23 February 2023
EMA/135534/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Opzelura

International non-proprietary name: ruxolitinib

Procedure No. EMEA/H/C/005843/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Abbreviation	Definition
^{14}C	radiocarbon
AD	atopic dermatitis
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
API	active pharmaceutical ingredient
ASR	application site reaction
AUC	area under the plasma concentration curve
$AUC_{ss,0-12h}$	area under the plasma concentration curve from time 0 to 12 hours
BID	twice daily
BMI	body mass index
BSA	body surface area
$C_{avg,ss}$	average steady-state plasma concentration
CD	cluster of differentiation
CDLQI	children's dermatology life quality index
CHMP	committee for medicinal products for human use
CHO	Chinese hamster ovary
CI	confidence interval
C_{max}	maximal concentration
COVID-19	coronavirus disease 2019 (SARS-CoV-2)
CPP	critical process parameter
CQA	critical quality attribute
CSF	cerebral spinal fluid
CSR	clinical study report
C_{ss}	steady-state concentration(s)
CXCL10	C-X-C motif chemokine ligand 10
CYP	cytochrome P450
CYP3A4	cytochrome P450 family 3 subfamily A member 4
DB	double-blind
DDI	drug-drug interaction
DLQI	dermatology life quality index
DoE	design of experiments
DVT	deep vein thrombosis
EC	European Commission
EC_{50}	half-maximal excitatory concentration
EMA	European Medicines Agency
E_{max}	maximal effect
EU	European Union
F-BSA	facial body surface area
FDA	Food and Drug Administration
F-PaGIC-V	facial assessment of patient global impression of change-vitiligo
F-PhGVA	facial assessment of physician global vitiligo assessment
FTIR	Fourrier transform infrared spectroscopy
F-VASI	facial vitiligo area scoring index
F-VASI50/75/90	50%/75%/90% improvement from baseline in F-VASI score
GC	gas chromatography
GCV	geometric coefficient of variation
GM-CSF	granuloocyte-macrophage colony-stimulating factor
HADS	hospital anxiety and depression scale
HDPE	high density polyethylene
HLT	high-level term
HPA	hypothalamic-pituitary-adrenal
HPLC	high performance liquid chromatography

IC	ion chromatography
IC_{50}	concentration resulting in 50% inhibition
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	inductively coupled plasma mass spectrometry
IFNγ	interferon gamma
IL	interleukin
IPC	in-process control
IR	infrared
IR	incidence rate
ISS	integrated summary of safety
ITT	intent-to-treat
IVRT	*In vitro* release test
JAK	Janus kinase
JAK1	Janus kinase 1
JAK2	Janus kinase 2
KF	Karl Fischer titration
LDPE	low density polyethylene
LFT	liver function test
LSM	least squares mean
MAA	marketing authorisation application
MACE	major adverse cardiac event
MedDRA	medical dictionary for regulatory activities
MI	multiple imputation
MO	major objection
MPV	mean platelet volume
NB-UVB	narrow-band ultraviolet B
NLT	not less than
NMR	nuclear magnetic resonance
NMT	not more than
NNT	number needed to treat
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NR	not reported
NRI	Non-responder imputation
PAR	proven acceptable range
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
PDE	permitted daily exposure
Ph. Eur.	European Pharmacopoeia
PhGVA	physician's global vitiligo assessment
PIP	paediatric investigation plan
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
pSTAT	phosphorylated signal transducer and activator of transcription
PT	preferred term
PUVA	psoralen and ultraviolet A
PY	person-years
QD	once daily
QTPP	quality target product profile
SAE	serious adverse event
SE	standard error
SmPC	summary of product characteristics
SMQ	standardized MedDRA query
SOC	system organ class
STAT	signal transducer and activator or transcription
STD	standard deviation
$t_{½}$	apparent terminal-phase elimination half-life

T-BSA	total body surface area
TE	treatment extension
TEAE	treatment-emergent adverse event
Tmax	time to maximum concentration
T-PaGIC-V	total body assessment of Patient Global Impression of Change-Vitiligo
T-PhGVA	total body assessment of Physician Global Vitiligo Assessment
TPO	thrombopoietin
TSQM	treatment satisfaction questionnaire for medication
T-VASI	total body vitiligo area scoring index
T-VASI50	50% improvement from baseline in T-VASI score
US	United States
USP/NF	United States Pharmacopoeia/National Formulary
UV	ultraviolet
UV	ultravioloet
VASI	vitiligo area scoring index
VitiQoL	vitiligo-specific quality of life
VNS	vitiligo noticeability scale
Vss	steady-state volume of distribution
WHO-5	World Health Organization-five well-being index
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Incyte Biosciences Distribution B.V. submitted on 30 September 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Opzelura, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 January 2021.

