EU RISK MANAGEMENT PLAN
FOR
RUXOLITINIB CREAM

RMP version to be assessed as part of this application: v 0.5

Data lock point for this RMP	20 JUN 2022	Version number	0.5
Date of final sign off	18 JUN 2025		

Rationale for submitting an updated RMP:

Updates to the RMP are made upon request by the EMA to submit a Type IB variation for INCB 18424-309 (*C.I.11.z Change in due date for category 1, 2 or 3 studies in the RMP and/or Annex II*) completion date.

Summary of significant changes in this RMP:

Part	Summary of changes in v 0.5 compared to RMP v 0.4
Part III: III.2	The due date for the LPLV for INCB 18424-309 has been updated from June 2024 to December 2027 to align with the due dates in the PIP modification EMEA-002618-PIP02-20-M01 approved by EMA on 12 April 2024.
Part III: III.3 (Table Part III-1)	The due date for the LPLV in study INCB 18424-309 has been updated to December 2027.
Annex 2 (Table Part VII.1)	The LPLV date for study INCB 18424-309 has been updated to December 2027.
Annex 3	Added information on the study status for INCB88888-037 and INCB 18424-308.

Other RMP versions under evaluation:

No RMP versions are currently under evaluation.

QPPV name: Achint Kumar

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	atopic dermatitis
AE	adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC code	Anatomical Therapeutic Chemical code
TNF-a	Tumor Necrosis Factor alpha
AUC	area under the plasma concentration-time curve
AUC_{0-12}	area under the steady-state plasma concentration-time curve from Hour 0 to 12
AUC_{0-24}	area under the steady-state plasma concentration-time curve from Hour 0 to 24
BID	twice daily
BMI	Body Mass Index
BSA	body surface area
$C_{avg,ss}$	average steady-state concentration
CD	cluster of differentiation
CDC	Center for Disease Control and Prevention
CDS	Core Data Sheet
CFR	Code of Federal Regulations
CHO	Chinese Hamster Ovary
Clcr	Creatinine Clearance
C_{max}	Maximum observed plasma concentration
CNS	Central Nervous System
COVID-19	Coronavirus disease 2019 (SARS-CoV-2)
C_{ss}	steady-state concentration
CTx	Carboxy-terminal collagen crosslinks
DB	double-blind
EC	European Commission
EEA	European Environment Agency
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EPAR	European public assessment report
ESRD	End Stage Renal Disease
EU	European Union
FDA	Food and Drug Administration

Abbreviation	Definition
F-BSA	Face body surface area
FPI	First patient in
F-VASI	Facial Vitiligo Area Scoring Index
GLP	Good Laboratory Practices
GVP	Good Pharmacovigilance Practices
HBV	Hepatitis B virus
HBV-DNA	Hepatitis B virus- Deoxyribonucleic Acid
HCP	Health Care professional
hERG	human ether-a-go-go-related gene
HIV	Human Immunodeficiency Virus
HLT	High Level Term
IC_{50}	Concentration resulting in 50% inhibition
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigator's Global Assessment
IL	interleukin
IR	Incidence rate
INN	International nonproprietary name
IV	Intravenous
JAK	Janus kinase
LD0-7	Lactation day 0-7
LFT	Liver Function Test
LoOI	List of outstanding issues
LPLV	Last patient, last visit
LPO	Last patient out
MACE	Major Adverse Cardiovascular Event
MAH	Manufacturing Authorization Holder
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MPV	Mean Platelet Volume
NB-UVB	Narrowband Ultraviolet B
nM	Nanomolar
NMSC	Non-melanoma skin cancer
NOAEL	No Observed Adverse Effect Level
OECD	Organization for Economic Co-operation and Development

Abbreviation	Definition
PASS	Post-authorisation safety studies
P1NP	Procollagen Type I Propeptides
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PL	Package Leaflet
pp	Postpartum
pQCT	Peripheral quantitative computed tomography
PSUR	Periodic Safety Update Report
PUVA	Psoralen Plus Ultraviolet A
PT	Preferred Term
PY	Person-Years
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Query
SOC	System Organ Class
STAT	Signal Transducers and Activators of Transcription
TB	Tuberculosis
TCI	Topical Calcineurin Inhibitor
TCS	Topical Corticosteroids
TEAE	Treatment-Emergent Adverse Event
Tmax	Time of Maximal Plasma Concentration
ULN	Upper Limit of Normal
µM	Micromolar
UV	Ultraviolet
VC	Vehicle-Controlled
VTE	Venous Thromboembolism

PART I PRODUCT(S) OVERVIEW

Table Part I.1: Product Overview

Active substance(s) (INN or common name)	ruxolitinib phosphate
Pharmacotherapeutic group(s) (ATC Code)	D11AH09
Marketing Authorisation Applicant	Incyte Biosciences Distribution B.V. Paasheuvelweg 25 1105 BP Amsterdam Netherlands
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Opzelura
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: Janus kinase (JAK) inhibitor
	Summary of mode of action: Ruxolitinib is a JAK inhibitor with selectivity for the JAK1 and JAK2 isoforms. Intracellular JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, and subsequent modulation of gene expression. Autoimmune IFNγ producing cytotoxic T lymphocytes are thought to be directly responsible for melanocyte destruction in human vitiligo. Recruitment of cytotoxic lymphocytes to lesional skin is mediated via IFNγ dependent chemokines. Downstream signaling of IFNγ is JAK1/2 dependent
	Important information about its composition: Ruxolitinib cream is formulated as an oil-in-water, solubilized emulsion cream for topical administration. The strength of 1.5% (15mg of ruxolitinib/1g of cream) is planned for commercial use in the proposed indication. All excipients in the ruxolitinib cream formulations are compendial grade or are approved for use in topical products. Ruxolitinib cream is packaged in 100 g tubes.
Hyperlink to the Product Information	See current/proposed Product Information.
Indication(s) in the EEA	Current: Ruxolitinib cream is indicated for the treatment of non-segmental vitiligo with facial involvement in adults and adolescents from 12 years of age.
	Proposed: Not Applicable

Dosage in the EEA	Current: A thin layer of cream applied twice daily to the depigmented skin areas up to a maximum of 10% body surface area (BSA), with a minimum of 8 hours between two applications of ruxolitinib cream.
	Proposed: Not Applicable
Pharmaceutical form(s) and strengths	Current: 1.5% cream (15 mg ruxolitinib/1 g of cream, equivalent to 19.8 mg ruxolitinib phosphate/1 g of cream)
	Proposed: Not Applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Vitiligo

Vitiligo is an autoimmune disease characterized by depigmented patches of skin with a selective loss of melanocytes (Krüger and Schallreuter 2012). Vitiligo is classified into 2 major forms: nonsegmental and segmental. The former is the most common type, accounting for up to 90% of cases (Taïeb and Picardo 2009), and is characterized by development of depigmented patches on both sides of the body. In contrast, depigmented patches in segmental vitiligo are typically limited to 1 side of the body. The main mechanism leading to nonsegmental vitiligo involves an immune-mediated destruction of melanocytes, whereas segmental vitiligo carries a different pathogenesis with most evidence indicating a mosaic skin disorder (Speeckaert and van Geel 2017). The natural course of vitiligo is generally unpredictable, but it is often progressive. Some degree of spontaneous repigmentation may occur in 10% to 20% of patients; however, for many of these patients, the repigmentation is not cosmetically acceptable (Castanet and Ortonne 1997).

Incidence:

Vitiligo occurs worldwide with an incidence rate between 0.1 and 2% irrespective of age, ethnic origin or skin color (Yaghoobi et al 2011). The incidence of vitiligo is not well established and existing estimates rarely originate from population-based studies.

Prevalence:

Worldwide prevalence estimates of vitiligo vary widely with estimates ranging from 0.004% to 2.28%. (Krüger and Schallreuter 2012, Zhang et al 2016). In a large general population survey study of more than 40,000 adults, aimed to estimate the point prevalence of vitiligo in the US, Gandhi et al (2022) found that the estimated point prevalence of vitiligo was 0.76% based on clinician adjudication and 1.38% based on self-report. The study also suggests that approximately 40% of adults with vitiligo in the US may be undiagnosed (Gandhi et al 2022).

Demographics of the population in the proposed indication and risks factors for the disease:

The onset of vitiligo is usually before age 30, with approximately a quarter of patients presenting by age 10 and nearly half of patients presenting with vitiligo between 10 and 20 years of age (Bergqvist and Ezzedine 2020, Rodrigues et al 2017, Silverberg 2015). Vitiligo affects people of all ethnicities and skin types with no clear differences in prevalence based on these characteristics (Alkhateeb et al 2003, Bergqvist and Ezzedine 2020, Ezzedine et al 2015, Picardo et al 2015); however, it has been noted that patients who were non-White (40.2% vs 31.5%) or Hispanic, Latino, or Spanish origin (21.3% vs 15.3%) were less likely to receive a diagnosis of vitiligo (Gandhi et al 2022). Men and women are equally affected, although women appear to seek treatment more often (Picardo et al 2015).

There is no generally accepted clinical definition of disease severity for vitiligo. The disease extent (ie, proportion of BSA with depigmentation) may be one consideration, but other clinical criteria, including location/visibility of lesions, the number of active lesions, and skin phototype, as well as subjective perception of disease impact on quality of life are also important. In a recent study by van Geel et al (2021), participants ranked location (ie, lesions in visible or sensitive areas) followed by disease extent and disease impact as the most important factors in the context of severity perception. Of note, there is a common perception that patients with darker skin tones are more affected by their vitiligo. However, research has shown that patients with lighter skin tones are also deeply affected by their vitiligo (Grimes and Miller 2018).

Risk factors for non-segmental vitiligo include family history of vitiligo and/or other autoimmune diseases, personal history of melanoma or non-Hodgkin lymphoma. Known triggers for vitiligo include a severe sunburn, injury to the skin and coming into contact with a strong chemical on the skin (American Academy of Dermatology 2022).

The main existing treatment options:

Currently, there is no approved drug treatment for repigmentation in vitiligo, with the exception of Opzelura (ruxolitinib) cream in the United States, and evidence for effectiveness of drug therapies used off-label is limited. There have been a limited number of randomized controlled clinical studies conducted to adequately support the efficacy of drug treatments in vitiligo. Based on a systematic review of randomized clinical trials evaluating interventions for vitiligo, factors that further limit the evidence for efficacy include variations in study design and outcome measures, small study size (the majority included fewer than 50 participants), and deficiencies in methodological quality (Whitton et al 2016). A systemic review of outcomes in vitiligo studies showed that 25 different outcomes had been measured in 54 randomized clinical studies. Although repigmentation was measured in 94% of studies, 48 different scales were used to measure repigmentation, making comparisons across studies impossible (Eleftheriadou et al 2012). The management of vitiligo is therefore empirical and based on the most recent consensus guidelines (American Academy of Dermatology 2020, Gawkrodger et al 2008, Taieb et al 2013, Vitiligo Research Foundation 2020).

