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HEALTH TECHNOLOGY BRIEFING AUGUST 2021

Ruxolitinib cream for vitiligo

NIHRIO ID	20418	**NICE ID**	10633
Developer/Company	Incyte Corporation	**UKPS ID**	Not Available

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Ruxolitinib cream is in development for the treatment of vitiligo. Vitiligo is a common chronic skin condition where white patches develop on the skin, commonly on the hands and face. The condition is not life-threatening but can have an impact on self-esteem and wellbeing of sufferers. Risk factors include other autoimmune diseases and family history of the disease. The cause of vitiligo is not fully understood but it is thought it may be an autoimmune condition. There are no licensed treatments specifically for vitiligo which highlights the unmet need of these patients.

Ruxolitinib cream is a topical formulation of the active substance ruxolitinib. Ruxolitinib works as a selective inhibitor by blocking the proteins which are involved in the downstream signalling of the immune system. Preventing the binding of these proteins reduces the immune response. If licensed, administered topically, ruxolitinib cream would offer a pharmacological treatment for patients with vitiligo who currently rely on non-specific and/or unlicensed medicines to treat their condition.

PROPOSED INDICATION

Treatment of vitiligo in patients aged 12 years and older.[1,2]

TECHNOLOGY

DESCRIPTION

Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2. These mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function.[3] JAK signal transducer and activator of transcription (JAK-STAT) proteins signalling is essential to transmit extracellular signals of many cytokines, including interferon gamma (IFN-γ), to the nucleus. Following ligation of the cytokine receptor, JAKs phosphorylate STATs proteins, which become activated and induce transcription of target genes. There are four members of JAK family, including JAK1, JAK2, JAK3, and Tyrosine kinase 2 (TYK2). JAK1 and JAK2 are directly involved in IFN-γ signalling, which activate STAT1 and thus induce the transcription of IFN-γ-induced genes.[4] Inhibiting these proteins results in a reduced immune response. Ruxolitinib cream is a proprietary formulation of the selective JAK1/JAK2 inhibitor ruxolitinib that has been designed for topical application.[5]

Ruxolitinib is currently in phase III clinical development. In phase III clinical trials (NCT04052425, NCT04057573, NCT04530344), ruxolitinib cream 1.5% is applied topically for 24 weeks followed by ruxolitinib cream 1.5% twice daily for an additional 28-week treatment extension period.[1,2]

INNOVATION AND/OR ADVANTAGES

There are no European Medicines Agency (EMA) approved drug therapies specifically for the treatment of vitiligo. There are also currently no approved JAK inhibitor treatments for repigmentation of vitiligo lesions.[6] Topical ruxolitinib would provide the first pharmacological approved treatment for patients with the disease.[5]

Previous research has reported that keratinocytes sense IFNγ in vitiligo lesions and promote T-cell recruitment, which can cause disease. As a result, a topical administration of a JAK inhibitor is a potential approach to diminish local inflammation and facilitate repigmentation in patients.[7]

Results from phase III trials have demonstrated the efficacy of ruxolitinib in comparison to a vehicle control with significantly more patients achieving ≥75% improvement from baseline in the facial vitiligo area scoring index.[8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Oral ruxolitinib currently has Marketing Authorisation in the EU/UK for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythemia myelofibrosis and for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.[3]

Topical ruxolitinib is currently in phase II/III trials for the treatment for a number of indications including atopic dermatitis, graft versus host disease and hidradenitis suppurativa.[9]

Common side effects of oral ruxolitinib include anaemia, thrombocytopenia, neutropenia, bruising, bleeding and headaches.[3]

PATIENT GROUP

DISEASE BACKGROUND

Vitiligo is a chronic condition where pale white patches develop on the skin surface. It can occur anywhere on the body but commonly forms on the face, neck, hands and in skin creases. Vitiligo can either be classified as segmental or non-segmental. Segmental vitiligo affects only one area of the body, whereas non-segmental mostly appear on both sides of the body as symmetrical patches.[10]

Vitiligo often starts as a pale patch of skin that gradually turns completely white. The centre of a patch may be white, with paler skin around it. If there are blood vessels under the skin, the patch may be slightly pink, rather than white. The edges of the patch may be smooth or irregular. They are sometimes red and inflamed, or have a brownish discolouration (hyperpigmentation). Vitiligo does not cause discomfort to your skin, such as dryness, but the patches may occasionally be itchy. The condition varies from person to person. Some people only get a few small, white patches, but others get bigger white patches that join up across large areas of their skin. There is no way of predicting how much skin will be affected. The white patches are usually permanent.[10]

Vitiligo is caused by the lack of a pigment called melanin in the skin. Melanin is produced by skin cells called melanocytes, and it gives your skin its colour. In vitiligo, there are not enough working melanocytes to produce enough melanin in the skin. This causes white patches to develop on the skin or hair. It is not clear exactly why the melanocytes disappear from the affected areas of skin. It is thought that non-segmental vitiligo is an autoimmune condition.[10]

Risk factors of non-segmental vitiligo include family history of vitiligo or other autoimmune conditions, having particular genetic changes and having melanoma or non-Hodgkin lymphoma. Vitiligo may be triggered by certain events including stress inducing events, skin damage or exposure to certain chemicals.[10]

Vitiligo is disfiguring, leading to loss of self-esteem, anxiety, significantly impaired quality of life and depression – in some patients to the point of suicide.[11-13]

CLINICAL NEED AND BURDEN OF DISEASE

Vitiligo is the most frequent case of depigmentation worldwide with estimations of around a 1 in 100 prevalence in the UK.[14,15] With 90% of sufferers affected by non-segmental vitiligo, it could be estimated that the eligible population would be around 603,731 in the UK.[10,16]