The applicant applied for the following indication: Opzelura is indicated for the treatment of non-segmental vitiligo with facial involvement in adults and adolescents from 12 years of age.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0145/2021 on the agreement of a paediatric investigation plan (PIP) and on the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP P/0145/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
29 May 2019	EMEA/H/SA/1155/3/2019/III	*Dr Caroline Auriche, Dr André Elferink*
29 January 2021	EMA/SA/0000068411	*Kerstin Wickström, Carin Bergquist*

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

Quality

- Acceptability of the proposed formulation from quality perspective, including physical stability and drug substance/product specifications, in relation to its intended clinical use
- Choice of cGMP starting material for the manufacture of ruxolitinib phosphate drug substance.

Non-clinical

- Sufficiency of the non-clinical programme to support a MAA

Clinical

- Acceptability of the clinical pharmacology data package and dermal tolerance studies to support an MAA
- Adequacy of phase 3 studies' design elements, including namely: intended treatment regimen, inclusion/exclusion criteria in relation to the indication intended for MAA, choice of primary outcome, study duration, statistical analyses, safety population and long-term efficacy follow-up

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Carla Herberts Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	30 September 2021
The procedure started on	28 October 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 January 2022
The CHMP Co-Rapporteur's Critique was circulated to all CHMP and PRAC members on	28 January 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 January 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 February 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	08 August 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	26 September 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 September 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	13 October 2022
The applicant submitted the responses to the CHMP List of Outstanding	24 January 2023

Issues on	
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	08 February 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Opzelura on	23 February 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Vitiligo is an autoimmune disease characterised by depigmented patches of skin with a selective loss of melanocytes (Krüger and Schallreuter 2012). Generalised (non-segmental) vitiligo is the most common type, accounting for up to 90% of cases (Taïeb and Picardo 2009). The natural course of the disease is generally unpredictable, but it is often progressive. Some degree of spontaneous repigmentation may occur in 10% to 20% of patients; however, often not to a cosmetically acceptable extent for many patients (Castanet and Ortonne 1997). 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). Men and women are equally affected, although women appear to seek treatment more often (Picardo et al 2015).

2.1.2. Epidemiology

The prevalence of vitiligo is about 0.5%-2%, with reported rates varying geographically (Bergqvist and Ezzedine, 2020). It can appear at any age, with a peak incidence in the second and third decade, with about 50% of the cases occurring before 20 years of age, and 70-80% before the age of 30 years. Non-segmental vitiligo (NSV) develops at all ages, but usually occurs between 10 and 30 years of age; segmental vitiligo (SV) tends to occur at a younger age than NSV; 41.3% before the age of 10 years with a mean onset of 15.6 and the latest onset at age 54 years (Than and Lee, J Am Acad Dermatol, 1996). There is no predominance of racial, ethnic, or socio-economic class (UptoDate), but there seem to be geographical differences (Bergqvist and Ezzedine, 2020).