In general, first-line treatments consist of off-label use of topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI), which are mostly used for treating limited disease (typically ≤10% BSA is treated). However, there are inconclusive (or insufficient) data supporting their efficacy, and many have restrictions on use due to tolerability concerns and adverse effects associated with these agents. TCS have been associated with local adverse effects, some of which may be irreversible such as skin atrophy and striae distensae, and an increased susceptibility to skin infections (Coondoo et al 2014, Taieb et al 2013). More potent TCS, through their percutaneous absorption and depot-like accumulation in the epidermis, may also produce systemic adverse events typical for oral corticosteroids. To minimize adverse effects, judicious use of high potency TCS is critical. In addition, the use of TCS on sensitive skin areas (eg, the face) and the long-term use of TCS are not recommended.

TCI are known for the induction of a skin burning sensation immediately after their application, which makes their use on the face problematic. TCI have also been implicated in their possible contribution to cutaneous malignancy when used long-term.

Second-line treatments consist of phototherapy (NB-UVB and PUVA) and off-label systemic steroid treatment. Phototherapy regimens typically require 2 to 3 treatments per week, and 12 to 24 months of continuous phototherapy may be necessary to achieve maximal repigmentation (Taieb et al 2013); relapses are common. Approximately 60% to 70% of patients experience depigmentation in areas repigmented by treatment within 1 year of stopping PUVA or NB-UVB therapy (Boniface et al 2018). There are also important safety limitations with phototherapy. PUVA carries a risk of phototoxic effects, nausea, and the potential risk for skin cancer.

Moreover, PUVA phototherapy is not recommended for children or pregnant women due to risks associated with systemic exposure of psoralen. NB-UVB phototherapy is considered to have safety advantages over PUVA but is also associated with adverse events such as erythema, itching, and mild burning or pain (Bae et al 2017). Excimer laser or monochromatic excimer lamp (both at 308 nm) which may reach deeper targets such as amelanotic melanocytes of the hair follicle, and also avoid irradiation of uninvolved skin, may improve clinical outcomes, however they are limited to localized treatment (Boniface et al 2018).

Third-line treatments consist of surgical grafting techniques and depigmenting treatments. Surgery is best indicated for stable and localized forms of vitiligo, and only a small number of patients with vitiligo are considered suitable candidates.

No available product or therapy is able to modify the course of vitiligo and produce long-lasting repigmentation. Currently available repigmenting drug therapies are immune-modulating, but no pharmacologic treatments have been successful at stimulating melanocytes to repopulate the areas depigmented by vitiligo. Recovery of pigment can depend on a reservoir of melanocyte precursors to repopulate and return functioning melanocytes to depigmented skin. Thus, repigmentation in vitiligo is generally recognized to be a slow biological process even with the use of immune-modulating treatments. For topical treatments, including TCI and TCS (with discontinuous treatment), a minimum of 6 to 12 months is often needed to achieve repigmentation (Taieb et al 2013). Phototherapy, which can produce effective results via immune-modulating effects and stimulation of melanocytes, can require 12 to 24 months of therapy to achieve satisfactory levels of repigmentation (Taieb et al 2013). Limited efficacy of current treatment options, together with important safety limitations of current drug treatments (eg, skin atrophy, striae distensae, skin burning, and increased risk of cutaneous malignancy), highlight that there is significant unmet need for safe and effective new treatments for vitiligo.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Vitiligo is associated with other autoimmune diseases such as thyroid disorders, juvenile diabetes mellitus, pernicious anemia, Addison's disease, and Halo nevus. Vitiligo can cause severe psychological distress, morbidity, and decreased quality of life.

Vitiligo affects people of all ethnicities and skin types with no clear differences in prevalence based on these characteristics (Alkhateeb et al 2003, Bergqvist and Ezzedine 2020, Ezzedine et al 2015, Picardo et al 2015). Studies have shown that the effect vitiligo has on quality of life, particularly psychological impairment, is similar to other skin diseases, such as psoriasis and atopic dermatitis (AD) (Linthorst et al 2009). Involvement of exposed skin, such as the face and hands, can have a major impact on self-esteem (Silverberg and Silverberg 2013). Self-esteem is more severely impacted in patients who have a greater extent of depigmentation

and in patients who started with stable disease that quickly spread later in life compared with patients who have less depigmentation and stable disease. Patients also report significantly lower quality of life when lesions are located on the head as opposed to lesions located elsewhere and not on the head (Bibeau et al 2022). In some societies, there is poor acceptance and understanding of the disease, to the extent of discrimination against affected individuals (Yazdani Abyaneh et al 2014). Approximately 75% of vitiligo sufferers feel their appearance is moderately to severely intolerable, and 41% of patients feel that there is little they can do to improve their condition, and feelings of hopelessness increase with time (Salzer and Schallreuter 1995). A majority of patients (66%) report being distressed by their disease, and 92% have experienced stigmatization (Krüger et al 2014). Feelings of anxiety, embarrassment, and fear of rejection can cause patients with vitiligo to withdraw and lead to social isolation in both personal and professional relationships. Indeed, a majority of patients with vitiligo have reported feelings of anxiety and embarrassment when meeting strangers or beginning a new sexual relationship (Porter et al 1990).

Important co-morbidities:

Clinical depression or depressive symptoms are associated with vitiligo. A systematic review of observational studies and clinical trials found that depression and anxiety were the most commonly reported psychosocial comorbidities; the prevalence of depression and anxiety in patients with vitiligo has been reported to be up to 62.3%, and the prevalence of anxiety or anxiety-related disorders up to 67.9%. The prevalence of most psychosocial comorbidities was significantly higher in people with vitiligo vs healthy individuals (Ezzedine et al 2021). Based on various meta-analyses, patients with vitiligo were approximately 5 times more likely to suffer from depression than healthy controls (Lai et al 2017, Osinubi et al 2018).

Studies also suggest that the onset of vitiligo beginning in childhood can be associated with significant psychological trauma that may have long-lasting effects on self-esteem. Furthermore, negative childhood experiences were significantly associated with more health-related quality-of-life impairment in early adulthood (Linthorst Homan et al 2008).

PART II: MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity Repeat-Dose Studies

The toxicity of ruxolitinib following oral administration was evaluated in rats for up to 6 months, and dogs for up to 52 weeks.

Primary findings in repeat-dose oral toxicology studies in rats and dogs were hematology and microscopic findings consistent with the pharmacologic activity of ruxolitinib, including decreased white blood cells (primarily lymphocytes with variable effects on other populations) and lymphoid depletion in various lymphoid tissues. In longer-term studies, findings considered secondary to pharmacology and immunosuppression were observed in dogs, which were associated with morbidity in the 52-week and 6-month studies, respectively. Exposures (based on AUC) at non-adverse levels in chronic toxicity studies were approximately 6 times in male rats, 221 times in female rats, and 12 times in dogs, the unbound plasma concentrations at the intended clinical strength of 1.5% applied twice daily in subjects with vitiligo. Ruxolitinib is rapidly metabolized in male rats with several active metabolites; therefore, plasma ruxolitinib exposures do not reflect total pharmacologic activity.

No evidence of systemic toxicity was observed in Gottingen minipigs following topical administration of 1.5% ruxolitinib cream formulation to 10% of body surface area twice daily for up to 9 months. Decreased peripheral lymphocyte counts were observed in the 9-month study, but there were no associated microscopic findings of lymphoid depletion, and no observations suggestive of immunosuppression. Clinical and microscopic findings in the skin were generally mild. Systemic ruxolitinib exposures in these studies were low.

Reproductive and Development Toxicity

Ruxolitinib was evaluated for fertility and early embryonic development following oral administration in Sprague-Dawley rats. No effect on reproductive outcome and sperm parameters after 10 weeks of dosing in males were observed at exposures up to 11 times the unbound plasma concentrations at the intended clinical strength of 1.5% applied twice daily in subjects with vitiligo. In female rats, no effect on estrous cycling, mating and fertility indices, or the numbers of corpora lutea or implantation sites were observed. An increase in postimplantation loss occurred at exposure approximately 63 times the unbound plasma concentration at the intended clinical strength of 1.5% applied twice daily in subjects with vitiligo.

Oral administration of ruxolitinib to pregnant Sprague Dawley rats from Gestation Day 7 through 20 resulted in maternal mortality and decreased fetal weights at exposures approximately 163 times the unbound plasma concentration at the intended clinical strength of 1.5% applied twice daily in subjects with vitiligo. No maternal or embryo-foetal toxicity was observed at 25 times the unbound plasma concentration in subjects with vitiligo. Ruxolitinib was not teratogenic at any dose.

Oral administration of ruxolitinib to pregnant New Zealand White rabbits from Gestation Day 8 through 21 resulted in maternal mortality, increased late resorptions, and lower fetal weights at 60 mg/kg per day at exposures approximately 3.8 times the unbound plasma concentration at the

intended clinical strength of 1.5% applied twice daily in subjects with vitiligo. In rabbits, low plasma ruxolitinib exposure was attributed to extensive metabolism to active metabolites. Thus, plasma ruxolitinib levels do not reflect the level of pharmacologic activity in rabbits.

When ruxolitinib was administered by oral gavage to pregnant and lactating female rats (F_0) from Gestation Day 6 through Lactation Day 20, there was no evidence of maternal toxicity and no adverse effects on postnatal development; maternal exposures were up to 29 times the unbound plasma concentration at the intended clinical strength of 1.5% applied twice daily in subjects with vitiligo.

Juvenile Toxicity

Oral administration of ruxolitinib to juvenile rats resulted in effects on overall growth as evaluated by body weight gain, and various bone density parameters as evaluated by peripheral quantitative computed tomography (pQCT). Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. When dosing was initiated at postpartum Day 21, which is considered approximately equivalent to a human at 2 years old, non-adverse findings in animals were observed at exposures approximately 35 times the unbound plasma concentration at the intended clinical strength of 1.5% applied twice daily in subjects with vitiligo.

Local Tolerance

Ruxolitinib cream was evaluated for skin and eye irritation in rabbits and found to be mildly to slightly irritating. Local application site reactions in dermal toxicology studies of ruxolitinib cream in minipigs were generally minimal to mild. Ruxolitinib showed no evidence of dermal sensitization in a mouse local lymph node assay. Ruxolitinib was not phototoxic and showed no evidence of photoallergy potential in in vivo studies in hairless guinea pigs.

Genotoxicity

Ruxolitinib was evaluated for potential genotoxicity in a Bacterial Reverse Mutation Assay, in vitro chromosomal aberrations assay in human peripheral blood lymphocytes, and an in vivo rat micronucleus study. Collective results of these studies showed no evidence of genotoxic potential of ruxolitinib.