Using hospital episode statistics data 2019/20, vitiligo (ICD-L80) accounted for 44 finished consultant episodes (FCEs), 43 admissions and 212 FCE bed days.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of vitiligo is based on changing the appearance of the skin by restoring its colour. However, these treatments are usually temporary and cannot always control the spread of

the condition. Patients are recommended treatments including vitamin D, skin camouflage, steroids, calcineurin inhibitors, phototherapy and depigmentation. Skin grafts may be offered to some patients. Many treatments for vitiligo are unlicensed.[18]

CURRENT TREATMENT OPTIONS

There are currently no licensed treatments for vitiligo.[19]

Current off-label pharmacological treatments are corticosteroids and calcineurin inhibitors.[18,19]

PLACE OF TECHNOLOGY

If licenced, ruxolitinib cream would offer a pharmacological treatment for patients aged 12 years and over with vitiligo.

CLINICAL TRIAL INFORMATION

Trial	**TRuE-V1;** NCT04052425; 2019-000846-37; Topical Ruxolitinib Evaluation in Vitiligo Study 1 (TRuE-V1): A Phase 3, Double-Blind, Randomised, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream Followed by an Extension Period in Participants With Vitiligo **Phase III** – Active, not recruiting **Location(s):** 6 EU countries. US and Canada **Primary completion date:** March 2021[a]
Trial design	Randomized, crossover assignment, triple-blinded, vehicle-controlled
Population	N=330; 12 years and older; clinical diagnosis of non-segmental vitiligo with depigmented area
Intervention(s)	Ruxolitinib cream 1.5% twice daily (BID) for 24 weeks followed by ruxolitinib cream 1.5% BID for an additional 28-week treatment extension period
Comparator(s)	Vehicle cream for 24 weeks followed by crossover to ruxolitinib cream 1.5% BID in a 28-week treatment extension period
Outcome(s)	Proportion of participants achieving ≥ 75% improvement from baseline in Face Vitiligo Area Scoring Index (F-VASI) score. [Time frame: Week 24] See trial record for full list of other outcomes
Results (efficacy)	Significantly more patients treated with ruxolitinib cream 1.5% BID achieved a ≥75% improvement from baseline in the facial vitiligo area scoring index (F-VASI75) compared to patients treated with a vehicle control at Week 24.[8]
Results (safety)	The most frequently reported TEAEs in participants who applied ruxolitinib 1.5% cream during the double-blind period were application site acne and application site pruritus. None

[a] Information provided by Incyte Corporation.

	of the treatment related TEAEs were reported as serious or Grade 3 or higher.[b]

Trial	**TRuE-V2;** NCT04057573; 2019-000847-28; Topical Ruxolitinib Evaluation in Vitiligo Study 2 (TRuE-V2): A Phase 3, Double-Blind, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream Followed by an Extension Period in Participants With Vitiligo **Phase III** – Active, not recruiting **Location(s):** 7 EU countries, US and Canada **Primary completion date:** March 2021[c]
Trial design	Randomized, crossover assignment, triple-blinded, vehicle-controlled
Population	N=344; 12 years and older; clinical diagnosis of non-segmental vitiligo with depigmented area
Intervention(s)	Ruxolitinib cream 1.5% BID for 24 weeks followed by ruxolitinib cream 1.5% BID for an additional 28-week treatment extension period
Comparator(s)	Vehicle cream for 24 weeks followed by crossover to ruxolitinib cream 1.5% BID in a 28-week treatment extension period
Outcome(s)	Proportion of participants achieving ≥ 75% improvement from baseline in Face Vitiligo Area Scoring Index (F-VASI) score. [Time frame: Week 24] See trial record for full list of other outcomes
Results (efficacy)	Significantly more patients treated with ruxolitinib cream 1.5% BID achieved a ≥75% improvement from baseline in the F-VASI75 compared to patients treated with a vehicle control at Week 24.[8]
Results (safety)	The most frequently reported TEAEs in participants who applied ruxolitinib 1.5% cream during the double-blind period were application site acne and application site pruritus. None of the treatment related TEAEs were reported as serious or Grade 3 or higher.[d]

Trial	NCT04530344; A Double-Blind, Vehicle-Controlled, Randomised Withdrawal and Treatment Extension Study to Assess the Long-Term Efficacy and Safety of Ruxolitinib Cream in Participants with Vitiligo **Phase III** – recruiting **Location(s):** 5 EU countries, US and Canada **Primary completion date:** January 2024
Trial design	Randomized, parallel assignment, double-blinded, vehicle-controlled
Population	N~500; 12 years and older; currently enrolled in TRuE-V1 or TRuE-V2

[b] Information provided by Incyte Corporation.
[c] Information provided by Incyte Corporation.
[d] Information provided by Incyte Corporation

Intervention(s)	Ruxolitinib cream (cohort A will be randomised 1:1, cohort B will continue on ruxolitinib cream)
Comparator(s)	Vehicle controlled
Outcome(s)	Cohort A: Time to Relapse [Time Frame: Extension period through Week 108]. See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of ruxolitinib cream is unknown.

RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract For Specialised Dermatology Services (All Ages). A12/S/a.

OTHER GUIDANCE

- NICE Clinical Knowledge Summary. Vitiligo. April 2020.[6]
- British Association of Dermatologists. British Association of Dermatologists guidelines for the management of people with vitiligo. 2021.[20]

ADDITIONAL INFORMATION

Incyte Corporation did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.