments. The effectiveness of these treatments varies greatly, and many patients report limited success, which compounds their frustration and emotional fatigue. Some treatments require frequent clinic visits, time off work, and financial strain, adding to the overall burden. The emotional toll of trying treatment after treatment with no guaranteed success leaves many feeling disillusioned and defeated.

"Uncomfortable engaging in activities that show my skin (swimming, short sleeves in summer, gym clothes etc). No longer living life to its fullest."

In terms of daily life, vitiligo affects even the simplest of activities. Vitiligo can affect any part of the skin, with where and how it appears being different for each person. Respondents shared that vitiligo affects their face, hands, feet, legs, arms, chest, abdomen, under arms, hair, lips, and genitals, with many sharing that their entire body is affected by vitiligo. Many patients avoid sun exposure due to a fear of worsening depigmentation and the sensitivity of the depigmented skin to UV radiation. This avoidance can limit outdoor activities and everyday outdoor social gatherings. The constant application of sunscreen, camouflage makeup, or other protective measures becomes part of the daily routine, adding another layer of mental fatigue to an already overwhelming experience. On top of this fatigue and frustration, the practicality of applying treatments and protective products can have financial and time burdens as well, with one respondent sharing that their clothes and vehicles are soiled by sunscreen, while another emphasized a desire for financial support for buying sunscreens and UV clothing. These examples demonstrate some of the unseen yet tangible costs associated with managing vitiligo. As a result, these experiences and effects on daily activities build day after day, impacting family relationships, intimate relationships, social life, and family planning, as reported by our survey respondents.

"Protecting my daughters self worth and helping her work through her struggles is devastating and heartbreaking"

Caregivers are also impacted, often witnessing their loved ones endure emotional pain, insecurity, and social withdrawal. The psychological burden on caregivers can be immense, as they provide ongoing emotional support and encouragement, while often feeling helpless themselves. Many caregivers express frustration at the lack of awareness and support for vitiligo, as well as the absence of consistently effective treatments. The caregiver also shared that their family balance/relationships, mental health, school/education, daily activities, and financial aspects of their life are affected by vitiligo, highlighting the range of psychosocial and financial impacts of vitiligo on the family and the need for more treatment options to reduce the family burden of disease.

"The entire family had to adapt to my needs (e.g., the hours I can go outside in the summer, picnic locations, vacation destinations, etc."

"My wife and kids afraid from me."

The burden on families was also noted, with some sharing that their families were impacted in significant ways. The social and personal impact of vitiligo was touched on most prominently by one patient who had tried most available treatments and shared that their wife and children are afraid of them because of their skin. Meanwhile, another's family has had to change how they do seemingly simple family activities like going for picnics, and also bigger, joyous milestones like family trips. These types of emotional deeply personal impacts can change how people perceive themselves, their self-worth, and their sense of identity, and they highlight yet another reason for the need for an increase in treatments tailored to vitiligo.

4. Experiences With Currently Available Treatments

Currently, vitiligo patients and their caregivers navigate a range of treatments with varying degrees of effectiveness and accessibility challenges. Many patients report limited success with existing therapies, highlighting the need for new, more effective treatments. In our survey, three respondents indicated that they had never used any treatment for vitiligo, while nine reported trying multiple therapies, including topical corticosteroids, vitamin D derivatives, oral steroids, topical immunomodulators, and calcineurin inhibitors. The responses emphasize the limited efficacy of these treatments: despite all nine having used topical corticosteroids in the past, none of the surveyed patients found them to work "well" or "very well." Instead, patients rated their experience as "did not work at all"

(44.44%), "did not work very well" (22.22%), or "no change" (33.33%). As topical corticosteroids are often the first-line therapy for vitiligo, this underscores the need for new and effective treatments that are accessible to patients.

Other treatments such as topical vitamin D derivatives also showed minimal effectiveness, with two respondents noting they "did not work at all" and one reporting "did not work very well." Oral steroids had similarly discouraging results, with all three users stating they "did not work at all." Topical immunomodulators and calcineurin inhibitors yielded similarly poor outcomes, with responses indicating "did not work at all" or "did not work very well." Two respondents reported having used “tattooing (micropigmentation)” to try to manage the appearance of their vitiligo, however both reported that it “did not work at all.” Moreover, there was one patient who reported having used all the treatments included in the survey in the past, including different types of transplant surgeries (minipunch skin transfer, blister grafting, and autologous melanocyte transplant) and they shared that the transplants did not work at all for them. One interesting thing to note with this patient is that they also shared that they currently don’t use a treatment for their vitiligo, demonstrating the fatigue and frustration among patients, further underscoring the importance of new and effective treatments becoming available for patients so that they are able to have more and better options for managing their condition.

Two treatments showed slightly more promising results for certain individuals yet still highlight significant variability in effectiveness. Depigmentation therapy with monobenzone, an option indicated for advanced cases only, was effective for one respondent ("worked very well"), while another reported no benefit at all. Phototherapy (narrow-band ultraviolet B, NB-UVB), a common treatment for vitiligo, had mixed reviews: one respondent found it "worked well," but others noted "no change" (n=1) or rated it as "did not work very well" (n=2) or "did not work at all" (n=1). Regarding other types of phototherapies, respondents also reported having tried Psoralen plus ultraviolet A (PUVA) photochemotherapy, however of the three, one reported that it “did not work at all,” another that it “did not work very well,” and another that they observed “no change.” Similarly, four respondents reported that they used phototherapy but we were unsure of which type, to which three reported that it “did not work at all,” and one reported that it “did not work very well.” This variability in responses suggests that while some patients may experience partial repigmentation, most find current treatment options inadequate for clinically significant improvement. The contrast in experiences with some of these treatments demonstrates the diverse needs of vitiligo patients. These results, although a small sample size, truly emphasize the significant gap in currently available treatments and the need for new, safe, effective treatments for supporting people who have vitiligo.

Regarding side effects, respondents reported experiencing skin thinning (n=1), skin irritation (n=2), and a burning sensation (n=1). Respondents also reported that their skin easily sunburned, and that they had an increase in nasal mucous production, sinus congestion, post-nasal drip from one treatment, and a fever from another. With two respondents having reported that they stopped treatments because of side effects, it’s important that new treatments are effective and that they have minimal side effects to better support patients in their treatment goals. Similarly, one patient reported that they stopped treatment because it was too difficult to take/apply, another because it was too expensive, and two others reported that it was not conducive to their daily schedule.

In addition to limited effectiveness, patients face practical challenges that hinder access to these treatments. Phototherapy, for example, requires frequent clinic visits, which can pose significant barriers in terms of cost, travel, and time away from work or other responsibilities. This burden is particularly heavy for individuals in rural and remote areas or regions with limited dermatology resources, where access to phototherapy or specialized care may require extended travel. The financial costs of these therapies, often compounded by additional expenses like camouflage makeup or sunscreen, place a further strain on patients and caregivers, especially when treatments fail to deliver results.

The psychological toll of repeatedly undergoing ineffective treatments cannot be overstated. Many respondents expressed frustration and emotional exhaustion from "getting their hopes up" only to experience little to no improvement. This cycle of optimism followed by disappointment leads some patients to discontinue treatment entirely, as the burden of constant trial-and-error becomes unsustainable. As one respondent noted, “I’m tired of getting my hopes up when treatments aren't guaranteed to work; I'm exhausted from trying treatments that don’t yield results.” When asked, participants overwhelmingly agreed or strongly agreed that they would be interested in a new treatment for vitiligo (10 out of 12 respondents) and that they wish there was a better vitiligo treatment option for them (10 out of 11 respondents). On the other side, only one respondent agreed that they felt satisfied with their current treatment for vitiligo, whereas 8/11 shared that they disagreed or strongly disagreed, and two neither agreed nor disagreed. These patient experiences highlight the need for new, effective, accessible treatments for patients so that they can manage their condition and reduce the mental health burdens so often experienced by people impacted by vitiligo.

5. Improved Outcomes

Vitiligo patients and caregivers have a clear vision of the improvements they hope to see in new treatments, underscoring the limitations of current options. When asked what aspects are most important in a new treatment, effectiveness emerged as the top priority for 83.33% of respondents. This focus on efficacy highlights the persistent gap in treatments that can reliably repigment skin and provide consistent, meaningful results. For many vitiligo patients, the ultimate goal is a treatment that not only restores pigment but also provides comprehensive, lasting repigmentation across depigmented areas, reducing the appearance of patches and the stark contrast between affected and unaffected skin. As one respondent shared, they desire “that the repigmentation process not be too long and that it be complete so that I don't have to go back for a long time to a mottled two-colour look (I'm almost entirely white at the moment).” This sentiment underscores the deeply personal impact of partial or inconsistent repigmentation, which can perpetuate the feeling of being “in between” two identities. Moreover, the lengthy period of time vitiligo patients are told to expect to have to wait for current treatments to begin significantly improving the appearance of their vitiligo can and often does greatly impact their health and wellbeing and adds to the burden of disease and the frustrations of trying treatment after treatment that are not as effective as they’d hoped they would be.

Fewer side effects were another priority, cited by 75% of respondents. Many patients have experienced or are wary of the side effects associated with treatments like topical steroids, immunosuppressants, and phototherapy, which can have cumulative health risks over time. The ideal treatment would be both effective and gentle, allowing patients to focus on their recovery without worrying about the long-term impact on their health. This consideration is particularly important for patients who might have been managing vitiligo for decades and are cautious about compounding the physical toll of treatment side effects.

Affordability is also a significant factor, with two-thirds (66.67%) of respondents highlighting cost as a key concern. Vitiligo treatments, especially those requiring specialized equipment or regular clinical visits, can quickly become financially burdensome. Accessibility issues arise not only from the cost of the treatment itself but also from associated expenses like travel, time off work, and the need for continuous treatment cycles. An affordable and accessible option would alleviate these financial stressors, making it possible for a broader range of patients to pursue and maintain effective treatment.

Beyond these core concerns, ease of use was noted as important by 50% of respondents, and 33% mentioned the importance of a treatment that fits into their schedule. The ease of applying a topical cream or the convenience of an at-home treatment could make a profound difference in adherence to and satisfaction with a therapy. A treatment that is simple to apply and integrates smoothly into daily life reduces the logistical and psychological burden on patients. This is particularly relevant for individuals managing the emotional weight of vitiligo, as well as any coexisting conditions or family responsibilities.

Vitiligo patients also express a desire for treatments that are inclusive of various skin tones and severities of depigmentation. Vitiligo manifests differently in individuals with different skin tones, making it imperative that new treatments offer consistent results across a diverse population. For those with richly pigmented skin, depigmentation is often more pronounced, and the cosmetic and emotional impact of uneven or partial repigmentation can be amplified. Effective treatment must address these variations, allowing all patients, regardless of skin tone, to achieve satisfying and confidence-boosting results.

Psychological and social relief are underlying motivations behind these desired outcomes. With a treatment that offers visible improvement and restores a sense of normalcy, patients anticipate a significant enhancement in quality of life, self-confidence, and social participation. Many hope to live free from the constant anxiety of covering up or explaining their condition, with one patient expressing frustration with the lingering need to camouflage their skin. By reducing the visible contrast of vitiligo, an effective treatment can empower patients to engage more fully in their personal and professional lives, thereby fostering greater well-being and self-esteem.

In terms of trade-offs, respondents indicated a clear preference for treatments that balance efficacy with safety and minimal side effects. While they are willing to invest time and energy into a treatment that works, many patients are hesitant to commit to options that impose a heavy burden on their schedule, health, or finances without guaranteed results. The ideal solution would therefore be a treatment that provides reliable and consistent repigmentation, is affordable, fits seamlessly into daily routines, and minimizes health risks.

Ultimately, our survey responses reveal that patients desire treatments that are not only clinically effective but also supportive of their holistic well-being. Effective, accessible treatments like Ruxolitinib have the potential to address the practical and emotional gaps in the current treatment landscape, allowing patients to regain a sense of agency over their condition and their lives.