Carcinogenicity

Ruxolitinib was not carcinogenic in a 26-week study oral study in Tg.rasH2 mice (doses 0, 15, 45, 125 mg/kg per day), a 2-year oral study in rats (doses of 0, 10, 20, and 60 mg/kg per day), or the 2-year dermal carcinogenicity study in mice (concentrations of 0.5%, 1.0% and 1.5% applied once daily to 10% BSA). Non-neoplastic findings in the oral studies were consistent with those reported in repeat-dose toxicology studies.

Safety Pharmacology

Adverse effects were observed following oral administration of ruxolitinib in the CNS study (darkened mucous membranes, decreased activity and body temperature) and respiratory study (decreased minute volume) in rats and a cardiovascular study in dogs (decreased arterial blood pressure). The NOAEL for these effects were associated with unbound Cmax values > 600-fold higher in female rats and > 900-fold higher in dogs than those observed in subjects with vitiligo. Collectively, these results indicate that the potential for unintended adverse pharmacological effects of ruxolitinib cream are low.

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

The evaluable population (N=2670[1]) includes participants who applied ruxolitinib cream at least once in Studies INCB 18424-102[2], INCB 18424-103, INCB 18424-201, INCB 18424-202, INCB 18424-203, INCB 18424-204, INCB 18424-206, INCB 18424-211, INCB 18424-303, INCB 18424-304, INCB 18424-306, INCB 18424-307, and INCB 18424-308 (Cohort B only) through 28 JAN 2022.

The vitiligo population (N=789) includes participants in Studies INCB 18424-211, INCB 18424-306, INCB 18424-307, and INCB 18424-308 (Cohort B only).

The AD population (N=1595) includes participants in Studies INCB 18424-102[3], INCB 18424-103, INCB 18424-206, INCB 18424-303, and INCB 18424-304.

The other indications population (N=286) includes participants in Studies INCB 18424-201 (plaque psoriasis), INCB 18424-202 (plaque psoriasis), INCB 18424-203 (plaque psoriasis), and INCB 18424-204 (alopecia areata).

Duration of exposure is defined as the duration from first cream application to last application.

Table Part II: Module SIII.1: Duration of Exposure (Any Dose)

Cumulative for All Indications (Patient Years)				
Duration of exposure (Continuous and Intermittent Dosing)	**Vitiligo N=789 (%)**	**Atopic Dermatitis (AD) [a] N=1595 (%)**	**Other Indications[b] N=286 (%)**	**Total[a] N=2670 (%)**
≤ 1 month	22 (2.8)	182 (11.4)	66 (23.1)	270 (10.1)
>1-3 months	35 (4.4)	373 (23.4)	141 (49.3)	549 (20.6)
>3-6 months	37 (4.7)	115 (7.2)	28 (9.8)	180 (6.7)
>6-9 months	83 (10.5)	105 (6.6)	16 (5.6)	204 (7.6)
>9-12 months	51 (6.5)	349 (21.9)	25 (8.7)	425 (15.9)
>12-15 months	186 (23.6)	471 (29.5)	5 (1.7)	662 (24.8)
>15-18 months	86 (10.9)	0 (0.0)	4 (1.4)	90 (3.4)
>18-21 months	117 (14.8)	0 (0.0)	1 (0.3)	118 (4.4)
>21-24 months	59 (7.5)	0 (0.0)	0 (0.0)	59 (2.2)
>24 months	113 (14.3)	0 (0.0)	0 (0.0)	113 (4.2)
Patient years (PY)	996.91	968.97	92.94	2058.83

[a] Includes all cohorts in the 18424-102 study

[b] alopecia areata, psoriasis

[1] Includes all cohorts in the 18424-102 study
[2] Includes all cohorts in the 18424-102 study
[3] Includes all cohorts in the 18424-102 study

Table Part II: Module SIII.2: Age Group and Gender

Age Group	**Vitiligo N=789 (%)**	**AD[a] N=1595 (%)**	**Other Indications[b] N=286 (%)**	**Total[a] N=2670 (%)**
Children (2 to 11 years)	0 (0.0)	50 (3.1)	0 (0.0)	50 (1.9)
Patient years (PY)	-	3.69	-	3.69
Adolescents (12 to 17 years)	70 (8.9)	281 (17.6)	0 (0.0)	351 (13.1)
Patient years (PY)	83.85	185.58	-	269.43
Adults (18 to 64 years)	657 (83.3)	1139 (71.4)	267 (93.4)	2063 (77.3)
Patient years (PY)	824.87	692.15	86.71	1603.72
65-74 years	59 (7.5)	107 (6.7)	18 (6.3)	184 (6.9)
Patient years (PY)	83.75	72.25	6.16	162.15
75-84 years	3 (0.4)	16 (1.0)	1 (0.3)	20 (0.7)
Patient years (PY)	4.44	13.31	0.08	17.84
85 + years	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Patient years (PY)	-	1.99	-	1.99
Gender	**Vitiligo N=789 (%)**	**AD[a] N=1595 (%)**	**Other Indications[b] N=286 (%)**	**Total[a] N=2670 (%)**
Males	365 (46.3)	642 (40.3)	150 (52.4)	1157 (43.3)
Patient years (PY)	466.76	365.96	36.59	869.30
Females	424 (53.7)	953 (59.7)	136 (47.6)	1513 (56.7)
Patient years (PY)	530.15	603.01	56.36	1189.52
Total Patients Dosed	789	1595	286	2670
Total Patient years (PY)	996.91	968.97	92.94	2058.83

[a] Includes all cohorts in the 18424-102 study.
[b] alopecia areata, psoriasis

Table Part II: Module SIII.3: Dose (Cream Strength)

All Population	1.5% BID N=(1819)	0.75% BID N=(623)	All Others[a] N=(445)	Total[b] N=(2670)
Patients	1819	623	445	2670
Patient years (PY)	1470.79	443.52	144.47	2058.83

[a] 0.15%, 0.5%, 1.0%
[b] Includes all cohorts in the 18424-102 study

Table Part II: Module SIII.4: Ethnic Origin

Ethnic origin	Vitiligo N=789 (%)	AD[a] N=1595 (%)	Other Indications[b] N=286 (%)	Total[a] N=2670 (%)
Hispanic or Latino	174 (22.1)	236 (14.8)	30 (10.5)	440 (16.5)
Patient years (PY)	212.15	111.27	8.59	332.01
Not Hispanic or Latino	578 (73.3)	1348 (84.5)	255 (89.2)	2181 (81.7)
Patient years (PY)	733.78	852.77	84.02	1670.57
Not Reported	30 (3.8)	0 (0.0)	1 (0.3)	31 (1.2)
Patient years (PY)	37.93	-	0.34	38.27
Unknown	5 (0.6)	3 (0.2)	0 (0.0)	8 (0.3)
Patient years (PY)	8.67	0.22	-	8.89
Other	2 (0.3)	8 (0.5)	0 (0.0)	10 (0.4)
Patient years (PY)	4.38	4.71	-	9.09

[a] Includes all cohorts in the 18424-102 study.
[b] alopecia areata, psoriasis

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Important exclusion criteria in INCB 18424-306 (TRuE-V1) and INCB 18424-307 (TRuE-V2) were:

Participants with concurrent conditions and history of other diseases:

- **Active acute bacterial, fungal, or viral skin infection (eg, herpes simplex, herpes zoster, chicken pox) within 1 week before baseline.**

  Reason for exclusion: Concurrent skin infections make it difficult to make accurate skin assessments.

  Is it considered to be included as missing information?: No

  Rationale: The decision to treat with ruxolitinib cream is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for ruxolitinib cream.

- **Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy or uncontrolled hypertension (blood pressure > 150/90 mmHg) unless approved by the medical monitor/sponsor.**

  Reason for exclusion: It is a standard practice to exclude participants from clinical trials who are medically unstable, and therefore, at higher risk of not being able to complete the trial. Participants who meet this criterion may need prompt medical attention, and any ongoing active medical issue may confound the assessment of efficacy and safety during the clinical trial.

  Is it considered to be included as missing information?: No

  Rationale: The decision to treat with ruxolitinib cream is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for ruxolitinib cream.

- **History of thrombosis, including deep venous thrombosis and pulmonary embolism.**

  Reason for exclusion: Oral JAK inhibitors, although not oral ruxolitinib, have been associated with venous thromboembolism. Patients with a history of VTE are considered to have a higher risk of recurrence. Due to lower systemic levels associated with topical administration, the risk is likely to be reduced compared to oral JAK inhibitors. To exercise an abundance of caution, the MAH excluded participants with a history of deep venous thrombosis and/or pulmonary embolism.

  Is it considered to be included as missing information?: No

Rationale: The decision to treat with ruxolitinib cream is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for ruxolitinib cream.

- **Participants with concurrent malignant disease or a history of that in the 5 years preceding the baseline visit except for adequately treated nonmetastatic malignancies.**

  Reason for exclusion: Long-term exposure to oral JAK inhibitors may increase the risk of malignancies, including non-melanoma skin cancers. A causal relationship to oral ruxolitinib has not been established. Due to lower systemic levels associated with topical administration, the risk is likely to be reduced compared to oral JAK inhibitors. To exercise an abundance of caution, the MAH excluded participants with a concurrent condition or medical history of malignancies. It is a standard practice to exclude participants from clinical trials who are medically unstable and have active malignancy. Participants who meet these criteria need prompt medical attention and may need chemotherapy or other medical treatments, which may make them immunocompromised. Ongoing active malignancy may confound the assessment of efficacy and safety during the clinical trial.

  Is it considered to be included as missing information?: No

  Rationale: The decision to treat with ruxolitinib cream is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for ruxolitinib cream.

- **Current and/or history of liver disease, including known hepatitis B or C, with hepatic or biliary abnormalities.**

  Reason for exclusion: It is a standard practice to exclude participants from clinical trials who are medically unstable and have active hepatitis. Participants who meet these criteria need prompt medical attention and treatments. Effective treatments are available for Hepatitis B, and Hepatitis C. Ongoing active hepatitis or its treatment may confound the assessment of efficacy and safety during the clinical trial. Hepatitis B viral load (HBV-DNA titre) increases have been reported in patients with chronic HBV infections taking oral ruxolitinib. Due to lower systemic levels associated with topical administration, the risk is likely to be reduced compared to oral JAK inhibitors.

  Is it considered to be included as missing information?: No

  Rationale: The decision to treat with ruxolitinib cream is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for ruxolitinib cream.