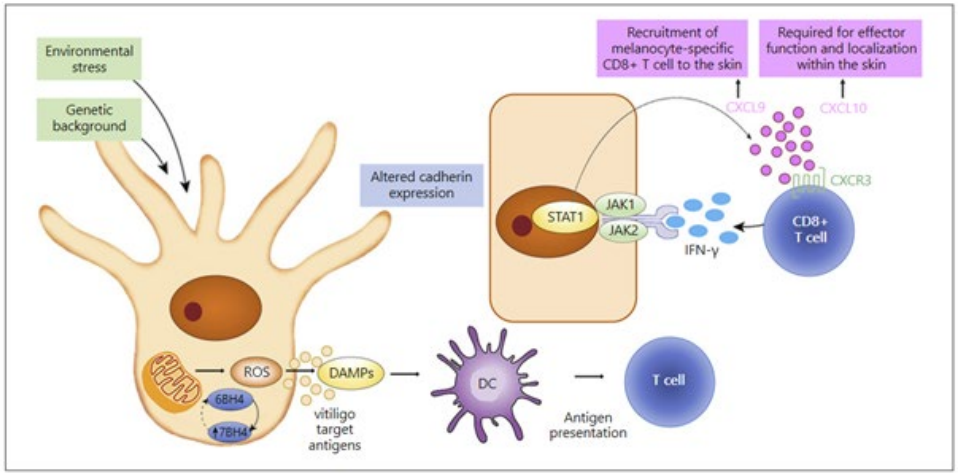
2.1.3. Aetiology and pathogenesis

The aetiology of vitiligo is unclear, but progress has been made in understanding the pathogenesis, which seems overlapping for segmental and non-segmental vitiligo. It is classified as an auto-immune disease associated with genetic and environmental factors together with metabolic, oxidative stress, and cell detachment abnormalities. It is a multistep process and involves initial release of pro-inflammatory cytokines and neuropeptides elicited by external or internal injury, with vascular dilatation and immune response. Both the innate and adaptive immune system are involved, but it is assumed to be a primary Th1-mediated process dependent on the production of INF-gamma to drive the response. CD8+ cells are found in sites of depigmentation, and there is evidence that they play a significant role in the destruction of melanocytes. T-cells express activation molecules in perilesional

vitiligo skin, as well as cytokines such as INF-gamma and TNF-alpha. Through these mechanisms, infiltrating T-cells kill melanocytes within the skin and cause loss of pigmentation in NSV. Observations in support of this hypothesis are that lesional CD8+ T-cells *in vitro* induce melanocyte apoptosis from unaffected skin and JAK1 expression (as downstream effector of IFN-gamma) is higher within vitiliginous skin compared to healthy skin.

As INFy signalling involves the JAK-STAT pathway, JAK-inhibition may be a useful strategy to treat vitiligo. Case reports on oral JAKi in inflammatory skin disease suggested efficacy but is limited due to side effects (mainly due to haematological side effects). As an alternative method of administration, topical treatment may be useful as it would locally inhibit disease activity and have at least potentially less systemic (adverse) effects.

Figure 1: The role of JAK inhibition in the pathogenesis of vitiligo



2.1.4. Clinical presentation, diagnosis and clinical course

The clinical presentation of vitiligo typically involves asymptomatic depigmented patches and macules, without clinical signs of inflammation. In some cases, sunburn, pregnancy, skin trauma or emotional stress precede presentation. The disease has a predilection for the face and areas around the orifices, genitals, and hands. Depigmented areas may show more than one colour shade (trichrome, quadrichrome, pentachrome). Classification is based on the Vitiligo Global Issues Consensus Conference (2012), which defined two broad categories: non-segmental (NSV; being the most common) and segmental vitiligo (SV). The two other categories are mixed (SV and NSV), and unclassified. NSV is further categorised into generalised, acro / acrofacial, focal, mucosal, or universal subtypes; the first being the most prevalent. SV typically occurs in a (quasi)dermatomal pattern, most frequently along the trigeminal nerve. It is less common than NSV and presents most often in childhood.

The clinical course of vitiligo is unpredictable, with stable disease, slow progression over years, flares, etc. Progression is more common in patients with a family history of NSV, longer disease duration, Koebner phenomenon, or mucosal involvement.

Diagnosis is usually quite straightforward, based on clinical presentation of well-demarcated, uniformly white macules surrounded by normal skin in the absence of inflammatory signs. The differential diagnosis is extensive and comprises chemically induced leukoderma, topical or systemic drug-induced depigmentation, post-inflammatory hypopigmentation, neoplasm-related hypomelanoses, idiopathic hypomelanosis, congenital hypomelanosis, and other conditions. The diagnosis may be facilitated by

using a Wood's lamp or dermoscopy. A skin biopsy is not often required but may be helpful in some cases. Histology then shows complete loss of melanin pigment in the epidermis and absence of melanocytes. Other findings may be vacuolar degeneration of keratinocytes, spongiosis, dermal lymphocyte infiltration. Immunohistochemical staining shows a predominance of CD8+ positive T-lymphocytes.

2.1.5. Management

There are no approved medicinal products for repigmentation in vitiligo, and evidence for the effectiveness of drug therapies used off-label is limited. Few randomised and controlled clinical studies have evaluated potential treatments, and interpretation of these studies is hampered by small study sizes as well as heterogeneity of study designs, methodologies, and measures (Eleftheriadou et al 2012, Whitten et al 2016). The current management of vitiligo is, therefore, empirical and based on 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 topical steroids and calcineurin inhibitors, which are most useful for treating limited disease (typically ≤ 10% BSA is treated). Second-line treatments consist of phototherapy (NB-UVB and PUVA) and systemic steroid treatment, and next-line treatments consist of surgical grafting techniques and depigmenting treatments. Responses to current treatment options vary and have limited durability. Treatments can also be time-intensive and burdensome to the patient and may produce cosmetically unacceptable results.