6. Experience With Drug Under Review

No respondents in our data collection reported having experience with the drug under review.

7. Companion Diagnostic Test

Not applicable.

8. Anything Else?

Given such significant impact of vitiligo on the lives of individuals living with the condition, it is important to explore effective and safe treatment options to improve the quality of life of those affected by vitiligo. There remains a great need for effective treatment options for vitiligo. Access to new and promising treatments is critical to helping patients gain a sense of control over their disease and begin to regain their quality of life. Presently, patients are told to anticipate at least 1-2 years of using a treatment to begin getting close to the treatment outcomes they want, leaving a significant need for new treatments for vitiligo.

Individuals with vitiligo have often attempted numerous treatments, therapies, and other strategies to manage the signs of their condition. When their vitiligo is well-treated, it becomes more manageable, and the psychological, cultural, and social impacts they experience because of this disease are reduced.

The nature of this disease requires ongoing care and a constellation of different approaches. Individuals with vitiligo incur considerable monetary expenses on items to hide their condition, as well as significant sociocultural costs of living with or being in a family with someone who has a skin pigmentation disorder, considerably impacting mental health, wellbeing, and a sense of identity/belonging for the individual and their family. For more information about the challenges of living with vitiligo, please see the following resources:

- CSPA information page for vitiligo
- Vitiligo Voices Canada

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

5. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No. CSPA and Vitiligo Voices Canada worked with staff and volunteers to complete this report. No funding was received to complete this submission.

6. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No. CSPA and Vitiligo Voices Canada worked with staff and volunteers to complete this report. No funding was received to complete this submission.

7. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Incyte Biosciences Canada				x

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Sabrina Ribau
Position: Programs Manager
Patient Group: Canadian Skin Patient Alliance
Date: October 28, 2024

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0835-000

Generic Drug Name (Brand Name): Ruxolitinib (Opzelura)

Indication: Nonsegmental vitiligo

Name of Clinician Group: Canadian Dermatology Association (CDA) with Co-Signatory Organizations: Dermatologist Association of Ontario, Dermatology Association of Saskatchewan

Author of Submission: CDA Pharmacy and Therapeutics Advisory Board

1. About Your Clinician Group

The Canadian Dermatology Association, founded in 1925, is the national medical specialty association that represents Canadian certified dermatologists. The association exists to advance the science and art of medicine and surgery related to the care of the skin, hair and nails; provide continuing professional development for its members; support and advance patient care; provide public education on sun protection and other aspects of skin health; and promote a lifetime of healthier skin, hair and nails. Clinical review and oversight is provided by the Canadian Dermatology Association's Pharmacy and Therapeutics Advisory Board.

Website: Home - Dermatologist Association of Ontario

The Dermatology Association of Ontario

- Is a unified voice for Ontario Dermatologists
- Promotes better patient care
- Supports the OMA Dermatology representatives
- Promotes Dermatology in Ontario
- Supports research and education

Website: Home - Dermatologist Association of Ontario

The Dermatology Association of Saskatchewan supports and promotes the interests of Saskatchewan Dermatologists.

Website: None

2. Information Gathering

Information that was gathered is from clinical experience, research and trial experience, medical literature, published trials and other research designs, national and international meetings.

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3. Current Treatments and Treatment Goals

There are no treatments approved for repigmentation of vitiligo in Canada, although the CADTH review of tacrolimus for vitiligo in 2017 could be interpreted as a tacit acknowledgement that there is an unmet need for treatment.[29] Specifically, there are no approved treatments for vitiligo in Canada.

There are no formalized clinical practice guidelines for vitiligo in Canada. However, a group of Canadian clinical experts in vitiligo worked on establishing consensus recommendations for its treatment. The results of this initiative are expected to be submitted shortly for publication in a peer reviewed journal. Current guidelines and expert recommendations for the management of vitiligo have been published respectively by the British Dermatology Association and the International Vitiligo Task Force.[12,27,28]

Canadian clinical experts agreed repigmentation is the foremost goal of therapy for their patients with vitiligo. In the international VALIANT study, both patients and physicians respectively identified repigmentation (22.5% and 37.2%) and stabilization to stop disease progression (24.7% and 18.5%) as core treatment goals.[9] These statistics may underestimate the true desire to repigment and reflect the belief that there is no effective means to achieve repigmentation.

The threshold for repigmentation treatment success is not well-established. Indeed, a systematic literature review and e-survey collated definitions of successful repigmentation that ranged from 'any repigmentation' to 100% repigmentation.[30] While some publications have defined successful repigmentation as ≥75% improvement, this is commonly a challenge to achieve in real-life practice. A threshold of 50% repigmentation at 6 months has been proposed for use in the context of clinical trials and a level of 25% repigmentation after 3 months has been reported to be indicative to patients of satisfactory results and reason to continue treatment.[27,31–34] Meaningful target repigmentation goals for the total body have been reported as lower than those for the face at 50% (vs 75%).[31] Overall, Canadian dermatologists recommend clinicians not adhere to a definitive threshold affirming that, in practice, any evidence of repigmentation (stippling and hyperpigmentation on margins of lesions) may be regarded by both clinicians and patients as meaningful and motivation to continue therapy. Maintenance treatment to prevent recurrence of depigmentation following successful repigmentation is also an important goal and there is data to suggest that continued treatment after repigmentation can reduce the risk of recurrence.[35] Rarely, in some exceptional cases (i.e, non-responsive, extensive vitiligo on visible areas), depigmentation may be considered as a treatment goal.[12]

Disease activity should be monitored during treatment and photography is useful to assess response.[12] While qualitative vitiligo-specific assessment tools such as vitiligo area scoring index (VASI), Vitiligo extent score (VES), vitiligo quality of life scale (VitiQOL), vitiligo impact scale (VIS), and vitiligo impact patient scale (VIP) have been used in clinical trials, they are neither essential nor practical in day-to-day clinical patient management. The patient experience and shared decision making should be critical to guide management of vitiligo.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

At the time of writing, there are no treatments approved in Canada for repigmentation of vitiligo lesions. In the absence of Canadian clinical practice guidelines, coupled with a paucity of well-designed clinical studies of vitiligo treatments, clinicians acknowledge that medications are prescribed arbitrarily on a trial-and-error basis.

The data show that people with vitiligo are underserved both in terms of healthcare and available treatments. Respondents in the VALIANT study reported they have not found treatment beneficial and felt that HCPs dismissed their vitiligo as a trivial or cosmetic condition.[9] Diagnosis is often delayed, with patients waiting a mean of 2.4 years before obtaining formal diagnosis. Previous misdiagnoses were reported by 44.9% of respondents, 44.6% said they had given up on finding an effective therapy and 56.7% reported being told by HCPs that vitiligo could not be treated. Of HCPs completing the survey, 26.3% said they did not believe an effective therapy for vitiligo exists. The most common reasons for treatment discontinuation according to HCPs were lack of treatment response (53.9%) and 68.4% of HCPs reported being frustrated by lack of effective treatments.

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While some publications have defined successful repigmentation as ≥75% improvement, a threshold of 50% repigmentation at 6 months has been proposed for use in the context of clinical trials and a level of 25% repigmentation after 3 months has been reported to be indicative to patients of satisfactory results and reason to continue treatment.[27,31–34]

In real-life practice experience, despite its physical and psychosocial burdens, vitiligo is one of the most challenging conditions to effectively treat with off-label therapies. It is well recognized amongst our colleagues that currently available off-label treatments demonstrate poor outcomes and/or poor tolerance, despite long treatment courses, leading to poor patient and clinician satisfaction. In experience, vitiligo patients are often the most adherent and compliant patients, indicating high motivations to pursue effective therapy due to disease impact.

The mainstay of first-line off label prescription therapy for vitiligo includes non-targeted topical corticosteroids (TCS) and topical calcineurin inhibitors (TCIs). Other than topical treatment efficacy failures, some require treatment discontinuation due to side effects. As vitiligo requires an extended treatment duration trial, particularly, use of TCS (available since the 1950's) has restricted use of applications to sensitive areas/areas of thin skin. Especially when escalated to higher strengths, TCS can come with increased risk of both local side effects, such as atrophy, striae, slowed wound healing, aggravation of secondary infection, steroid-induced acne, rosacea, perioral dermatitis, and pigmentary changes, tachyphylaxis, amongst others, and systemic side effects in more extreme cases such as those associated with Cushing syndrome. Common adverse events seen with TCIs, such as stinging, burning and irritation reported by some users can prohibit compliance and effective use for those with vitiligo. Many patients report not being able to tolerate the greasiness of steroid and topical tacrolimus ointments (e.g. stains clothes), which may decrease compliance (e.g. there is a need for better tolerated cream-based formulations).

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Based on the results of the TRuE-V studies, Canadian dermatologists concurred ruxolitinib cream could transform the treatment paradigm in vitiligo. Given its potential to simplify treatment and significantly improve outcomes for patients with vitiligo, dermatologists agreed ruxolitinib cream should be used as a first-line treatment for all patients ≥12 years old with vitiligo. Furthermore, ruxolitinib can be used on all areas of body skin (compared to topical steroids) and as monotherapy. It is the only targeted therapy for vitiligo that, through inhibition of the JAK-STAT pathway, blocks synthesis of IFN-gamma – the underlying pathological mechanism for melanocyte destruction and depigmentation.[28,58] While other treatments have anti-inflammatory effects, their spectrum of activity is less precisely targeted to the vitiligo underlying pathogenic pathway.

In a robust phase III clinical trial program that enrolled 674 patients, ruxolitinib cream as monotherapy has been demonstrated to provide clinically meaningful levels of repigmentation (F-VASI75 and F-VASI90) in significantly higher proportions of patients compared with vehicle after 24 weeks of continuous use,[13] with findings unprecedented compared to commonly used off-label therapies. Ruxolitinib was well tolerated with mild to moderate localized adverse effects and as such, has the potential for prolonged use as maintenance therapy. In the long term extension study (LTE), ruxolitinib cream demonstrated continuous improvements in patients through week 104. Overall favorable and well tolerated safety profiles (including low rates of application site events) are also demonstrated in long-term extension atopic dermatitis Phase III (True-AD1&2) controlled trials. Unlike topical calcineurin inhibitors (TCI) and topical corticosteroids (TCS) treatments, ruxolitinib cream does not appear to be associated with dose-limiting toxicities. Additionally, mean plasma concentrations of ruxolitinib in TRuE-V1 and TRuE-V2 were well below half-maximal concentrations for thrombopoietin-stimulated STAT3 phosphorylation, which is used as a proxy for determining JAK-related bone marrow myelosuppression.

Canadian experts agreed ruxolitinib cream could be appropriately used as monotherapy and potentially in combination with narrow band-ultraviolet B (NB-UVB) phototherapy for enhanced repigmentation effect. Although it was not evaluated in the pivotal trials TRuE-V1 and TRuE-V2, the combination of ruxolitinib cream and phototherapy was examined in a subset of patients in the long-term extension phase II study of ruxolitinib cream.

The expert panel also felt ruxolitinib cream has the potential to be used in combination with antioxidants for a two-pronged anti-pathogenic approach, targeting IFN-gamma and ROS. The panel concurred that there would be some patients with vitiligo who would not respond to treatment with ruxolitinib cream, although opinions were mixed at which point to recommend discontinuation of

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treatment. Based on clinical experience, some of the experts believed that patients with no evidence of repigmentation after 6 months of treatment would be unlikely to respond at all, while others believed signs of repigmentation could take as long as 18 months to emerge. All agreed that repigmentation is a lengthy process and that any signs of repigmentation are clinically meaningful, being indicative of melanocyte recovery. The clinicians also reported that patients may interpret any sign of repigmentation as reason for hope and are highly motivated to continue treatment. While the panel thought F-VASI75 at 24 weeks was an appropriate endpoint within a clinical trial setting, they indicated that in practice, it should not be used as a cut-off point as this would exclude patients who were achieving meaningful improvement.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Dermatologists agreed ruxolitinib cream should be used as a first-line treatment for all patients ≥12 years old with vitiligo. It is the only targeted therapy for vitiligo that, through inhibition of the JAK-STAT pathway, blocks synthesis of IFN-gamma – the underlying pathological mechanism for melanocyte destruction and depigmentation.[28,58] While other treatments have anti-inflammatory effects, their spectrum of activity is less precisely targeted to the vitiligo underlying pathogenic pathway.