- **Current and/or history of tuberculosis (TB).**

  Reason for exclusion: It is a standard practice to exclude participants from clinical trials who are medically unstable and have active TB or a past history of TB. Participants who meet this criterion need prompt medical attention and treatments. Effective treatments are available for TB. In addition, ongoing active TB may confound the assessment of efficacy and safety during the clinical trial. Tuberculosis

infection complication has been reported in patients receiving oral ruxolitinib. Due to lower systemic levels associated with topical administration, the risk is likely to be reduced compared to oral JAK inhibitors.

Is it considered to be included as missing information?: No

Rationale: The decision to treat with ruxolitinib cream is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for ruxolitinib cream.

Participants with clinically significant abnormal laboratory values at screening:

- **Hemoglobin (< 10 g/dL).**

  Reason for exclusion: It is a standard practice to exclude participants from clinical trials who are medically unstable and have current moderate to severe anaemia or cytopenias. Oral JAK inhibitors including ruxolitinib are associated with anaemia. Due to lower systemic levels associated with topical administration, the risk is likely to be reduced compared to oral JAK inhibitors. The discovery of anaemia requires further investigation for the possible cause. Participants who meet this criterion need prompt medical attention and treatments. Effective treatments are available for anaemia. In addition, ongoing active anaemia may confound the assessment of safety during the clinical trial.

  Is it considered to be included as missing information?: No

  Rationale: The decision to treat with ruxolitinib cream is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for ruxolitinib cream.

- **Liver function tests:**
  - AST or ALT ≥ 2 × ULN.
  - Alkaline phosphatase and/or bilirubin > 1.5 × ULN (isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%).

  Reason for exclusion: It is a standard practice to exclude participants from clinical trials who are medically unstable and are discovered to have liver abnormalities such as elevated AST and/or ALT or bilirubin. These participants require further assessment for the possible cause and may need medical management of elevated liver enzymes. Elevated bilirubin may confound efficacy and safety assessment of ruxolitinib due to the presence of jaundice. Elevations in LFT parameters, including ALT and AST, have been observed with oral ruxolitinib treatment. Due to lower systemic levels associated with topical administration, the risk is likely to be reduced compared to oral JAK inhibitors.

  Is it considered to be included as missing information?: No

  Rationale: The decision to treat with ruxolitinib cream is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for ruxolitinib cream.

- **Severe renal disease (with creatinine clearance < 30 ml/min) or renal disease requiring dialysis.**

  Reason for exclusion: It is a standard practice to exclude participants from clinical trials who are medically unstable and are discovered to have renal impairment. These participants require further assessment for the possible cause and may need medical management. Renal impairment and its associated metabolic derangements may confound the efficacy and safety assessment of ruxolitinib. After treatment with oral ruxolitinib, total exposure of ruxolitinib and its active metabolites increased with severe (CLcr 15 mL/min to 29 mL/min) renal impairment and ESRD on dialysis (Chen et al 2014). Due to lower systemic levels associated with topical administration, the risk is likely to be reduced compared to oral JAK inhibitors.

  Is it considered to be included as missing information?: No

  Rationale: The decision to treat with ruxolitinib cream is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for ruxolitinib cream.

- **Clinically significant abnormal TSH or free T4 at screening as determined by the investigator.**

  Reason for exclusion: Some vitiligo patients may have concurrent autoimmune thyroid disorders. Clinically significant, especially symptomatic thyroid disease such as hypothyroidism, is an easily diagnosed and treated condition. It will be considered unethical to delay the treatment of thyroid disorders. Untreated thyroid conditions may increase medical risk and confound potential response to ruxolitinib (repigmentation).

  Is it considered to be included as missing information?: No

  Rationale: The decision to treat with ruxolitinib cream is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for ruxolitinib cream.

- **Positive serology test results at screening for HIV antibody.**

  Reason for exclusion: HIV is an easily diagnosed and treatable condition which can have serious consequences if not treated in a timely manner. It will be considered unethical to delay treatment of HIV. Participants who may have concurrent HIV were excluded to enhance participants' safety and to avoid delay in treatment.

  Is it considered to be included as missing information?: No

  Rationale: The decision to treat with ruxolitinib cream is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for ruxolitinib cream.

Participants who have previously received JAK inhibitors, systemic or topical.

Reason for exclusion: This was to avoid confounding factors for efficacy caused by prior use of other drugs with a similar mode of action to ruxolitinib cream.

Is it considered to be included as missing information?: No

Rationale: This was due to confounding factors for efficacy and not for safety.

Body mass index < 17 or > 40 kg/m^2 for adult participants (age ≥ 18 years). BMI-for-age in the < 5th percentile or ≥ 85th percentile range for adolescent participants (age ≥ 12 to < 18 years) according to according to the CDC BMI Percentile Calculator for Child and Teen (2019).

Reason for exclusion: Severely underweight and morbidly obese participants may require diagnostic workup and treatment. Participants who are emaciated or malnourished may have underlying undiagnosed medical condition and require a medical assessment and nutrition supplementation. Similarly, morbid obesity is associated with adverse health outcomes and requires close follow-up and treatment such as dietary counselling, exercise regimen, and referral to bariatric surgery. Participants who were severely underweight or were morbidly obese were excluded to enhance participants' safety and to avoid delay in treatment.

Is it considered to be included as missing information?: No

Rationale: The decision to treat with ruxolitinib cream is to be made by the HCP, after consideration of the patient's medical history/present medical condition and the product information for ruxolitinib cream.

Pregnancy and lactation

Reason for exclusion: When pregnant rats and rabbits were administered oral ruxolitinib during the period of organogenesis, adverse developmental outcomes occurred at doses associated with maternal toxicity.

Is it considered to be included as missing information?: No

Rationale:

No adequate and well-controlled studies of ruxolitinib cream have been conducted in pregnant women to inform drug-associated risks. Women who were pregnant or lactating were excluded from all clinical studies. Women of childbearing potential were required to use effective contraception, and men must have been willing to abide by protocol-specified methods throughout the study to avoid fathering a child. No data are available regarding the presence of ruxolitinib in human milk, the effects on the breast-fed child, or the effects on milk production. Ruxolitinib and/or its metabolites were present in the milk of lactating rats. The SmPC contraindicates the use of ruxolitinib cream in pregnant or breastfeeding women. Considering this contraindication, use in this patient population is not considered to be relevant for inclusion as missing information.

Participants with known allergy or reaction to any component of the study formulation.

Reason for exclusion: Patients with a history of such hypersensitivities could have been at increased risk of hypersensitivity reactions to ruxolitinib cream.

Is it considered to be included as missing information?: No

Rationale: Use of ruxolitinib cream is contraindicated in patients with hypersensitivity to the active substance(s) or to any of the excipients (SmPC Section 4.3). This is considered sufficient.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The safety database is adequate to characterize the safety profile of ruxolitinib cream in patients with vitiligo. The numbers of participants with ruxolitinib cream exposures at the proposed strength and regimen (ie, 1.5% BID) exceed those recommended in the ICH E1A guideline.

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

This section aims to present the size of the safety database in each of the populations that are under-represented.

Table Part II: Module SIV.5: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Ruxolitinib cream clinical trials have been conducted globally with multiple clinical trials conducted in a variety of ethnic groups (Table Part II: Module SIII.4). The majority of participants in ruxolitinib cream clinical trials were Not Hispanic or Latino.

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 Post-Authorisation Exposure

Opzelura® (ruxolitinib cream) was approved on 21 SEP 2021 in the US and is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Opzelura (ruxolitinib) cream was approved in the US for the topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older. Approval for this indication was received on 18 JUL 2022, after the clinical cutoff date for this RMP.

Ruxolitinib cream is not approved in any other country.

SV.1.1 Method Used to Calculate Exposure

In order to calculate the worldwide postmarketing exposure for Opzelura, an estimated standard monthly dose of 60g was selected for the indication of atopic dermatitis as approved in the United States.

SV.1.2 Exposure

The worldwide postmarketing exposure for Opzelura as of 20 JUN 2022, was approximately 8,665 patient years of treatment (PYT).

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

While no clinical trials have been conducted to evaluate dependence potential for ruxolitinib cream, no evidence has emerged that would suggest a potential for abuse or dependence.

Drug products with abuse potential generally contain drug substances that have central nervous system (CNS) activity and produce euphoria (or other changes in mood), hallucinations, and effects consistent with CNS depressants or stimulants (FDA 2017).

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

An evaluation of the risks for ruxolitinib cream was conducted in accordance with Revision 2 to the guideline on GVP Module V – Risk Management Systems (31 March 2017). A careful review of the available data was performed to determine if the identified and potentials risks met the criteria for important, in line with the revised GVP Module V. Based on this review, the following risks were not considered to have an impact on the risk-benefit balance of the product and therefore do not qualify for inclusion into the list of safety concerns for the purpose of risk management planning.

Adverse reactions with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Application site acne

The following are potential risks that require no further characterisation and will be followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting.

Significant systemic exposure to the active ingredient following dermal penetration

A critical safety consideration for topical drugs is whether application to the skin results in significant systemic exposure to the active ingredient following dermal penetration. To this end, plasma ruxolitinib concentrations following topical application of ruxolitinib cream were evaluated.

Consistent with the low systemic availability of ruxolitinib following topical administration, no evidence of systemic toxicity was observed in Gottingen minipigs following topical administration of 1.5% ruxolitinib cream formulation to 10% of body surface area twice daily for up to 9 months. Refer to Part II: Module SII Repeat-Dose Studies for additional information on systemic exposure from pre-clinical studies.

The likelihood of adverse effects caused by systemic exposure is low based on the low plasma concentrations following topical applications of ruxolitinib cream in the Phase 3 vitiligo studies. Specific instructions on how to use ruxolitinib cream are provided in Section 4 of the SmPC. The MAH will continue to monitor for known systemic effects of oral JAKs through routine ongoing safety surveillance.

In the Phase 3 studies in participants with vitiligo, both arithmetic and geometric mean trough concentrations of ruxolitinib in plasma (C_{ss}; 56.9 nM and 27.4 nM, respectively, for the DB period of the Phase 3 studies) following topical applications of 1.5% ruxolitinib cream BID to 3% to 10% BSA were low. The mean daily average application amount of ruxolitinib free base equivalent was 65.8 mg, that is, 4.4 grams of 1.5% ruxolitinib cream per day. Considering the modest peak/trough ratio, the ruxolitinib $C_{avg,ss}$ in plasma following topical applications of 1.5% ruxolitinib cream BID would be marginally higher than the trough concentrations. However, steady-state daily exposure levels for participants with vitiligo who applied ruxolitinib 1.5% cream BID (geometric mean C_{ss} = 27.4 nM) were ~ 12.6% of levels observed following oral administration of ruxolitinib 15 mg BID (geometric mean $C_{avg,ss}$ = 218 nM as derived from $AUC_{ss,0-12h}$ = 2610 h·nM) in healthy participants. Likewise, they are ~10% of the ruxolitinib IC_{50} for JAK2 inhibition in whole blood assays (281 nM; Quintás-Cardama et al 2010).