Being a disease with high psychological burden, there is a need for effective repigmentation treatment options in vitiligo. Current treatment is based on off-label application of topical corticosteroids and calcineurin inhibitors, whether or not combined with phototherapy, and when insufficient effect is achieved, systemic corticosteroids and phototherapy are applied. Finally, surgery and depigmentation treatment may be considered in severe cases. Use of topical therapies (corticosteroid and calcineurin inhibitors), which are usually applied in limited disease (< 10% BSA), is hampered by side effects and their effectiveness is still inconclusive. Research on vitiligo treatment is characterised by the absence of uniform outcome measures, small sample sizes, and deficiencies in methodological quality. As a result, there is an unmet need for safe and effective treatment options.

2.2. About the product

Ruxolitinib phosphate (INCB018424) is a potent and selective inhibitor of the JAKs with selectivity for JAK1 and JAK2. Pharmacological data obtained in both *in vitro* and *in vivo* model systems support the use of ruxolitinib in the treatment of vitiligo. Ruxolitinib potently inhibits the expression of several vitiligo-relevant immune mediators, including IFNγ, CXCL10, and Granzyme B.

Ruxolitinib is a well-known active substance, already approved as an oral drug for the treatment of moderate / severe myelofibrosis, polycythemia vera and Graft versus host disease (Jakavi, EMEA/H/C/002464).

Ruxolitinib cream is a topical formulation of ruxolitinib phosphate.

The recommended dose is a thin layer of cream applied twice daily to the depigmented skin areas up to a maximum of 10% of body surface area (BSA), with a minimum of 8 hours between two applications (see SmPC section 4.2 for full text).

The Article 20 referral procedure for JAK inhibitors used in chronic inflammatory disorders finalised on January 2023 (CHMP opinion; EC decision pending) recommended measures to minimise the risk of serious side effects with JAKi. The data currently available for ruxolitinib cream do not support the

need to include specific warnings in the SmPC regarding those class effects as the systemic exposure, given the different route of administration of Opzelura (ruxolitinib cream), is considered to be sufficiently low, not to lead to systemic effects including VTE, MACE, malignancy other than NMSC, and serious infections.

2.3. Type of application and aspects on development

The application was submitted under the legal basis 8(3) of Directive 2001/83/EC which corresponds to a complete and independent application.

The applicant requested EMA scientific advice for ruxolitinib in the treatment of vitiligo. The questions concerned the quality, clinical and non-clinical development (see section 1.5. 'Scientific advice').

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a cream containing 15 mg/g ruxolitinib as active substance. The product contains the phosphate salt.

Other ingredients are purified water, light liquid paraffin (E905), white soft paraffin (E905), medium chain triglycerides, propylene glycol (E1520), macrogol, xanthan gum (E415), polysorbate 20 (E432), cetyl alcohol, dimeticone (E900), disodium edetate (E385), self-emulsifying glyceryl stearate, methyl parahydroxybenzoate (E218), phenoxyethanol, propyl parahydroxybenzoate, stearyl alcohol, butylated hydroxytoluene (E321).

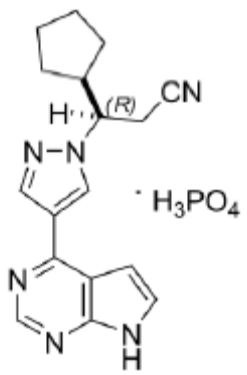
Ruxolitinib cream is packaged in aluminium tubes with internal lacquer coating with a polypropylene puncture cap as described in section 6.5 of the SmPC.

2.4.2. Active substance

General information

The chemical name of ruxolitinib phosphate is (*R*)-3-(4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate corresponding to the molecular formula $C_{17}H_{18}N_6.H_3PO_4$. It has a relative molecular mass of 306.37 g/mol (free base), 404.36 g/mol (phosphate salt) and the following structure:

Figure 2: active substance structure



The chemical structure of ruxolitinib phosphate was elucidated by a combination of elemental analysis, IR spectroscopy, NMR spectroscopy (^{1}H and ^{13}C), mass spectrometry and UV spectroscopy. The obtained spectra are in agreement with the assigned structure. The molecular structure of ruxolitinib phosphate active substance was independently confirmed using single crystal X-ray diffraction.

The solid-state properties of the active substance were measured by XRPD, differential scanning calorimetry, scanning electron microscopy and thermogravimetric analysis.