In a robust phase III clinical trial program that enrolled 674 patients, ruxolitinib cream as monotherapy has been demonstrated to provide clinically meaningful levels of repigmentation (F-VASI75 and F-VASI90) in significantly higher proportions of patients compared with vehicle after 24 weeks of continuous use.[13] It was well tolerated with mild to moderate localized adverse effects and as such, has the potential for prolonged use as maintenance therapy. In the LTE, ruxolitinib cream demonstrated continuous improvements in patients through week 104. Unlike TCI and TCS treatments, ruxolitinib cream does not appear to be associated with dose-limiting toxicities.

Canadian experts agreed ruxolitinib cream could be appropriately used as monotherapy and potentially in combination with NB-UVB phototherapy for enhanced repigmentation effect. Although it was not evaluated in the pivotal trials TRuE-V1 and TRuE-V2 , the combination was examined in a subset of patients in the long-term extension phase II study of ruxolitinib cream. The expert panel also felt ruxolitinib cream has the potential to be used in combination with antioxidants for a two-pronged anti-pathogenic approach, targeting IFN-gamma and ROS.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

The clinicians reported that patients may interpret any sign of repigmentation as reason for hope and are highly motivated to continue treatment. While the panel thought F-VASI75 at 24 weeks was an appropriate endpoint within a clinical trial setting, they indicated that in practice, it should not be used as a cut-off point as this would exclude patients who were achieving meaningful improvement and experiencing improved psychosocial health. If patients have involvement in highly visible sites this also can be incredibly impactful with regards to repigmentation. It is worth noting that by the nature and pathophysiology of vitiligo, treatment response is not necessarily ‘rapid’ compared to other disease states such as psoriasis. Therefore, up to a 52 week or even longer reassessment period treatment response would be appropriate for re-evaluation.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

The panel concurred that there would be some patients with vitiligo who would not respond to treatment with ruxolitinib cream, although opinions were mixed at which point to recommend discontinuation of treatment. Based on clinical experience, some of the experts believed that patients with no evidence of repigmentation after 6 months of treatment would be unlikely to respond at all, while others believed signs of repigmentation could take as long as 18 months to emerge. All agreed that repigmentation is a lengthy process and that any signs of repigmentation are clinically meaningful, being indicative of melanocyte recovery.

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5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Patients with Vitiligo are expected to be diagnosed, treated and monitored by dermatologists, thus ruxolitinib cream for this indication is expected to be prescribed by dermatologists, although it should not be restricted as such.

In light of the substantial psychosocial burden of disease associated with vitiligo, it is essential that patients should have access to this effective, well-tolerated and easy-to-use therapy following its approval by Health Canada.

6. Additional Information

Call Outs from Clinician Group Members

"It is important that vitiligo not be trivialized and dismissed as a cosmetic complaint."

"While vitiligo is not painful and poses no immediate danger to life expectancy, it can be symptomatic and is considered by many patients to be unacceptably disfiguring and stigmatizing."

"(Compared to individuals without vitiligo), patients with vitiligo have a higher prevalence of anxiety, depression, and suicidal ideation/behaviour. Psychosocial burdens are greatest among women, younger patients, and those with visible or genital lesions and/or extensive body surface area involvement."

"Given that the contrast between darker pigmented and depigmented skin may be more pronounced, the impact of vitiligo disproportionately affects patients with skin of colour."

"High rates of stigmatization attached to vitiligo have been reported in South Asian cultures… some women spoke of family shame and being hidden away and isolated from their community."

"These findings have strong implications for Canada in which a growing proportion of the population has skin of colour. Canada is ranked among the most ethnically and culturally diverse countries in the world."

"Currently, there are no treatments approved in Canada for repigmentation of vitiligo lesions."

"Ruxolitinib cream 1.5% represents a significant addition to the treatment armamentarium and has the potential to improve quality of life for many patients who are currently under-served."

Introduction

Vitiligo is a chronic, autoimmune disorder of pigmentation in which progressive destruction of melanocytes manifests as milky-white, non-scaly lesions with distinct margins on the skin surface **(Figure 1).**[1–5]

Vitiligo is classified according to lesion distribution as non-segmental, segmental, and mixed vitiligo.[1,6] The most common form is non-segmental vitiligo, characterized by bilateral, symmetrical depigmented patches typically distributed in an acrofacial (hands, feet and face) pattern or over the entire body surface.[2] Loss of pigmentation in hairs on involved skin (i.e. leukotrichia) may develop over time.

Vitiligo is estimated to affect approximately 0.5 to 2% of the worldwide population.[2,7] Under-reporting and misdiagnosis is common, and the actual prevalence may be higher. [3] Of note, Statistics Canada has not undertaken an estimation of the prevalence of vitiligo in the Canadian population.

While vitiligo is not painful and poses no immediate danger to life expectancy, it can be symptomatic and is considered by many patients to be unacceptably disfiguring and stigmatizing.[8,9] As such, vitiligo carries a substantial burden of psychological distress – self-reported quality of life impairment was higher for patients with greater extent of disease (>5% body surface area), darker skin and lesions on visible areas including the face or hands. Patients' perception of changes in vitiligo was increased 7-fold when lesions were on the face, compared with other areas of the body.[10] Given that the contrast between darker pigmented and depigmented skin may be more pronounced, the impact of vitiligo disproportionately affects patients with skin of colour. [8,11]

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It is, therefore, important that vitiligo not be trivialized and dismissed as a cosmetic complaint. At the time of writing, there are no treatments approved in Canada for repigmentation of vitiligo lesions. In the absence of Canadian clinical practice guidelines, coupled with a paucity of well-designed clinical studies of vitiligo treatments, clinicians acknowledge that medications are prescribed arbitrarily on a trial-and-error basis.

Ruxolitinib 1.5% cream, a JAK 1/JAK 2 inhibitor, has recently been approved for the repigmentation of vitiligo in the United States and Europe based on the results of two phase III, randomized, placebo-controlled clinical trials (RCT).[12,13] Incyte Biosciences Canada is currently preparing a submission to Health Canada for market authorization of ruxolitinib cream for the treatment of vitiligo. Recently a group of Canadian dermatologists with expertise in the treatment of vitiligo met to review unmet needs for Canadian patients with vitiligo and determine the projected place in the vitiligo treatment paradigm for ruxolitinib cream.

The purpose of this review is to call attention to unmet needs in the management of vitiligo in Canada. It will argue that ruxolitinib cream 1.5% represents a significant addition to the treatment armamentarium and has the potential to improve quality of life for many patients who are currently under-served. This review will present data highlighting the psychosocial impact of vitiligo. It will also provide an overview of the pathophysiology of vitiligo, describe treatment options currently used by Canadian clinicians as well as present data from the phase III RCTs of ruxolitinib cream.

Psychosocial impact of vitiligo

Studies in people with vitiligo have observed that the prevalence of most psychosocial comorbidities is significantly higher compared to those without vitiligo as well as those with other dermatological disorders including acne, alopecia areata, psoriasis, atopic dermatitis and urticaria.[14,15] Psychosocial burdens are greatest among women, younger patients, and those with visible or genital lesions and/or extensive body surface area (BSA) involvement.[14] Patients with vitiligo have a higher prevalence of anxiety, depression, and suicidal ideation/behaviour.[14,16,17] In some communities, entire families may be affected by one member's vitiligo due to social stigma. [8,11]

The Vitiligo and Life Impact Among International Communities (VALIANT) study was a qualitative, cross-sectional population-based survey study recruiting participants from 17 countries in North America, South America, Asia, Europe, and Australia. In total, 3541 patients with vitiligo and 1203 healthcare providers (HCPs) were included in the analysis.[8,9] More than half of the patient respondents reported diagnosed mental health conditions including anxiety (28.8%), and depression (24.5%). Of these, 55% had moderate to severe depression.[8] Moderate to severe depressive symptoms affected high numbers of patients in Africa /Middle East regions (56.2%), Asia (61.9%), Europe (49.6%), and Canada (54.5%). The largest depressive subgroup was based in India (89.4%). Quality of life (QoL) burden was more profound for patients with darker skin tones (Fitzpatrick skin types IV to VI), younger age, disease duration ≤2 years, affected BSA ≥5% and the presence of facial depigmentation (Bibeau 2023).

At least 40% of patients reported that vitiligo increased stress associated with daily living including choosing which clothes to wear, attending social activities, shaking hands and being intimate with their partner.[8] In the VALIANT study, at least 50% of respondents agreed with statements including: "People often avoid shaking my hand because of my vitiligo"; "My family and friends feel pity for me because of my vitiligo"; "My community has not fully accepted me due to my vitiligo"; "My vitiligo keeps me up at night causing me to have trouble sleeping"; "People in my family experience discrimination/judgement due to my vitiligo".

Vitiligo has been found to have a more negative impact in some cultures compared to others. Notably, high rates of stigmatization attached to vitiligo have been reported in South Asian cultures.[8,11,18] In a qualitative study of British women of South Asian descent living with vitiligo (n=7), experiences of stigmatization were perceived to be associated with cultural values related to appearance (considered disfigurement), social status and myths about vitiligo.[11] Some of the women spoke of family shame and literally being hidden away and isolated from their community. They reported that older generations particularly regard vitiligo as a stigma. The importance of appearance was most evident in the context of arranged marriage, which significantly affects the individual and their families. According to one of the study participants, "Once we had this huge argument…when my mum just said, well who's going to marry you with your skin like that, because a lot of arranged marriages are pretty much based on looks and status".

These findings have strong implications for Canada in which a growing proportion of the population has skin of colour. Canada is ranked among the most ethnically and culturally diverse countries in the world.[19] The 2021 census conducted by Statistics Canada

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reported 30% of the population identifies as non-white, from ethnic backgrounds including South Asian (7.1%), Indigenous (5%), Chinese (4.7%), Black (4.3%), and Filipino (2.6%).[20]

The data show that people with vitiligo are underserved both in terms of healthcare and available treatments. Respondents in the VALIANT study reported they have not found treatment beneficial and feeling that HCPs dismissed their vitiligo as a trivial or cosmetic condition.[9] Diagnosis is often delayed, with patients waiting a mean of 2.4 years before obtaining formal diagnosis. Previous misdiagnoses were reported by 44.9% of respondents, 44.6% said they had given up on finding an effective therapy and 56.7% reported being told by HCPs that vitiligo could not be treated. Of HCPs completing the survey, 26.3% said they did not believe an effective therapy for vitiligo exists. The most common reasons for treatment discontinuation according to HCPs were lack of treatment response (53.9%) and 68.4% of HCPs reported being frustrated by lack of effective treatments.