Maximum Use Study

In the maximum-use study, INCB 18424-103, where ruxolitinib 1.5% cream BID was applied onto extensive skin lesions (mean total BSA involvement at baseline was 38.1% [range: 25%-90%]) in adolescents and adults with atopic dermatitis, the mean plasma concentration-time profile was nearly flat, and the mean peak/trough ratio was 2.72. Considering the modest peak/trough ratio, the ruxolitinib $C_{avg,ss}$ following topical applications of ruxolitinib 1.5% cream BID would be marginally higher than the trough concentrations. Despite treatment being under conditions of "exaggerated" (maximum) use, such levels are only a small fraction of $C_{avg,ss}$ (arithmetic and geometric mean at 226 nM and 218 nM, respectively) in healthy participants treated with multiple oral doses of ruxolitinib 15 mg BID, as well as a small fraction of the ruxolitinib IC_{50} for JAK2 inhibition in whole blood assays (281 nM). The likelihood of adverse effects caused by systemic exposure following topical application of ruxolitinib cream is therefore low.

Adverse events of interest for oral ruxolitinib and other oral JAK inhibitors

The following are adverse events of interest for oral ruxolitinib and other oral JAK inhibitors that have been evaluated as potential risks for ruxolitinib cream. Due to lower systemic levels associated with topical administration, the risk of these events is likely to be reduced compared to oral JAK inhibitors. Overall, the events of interest (ie, cytopenias [erythropenia, neutropenia, and thrombocytopenia], infections including serious infections, herpes zoster and other viral skin infections and malignancies, LFT elevations, MACE, and arterial and venous thromboembolic and thrombocytosis events) were infrequent and mostly considered unrelated to study drug by the investigators. Incidence rates of these events were consistent with the expected rates (when available) in the general population and/or the patient populations under investigation. Based on review of all available evidence from the clinical and safety databases, including the addition of treatment extension period data from the Phase 3 studies, a causal relationship between the

events of interest and ruxolitinib cream could not be established. Following review, these adverse events of interest for oral ruxolitinib and other oral JAK inhibitors require no further characterisation and will be followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting. A detailed justification for not including as a potential risk in the list of safety concerns is provided for each topic below.

Safety data were analyzed for 4 pooled populations as follows:

Phase 3 Vitiligo Vehicle-Controlled Population: Adolescent and adult participants who applied vehicle cream (224 participants) or 1.5% ruxolitinib cream (449 participants) at least once during the 24-week double-blind period in the Phase 3 studies in participants with vitiligo (INCB 18424-306 and -307); 673 participants).

Phase 3 Vitiligo 52-Week Population: Adolescent and adult participants who applied study drug at least once during 52-week treatment period in the Phase 3 studies (INCB 18424-306 and -307; 673 participants).

Phase 2/3 Vitiligo Population: Adolescent and adult participants who applied vehicle cream or ruxolitinib cream at least once during any treatment period in the Phase 2 and Phase 3 studies in participants with vitiligo (Studies INCB 18424-211, -306, -307, and -308 [Cohort B only]); 830 participants).

All Ruxolitinib Cream Population: Adolescent and adult participants with inflammatory skin diseases (vitiligo, atopic dermatitis, other indications) who applied ruxolitinib cream at least once (Studies INCB 18424-102 [Cohorts 1 and 2 only], -201, -202, -203, -204, -206, -211, -303, -304, -306, -307 and -308 (Cohort B only); 2579 participants).

Cytopenias (erythropenia, thrombocytopenia, neutropenia)

The dependence of erythropoietin and thrombopoietin signaling on JAK2 and the dependence of granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor signaling on JAK2 and JAK1, respectively, result in a potential for cytopenias as consequences of prolonged JAK1 and JAK2 inhibition (Parganas et al 1998, Schindler et al 2007, Shimoda et al 1997). Such hematological events were not anticipated with ruxolitinib cream, owing to the low bioavailability and plasma concentrations of ruxolitinib cream after topical application.

To evaluate specific hematologic TEAEs, the hematopoietic erythropenia, hematopoietic thrombocytopenia, and hematopoietic leukopenia SMQs were reviewed, and clinically relevant terms were identified for erythropenia, thrombocytopenia, and neutropenia. These focused MedDRA queries were run against the integrated clinical database. Other data that inform the analysis of cytopenia events include laboratory and PK data. Analyses of data from the Phase 2 and 3 studies in participants with vitiligo were performed to explore and summarize the relationships between the trough plasma concentrations of ruxolitinib after topical application and the clinical laboratory test results (platelet count, MPV, hemoglobin, and neutrophil count) by visit during the double-blind period.

The results of the analyses demonstrate that treatment-emergent erythropenia, thrombocytopenia, and neutropenia AEs were infrequent, and there were no meaningful trends (decreases) in the corresponding laboratory parameters.

Plasma concentration-safety analyses in the 3 vitiligo studies demonstrated that there was no correlation between C_{ss} categories (quartiles) and decreases in hemoglobin levels, absolute neutrophil counts, MPVs, and platelet counts.

All cytopenia events in participants in the Phase 2/3 Vitiligo Population were nonserious and were Grade 1 or 2 in severity. The majority of erythropenia, neutropenia, and thrombocytopenia events resolved with no action taken with the study drug due to the event.

The MAH will continue to monitor cytopenias (erythropenia, thrombocytopenia, neutropenia) through routine ongoing safety surveillance.

Liver enzyme elevations

Elevations in LFT parameters, including ALT and AST, have been observed with oral ruxolitinib treatment (Jakafi 2022). To evaluate the potential of ruxolitinib cream to induce LFT elevations, the integrated clinical database was queried for AEs in the liver-related investigations, signs and symptoms SMQ. The results of these analyses demonstrate that LFT elevation TEAEs were infrequent, as were worsening shifts from baseline in the corresponding clinical chemistry laboratory test values. In addition, no clinically relevant trends in changes in LFTs were observed in participants in the pooled populations. No TEAEs met the criteria for Hy's law.

In the Phase 2/3 Vitiligo population, the incidences of TEAEs in the liver-related investigations, signs and symptoms SMQ through the data cutoff date were low (0.8%, 2.3%, and 2.2% of participants in the vehicle cream BID, ruxolitinib 1.5% cream QD and ruxolitinib 1.5% cream BID groups, respectively). All TEAEs identified were related to LFT elevations (most frequently ALT and AST elevations), none of which occurred in ≥ 2% of participants in any treatment group. Liver function test elevation TEAEs were nonserious and Grade 1 or 2 in severity and the majority of LFT elevation TEAEs resolved with no action taken with the study drug. The MAH will continue to monitor liver enzyme elevations through routine ongoing safety surveillance.

Infections (including Herpes Zoster and other viral skin infections)

Infections

An analysis of TEAEs in the infections and infestations SOC among participants with vitiligo was conducted.

In the Phase 2/3 Vitiligo Population, the majority of infection and infestation events were Grade 1or 2 in severity and nonserious. The most frequently reported TEAEs were COVID-19, nasopharyngitis, and upper respiratory tract infection. The TEAEs of COVID-19, nasopharyngitis, upper respiratory tract infection, and urinary tract infection were slightly more common in the ruxolitinib 1.5% cream BID group than in the vehicle cream BID group, which can be expected given the much shorter duration of exposure. Adjusting for study size and exposure, the difference in the crude incidence of COVID-19 and urinary tract infection is reduced (< 2 events per 100 PY) and the difference in the crude incidence of nasopharyngitis and upper respiratory tract infection is no longer evident. No other events had a higher frequency (≥ 2% difference) and no event had a higher IR (≥ 2 events per 100 PY) in the ruxolitinib cream total group compared to the vehicle cream group.

Serious Infections

Serious infections due to bacterial, mycobacterial, invasive fungal, viral or other opportunistic pathogens have been reported in patients receiving oral JAK inhibitors. Although the likelihood of such events following application of ruxolitinib cream was low given the observed plasma concentrations, which tended to be low and at levels unlikely to have any impact on the progenitor blood cells in the bone marrow, a review of the clinical database was performed to determine if there were any serious infections with possible relationship to the study drug.

Serious TEAEs in the infections and infestations SOC among participants with vitiligo included the following: serious events of appendicitis (Grade 4), appendiceal abscess (Grade 4), hepatitis infectious mononucleosis (Grade 3), COVID-19 (Grade 4), and COVID-19 pneumonia (Grade 4) in 1 participant each in the ruxolitinib 1.5% cream BID treatment group. None of these events was considered related to the study drug by the investigator, and each of these events resolved. Only the events of hepatitis infectious mononucleosis and the serious event of COVID-19 led to a modification to the study treatment: study drug interruption. Serious infections that are typically of concern with oral JAK inhibitors were not observed among participants in the Phase 2/3 Vitiligo Population.

As assessment of the ruxolitinib concentrations for participants with serious TEAEs in the infections and infestations SOC yielded no clear pattern; all concentrations were below the IC_{50} for JAK2 inhibition (281 nM). Two of the participants with COVID-19-related TEAEs had moderate plasma ruxolitinib concentrations (Css for each participant: 97.6 and 135 nm). Of note, each of the events related to COVID 19 occurred in a participant with risk factors for severe disease (diabetes mellitus, BMI > 30 kg/m2, and/or extensive history of cardiovascular disease) and no record of having received the COVID 19 vaccine.

Altogether, there is no evidence that events of serious and severe infections observed in the ruxolitinib cream program were caused by ruxolitinib cream. The rate of serious and severe infections was low, and an assessment of the ruxolitinib concentrations for participants with serious and/or severe infections yielded no clear pattern. The MAH will continue to monitor serious infections through routine ongoing safety surveillance.

Herpes Zoster

Herpes zoster (caused by varicella zoster virus), the incidence of which appears to be increasing in recent decades, is not infrequent in the general population (7.2 per 1000 PY in adults aged ≥ 35 years in 2016; Hales et al 2013, Harpaz and Leung 2019, Kawai et al 2016), and the probability of herpes zoster recurrence is correlated with increasing age (Harpaz and Leung 2019).

A focused MedDRA query for herpes zoster events was developed to aggregate AEs (PTs) that are similar in nature, and was used to search the integrated clinical database. The following PTs were included in the query for herpes zoster events: genital herpes zoster, herpes zoster, herpes zoster cutaneous disseminated, herpes zoster disseminated, herpes zoster infection neurological, herpes zoster meningitis, herpes zoster meningoencephalitis, herpes zoster meningomyelitis, herpes zoster meningoradiculitis, herpes zoster necrotising retinopathy, herpes zoster oticus, herpes zoster pharyngitis, ophthalmic herpes zoster, and post herpetic neuralgia.