Ruxolitinib phosphate is a white to off-white to light pink powder. Relevant physicochemical properties (hygroscopicity, solubility at different pH buffer solutions and organic solvents, melting point, dissociation constants and partition coefficients) have been investigated. Ruxolitinib phosphate is very slightly soluble in aqueous medium (pH 1-8), slightly soluble in isopropanol and sparingly soluble in ethanol.

Ruxolitinib phosphate contains a single chiral centre in the (*R*)-configuration. The stereocentre is introduced selectively in the manufacturing process and routinely controlled in relevant intermediates and the active substance.

Manufacture, characterisation and process controls

Ruxolitinib phosphate is synthesized using well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in double LDPE bags inside a HDPE drum. Relevant materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for description, identity, chiral purity, assay, impurities, residual solvents, elemental impurities, water content, and phosphate content.

The specifications adopted for ruxolitinib phosphate active substance are derived from ICH guidelines, the Ph. Eur. and batch data. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from production scale batches of active substance, stored in the intended commercial package up to 60 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The following

stability-indicating parameters were tested: description, chiral purity, water content, related substances and assay. No significant changes or trends to any of the measured parameters were observed.

Photostability testing following the ICH guideline Q1B was performed on two batches. No degradation was observed, ruxolitinib phosphate is photostable. Forced degradation studies indicate that ruxolitinib is generally stable and is most susceptible to alkaline degradation.

The stability results indicate that the active substance is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.4.3. Finished medicinal product

Description of the product and pharmaceutical development

Opzelura is a white to off-white oil-in-water, solubilised emulsion cream containing 15 mg ruxolitinib per 1 g of cream (1.5 wt%), stored in a lined aluminium tube. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report.

The finished product was developed to a physically and chemically stable multi-use topical formulation for the treatment of vitiligo. The phosphate salt of ruxolitinib was selected relative to other salt forms. Furthermore, the active substance was shown to be extremely stable during stability studies and no incompatibility with any of the excipients was observed. The key physicochemical parameters of ruxolitinib cream are homogeneity and emulsion stability. An appropriate quality target product profile (QTPP) has been provided for the development of a cream formulation.

Description, identification, absence of crystals, assay, degradation products, uniformity in container, viscosity, package integrity, preservative content, *in vitro* release test (IVRT) and microbial purity were identified as the critical quality attributes (CQAs), which is acceptable for a cream. An acceptable justification for the selection of the finished product CQAs was provided in the dossier. All CQAs are routinely controlled in the finished product specification.

The excipients and container closure system are common for this type of dosage form. The components of the cream, their functions and references to standards were provided and explained. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report.

The preservative system comprises a combination of phenoxyethanol, methyl- and propylparaben. The need for a preservative is justified given the high (50%) water content and that the product is a multi-use formulation. However, the applicant did not justify that the content had been minimised as per EU guidance and this resulted in a major objection (MO) during the procedure. In response, the applicant demonstrated that there is no concern from a safety point of view. Nonetheless, the applicant is recommended to investigate alternative formulations post-approval with reduced preservative content and amend the formulation as dictated by the study results (REC). The applicant has provided a development plan to investigate low preservative formulations which was reviewed and considered acceptable. The finished product is indicated for use in in adults and adolescents from age 12. The Paediatric Investigation Plan (PIP) has been endorsed and the formulation is considered appropriate for use in children aged 6 and above.

The formulations and manufacturing process have not changed over the course of product development comprising material used in clinical trials. Overall, the formulation development has been sufficiently described.

The finished product manufacturing process was developed based on the QTPP. It essentially consists of the preparation of various liquid components by either melting or dissolution followed by the key emulsification step. The proposed CQAs and the critical steps in the manufacturing process have been thoroughly evaluated at the initially proposed manufacturing site. Design of Experiment (DoE) studies were conducted to study the connection between process critical process parameters (CPPs) and product CQAs. Based on those results and prior knowledge IPCs, CPPs and PARs were determined establishing the overall control strategy for the manufacturing process of ruxolitinib cream. Therefore, batches were manufactured at production scale including the official validation batches. All batches met with the acceptance criteria indicating a robust process at the intended commercial scale. During development, a second manufacturing site was introduced. Small modification to several unit operations were implemented to accommodate the different equipment. The applicant submitted comparability data including IVRT results in an effort to demonstrate the sameness of product manufactured at the two sites. Initially, the CHMP judged that the sameness had not been sufficiently demonstrated as there were differences in some measured parameters (e.g. non-Newtonian behaviour, active substance release profiles) resulting in a MO. In addition, the IVRT methods in place at both sites were not considered sufficiently robust and the CHMP requested to see comparability data on more parameters. In response, the applicant developed a new IVRT method which is used to measure the release profiles of batches from both sites. The new method is considered to be suitably validated and is sufficiently discriminatory. The IVRT data, allied to the totality of batch data in line with the draft "*Guideline on the quality and equivalence of topical products*" demonstrates the sameness of the creams manufactured at both sites. The MO was resolved and finished product is considered equivalent to that used in the clinical trials.