Pathophysiology of vitiligo: the role of the JAK-STAT pathway and IFN-gamma

During the past ten years, our understanding of the pathogenesis of vitiligo has advanced substantially.[3] Vitiligo is a complex condition with a multifactorial etiology including genetic and autoimmune/inflammatory responses, oxidative stress, and melanocyte dysfunction.[3,4,6,21–23] The pro-inflammatory cytokine IFN-gamma, which is mediated by the JAK-STAT pathway, plays a key role in the initiation, progression, and persistence of vitiligo **(Figure 2)**.[3]

Initiation

Impaired melanocytes in vitiligo have decreased adhesiveness and are more susceptible to oxidative stress which impairs the function of membrane lipids and cellular proteins. These stressed melanocytes secrete exosomes which activate an innate immune response bringing natural killer and ILC1 cells to the skin surface where they produce IFN-gamma.[24]

Progression

IFN-gamma is central to vitiligo pathogenesis, promoting autoreactive CD8+ T cell recruitment to the dermis and epidermis through a feedback loop. Once localized in the skin, CD8+ T cells generate more IFN-gamma. Disease progression is accelerated as IFN-gamma activates the JAK-STAT signalling pathway promoting transcription of IFN-gamma-inducible genes. JAK1 expression is more intense in skin tissue with vitiligo lesions compared to regular skin. IFN-gamma inhibits melanogenesis and induces melanocyte apoptosis.[24]

Maintenance

Established vitiligo is maintained through the melanocyte-reactive T_{RM} (resident memory) cells of the adaptive immune system. Regulatory T cells (Tregs) which suppress auto-immune response, are impaired and less abundant in vitiligo-affected skin.[24]

Vitiligo shares genetic loci with several other autoimmune disorders.[24] Consequently, patients with vitiligo are at a higher risk of comorbid autoimmune disorders including thyroid disease, type 1 diabetes mellitus, rheumatoid arthritis, pernicious anemia, and alopecia areata.[25,26]

To date, treatments for vitiligo have demonstrated limited efficacy and tolerability. Current therapeutic options, including topical and systemic corticosteroids and topical calcineurin inhibitors act non-specifically on immune/inflammatory pathways.[24]

Topical treatments

Therapy with topical corticosteroids (TCS) and calcineurin inhibitors (TCI) is currently used as first-line monotherapy for the treatment of any form of vitiligo.[28]

Topical corticosteroids

TCS such as betamethasone valerate, clobetasol propionate, mometasone furoate, and triamcinolone acetonide have multifactorial mechanisms of action, including anti-inflammatory, vasoconstrictive, anti-mitotic, and immunomodulatory effects. [36] TCS also act on DNA to increase anti-inflammatory genes and decrease expression of pro-inflammatory genes. TCS are considered more effective for stabilization than repigmentation, although robust evidence from clinical trials for the use of TCS in vitiligo is lacking to support

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this observation.[12] Most studies with TCS used potent to very potent corticosteroids once daily for 3 – 6 months.[28] Mild TCS are considered insufficiently potent to be effective for repigmentation. According to expert clinical experience, intermittent treatment (2 weeks on/2 weeks off) can reduce the frequency of local side effects associated with TCS such as skin atrophy, telangiectasia, hypertrichosis, acne, and striations, but may therefore be less effective in vitiligo compared to consistent daily application. TCS should be used with caution on sensitive areas such as the eyelids, face, and genitals. Systemic absorption can be a concern if TCS are used on large areas over prolonged periods of time. Limited duration of use precludes use of TCS as maintenance therapy

Topical calcineurin inhibitors

TCIs provide a broad spectrum of activity against proinflammatory cytokines, including IL-2, IL-3. IL-4, Il-5, INF-y and TNF-a.[37] TCI are used as first-line treatment for patients with limited involvement – especially for sensitive areas such as the face, neck, and body folds with thin skin.[28] While TCI may offer comparable efficacy to TCS, TCI may be less effective for use on extra-facial lesions. The safety profile of TCI may be more favourable than TCS in presenting reduced risk of skin atrophy and may therefore be useful when prolonged use of potent TCS is contraindicated.

Studies have shown TCI monotherapy induces ≥25% repigmentation in 55% of patients and ≥75% repigmentation in 18.1% after three months).[28,38]

Van Geel et al observe that combining TCI with ultraviolet (UV) light may be considered for optimal repigmentation, but caution that safety considerations must be assessed against the benefits. This is underscored by the language in the Protopic® Product Monograph (2022) stating “patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment”), although combined use of TCIs with phototherapy is not specifically contraindicated.[39] However, physicians should be aware, and patients should be informed of the official warning against the concomitant use of TCIs and intentional ultraviolet light exposure.

The most common side effects associated with TCIs include local reactions such as burning, pruritus and erythema, which can be significant limiting factors. While no association with systemic immunosuppression, infection or increased risk for malignancies has been noted in clinical vitiligo trials with TCI, higher risks have been observed in patients with other skin conditions such as atopic dermatitis.[12,40,41]

Anecdotal reports attest patients dislike the texture of TCI ointment deeming it aesthetically unattractive. This contributes to limited use at night and increased risk of discontinuation.

In Canada, TCIs are not covered for vitiligo by most provincial health insurance plans and are accessible only to patients with private insurance or those willing to pay out of pocket.

Phototherapy and other light therapy

Narrow Band-UVB phototherapy is preferred first-line therapy for widespread or rapidly progressing vitiligo.[28] NB-UVB (total body treatment) and excimer laser/lamp therapy (limited vitiligo) are the recommended forms of light treatment for patients with vitiligo. Early initiation of NB-UVB is encouraged because it has been shown in an RCT to effectively arrest disease activity and induce repigmentation.[28,42] Limitations include lack of effect at resistant sites such as fingers and toes, and areas with no melanocyte reservoir, often indicated by leukotrichia. [28] Common side effects include erythema, lentigines, UV burn, xerosis, and hyperpigmentation of normal skin, but no significant associations with basal or squamous cell carcinoma have been identified.

In Canada, access to phototherapy is limited by a small number of clinics which tend to be located only in large, urban centres.[43] The introduction of home phototherapy has potential to provide better access and save patients the inconvenience of multiple visits to phototherapy centres, but this option is not widely available to patients in Canada and not publicly covered by provincial/territorial public health insurance programs.

Unlike phototherapy for other dermatologic disorders, phototherapy for vitiligo typically requires a protracted treatment course of at least 6-12 months and many phototherapy centres will only treat vitiligo for 6 months at a time, often due to wait times.

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There are efficacy and safety data to support the use of clinic-based excimer laser/lamp therapy either alone or in combination with other therapies for the treatment of patients with vitiligo; however, this treatment modality is not widely available and also not covered publicly or privately, which can be cost restrictive.[28,44,45]

Systemic therapy

Use of systemic immunomodulators can be considered for patients with unstable or rapidly progressive vitiligo. Systemic therapies may include corticosteroids such as betamethasone or dexamethasone, given as oral mini pulse (OMP) twice weekly on 2 consecutive days per week for 3 months with a maximum of 6 months due to risk of adverse effects. Prednisone and prednisolone may also be considered.[28]

OMP has been shown to arrest disease activity in >80% of patients but does not often result in repigmentation unless combined with phototherapy.[28]

Patients need to be aware of potential adverse effects associated with short- and long-term OMP corticosteroids. These can include weight gain, insomnia, agitation, menstrual disturbances, hypertrichosis, immunosuppression, and growth inhibition in children.[28]

Immunomodulators (methotrexate, cyclosporine, azathioprine, minocycline) have been used in vitiligo although strong evidence for their efficacy and safety is lacking. TNF-alpha and IL-17 are not recommended for patients with vitiligo, but systemic Janus kinase (JAK) inhibitors are showing promise. [28]

Surgical therapy

Surgical interventions should be reserved for segmental vitiligo and NSV patients with localized, stable disease that has not responded to topical, systemic, or light therapy.[28] Surgical options for vitiligo include mini punch grafting, suction blister grafting, and cellular grafting. Each technique has benefits and drawbacks, but all are associated with some risk of relapse. Surgery for patients with vitiligo is not routinely conducted or available in Canada.

Depigmentation

Although monobenzyl ether of hydroquinone (MBEH) is approved for depigmentation therapy in the treatment of vitiligo, it should only be considered in people with extensive vitiligo on visible sites in whom the condition is having a negative psychological impact.[27] Even though MBEH is putatively irreversible, physicians and patients should be aware that 78% of patients may experience repigmentation following the procedure.[46]

Complementary and alternative (CAM) medicines

Treatment with antioxidants is believed to reduce excess production of the ROS thought to play an active role in the pathogenesis of vitiligo (Bergqvist).[24] Antioxidants including gingko biloba, alpha lipoic acid, panthotenic acid, vitamin C, Vitamin E, polypodium leucotomos and gliadin-protected superoxide dismutase (SOD) have been used alone and in combination with phototherapy with the goal of stabilization and repigmentation in vitiligo. Evidence of vitiligo improvement has been seen in studies of polypodium leucotomos and GP-SOD, however, the quality of evidence is poor.[28,47,48]

Ruxolitinib cream 1.5%

Ruxolitinib is a non-steroidal, anti-inflammatory, selective and potent JAK1 and JAK2 inhibitor (Howell 2019; Howell 2018; Lee 2016; Kim 2020; Covington 2020).[48–53] Ruxolitinib cream 1.5% is a topical formulation of ruxolitinib.

Ruxolitinib cream locally targets the pathogenic pathways that underlie vitiligo by disrupting IFN-gamma signalling though JAK1 and JAK2 inhibition and the STAT pathway **(figure 4)**.[49–54]

Ruxolitinib cream was evaluated as a treatment for vitiligo in two phase 3, double-blind vehicle-controlled trials (Topical Ruxolitinib Evaluation in Vitiligo Study [TRuE-V1 and TRuE-V2] in 674 patients ≥12 years with non-segmental vitiligo covering ≤10% of body area).[13] Patients were randomized 2:1 to apply ruxolitinib cream 1.5% or vehicle twice daily (bid) for 24 weeks after which all patients continued with ruxolitinib cream through Week 52. The primary endpoint was an improvement of at least 75% from baseline in facial vitiligo (F-VASI75) response at Week 24. There were five key secondary end points including at least 50% improvement in total body

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vitiligo (T-VASI50) and improved responses on the Vitiligo Noticeability Scale (VNS), a patient-reported outcome measure of vitiligo treatment response (Batchelor 2016).[55]

In TRuE-V1 29.8% patients achieved F-VASI75 response at Week 24 vs 7.4% in the vehicle group (RR 4.0; 95% CI 1.9–8.4; p<0.001).[13] In TRuE-V2, the percentages were 30.9% and 11.4% respectively (RR 2.7; 95% CI 1.5–4.9; p<0.001). F-VASI90 at Week 24 occurred in 34/221 (15.3%) patients in TRuE-V1 and 36/222 (16.3%) patients in TRuE-V2 compared with 2/109 (2.2%) and 1/109 (1.3%) with vehicle (RR 7.3, 95% CI 1.8to 29.5; p=0.004) and (RR 13.1; 95%CI 1.9–90.2; p=0.006) respectively. T-VASI50 at Week 24 was observed in 46/221 (20.6%) and 53/222 (23.9%) patients in the treatment arms vs 6/109 (5.1%) and 7/109 (6.8%) patients in the vehicle arms (RR 4.1, 95% CI 1.6 to 10.5; p=0.002) and (RR 3.5, 95% CI 1.7 to 7.5; p<0.001) in TRuE-V1 and True-V2 respectively. A significantly higher proportion of patients in the active treatment arm reports VNS scores of 4 and 5 ("a lot less noticeable" and "no longer noticeable") at Week 24. A complete presentation of the primary and secondary endpoints appears on **Table 1** and successive improvements in one patient's facial vitiligo is shown in **Figure 5.**

In the TRuE-V studies, treatment with ruxolitinib cream 1.5% resulted in repigmentation in all body regions including challenging areas e.g., hands and feet.[56]

By Week 52, T-VASI75 was achieved by approximately 50% of patients who applied ruxolitinib cream from Day 1, and in approximately 30% of the patients who had crossed over to treatment from the vehicle arm at Week 24 (Rosmarin 2022).[13] Responses did not plateau and patients continued to experience increasing improvements from baseline at Week 52.