There were no participants with herpes zoster in the Phase 3 Vitiligo Vehicle-Controlled Population. The proportions of participants with herpes zoster in the Phase 2/3 Vitiligo Population (0.5% of participants in the ruxolitinib cream total group; exposure-adjusted IR of 6 per 1000 PY) were low and comparable to the general population (7.2 per 1000 PY in adults aged ≥ 35 years in 2016; Hales et al 2013, Harpaz and Leung 2019, Kawai et al 2016).

All herpes zoster events in participants with vitiligo resolved without interruption of the study drug. Clinical manifestations for the events of herpes zoster in participants with vitiligo were limited to cutaneous uncomplicated disease for all participants except for 1 participant who had post-herpetic neuralgia.

The majority of the events were reported in participants ≥ 50 years of age. Increased age is a risk factor for herpes zoster (Harpaz and Leung 2019).

The MAH will continue to monitor herpes zoster infections through routine ongoing safety surveillance.

Other Viral Skin Infections

The integrated clinical database was queried for AEs using the HLT skin and subcutaneous tissue viral infections. The overall incidences of TEAEs in the skin and subcutaneous viral skin infections HLT are inclusive of TEAEs of herpes zoster.

The global prevalence of herpes simplex Type 2 is approximately 11.3%, with a global incidence in the general population of approximately 0.5% (Looker et al 2015b). The global burden of herpes simplex Type 1 is much more substantial, with an approximate prevalence of 67% and a global incidence in the general population of approximately 2% (Looker et al 2015a). In comparison, the overall incidence of herpes simplex for the largest integrated dataset, the All Ruxolitinib Cream Population, remained low (0.4% for all ruxolitinib cream treatment groups). The below refers only to other viral skin infections that were identified in the clinical database for vitiligo: herpes simplex and varicella. These other viral skin infections were infrequent, Grade 1 or 2 in severity, and nonserious. The majority of events were not considered related to the study drug by the investigator.

Herpes Simplex

In the combined Phase 3 Vitiligo Vehicle-Controlled Population and the Phase 2/3 Vitiligo Population, 1 participant in the ruxolitinib 1.5% cream BID treatment group had 2 events of herpes simplex; 1 during the double-blind period and 1 during the treatment extension period. Both events were nonserious and resolved with concomitant medication and with no action taken with the study drug within 10 days; neither event was considered related to study drug. In the Phase 2/3 Vitiligo Population, an additional 2 participants in the ruxolitinib 1.5% cream BID treatment group had a TEAE of herpes simplex. Both events were nonserious and considered not related to the study drug. One event had recovered/resolved and the other event was recovering/resolving; both participants were ongoing in the treatment extension study.

Varicella

One participant, a 29-year-old man in the ruxolitinib 1.5% cream BID treatment group, had a Grade 2, nonserious TEAE of varicella during the treatment-extension period. The event resolved with concomitant medication within 14 days and with no action taken with the study

drug; the event was considered not related to the study drug. This was the only event of varicella among participants in the All Ruxolitinib Cream Population.

The MAH will continue to monitor other viral skin infections through routine ongoing safety surveillance.

Malignancies (excluding NMSC)

Analyses were performed against the integrated clinical database for the ruxolitinib cream studies to evaluate the additional category of malignancies in response to results from a randomized study that showed a higher occurrence of cancer in rheumatoid arthritis patients treated with both doses of oral tofacitinib compared to patients treated with aTNF inhibitor (Ytterberg et al 2022). NMSC at long-term use is considered an important potential risk and is presented in Section Part II: Module Section SVII.3.1. The following is an analysis of malignancies, excluding NMSC.

To evaluate TEAEs of malignancies, events under the SOC of neoplasms benign, malignant, and unspecified (including cysts and polyps) were reviewed.

An analysis of the malignancies in the Phase 3 Vitiligo Vehicle-Controlled Population, Phase 3 Vitiligo 52-Week Population, and Phase 2/3 Vitiligo Population showed a very low incidence of malignancies and no significant differences between groups (1 participant [0.4%] in the vehicle cream BID group and 3 participants [0.5%] in the ruxolitinib 1.5% cream group. Malignancies among participants with vitiligo included breast cancer, ovarian cancer (nonserious), papillary thyroid cancer, and prostate cancer in 1 participant each. These events were rare and sporadic, all occurred in unrelated organ systems, and could be explained by alternate etiologies. Based on this analysis, no association of malignancies and ruxolitinib cream was evident. The MAH will continue to monitor malignancies through routine ongoing safety surveillance.

Arterial and venous thromboembolic events and major adverse cardiovascular events (MACE)

Concerns have been raised regarding a class effect of venous and arterial thromboembolism and MACE with oral JAK inhibitors. The mechanism that would link JAK1 or JAK2 inhibition with thromboembolic events or MACE, is not known. Oral ruxolitinib has not been associated with an elevated risk for venous thromboembolic events and MACE, or for arterial thromboembolic events or thrombocytosis. In order to assess these potential risks for ruxolitinib cream, multiple approaches were used including:

- Querying the integrated ruxolitinib cream clinical database for arterial and venous thromboembolic events (embolic and thrombotic events SMQ) and thrombocytosis events.
- Reviewing the integrated ruxolitinib cream clinical database for MACE (the full list of MedDRA HLTs and Preferred Terms, by FDA MACE definition, are provided for reference in Appendix B of the ruxolitinib cream 2.7.4 Summary of Clinical Safety).
- Assessing the risks of these arterial and venous thromboembolic events as measured by clinical laboratory data in the integrated ruxolitinib cream clinical database, specifically increases in platelet counts and MPV, as well as assessing the relationship between the trough plasma concentrations of ruxolitinib after topical

application and platelet counts and MPV during the double-blind period of the Phase 3 studies.

A limited number of events representing arterial and venous thromboembolic events and MACE were retrieved. The majority of the cases were confounded by significant risk factors (including but not limited to personal and/or family history of hypertension, hyperlipidaemia, heart disease, diabetes mellitus, smoking). None of the cases were considered to be related to ruxolitinib cream or vehicle by the investigator or the sponsor.

Based on the available evidence from these various data sources, no causal relationship between thromboembolic events or MACE and topical ruxolitinib has been established. The MAH will continue to monitor arterial and venous thromboembolic events and MACE through routine ongoing safety surveillance.

Withdrawal/rebound effect

"Rebound and withdrawal are phenomena, which are due to tolerance/dependence on and/or discontinuation of the medicinal product. Rebound is defined as an increase of symptoms immediately after treatment is stopped, whereas withdrawal is the development of symptoms different from the original ones" (EMEA 2002).

Withdrawal or rebound is a systemic safety consideration based on oral ruxolitinib. In Section 7 'Adverse drug reactions' of the oral ruxolitinib CDS, it has been stated that upon discontinuation, MF patients may experience a return of MF-symptoms. No withdrawal or rebound effects were observed in PV patients treated with oral ruxolitinib. The topic 'AEs after discontinuation of ruxolitinib (with return of MF symptoms)' was previously included in the oral ruxolitinib RMP as an important potential risk. In compliance with the GVP Module V, Revision 2, 'AEs after discontinuation of ruxolitinib (with return of MF symptoms)' has been removed as an important potential risk in the in the approved oral ruxolitinib RMP version 12.1.

An ad hoc analysis to gain insight into rebound effects following discontinuation of ruxolitinib cream was performed using longer term data collected from participants in Study INCB 18424-211 who applied ruxolitinib 1.5% cream at least once during the open-label extension period (Weeks 52 to 156) and had at least 1 nonmissing value during the follow-up period of up to 6 months; a total of 70 participants were included in this analysis. Rebound was conservatively defined as an F-VASI score during the follow-up period that was ≥ 25% higher than the F-VASI score at baseline. No true case of rebound was identified.

A review of treatment-emergent AEs reported during the follow-up period revealed few in number (4 participants had a total of 7 events), and an analysis of the events demonstrated no evidence of rebound of vitiligo and no safety concerns associated with discontinuing treatment with ruxolitinib cream.

The results from these analyses suggest that the likelihood of rebound after treatment discontinuation is low. The MAH will continue to monitor withdrawal/rebound effect through routine ongoing safety surveillance.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk:

There are currently no Important Identified Risks for ruxolitinib cream.

Important Potential Risk: Non-melanoma skin cancer (NMSC) at long-term use

Risk-benefit impact:

Non-melanoma skin cancer (NMSC) is considered a potential class effect of oral JAK inhibitors, and 52 weeks of follow-up is not considered sufficient to determine if ruxolitinib cream could contribute to the induction of NMSC. The risk-benefit impact of ruxolitinib cream remains favourable when used in accordance with the proposed SmPC. NMSC will continue to be monitored as an important potential risk.

Important Potential Risk: Embryo-foetal toxicity

Risk-benefit impact:

Embryo-foetal toxicity was observed following oral administration of ruxolitinib to rats and rabbits during gestation; similar findings have been identified in nonclinical studies with other JAK inhibitors. The conclusions from the non-clinical data point to a potential relevant risk in humans. Additionally, human PK data show that there is a non-negligible systemic exposure after ruxolitinib cream application, so negative effects from dermal use of ruxolitinib during pregnancy on developing foetus cannot be entirely excluded.

No adequate and well-controlled studies of ruxolitinib cream have been conducted in pregnant women to inform drug-associated risks. Women who were pregnant or lactating were excluded from all clinical studies. Women of childbearing potential were required to use effective contraception, and men must have been willing to abide by protocol-specified methods throughout the study to avoid fathering a child.

In the absence of data, ruxolitinib cream should not be used by pregnant women. The risk-benefit impact of ruxolitinib cream remains favourable when used in accordance with the proposed SmPC.

Missing Information: Impaired bone growth and development in paediatric patients < 18 years of age

Risk-benefit impact:

Based on currently available data, it is difficult to assess and draw a conclusion on the impact of long-term use of ruxolitinib cream on growth in children. The risk-benefit impact of ruxolitinib cream remains favourable when used in accordance with the proposed SmPC.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

This section is not applicable as this is an initial RMP.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk:

There are currently no Important Identified Risks for ruxolitinib cream.

Important Potential Risk: Non-melanoma skin cancer (NMSC) at long-term use

PT(s):

HLT skin neoplasms malignant and unspecified (excluding melanoma)

Potential mechanisms:

Unknown

Evidence source(s) and strength of evidence:

NMSC is considered a potential class effect of oral JAK inhibitors. A causal relationship between NMSC and oral ruxolitinib has not been established.

NMSCs, predominantly basal cell carcinomas, have been reported in patients treated with topical ruxolitinib. Most of these patients had risk factors, such as prior phototherapy or prior NMSC. A causal relationship to topical ruxolitinib has not been established based on available safety data. A 52-week follow-up is not considered sufficient to determine if ruxolitinib cream could contribute to the induction of NMSC.