The primary packaging is an aluminium tube with internal lacquer coating with a polypropylene puncture cap. The materials comply with Ph. Eur. and EC requirements. The suitability of the selected container closure system was evaluated in terms of protection, compatibility and safety. Extractable and leachable studies have been conducted, considering both mutagenic and elemental impurities. There is negligible risk from the container closure. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of several main steps: preparation of a melted oil phase; preparation of the aqueous solution; compounding of the oil and aqueous phases; emulsification and cooling; mixing and cooling. The process is considered to be a standard manufacturing process.

Initially, the CHMP considered the process to be non-standard given the low active substance content and emulsified formulation and therefore requested formal validation data in addition to the provided validation scheme, resulting in a MO. In response, the applicant argued that the extent of batches manufactured to date at large scale, the consistent content uniformity data, and the experience with similar products at the proposed commercial manufacturer justified the process being considered standard. The CHMP agreed with the arguments provided. Major steps of the manufacturing process have been validated on over 20 production scale batches across both sites. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Critical steps of the manufacturing process have been defined. The IPCs which focus on critical unit operations are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including description, identification, assay, degradation products, uniformity of active ingredient, pH, viscosity, globule size, absence of ruxolitinib crystals, IVRT, minimum fill, weight loss, package

integrity, preservative content, and microbial limits. The finished product specification is in compliance with ICH Q6A on specifications. The limits set are based on the data obtained during development, batch analysis and stability studies. A justification has been presented for each parameter of the specification. The provided release and shelf-life specifications list adequate parameters for a cream.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment, considering the limits for relevant impurities already included in the active substance specification and taking into account the cutaneous administration route, it was be concluded that there is no risk of elemental impurities above their respective PDEs and no limits are needed in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004 - Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no confirmatory testing was requested, nor specific control measures deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis results are provided for production scale batches and supportive data from batches used in clinical development confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from production scale batches of finished product stored for up to 21 months under long term conditions (25ºC / 60% RH), for up to 12 months under intermediate conditions (30ºC / 75% RH), and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Supportive data from a previous manufacturer was also provided. The following parameters were tested: description, assay, degradation products, uniformity in container, pH, viscosity, globule size, weight loss, package integrity, preservative content, microbial limits, and IVRT. No significant changes or trends to any of the measured parameters were observed, other than a steady decrease in viscosity under all conditions. In addition, 1 batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. In the absence of the packaging, a slight increase in impurities was observed. However, the aluminium tube was shown to provide adequate protection.

A freeze-thaw study was conducted, cycling the tubes of cream between accelerated conditions and -20ºC. Little or no impact on any measured parameters were observed.

An in-use study was conducted on batches of differing storage time (7 months and 29 months). Tubes were opened, cream dispensed, and the tubes re-sealed weekly for 26 weeks. No significant quality

changes were observed. The proposed in-use shelf-life of 6 months (SmPC section 6.3) is deemed acceptable.

Based on available stability data, the proposed shelf-life of 21 months and the in-use shelf-life of 6 months, stored at or below 30ºC as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The applicant provided additional justification that the process can be considered as standard to resolve the MO on process validation. In addition, the IVRT method was re-developed and used, among other tests, to demonstrate the sameness of the creams manufactured at the different manufacturing sites. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

It has not yet been justified from a quality point of view that the preservative content of the cream is as low as possible, while maintaining effectiveness. While preservative levels are considered acceptable from a safety point of view, the applicant should conduct post-approval studies to determine whether a lower effective preservative level is possible and re-develop the formulation accordingly. This point is put forward and agreed as a recommendation for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant is recommended to investigate alternative formulations post-approval with reduced preservative content in line with the provided development plan and to re-formulate the product as dictated by the study results.