The most common adverse events were acne (6.3%), nasopharyngitis (5.4%) and application site pruritus (5.4%).[13] All events were mild and moderate in severity and comparable to placebo. No serious treatment emergent adverse events (TEAEs) emerged throughout 2 years of treatment, which included a long-term extension (LTE) of 52 weeks to Week 104.

While directional improvements in the Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI) (administered to patients <16 years old) were observed, the differences were not statistically significant.[13] However, the DLQI and CDLQI include scores for itch and pain which may decrease their sensitivity as patient scoring systems for vitiligo. In clinical practice, it may be assumed that repigmentation correlates with improved QoL, but clinicians acknowledge that vitiligo-specific aspects of quality of life such as social ostracization are difficult to quantify with standard quality of life measurements.

In the LTE phase, continued improvement in F-VASI75 responses was observed with ruxolitinib cream to Week 104 in the cohort of patients who continued ruxolitinib cream.[13] The cohort of patients achieving ≥F-VASI90 in the parent studies were re-randomized to receive either vehicle (ruxolitinib withdrawal) or continue with ruxolitinib cream. The probability of maintaining repigmentation was higher in patients who applied ruxolitinib cream continuously for the duration of the study vs. those who were randomised to vehicle. In this cohort, patients who lost response after treatment discontinuation were able to regain response following re-treatment with ruxolitinib cream. The median time to recaptured response was approximately 12 weeks for F-VASI75 and 15 weeks for F-VASI90 (Harris 2023).[57] Canadian experts commented that the data showing that more patients achieved F-VASI75 at Week 52 (≈ 50%) vs Week 24 (≈ 30%) in those who applied ruxolitinib cream continuously from Day 1) suggested non-responders after 24 weeks may nonetheless obtain repigmentation if they persist with treatment for longer periods.

Conclusion

Vitiligo should not be dismissed as a trivial cosmetic complaint. Patients find it unacceptably disfiguring and it has been shown to be linked with significant psychological distress. Due to greater contrast between darker skin tones and areas of depigmentation, the effects of vitiligo on mental health disproportionately affect patients with skin of colour.[8] Vitiligo may be particularly challenging for those from cultural communities who have stigmatized the condition. In Canada, the non-white population, including people from indigenous, Indian, Southeast Asian, and Black ethnic backgrounds, accounts for 30% of the total population and continues to grow.[20]

Treatments for dyspigmentation and vitiligo are limited in Canada, especially when compared to the numerous reimbursed treatment options for disorders affecting lighter skin such as rosacea. There is a clear ethical imperative to address this disparity in access to treatment for people of racialized backgrounds.

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Patients living with vitiligo in Canada are under-served. Vitiligo remains poorly understood, and under-diagnosed, although experts agreed this could be rectified through educational initiatives to help HCPs recognize the clinical features of vitiligo. Diagnosis of vitiligo is relatively straightforward with no companion diagnostic test required. There are currently no treatments approved to treat vitiligo in Canada. Treatments are currently prescribed off label and often on a haphazard basis of trial and error. Current treatments are also considered unsatisfactory by patients and physicians. Repigmentation efficacy is disappointing and the repigmentation process itself is lengthy, varying according to body area location.[32] Distal areas such as hands and feet tend to be more resistant to repigmentation as they have a lower density of hair follicles.[59] Concerns with over-exposure resulting from prolonged treatment are associated with TCS and phototherapy. Access to TCI and phototherapy is also limited by lack of reimbursement and clinics.

Ruxolitinib cream 1.5% is the first topical treatment to target the JAK-STAT pathway, which plays a key role, in the pathogenesis of vitiligo. It was demonstrated to induce significant levels of repigmentation in two phase III randomized clinical trials and was well tolerated over two years of continuous use.

In light of the substantial psychosocial burden of disease associated with vitiligo, it is essential that patients should have access to this effective, well-tolerated and easy-to-use therapy following its approval by Health Canada.

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TABLES AND FIGURES

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Table 1. Primary and secondary key efficacy end points at Week 24 in TRuE V1 and TRuE-V2

Table 2. Primary and Key Secondary Efficacy End Points (Double-Blind Period; Modified Intention-to-Treat Population).*

End Point	TRuE-V1				TRuE-V2			
	Vehicle (N = 109)	1.5% Ruxolitinib Cream (N = 221)	Relative Risk (95% CI)	P Value	Vehicle (N = 109)	1.5% Ruxolitinib Cream (N = 222)	Relative Risk (95% CI)	P Value
Primary end point								
F-VASI75 response at wk 24 — % (95% CI)†	7.4 (2.2 to 12.6)	29.8 (23.5 to 36.1)	4.0 (1.9 to 8.4)	<0.001	11.4 (5.2 to 17.7)	30.9 (24.5 to 37.3)	2.7 (1.5 to 4.9)	<0.001
Key secondary end points								
F-VASI50 response at wk 24 — % (95% CI)†	16.9 (9.3 to 24.6)	51.2 (44.4 to 58.0)	3.0 (1.9 to 4.8)	<0.001	20.9 (12.9 to 28.9)	51.4 (44.6 to 58.3)	2.5 (1.6 to 3.7)	<0.001
F-VASI90 response at wk 24 — % (95% CI)†	2.2 (0 to 5.1)	15.3 (10.4 to 20.2)	7.3 (1.8 to 29.5)	0.004	1.3 (0 to 3.8)	16.3 (11.2 to 21.5)	13.1 (1.9 to 90.2)	0.006
T-VASI50 response at wk 24 — % (95% CI)†	5.1 (0.6 to 9.7)	20.6 (15.2 to 26.0)	4.1 (1.6 to 10.5)	0.002	6.8 (1.9 to 11.7)	23.9 (18.1 to 29.8)	3.5 (1.7 to 7.5)	<0.001
VNS response at wk 24 — % (95% CI)†‡	3.3 (0 to 6.9)	24.5 (18.5 to 30.4)	7.5 (2.4 to 23.5)	<0.001	4.9 (0.7 to 9.2)	20.5 (14.9 to 26.1)	4.2 (1.7 to 10.2)	0.001
LSM percentage change from baseline in facial BSA affected by vitiligo at wk 24 (95% CI)§	−9.5 (−15.9 to −3.2)	−28.9 (−33.2 to −24.5)	NA	<0.001	−7.0 (−14.5 to 0.5)	−26.4 (−31.5 to −21.4)	NA	<0.001

* F-VASI50 denotes a decrease (improvement) of at least 50% in the F-VASI from baseline, F-VASI75 a decrease of at least 75% in the F-VASI from baseline, F-VASI90 a decrease of at least 90% in the F-VASI from baseline, NA not applicable, and T-VASI50 a decrease of at least 50% in the T-VASI from baseline.
† Multiple imputation was applied to account for missing values.
‡ A Vitiligo Noticeability Scale (VNS) response was defined as a rating of a lot less noticeable or no longer noticeable.
§ An analysis of covariance model was applied to determine least-squares mean (LSM) and P value.

Rosmarin D, et al. *N Engl J Med* 2022; 387(16):1445-1455.

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Figure 1. Depigmented vitiligo lesions

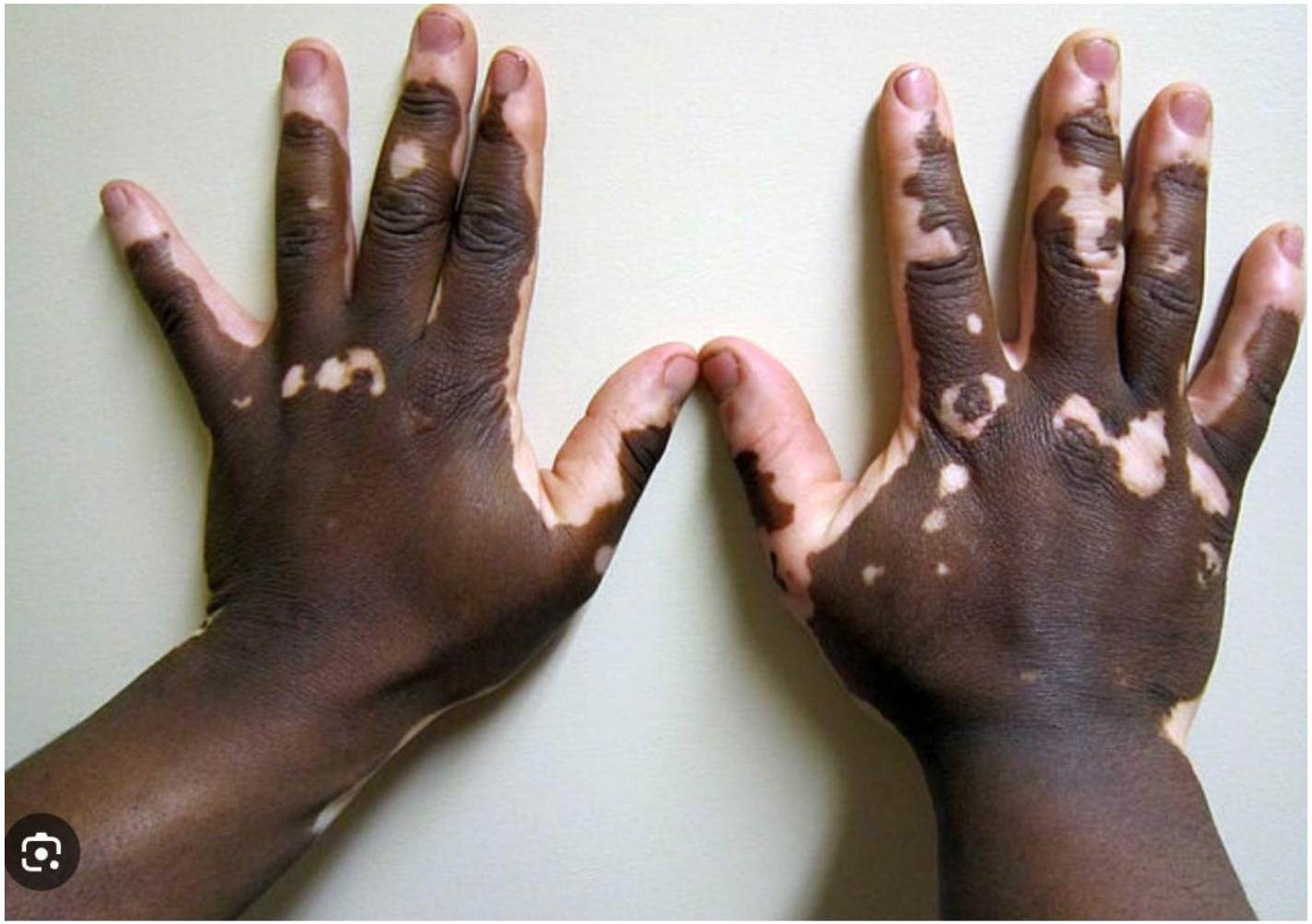

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Figure 2. Pathogenesis of vitiligo. A. Initiation: Melanocytes in patients with vitiligo have decreased adhesiveness and are more susceptible to oxidative stress. Oxidative stress impairs the function of membrane lipids and cellular proteins and causes melanocytes to secrete exosomes which contain melanocyte-specific antigens leading to T-cell homing to the skin. In response to oxidative stress, NK and ILC1 cells produce IFN-gamma that induces the expression of chemokines in melanocytes. B. Progression: CD8+ T cells from vitiligo lesions produce cytokines including IFN-gamma which binds to its receptor and activates the JAK-STAT pathway. Resultant chemokine secretion promotes bulk recruitment of melanocyte specific CD8+ T cells to the skin increasing inflammation through a positive feedback loop and inducing melanocyte apoptosis. C. Maintenance: Melanocyte-reactive T_{RM} cells maintain vitiligo disease activity and remain long-lived in the skin through IL-15-dependent signalling.