Based on the limited long-term follow-up and because NMSC is considered a potential class effect of oral JAK inhibitors, NMSC at long-term use of topical ruxolitinib will continue to be monitored as an important potential risk.

Characterisation of the risk:

To evaluate the risk of nonmelanoma skin neoplasms, the integrated clinical database was queried for AEs using the HLT skin neoplasms malignant and unspecified (excluding melanoma). A total of 6 participants had a TEAE of nonmelanoma skin neoplasms across the vitiligo studies: 1 participant in the Phase 3 Vitiligo Vehicle-Controlled Population (vehicle cream BID treatment group; squamous cell carcinoma), 1 participant in the Phase 3 Vitiligo 52 Week Population (ruxolitinib 1.5% cream BID group; basal cell carcinoma), and 4 participants in the Phase 2/3 Vitiligo Population (all from study 211 whom received ruxolitinib cream, had either basal cell carcinoma or Bowen's disease). In one participant, the event(s) did not occur at an application site. All of participants had at least 1 risk factor including but not limited to personal medical history of basal cell carcinoma, prior treatment with corticosteroids, photochemotherapy, phototherapy, UVA, and/or topical tacrolimus that may have predisposed them to the events.

The frequency of nonmelanoma skin neoplasms was 0.6% in the Phase 2/3 Vitiligo Population (5 of 789 participants [0.6%] in the ruxolitinib cream treatment group and 1 of 256 participants [0.4%] in the vehicle cream treatment group) compared with approximately 5% in the general US population (Stern 2010), while the background rate of basal cell carcinoma was estimated to

be 1.4% and almost 4 times higher (5.4%) in the oldest age subgroup (≥ 65 years) in the Netherlands (Flohil et al 2011).

Risk factors and risk groups:

While the role of ultraviolet radiation in the pathogenesis of squamous cell carcinoma is undisputable, it has also been cited as the most important risk factor in the development of basal cell carcinoma (Bhari et al 2016, Situm et al 2008). Basal cell carcinoma, has been reported in patients with vitiligo treated with phototherapy. This may be explained by the mechanism of thymine dimer formation and cumulative DNA damage by ultraviolet light, which results in numerous mutations and local immune system depression leading to decreased immune surveillance for new tumor cells (Situm et al 2008). In the Phase 2/3 Vitiligo Population, 29.6% of participants had received phototherapy prior to enrolling in the studies.

Other risk factors include patients with a personal or family history of NMSC or pre-malignant skin lesions, sun beds, skin type 1 or 2, immunosuppression, occupational exposure to chemicals (coal tar, creosote, arsenic, radium or pitch) and previous radiotherapy (Situm et al 2008, Perera 2014).

Preventability:

Periodic skin examination is recommended for patients who are at increased risk for skin cancer. Limiting sun exposure, wearing UV protective clothing and sunscreen can also help reduce risk factors for NMSC (Perera 2014).

Impact on the risk-benefit balance of the product:

The likelihood of adverse effects caused by systemic exposure following topical application of ruxolitinib cream is low. The benefit-risk balance of ruxolitinib cream remains favourable when used in accordance with the SmPC.

Public health impact:

Due to lower systemic levels associated with topical administration, the risk of these events is likely to be reduced compared to oral JAK inhibitors. Since these patients are usually under the care of dermatologists, who provide guidance on the avoidance of UV damage to the skin and can monitor the skin for early lesions, the potential public health impact is low.

Important Potential Risk: Embryo-foetal toxicity

PT(s):

SMQ Pregnancy and Neonatal Topics (broad)

Potential mechanisms:

Unknown

Evidence source(s) and strength of evidence:

There are limited data from the use of ruxolitinib in pregnant women. Data on systemic absorption of topical ruxolitinib during pregnancy are lacking. There could be individual factors (e.g. damaged skin barrier, excessive use) that contribute to an increased systemic exposure.

Embryo-foetal toxicity was observed following oral administration of ruxolitinib to rats and rabbits during gestation; similar findings have been identified in nonclinical studies with other JAK inhibitors. The conclusions from the non-clinical data point to a potential relevant risk in humans. Additionally, human PK data show that there is a non-negligible systemic exposure after ruxolitinib cream application, so negative effects from dermal use of ruxolitinib during pregnancy on developing foetus cannot be entirely excluded.

Characterisation of the risk:

In embryo-foetal development studies, oral administration of ruxolitinib to rats and rabbits during gestation resulted in decreased foetal weight and increased post-implantation loss at doses associated with maternal toxicity. There was no evidence of a teratogenic effect in rats and rabbits. Margins (based on unbound AUC) at non-adverse levels for developmental toxicity in rats were approximately 25-fold the systemic exposure observed in patients with vitiligo that applied 1.5% ruxolitinib cream twice daily. No effects of oral ruxolitinib were noted on fertility in male or female rats. In a pre- and post-natal development study, a slightly prolonged gestation period, reduced number of implantation sites, and reduced number of pups delivered were observed. In the pups, decreased mean initial body weights and short period of decreased mean body weight gain were observed. The potential risk for humans is unknown.

A total of 11 pregnancies and 4 pregnancies of a partner have been reported across the ruxolitinib cream clinical development program as of the data cutoff dates for the ongoing studies. When pregnancy outcomes were known, 5 pregnancies resulted in a term birth and healthy infant, and 2 participants had TEAEs of abortion spontaneous. Both spontaneous abortions were assessed as unrelated to study drug by the investigator.

The proposed product label lists pregnancy under “Contraindications”.

Risk factors and risk groups:

Women of child bearing potential not using effective contraception.

Preventability:

Exposure during pregnancy can be prevented by ensuring women of child bearing potential use effective contraception and that ruxolitinib is not used during pregnancy. Use of ruxolitinib cream during pregnancy is contraindicated in the SmPC.

Impact on the risk-benefit balance of the product:

The benefit-risk balance of ruxolitinib cream remains favourable when used in accordance with the SmPC.

Public health impact:

The potential public health impact is minimal if taking preventative measures as outlined in the SmPC.

SVII.3.2 Presentation of the Missing Information

Missing information: Impaired bone growth and development in paediatric patients < 18 years of age

PT(s):

'Bone development abnormal' and paediatric patients < 18 years of age.

Evidence source:

Based on non-clinical data in juvenile animals, a risk for detrimental bone effects is unlikely for children and adolescents, also because the effects were only seen at exposures 35x higher than the human exposure after topical use. Bone development abnormality has not been identified for topical ruxolitinib in adolescents. Based on currently available data, it is difficult to assess and draw a conclusion on long-term use of ruxolitinib cream regarding the growth in children. Therefore, 'impaired bone growth and development in paediatric patients <18 years' is included in the RMP as missing information.

Anticipated risk/consequence of the missing information:

The anticipated risk cannot be characterized due to limited information. To further characterize the safety concern, the routine pharmacovigilance activities will be supplemented with additional pharmacovigilance activities: study INCB 18424-308 (ongoing) and study INCB 18424-309 (planned). Further characterization will also occur based on continuous monitoring of this topic in PSURs.

PART II: MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Table Part II: Module SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Non-melanoma skin cancer at long-term use Embryo-foetal toxicity
Missing information	Impaired bone growth and development in paediatric patients < 18 years of age

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

In order to address the Important Potential Risk of embryo-foetal toxicity, the MAH has an established process, including multiple attempts for the collection of follow-up information, from clinical trials or post-marketing for both Prospective and Retrospective Pregnancy Reports using standard pregnancy forms. With each follow-up attempt, a clinical trial or post-marketing pregnancy form is provided to the reporter/HCP to ensure all relevant information pertaining to the pregnancy and outcomes of the pregnancy (e.g. complications, congenital anomalies, etc.) are collected. The Standard Pregnancy Forms are provided in Annex 4.

Other forms of routine pharmacovigilance activities:

There are currently no other forms of routine pharmacovigilance activities for ruxolitinib cream.

III.2 Additional Pharmacovigilance Activities

To further address the Important Potential Risk of NMSC at long-term use, the below post-authorisation safety study (PASS) is proposed as an additional pharmacovigilance activity:

Study INCB88888-037: Evaluation of the Incidence of Non-Melanoma Skin Cancer after Long-term exposure to Ruxolitinib Cream

Study Rationale: Vitiligo and Non Melanoma Skin Cancer

Recent data have been published that draw a relationship between JAK inhibitors and non-melanoma skin cancers, including basal cell and squamous cell carcinomas (Lin et al 2022, Greif et al 2021). Such literature findings have suggested that in chronic inflammatory conditions, patients with such underlying disease may also be at risk for outcomes of NMSC. Upon review of the marketing application for ruxolitinib cream, and in alignment with previously published safety risks concerning oral JAK inhibitors, the European Medicines Agency requested consideration of a non-interventional clinical study to evaluate the relationship between the long-term use of ruxolitinib cream for vitiligo, and the development of non-melanoma skin cancers.

Study Objectives:

Primary Objective: The objective of this study is to evaluate the safety of long-term ruxolitinib cream use with respect to incidence of non-melanoma skin cancers.

Endpoints for evaluation of the primary objective are Incident Non-melanoma skin cancers in a cohort exposed to ruxolitinib cream as compared to those unexposed to ruxolitinib cream.

Study Design:

This is a post-authorisation, observational cohort study using an accumulated approach reported annually to describe the incidence of NMSC.

Study Population:

The population of this study will be defined using the following categories.

Exposed to Ruxolitinib cream: Patients with at least 12 months of expected exposure to ruxolitinib cream will be identified using algorithms based on prescribed dose and frequency and days supply. Patients exposed to ruxolitinib cream will separated into two categories:

1. Patients with exposure to ruxolitinib cream and evidence of concurrent or recent phototherapy
2. Patients with exposure to ruxolitinib cream and no evidence of concurrent or recent phototherapy

Patients will also be grouped into a full cohort of patients comprising all patients who have been exposed.

Unexposed to Ruxolitinib cream: Those patients comprising the unexposed cohort will be further stratified into four groups of unexposed patients. These include the following:

1) Those with diagnosed vitiligo but who have no evidence of treatment;

2) Those with diagnosed vitiligo with exposure to TCI/TCS and no phototherapy;

3) Those with diagnosed vitiligo with exposure to TCI/TCS with phototherapy, and

4) Those with diagnosed vitiligo with exposure to phototherapy alone.

Patients will also be grouped into a full cohort representing all patients without exposure to ruxolitinib cream.