2.5. Non-clinical aspects

2.5.1. Introduction

Ruxolitinib has been developed as a cream for the topical treatment of vitiligo with the aim of impeding the CD8+ T-cell-mediated pathogenesis of vitiligo. In support to this MAA the applicant submitted a comprehensive panel of *in vitro* and *in vivo* pharmacology and pharmacokinetic studies, including those that were conducted for Jakavi (EMEA/H/C/002464), oral tablets. Besides primary pharmacodynamic studies, ruxolitinib was evaluated in a non-GLP Cerep ExpresSProfile screen against various kinases,

receptors, transporters for potential cross-reactivity. Pharmacokinetics of ruxolitinib following oral or dermal administration has been determined in mice, rats, rabbits, dogs, monkeys and minipigs.

Toxicology of ruxolitinib following oral administration has been previously evaluated for Jakavi tablets for oral use (EMEA/H/C/002464). The dossier included the safety pharmacology studies, general toxicity studies in rats (up to 6 months) and dogs (up to 1 year), *in vitro* and *in vivo* genotoxicity studies, carcinogenicity study in Tg.rasH2 mice (26-weeks), fertility and early embryonic development study in male and female rats, embryo-foetal development studies in rats and rabbits, a pre- and postnatal development study in rats, juvenile toxicity studies in rats.

Newly submitted studies to evaluate safety of topical use of ruxolitinib for the indication of vitiligo included repeat dose dermal toxicity studies in CD-1 mice and Göttingen minipigs, *in vitro* photoclastogenicity study, dermal 2-year carcinogenicity study in CD-1 mice, 2-year carcinogenicity study in rats, acute dermal and ocular irritation studies in rabbits, the mouse local lymph node hypersensitivity study, phototoxicity and photo-allergy studies in hairless albino guinea pigs.

For topical studies, the cream formulation used was the same as the clinical ruxolitinib cream formulation. The excipients contained in the drug product are well known, commonly used in the manufacture of medicinal products intended for cutaneous use and of the Ph. Eur. quality, except for glyceryl stearate SE.

In general, findings in toxicology studies were limited to those expected based on the pharmacologic activity of ruxolitinib and associated effects on the immune system.

2.5.2. Pharmacology

The pharmacology of ruxolitinib has been studied *in vitro* and *in vivo*. Information on oral dose as well as after dermal application is provided. The systemic exposure from ruxolitinib 1.5% cream may overlap with that from orally administered ruxolitinib, and therefore, non-clinical information from oral dose as well as after dermal application is considered relevant. Extensive non-clinical information on the pharmacological activity of ruxolitinib evaluated *in vitro* as well as *in vivo* following oral administration had already been assessed previously during the registration procedure of the medicinal product Jakavi, tablets. To evaluate the pharmacology activity of topical ruxolitinib in view of the proposed indication vitiligo, the applicant performed a new *in vitro* study using activated human CD8+ T-cell and melanocyte cultures and new *in vivo* studies using preclinical mice models of dermatitis. In addition, previously assessed *in vivo* studies using mouse models of inflammatory disease (IL-23 induced psoriasis and dorsal delayed-type hypersensitivity (DTH) were submitted. Information from literature presenting the pharmacological activity of ruxolitinib in a mouse model of vitiligo following oral administration was also provided.

2.5.2.1. Primary pharmacodynamic studies

Literature showed that ruxolitinib is a potent and selective inhibitor of JAK1 and JAK2 tyrosine kinases. JAK signalling involves activation of the JAK-STAT pathway, leading to recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, and subsequent modulation of gene expression. According to literature data, IFNγ-driven inflammation in vitiligo is JAK-mediated. Activated CD8+ T cells produce IFNγ which trigger more CXCL9 and CXCL10 production through JAK1 and JAK2 signalling and recruit more CD8+ T-cells to the inflammatory sites. CD8+ T-cells then destruct melanocytes and lead to depigmentation.

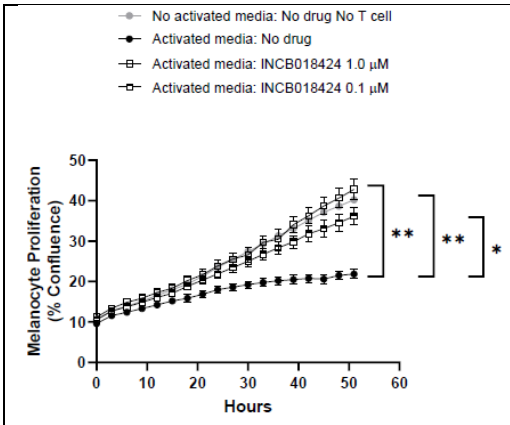
In enzyme-based assays at a cellular concentration of ATP (1 mM), the potency of ruxolitinib against human JAK family members (JAK1, JAK2, JAK3 and TYK2) was demonstrated by the following mean

IC50 values: 3.3 ± 1.2 nM for JAK1, 2.8 ± 1.2 nM for JAK2, 19 ± 3.2 nM for TYK2 and 428 ± 243 nM for JAK3.