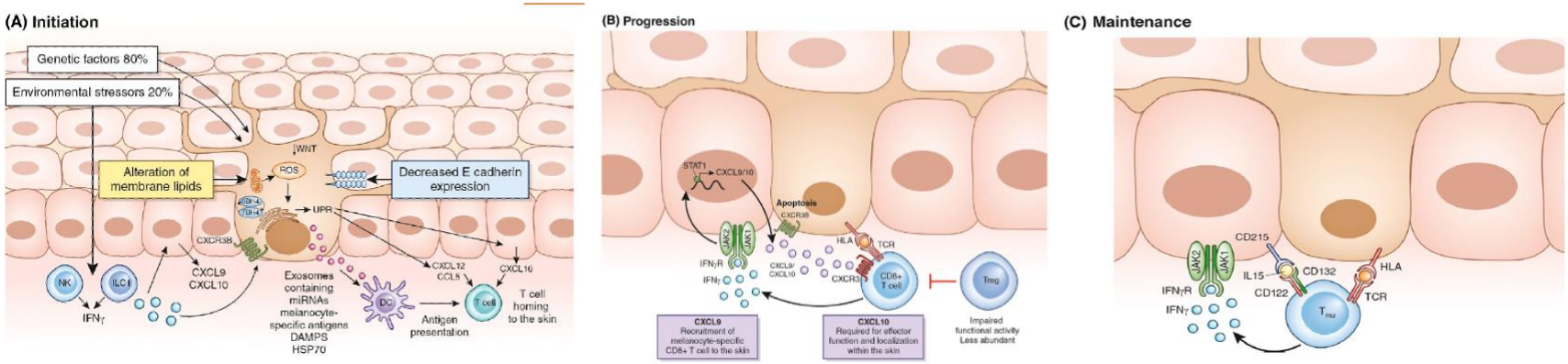

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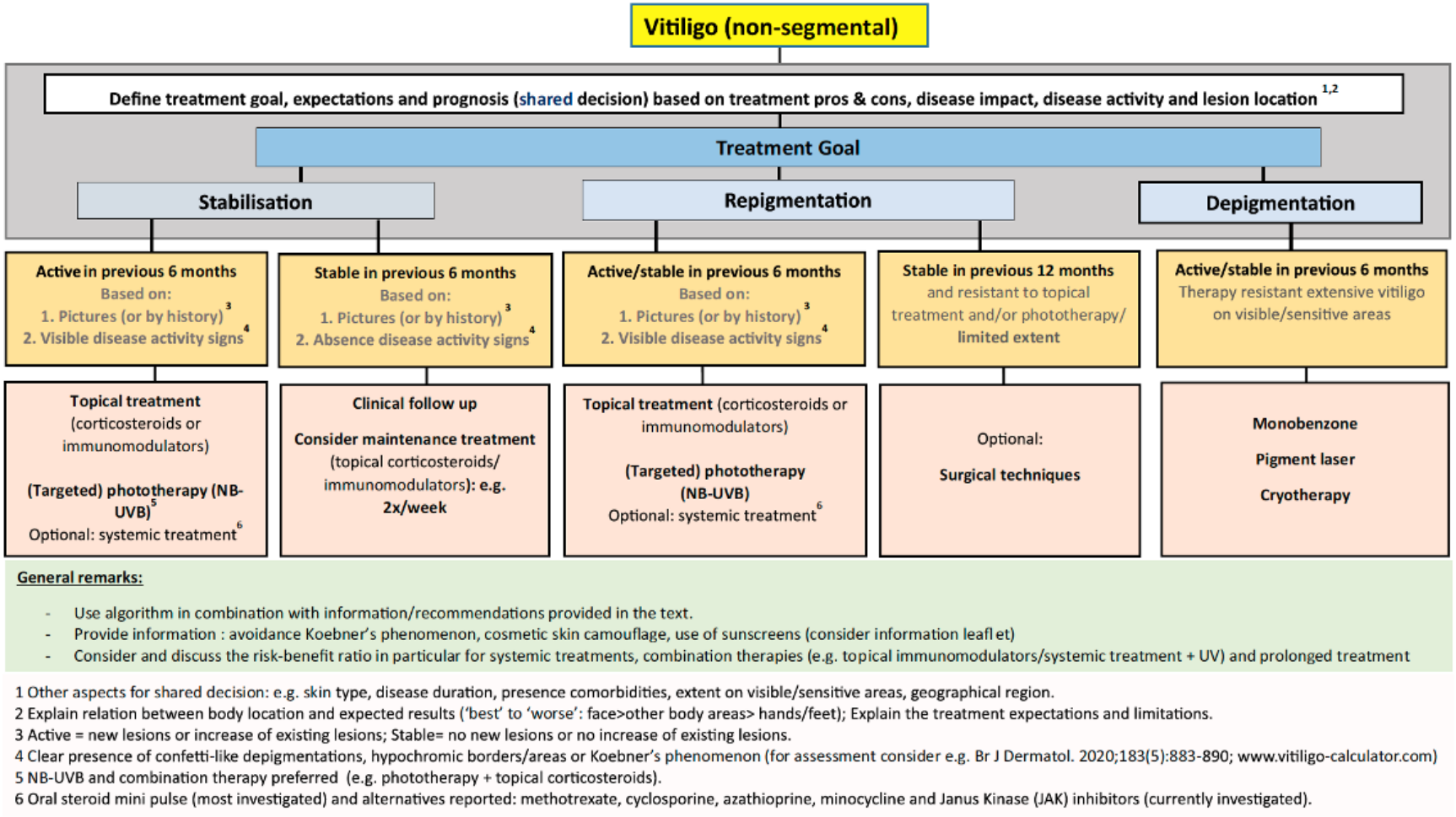
Figure 3. Recommendation for the management of non-segmental vitiligo



Reproduced with permission from van Geel N, et al. *J Eur Acad Dermatol Venereol* 2023;37:2173–2184

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Figure 4: Ruxolitinib mechanism of action: selective JAK 1/JAK2 inhibition (Smith et al.)

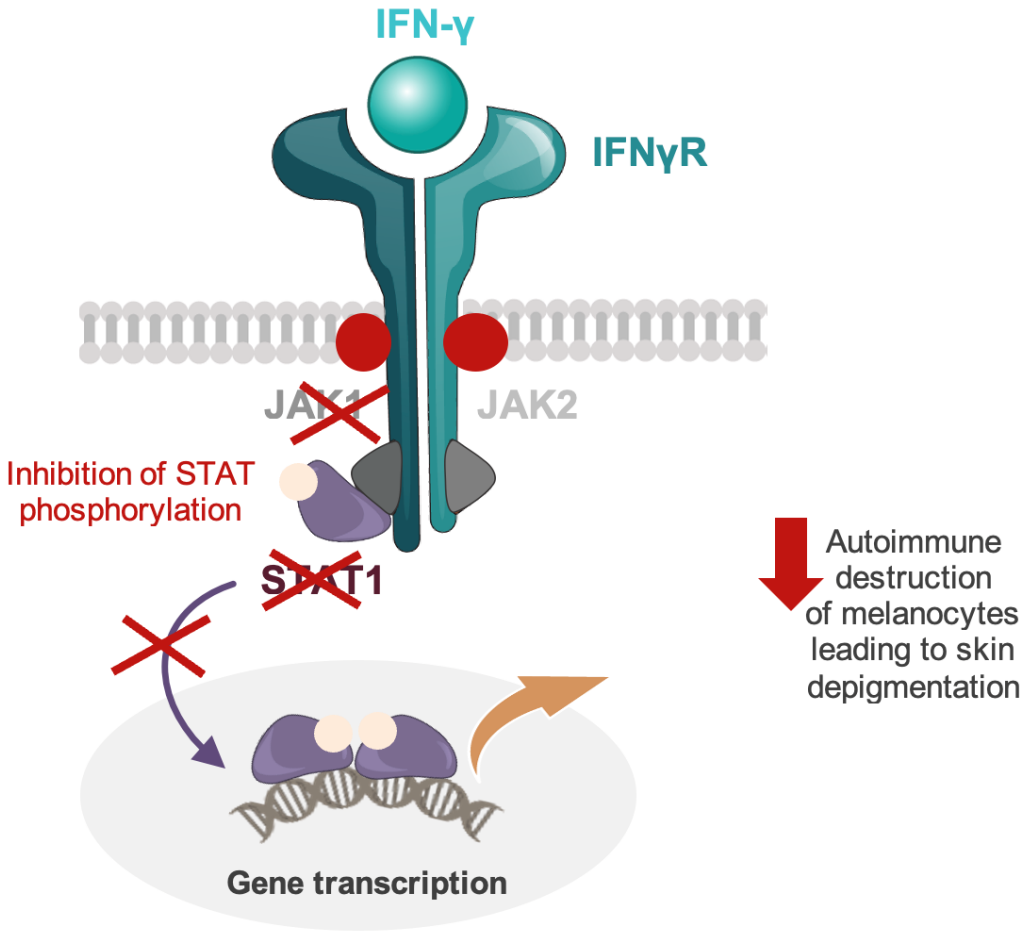

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Figure 5. F-VASI 90 response achieved at Week 24 after application of ruxolitinib cream 1.5% bid. The patient is a 56-year-old man with disease duration of 21.6 years

Reproduced with permission from Rosmarin D. *N Engl J Med*. 2022;387:1445–1455.

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7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No. This was written by clinicians with a clinical and academic interest in vitiligo, based on the resources as referenced.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

N/A

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Rachel Asiniwasis MD MSHS FRCPC FAAD
Position: 1. CDA Pharmacy and Therapeutics Advisory Board Member, 2. Saskatchewan Dermatology Association
Date: 11-10-2024

X **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Incyte		X Vitiligo Advisory		
N/A (No other company makes on-label Vitiligo treatments)				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: David N. Adam MD FRCPC
Position: Dermatologist and President , Dermatology Association of Ontario
Date: 13-10-2024

x I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Incyte		x		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Maxwell Sauder
Position: Dermatologist and Secretary, Dermatology Association of Ontario
Date: 12 Oct 2024

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Incyte		X		
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Jensen Yeung
Position :Dermatologist, Member of the Dermatology Association of Ontario
Date: 14 Oct 2024

x I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Incyte			x	
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Reetesh Bose
Position: Dermatologist, Secretary Ottawa Dermatology Society, EDI committee member Canadian Dermatology Association
Date: 14-10-2024

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Incyte		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Benjamin Barankin, MD, FRCPC
Position: Dermatologist, Member of the Dermatology Association of Ontario
Date: 16-10-2024

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
INCYTE	X			
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

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Declaration for Clinician 7

Name: Patricia Ting, MSc, MD, FRCPC, DABD
Position: Dermatologist, CDA Pharmacy and Therapeutics Advisory Board Member
Date: 23-10-2024

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 7

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Incyte	X			
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Sam Hanna, MD, DABD
Position: Dermatologist, Member of the Dermatology Association of Ontario
Date: 19-10-2024

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Incyte			X	
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

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Clinician Group Input

CADTH Project Number: **SR0835-000**
Generic Drug Name (Brand Name): **Ruxolitinib**
Indication: **Nonsegmental vitiligo**
Name of Clinician Group: South Western Ontario Dermatologists Group
Authors of Submission: Dr. Ajith Cy, Dr. Cathryn Sibbald, Dr. Jeff Cowger, Dr. Dusan Sajic

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

The purpose of our group of dermatologists is to engage and learn from each other through interactive discussions of topics of clinical interest, real world cases and treatments. We share real world cases, challenging clinical scenarios, and discuss optimal treatment strategies. These regular meetings have provided us significant learning, and more importantly, optimized patient care.

2. Information Gathering

Please describe how you gathered the information included in the submission.

By reviewing the published articles pertaining to vitiligo, treatments for vitiligo, and topical ruxolitinib in vitiligo

3. Current Treatments and Treatment Goals

Please describe the current treatment paradigm for the disease.