Milestones:

Protocol submission - within 6 months of EC decision

Start of data collection - June 2025

End of data collection – June 2029

Registration in the EU PAS Register – Before the start of the study

Final report of study results – 2030

To further characterize the Missing Information, the below studies are proposed as additional pharmacovigilance activities:

Study INCB 18424-308: A Double-Blind, Vehicle-Controlled, Randomized Withdrawal and Treatment Extension Study to Assess the Long-Term Efficacy and Safety of Ruxolitinib Cream in Participants with Vitiligo (TRuE-V LTE)

Study Rationale:

This study is designed to evaluate the duration of response following withdrawal of ruxolitinib cream (Cohort A vehicle group) and maintenance of response with continued use of ruxolitinib cream in individuals with vitiligo who have experienced repigmentation with ruxolitinib cream

treatment. This study is also designed to characterize the long-term efficacy and safety profile of ruxolitinib cream in individuals with vitiligo treated for up to a total of 104 weeks.

Study Objectives:

To evaluate the duration of clinical response of ruxolitinib cream in participants with vitiligo.

Study Design:

Double-blind, vehicle-controlled, randomized withdrawal (Cohort A) and treatment extension (Cohort A and Cohort B).

Study Population:

Male and female participants from Study INCB 18424-306 or Study INCB 18424-307 (parent studies) conducted in adults and adolescents with vitiligo who adequately completed the visits and assessments required for the treatment periods, as defined in the parent study protocol, and tolerated ruxolitinib cream treatment without safety concern for continuation.

Milestones:

Study completed – December 2022

CSR completion – June 2023

Study INCB 18424-309: Double-blind, randomised, placebo-controlled trial to evaluate efficacy and safety of ruxolitinib cream in children from 6 years to less than 12 years of age with non-segmental vitiligo

Study Rationale/Objectives:

To evaluate efficacy and safety of ruxolitinib cream in children from 6 years to less than 12 years of age with non-segmental vitiligo

Study Design:

Double-blind, randomised, placebo-controlled trial

Study Population:

Males and females, aged 6 to less than 12 years, diagnosed with non-segmental vitiligo and with proven psychological impairment due to vitiligo

Milestones:

LPLV: December 2027

Milestones will be aligned with the Paediatric Investigation Plan.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III-1: Ongoing and Planned Additional Pharmacovigilance Activities

Study **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Study INCB88888-037 (PASS) Planned	To evaluate the safety of long-term ruxolitinib cream use with respect to incidence of non-melanoma skin cancers	NMSC at long-term use	Protocol submission - within 6 months of EC decision First report to contain data on use of ruxolitinib cream from 2023-mid 2025 Interim reports to be provided yearly with updated available data for period of 5 years.	First report expected availability Dec 2025 Interim reports provided annually from 2026 to 2029
			Final report	2030

Study **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Study INCB 18424-308 Completed	To evaluate the duration of clinical response of ruxolitinib cream in participants with vitiligo.	Impaired bone growth and development in paediatric patients < 18 years of age	Final CSR	June 2023
Study INCB 18424-309 Planned	To evaluate efficacy and safety of ruxolitinib cream in children from 6 years to less than 12 years of age with non-segmental vitiligo	Impaired bone growth and development in paediatric patients < 18 years of age	LPLV Milestones will be aligned with the Paediatric Investigation Plan.	December 2027

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1 Routine Risk Minimisation Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Non-melanoma skin cancer at long-term use	Routine risk communication: SmPC section 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Periodic skin examination is recommended for patients who are at increased risk for skin cancer (see section 4.4). Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription. Per SmPC: Opzelura should be initiated and supervised by physicians with experience in the diagnosis and treatment of non-segmental vitiligo.
Embryo-foetal toxicity	Routine risk communication: SmPC sections 4.3 and 4.6 Routine risk minimisation activities recommending specific clinical measures to address the risk: Women of childbearing potential have to use effective contraception during treatment and for 4 weeks after discontinuation of treatment. Opzelura is contraindicated during pregnancy (see section 4.3 and 4.6). Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription. Per SmPC: Opzelura should be initiated and supervised by physicians with experience in the diagnosis and treatment of non-segmental vitiligo.

Safety concern	Routine risk minimisation activities
Impaired bone growth and development in paediatric patients < 18 years of age	Routine risk communication: SmPC section 4.2 Paediatric Population SmPC section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription. Per SmPC: Opzelura should be initiated and supervised by physicians with experience in the diagnosis and treatment of non-segmental vitiligo.

V.2 Additional Risk Minimization Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimization Measures

Table Part V.2: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Non-melanoma skin cancer at long-term use	Routine risk minimisation measures: • SmPC Section 4.4 Additional risk minimisation measures: No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study INCB88888-037 (PASS)
Embryo-foetal toxicity	Routine risk minimisation measures: • SmPC Sections 4.3 and 4.6 Additional risk minimisation measures: No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Standard Pregnancy Forms Additional pharmacovigilance activities: None
Impaired bone growth and development in paediatric patients < 18 years of age	Routine risk minimisation measures: • SmPC Section 4.2 Paediatric population • Section 5.3 Additional risk minimisation measures: No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study INCB 18424-308 Study INCB 18424-309

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR RUXOLITINIB CREAM

This is a summary of the risk management plan (RMP) for ruxolitinib cream. The RMP details important risks of ruxolitinib cream, and how more information will be obtained about ruxolitinib cream's risks and uncertainties (missing information).

Ruxolitinib cream's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ruxolitinib cream should be used.

This summary of the RMP for ruxolitinib cream should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of ruxolitinib cream's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

Ruxolitinib cream is authorised for the treatment of non-segmental vitiligo with facial involvement in adults and adolescents from 12 years of age (see SmPC for the full indication). It contains ruxolitinib phosphate as the active substance and it is applied topically.

Further information about the evaluation of ruxolitinib cream's benefits can be found in ruxolitinib cream's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of ruxolitinib cream, together with measures to minimise such risks and the proposed studies for learning more about ruxolitinib cream's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of ruxolitinib cream is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of ruxolitinib cream are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely applied. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ruxolitinib cream. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table II.1: Lists of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	Non-melanoma skin cancer at long-term use Embryo-foetal toxicity
Missing information	Impaired bone growth and development in paediatric patients < 18 years of age

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important potential risk: Non-melanoma skin cancer at long-term use	
Evidence for linking the risk to the medicine	Non-melanoma skin cancer (NMSC) is considered a class effect of oral JAK inhibitors. A causal relationship between NMSC and oral ruxolitinib has not been established. Non-melanoma skin cancers, predominantly basal cell carcinomas have been reported in patients treated with topical ruxolitinib. Most of these patients had risk factors, such as prior phototherapy or prior NMSC. A causal relationship to topical ruxolitinib has not been established based on available safety data. A 52-week follow-up is not considered sufficient to determine if ruxolitinib cream could contribute to the induction of NMSC. Based on the limited long-term follow-up and because NMSC is considered a potential class effect of oral JAK inhibitors, NMSC at

Important potential risk: Non-melanoma skin cancer at long-term use	
	long-term use of topical ruxolitinib will continue to be monitored as an important potential risk.
Risk factors and risk groups	While the role of ultraviolet radiation in the pathogenesis of squamous cell carcinoma is undisputable, it has also been cited as the most important risk factor in the development of basal cell carcinoma (Bhari et al 2016, Situm et al 2008). Basal cell carcinoma, has been reported in patients with vitiligo treated with phototherapy. This may be explained by the mechanism of thymine dimer formation and cumulative DNA damage by ultraviolet light, which results in numerous mutations and local immune system depression leading to decreased immune surveillance for new tumor cells (Situm et al 2008). In the Phase 2/3 Vitiligo Population, 29.6% of participants had received phototherapy prior to enrolling in the studies. Other risk factors include patients with a personal or family history of NMSC or pre-malignant skin lesions, sun beds, skin type 1 or 2, immunosuppression, occupational exposure to chemicals (coal tar, creosote, arsenic, radium or pitch) and previous radiotherapy (Situm et al 2008, Perera 2014).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 Additional risk minimisation measures: No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study INCB88888-037 (PASS) See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	There are limited data from the use of ruxolitinib in pregnant women. Data on systemic absorption of topical ruxolitinib during pregnancy are lacking. There could be individual factors (e.g. damaged skin barrier, excessive use) that contribute to an increased systemic exposure. Embryo-foetal toxicity was observed following oral administration of ruxolitinib to rats and rabbits during gestation; similar findings have been identified in nonclinical studies with other JAK inhibitors. The conclusions from the non-clinical data point to a potential relevant risk in humans. Additionally, human PK data show that there is a non-negligible systemic exposure after ruxolitinib cream application, so negative effects from dermal use

Important potential risk: Embryo-foetal toxicity	
	of ruxolitinib during pregnancy on developing foetus cannot be entirely excluded.
Risk factors and risk groups	Women of child bearing potential not using effective contraception.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.3 • SmPC Section 4.6 Additional risk minimisation measures: No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Missing information: Impaired bone growth and development in paediatric patients < 18 years of age	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 5.3 Additional risk minimisation measures: None

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorisation or specific obligation of ruxolitinib cream.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study INCB88888-037: Evaluation of the Incidence of Non-Melanoma Skin Cancer after Long-term exposure to Ruxolitinib Cream

Purpose of the Study: Recent data have been published that draw a relationship between JAK inhibitors and NMSC, including basal cell and squamous cell carcinomas (Lin et al 2022, Greif et al 2021). Such literature findings have suggested that in chronic inflammatory conditions, patients with such underlying disease may also be at risk for outcomes of NMSC. Upon review of the marketing application for ruxolitinib cream, and in alignment with previously published safety risks concerning oral JAK inhibitors, the European Medicines Agency requested consideration of a non-interventional clinical study to evaluate the relationship between the long-term use of ruxolitinib cream for vitiligo, and the development of non-melanoma skin cancers.

Study INCB 18424-308: A Double-Blind, Vehicle-Controlled, Randomized Withdrawal, and Treatment Extension Study to Assess the Long-Term Efficacy and Safety of Ruxolitinib Cream in Participants with Vitiligo (TRuE-V LTE)

Purpose of the Study:

This study is designed to evaluate the duration of response following withdrawal of ruxolitinib cream (Cohort A vehicle group) and maintenance of response with continued use of ruxolitinib cream in individuals with vitiligo who have experienced repigmentation with ruxolitinib cream treatment. This study is also designed to characterize the long-term efficacy and safety profile of ruxolitinib cream in individuals with vitiligo treated for up to a total of 104 weeks.

Study INCB 18424-309: Double-blind, randomised, placebo-controlled trial to evaluate efficacy and safety of ruxolitinib cream in children from 6 years to less than 12 years of age with non-segmental vitiligo

Purpose of the Study:

To evaluate efficacy and safety of ruxolitinib cream in children from 6 years to less than 12 years of age with non-segmental vitiligo.

PART VII ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Follow-up forms

Standard Pregnancy Forms:

PHV Form Clinical Trial Report of Pregnancy or Drug Exposure via Breastmilk

PHV Form for Report of Drug Exposure via Pregnancy or Breastmilk

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

Not applicable.

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