- Focus on the Canadian context.
- Please include drug and non-drug treatments.
- Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Treatments available through special access programs are relevant. Are such treatments supported by clinical practice guidelines?
- Do current treatments modify the underlying disease mechanism? Target symptoms?
- What are the most important goals that an ideal treatment would address?
- **Examples:** Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Vitiligo is characterized by chronic depigmented patches due to selective loss of melanocytes. The estimated prevalence of vitiligo is 0.5 to 2% worldwide and, is often associated with profound psychological distress, in addition to its significant cosmetic effect.

Current vitiligo treatments in Canada include primarily topical agents with the most common being topical corticosteroids and calcineurin inhibitors. This may be followed by Phototherapy with Narrow Band Ultra Violet B (NBUVB) where accessible. However, phototherapy is not widely available in many provinces in

Canada. Systemic agents for vitiligo are not widely prescribed in Canada. Systemic agents used include prednisone, oral dexamethasone as oral mini pulse therapy, followed by other systemic immunosuppressants such as methotrexate and cyclosporine. The current treatment landscape is not adequate for many patients resulting in substandard outcomes and patient care. These leaves some patients to resort to measures like using cosmetic camouflage or tattooing to cover the disease, especially in special sites like the face and hands. Inability to adequately treat the disease is a significant mental health stress for many patients. Various studies have demonstrated the impact vitiligo has on patient's general health and especially mental health. Many patients make life altering decisions for their personal life, career, or both based on the severity and location of the disease. Additionally, given the lack of effective treatments available in Canada, some patients will purchase products abroad which are often laced with ingredients that are associated with adverse effects.

Current Treatment Options:

Current treatment modalities in Canada are being used off-label, as there have been no approved pharmacologic agents for Vitiligo until October 2024. The 3 main goals of treatment include:

1. Attaining stability of disease process and thereby limit spread of disease by using topical and /or systemic immunosuppressants / immunomodulators
2. Inducing re-pigmentation by stimulating melanogenesis (phototherapy, afamelanotide, and surgical treatments)
3. Reducing intrinsic stress on melanocytes by use of oral antioxidants

Most treatment agents provide varying levels of impact in one or more of the above targets and current treatment modalities can broadly be classified into medical (topical & systemic agents), phototherapy, laser and surgical methods.

Topical Medications

Topical corticosteroids

Corticosteroids are the most commonly used topical medications for vitiligo worldwide. Corticosteroids act by blocking cytotoxic T-lymphocyte activation. Among the various topical corticosteroids used, the literature has shown that mometasone has similar efficacy to clobetasol propionate but with the advantage of fewer side effects and a better safety profile in both the pediatric and adult population.

Topical Calcineurin Inhibitors (TCI)

TCIs, such as Tacrolimus, play an important role in the treatment of vitiligo by exerting an immunomodulatory effect through the blockade IL-2 and IFN- γ, thereby inhibiting cytotoxic T-cells. Tacrolimus also helps in promoting melanogenesis by reducing systemic

anti-oxidant stress. Tacrolimus 0.1% ointment has shown superior results to Pimecrolimus 1% cream. TCIs are effective and safe, may be used long term and work best in the management of vitiligo when used in combination with other modalities of treatment.

Latanoprost

When originally used as a treatment for glaucoma, topical prostaglandin analogues caused hyperpigmentation as a side effect which prompted studies in vitiligo. Its mechanism of action involves the induction of tyrosinase and an upregulation of melanocyte proliferation. Latanoprost has shown statistically superior results to placebo on both facial and non-facial skin but is likely more effective on the face and is safe for periocular vitiligo. Similar to tacrolimus, the cost and off-label prescribing present barriers to its use in real world.

Phototherapy

Phototherapy is a first-line treatment modality for those with extensive vitiligo. Narrowband UVB (NBUVB) has mostly replaced PUVA as the primary phototherapy modality. Its mechanism of action is to induce tyrosinase enzyme and it has shown superior efficacy than PUVA in achieving disease stability and repigmentation. Advantages include the lack of immunosuppression and good efficacy. However, the significant time commitment (2-3 times weekly at a clinic) and lack of access in Canada poses significant barriers to its use.

Lasers

An FDA-approved laser used for treating vitiligo is the monochromatic excimer light (MEL) 308nm laser with peer-reviewed results suggesting that the face responds better than other regions. Compared to NBUVB, the MEL laser may deliver superior clinical outcomes, but this treatment modality is more expensive and challenging to use for those with extensive vitiligo. Another laser that has been tested for vitiligo is the Helium-neon laser (632.8nm). In use for head and neck segmental vitiligo, the He-Ne laser has shown greater than 50% repigmentation in 60% of patients. However, there is very limited access in Canada.

Systemic Treatments

Systemic Corticosteroids

For patients who have failed topicals and NBUVB, systemic immunosuppressants may be the next option to consider. The primary aim of systemic immunosuppressants is to attain disease stability (i.e. no newer / progressing lesions), and also to help with repigmentation. With this in mind, the most commonly used agents are systemic corticosteroids. Longer acting systemic corticosteroids used at a lower dose are commonly referred to as oral mini pulse (OMP) treatment, which involves giving either oral dexamethasone 4mg or oral betamethasone 2.5mg or 5mg on 2 consecutive days in a week for up to 6 months. Several studies have shown the arresting of disease activity with OMP treatment in up to 90% of patients with recurrence upon discontinuation of the OMP regimen being noted in about 13% of patients. Compared to regular-dosed prednisone, much of the peer-reviewed literature suggests that OMP is better tolerated for arresting progressive unstable vitiligo

with minimal adverse events. Adverse events reported were similar to those seen with corticosteroids including weight gain, acneiform eruptions, and lethargy.

Cyclosporine

As interleukin 2 is a major cytokine for recruitment of T-Cells, cyclosporine can be a therapeutic choice in the treatment of vitiligo for achieving stability in progressive and unstable disease. Taneja et al showed a significant improvement in the vitiligo area severity index (VASI) score with the use of cyclosporine at 3mg/kg/day for 3 months. Significant side effects are well recognized with the use of cyclosporine, including hypertension, hyperlipidemia, and renal compromise, resulting in significant morbidity in patients, requiring regular monitoring, and recommendations to limit its use to 2 years.

Methotrexate

In some patients with extensive disease that tends to follow a progressive unstable course over many years, immunosuppressants may be needed long term. In these patients, methotrexate is an option. A comparative study of low-dose methotrexate (10mg weekly) demonstrated that it was well tolerated by patients and resulted in comparable outcomes to OMP with betamethasone. Methotrexate can have a longer onset to efficacy and is also associated with significant side effects including bone marrow toxicity and liver fibrosis if used long term and in the setting of some concurrent medications or liver insults. Its use requires regular bloodwork and liver scans once a threshold exposure is met.

Surgical Methods

Surgical treatments in vitiligo involve reintroducing melanocytes harvested from pigmented skin of the same person. One of the most important aspects of utilizing surgical methods for the treatment of vitiligo is appropriate patient selection, with the specific aim of ensuring that the disease is stable for at least 1 year (i.e. no new or progressive lesions in the past 1-year period). In unstable / progressive disease, surgery may cause Koebnerization and induce new lesions. Two categories of surgical treatments are tissue grafting and cellular grafting with cellular grafting providing significantly better patient outcomes but requiring more expertise, and laboratory support.

Depigmenting Treatment:

In patients with extensive vitiligo not responding to treatment, the option of depigmenting remaining normal skin may give better cosmetic outcomes. Monobenzyl ether of hydroquinone (MBEH) 20% is a FDA-approved depigmenting agent for vitiligo. The mechanism of action involved with MBEH involves the induction of lysosomal degradation and oxidative stress of melanocytes leading to immune destruction of the remaining melanocytes. The possible adverse events associated with the use of MBEH are rare but can include conjunctival melanosis and irritant contact dermatitis.

Emerging treatment options in Vitiligo:

Newer options currently in development include targeted immunotherapeutic agents such as JAK / STAT inhibitors, and newer phototherapy and laser options which will be reviewed below.

JAK Inhibitors:

Janus kinases (JAKs) are a family of 4 proteins: JAK1, JAK2, JAK3, and TYK2. These proteins cause immunomodulation by activation of intracytoplasmic transcription factors called signal transducer and activator of transcription (STAT). Once activated, they dimerize and move to the nucleus where they modulate gene expression. Laboratory work in mice with vitiligo has helped illuminate the crucial role of the JAK/STAT pathway in the pathogenesis of vitiligo.

JAK inhibitors (JAKI) are broadly classified into first and second generation agents. First generation JAK inhibitors block more than 1 or all of the Janus kinase family of proteins and have been the agents used with greatest frequency for vitiligo to date.

Tofacitinib

Tofacitinib is a JAK 1/3 inhibitor. Both systemic and topical Tofacitinib have been used in vitiligo. In various case series', the use of oral tofacitinib at doses of 5mg po OD – BID for 3 to 6 months has demonstrated significant improvement in repigmentation. Topical tofacitinib citrate 2% given for facial vitiligo achieved a mean improvement of 70% based on the difference in mean facial VASI at baseline and at follow-up (mean follow-up of 112 days).

Ruxolitinib

Topical ruxolitinib 1.5% cream has shown great response in vitiligo, especially for facial vitiligo. In an open-label trial, a mean improvement of 92% was observed in facial lesions calculated as improvement in overall VASI for enrolled patients (n = 8) at week 52 from baseline. Transient acneiform eruption, worsening of acne, and mild erythema were the most commonly reported side effects.

It is worth noting that there are better repigmentation rates in patients who received both JAK inhibitors and NBUVB at sites of chronic UV exposure such as the face and extensor forearms. Clinical trials examining this are ongoing with JAK inhibitors and NBUVB.

Alpha-melanocyte-stimulating hormone (α-MSH) analogue

Afamelanotide is a synthetic analogue of alpha-melanocyte-stimulating hormone (α-MSH) which induces melanogenesis. A clinical trial involving the use of afamelanotide with NBUVB vs NBUVB alone has shown that afamelanotide with NBUVB had superior repigmentation rates.

Basic Fibroblast Growth Factor (b-FGF)

In vitro studies have shown that b-FGF is capable of stimulating melanogenesis and a recent phase IV double blind randomized control trial has shown b-FGF with NBUVB to be superior to NBUVB alone with a very good tolerability profile.

Bioskin evolution micro phototherapy

Bioskin evolution is a targeted 311-nm narrowband micro phototherapy device that is suitable for lesions involving <10% body surface area (BSA). The advantages of this device are that it can be used in patients with limited disease including sensitive areas such as eyelid skin and it is more convenient than having to expose the whole body to NBUVB treatment.

311nm Titanium: Sapphire laser (TSL)

A 311nm TSL for vitiligo along with topical tacrolimus 0.1% ointment has shown significant benefit to complete repigmentation in 79% of patients. Results from TSL were similar to 308nm excimer laser (EL), but with better safety profile.

UVA-1 lasers

The Laser Alba 355®, a UVA-1 laser with 355nm spectrum has shown successful repigmentation in up to 75% patients. Utilization of a UVA-1 laser works well due to its deeper penetration and immunomodulatory properties.

Oral Antioxidants

Oral antioxidants are now part of first line management of vitiligo, as they may help to decrease the oxidant stress on melanocytes. Oral gingo biloba, polypodium leucotomus, vitamin E, vitamin C, alpha lipoic acid have all been shown to promote repigmentation.

Future Treatment Prospects

Programmed cell death-1 ligand (PDL-1) is currently being studied for psoriasis and inflammatory bowel disease and might be beneficial for vitiligo as well, as it helps to maintain immune balance.

IL-15 causes oxidative stress mediated destruction of melanocytes; therefore inhibiting IL-15 may be explored as a future potential mechanism of action in the treatment of vitiligo. Inducing mi-RNA via a miR-155 agonist has also shown to improve melanocyte regeneration. Hence mi-RNA induction may be a future treatment option for vitiligo.

Conclusion

The treatment of vitiligo cannot be addressed as one size fits all, but must be individualized to address patient expectations, impact of disease, and compliance. The effective treatment of vitiligo requires a multimodal approach including minimizing oxidative stress with anti-oxidants, implementing topical or systemic immunomodulatory agents, and initiating treatment modalities to regenerate melanocyte function by phototherapy and surgical methods. Future treatments, especially those involving the JAK-STAT pathway, hold promising potential.

There were no Health Canada approved treatments for vitiligo until the recently approved Ruxolitinib 1.5% cream. The current treatment landscape in Canada of off label medications does not adequately address the patient suffering. The majority of currently available treatments take time, and mostly provide mild to moderate success rates at best. This has resulted in many Canadian dermatologist no longer accepting consults for vitiligo. However, with the approval of Ruxolitinib and the promise of new and emerging medications there is renewed interest in treatment of vitiligo in Canada.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Please describe goals (needs) that are not being met by currently available treatments. Examples of unmet needs:

- Not all patients respond to available treatments
- Patients become refractory to current treatment options
- No treatments are available to reverse the course of disease
- No treatments are available to address key outcomes
- Treatments are needed that are better tolerated
- Treatments are needed to improve compliance
- Formulations are needed to improve convenience

Please describe limitations associated with current treatments (e.g., adverse events, administration, etc., if applicable).

The majority of available treatments do not adequately address the complete pathophysiology of vitiligo. Only a minority of patients respond adequately to the currently available treatment options, and even then, the onset of effect is quite long, leading to significant time and financial constraints to the patient.
The limitations of current treatment including topical corticosteroids are its inability to be used for long term treatment due to the risk of steroid atrophy and tachyphylaxis. Most Canadian dermatologists will use topical corticosteroids alternating with calcineurin inhibitors to minimize the long term risks of topical corticosteroid. Public coverage plans do not currently reimburse /cover access for topical calcineurin inhibitors.
Even if successfully treated to patient's satisfaction, there is no current treatment that reverses the disease process, and at least 40% of patients are prone to recurrence of the disease.
These reasons highlight a necessity for patients suffering from vitiligo to have access to new treatments that may have better efficacy and are safe for long term use including the recently approved ruxolitinib. >

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?
Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?
Would the drug under review be reserved for patients who are intolerant to other treatments or in whom other treatments are contraindicated?
Is the drug under review expected to cause a shift in the current treatment paradigm?
Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with drug under review. Please provide a rationale for your perspective.

Ruxolitinib 1.5% cream acts to provide repigmentation in vitiligo by inhibiting the deleterious effects of CD8+T cells. Depigmentation that characterizes vitiligo is caused by progressive melanocyte destruction. Melanocyte-specific $CD8^+$ T cells predominantly infiltrate the dermal-epidermal junction adjacent to melanocytes in the border of depigmented lesions and participate in the elimination and destruction of melanocytes. Interferon gamma (IFN-γ) is the key cytokine produced by $CD8^+$ T cells, that plays a central role in the pathogenesis of the disease. The expression of IFN-γ-induced genes including the T cell chemokine receptor (CXCR3) and its multiple ligands, CXCL9, CXCL10, and CXCL11, is upregulated in depigmented skin lesions.

Based on multiple studies conducted in mouse vitiligo models, the IFN-γ-chemokine axis, with its associated positive feedback loop, has been identified as a potential pathway in the initiation and progression of vitiligo. Autoreactive $CD8^+$ T cells produce IFN-γ, which promotes depigmentation. IFN-γ simultaneously stimulates keratinocytes to express CXCR3, which binds to CXCL9 to recruit more melanocyte-reactive T cells. In addition, CXCL10 recruits T cells within the skin through the CXCR3 receptor, which prolongs and exacerbates the established vitiligo lesion.

Ruxolitinib (INCB-018424) is a small-molecule inhibitor that selectively targets JAK1 and JAK2. The oral form of ruxolitinib was first approved in 2011 to treat polycythemia vera, essential thrombocythemia, and myelofibrosis. Although oral ruxolitinib has been shown to improve skin conditions, such as alopecia areata, topical administration of ruxolitinib resulted in higher concentrations in both the epidermis and dermis with minimal deleterious systemic effects versus oral administration, demonstrating sustained and near-complete blockage of the JAK/STAT signaling pathway in the tissues to which it was applied, with no significant plasma concentrations.

Skin re-pigmentation was observed in patients with vitiligo treated with oral ruxolitinib, with marked declines in serum CXCL10 levels after administration, indicating that ruxolitinib's mechanism of action may involve disruption of IFN-γ signaling and JAKs.

Studies on mice and human tissues on the mechanism of action of ruxolitinib cream in the treatment of vitiligo, have found that in addition to blocking IFN-γ and its downstream effector, JAKs, ruxolitinib also inhibited the differentiation and migration of human dendritic cells (DCs) *ex vivo.* This reduced DC-induced antigen-specific $CD4^+$ and $CD8^+$ T cell responses and the induction of $CD8^+$ cytotoxic T cell responses, which are the key cell responses that are hypothesized to participate in the pathogenesis of vitiligo, *in vivo*.

In another double-blind phase 2 trial, 157 adult patients with vitiligo from 26 hospitals in the United States were randomly assigned 1:1:1:1:1 to receive topical ruxolitinib cream 1.5% twice daily, 1.5% once daily, 0.5% once daily, 0.15% once daily, or a vehicle for 24 weeks, respectively. The percentage of patients who achieved more than 50% improvement from baseline in Facial VASI (F-VASI 50) at week 24 was set as the primary endpoint to evaluate treatment efficacy in each group. After the 24-week treatment period,

significantly more patients in the groups receiving ruxolitinib cream 1.5% twice daily, 1.5% once daily, and 0.5% once daily achieved F-VASI50 than patients in the control groups. Patients who were assigned in the three positive responsive groups receiving ruxolitinib cream 1.5% twice daily, 1.5% once daily, and 0.5% once daily were asked to remain their original treatment dose up to 52 weeks. At week 52, patients in these three treatment groups showed substantial repigmentation of vitiligo lesions and good dose tolerance, indicating that topical ruxolitinib may be a good option for vitiligo management.
Ruxolitinib cream offers a medication that is directly targeting the known pathogenesis and has successfully completed phase 3 randomized double-blind placebo controlled clinical trials and shows both safety and efficacy for vitiligo patients. Ruxolitinib 1.5% cream is the 1st treatment approved for vitiligo in Canada.
If accessible, Ruxolitinib 1.5% cream should serve as the first line treatment for vitiligo, as it addresses the proven specific pathogenesis mechanism for vitiligo, thereby primarily targeting the specific disease process.
Due to the mechanism of action and data available Re efficacy and safety from already completed phase 3 clinical trials, the medication should serve as first line agent to treat vitiligo, rather than second- or third-line agent.
For patients with significant vitiligo, including those with involvement of special sites (Face, hands or genitals) or those with progressive vitiligo Ruxolitinib 1.5% cream is the best first line treatment. In other cases of vitiligo, Ruxolitinib 1.5% cream may be considered a second line therapy after failing a combination of topical corticosteroid cream and topical calcineurin inhibitor cream / ointment.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Which patients are most likely to respond to treatment with drug under review?
Which patients are most in need of an intervention?
Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?
How would patients best suited for treatment with drug under review be identified (e.g., clinician examination/judgement, laboratory tests (specify), diagnostic tools (specify))
Are there any issues related to diagnosis?
Is a companion diagnostic test required?
Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?
Is it possible to identify those patients who are most likely to exhibit a response to treatment with drug under review?

Patients with mild to moderate extent of disease would be ideal candidates for Ruxolitinib cream. Patients with vitiligo especially on visible and special sites that impact patient daily life significantly such as vitiligo on the face, hands, forearms, feet, lower legs, genitals would also benefit from having access to the medication.
Those patients with rapidly spreading and extensive vitiligo involving > 50% BSA may not be ideal candidates in the beginning, as these patients initially require systemic immunosuppressant agents.
Patients can be best identified by clinical history and physical examination by physicians experienced in the treatment of vitiligo.
Diagnosis is usually straightforward and mostly made by clinical examination. Only rarely do patients need tests like skin biopsy for diagnosis. Physicians not familiar with skin

diseases or have not had experience with vitiligo may have difficulty correctly confirming the diagnosis.
Patients with disease mostly localized to face, hands, forearms, feet, lower legs, or hair bearing areas on trunk, extremities are more likely to benefit from the medication>

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Are outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?
What would be considered a clinically meaningful response to treatment? Consider the magnitude of the response to treatment. Is this likely to vary across physicians?
Examples: improved survival; reduction in the frequency/severity of symptoms (provide specifics regarding changes in frequency, severity, etc.); attainment of major motor milestones; ability to perform activities of daily living; improvement of symptoms; and stabilization (no deterioration) of symptoms.

Most measures in clinical practice to assess disease response to treatment are based on repigmentation and halting the spread of disease.
The best among currently available treatment outcome measure will be Vitiligo Area Severity Index (VASI) – Both Facial VASI and Total body VASI, Investigator Global Assessment (IGA), Facial IGA, and also patient reported outcome like Vitiligo noticeability scale (VNS), facial global impression of change-vitiligo (F-PaGIC-V) and total body global impression of change-vitiligo (T-PaGIC-V)
A 50% improvement in Facial VASI score and Total body VASI score at 1 year is considered a clinically meaningful response to treatment.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Examples: disease progression (specify, e.g. loss of lower limb mobility); certain adverse events occur (specify type/frequency/severity); or additional treatment becomes necessary (specify).

< If no adequate response to patient's satisfaction based on above patient reported outcome measures, and on 1 of the above physician outcome measures after 1 year of treatment – then it is worth considering discontinuing treatment >

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Examples: Community setting, hospital (outpatient clinic), specialty clinic
If a specialist is required, which specialties would be relevant?

Vitiligo can be diagnosed by any physician and can be treated in any setting including outpatient clinics and hospital setting.
Though it is easy to diagnose by physicians with training in dermatology, the lack of adequate treatments is currently the main negative impact for patients with vitiligo. Dermatologists would be ideal to help with the diagnosis, decide on which treatment to use, outcome measures monitoring, and what would provide the best outcome for patients in the long term.

6. Additional Information

Is there any additional information you feel is pertinent to this review?

Vitiligo significantly affects patients' lives both physically and mentally. Several studies have confirmed the significant mental and emotional impact vitiligo has on patient's life. The change in appearance due to vitiligo, especially when it affects easily visible sites like face and hands, makes patients very self-conscious, affects their confidence, prompts many patients to make major life changing decisions in their personal and professional lives. Historically available treatment options are not adequately addressing the pathogenesis specifically, and is also associated with significant time constraints, financial burden and risk of side effects. No Health Canada approved treatment was available until the recent approval of Ruxolitinib 1.5% cream. Ruxolitinib 1.5 % cream is expected to cause a shift in the current treatment landscape for vitiligo treatments in Canada, as this will likely become the preferable first line agent for treatment of vitiligo. This will depend a lot on access for vitiligo patients to receive Ruxolitinib 1.5% cream. Based on the above data and information provided please consider providing access to Ruxolitinib 1.5% cream for at least one year.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict-of-interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No. I confirm that no outside help was received in the preparation of this document or for its submission

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

Collection and analysis of the information was done entirely by the clinician group. No outside help was received for this

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Ajith Cy
Position: Dermatologist, Waterloo, ON, Canada
Date: 17-10-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Incyte		x		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Cathryn Sibbald
Position: Dermatologist, University of Toronto, ON, Canada
Date: 19-10-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Incyte		x		
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Jeffrey Cowger
Position: Dermatologist, London, ON, Canada
Date: 27-10-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Incyte		x		
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dusan Sajic
Position: Dermatologist, Guelph, ON, Canada
Date: 27-10-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Incyte		x		
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.