In cell-based assays, ruxolitinib potently inhibited IL-6, TPO or GM-CSF stimulated phosphorylation of STAT3 in primary human peripheral blood mononuclear cells (PBMCs) and primary human neutrophils at a concentration lower than 100 nM. It also inhibited the IL-23 stimulated production of IL-22,a cytokine implicated in the pathogenesis of multiple auto-immune inflammatory disease, in primary human T-cells with an IC50 value of 50 nM. By using human whole blood, where serum protein binding can be a significant factor, exogenous ruxolitinib blocked TPO or IL-6 induced STAT3 phosphorylation with IC50 values of 281 nM and 280 nM. In addition, ruxolitinib inhibited IL-6 stimulated STAT3 phosphorylation in whole blood from dogs (IC50 = 119 nM), rats (IC50 = 95 nM) and rabbits (IC50 = 600 nM), confirming that ruxolitinib is pharmacologically active in human test systems and across the different species used in toxicology studies.

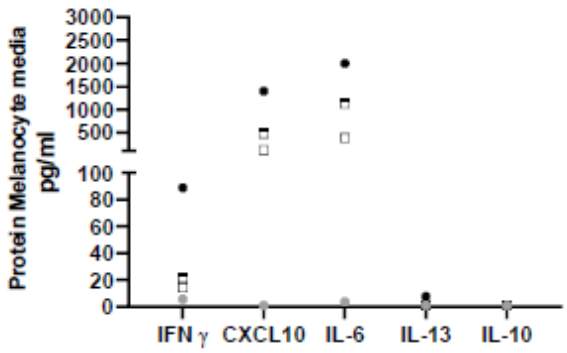
In vitro assay using activated human CD8+ T-cell and melanocyte cultures showed the implication of IFN-γ/CXCL10 signalling pathway in conditions resembling vitiligo. Activated CD8+ T-cell conditioned media contained increased immune mediators, including IFNγ, IL-2, CXCL10 and Granzyme B, as also documented in literature. Subsequent CD8+ -cell conditioned media transfer to primary melanocytes resulted in rapid, and sustained, inhibition of spontaneous proliferation. Subsequent analysis of the melanocyte culture supernatants revealed a distinct inflammatory cytokine profile, including IL-6, CXCL10 and IL-8, induced by activated CD8+ T-cell conditioned media. Ruxolitinib significantly reduced the levels of T-cell derived cytokines, normalised melanocyte proliferation and ameliorated the melanocyte inflammatory milieu (Figure 3). These results were consistent with the observation that a dose-dependent reduction of circulating CXCL10 concentrations in vitiligo patients was associated with ruxolitinib cream treatment.

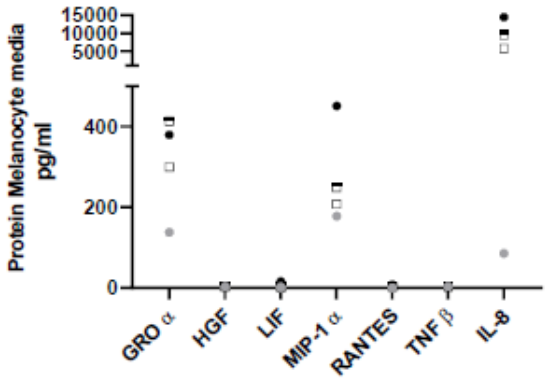
Figure 3: Melanocyte proliferation modulated by CD8+ T-cell conditioned media and the effect of Ruxolitinib



Transfer of anti-CD3 anti-CD28 activated CD8+ T-cell conditioned media to *in vitro* cultured human melanocytes resulted in rapid, and sustained, inhibition of spontaneous proliferation compared to nonactivated media control. In contrast, ruxolitinib when cocultured with the CD8+ T cells, significantly attenuated the activated CD8+ T-cell conditioned media inhibitory response, and normalized melanocyte proliferation. *P<0.05, **P<0.01.

Figure 4: Proteomic analysis of melanocyte culture supernatant that had been treated with CD8 T-cell conditioned media and the effect of ruxolitinib



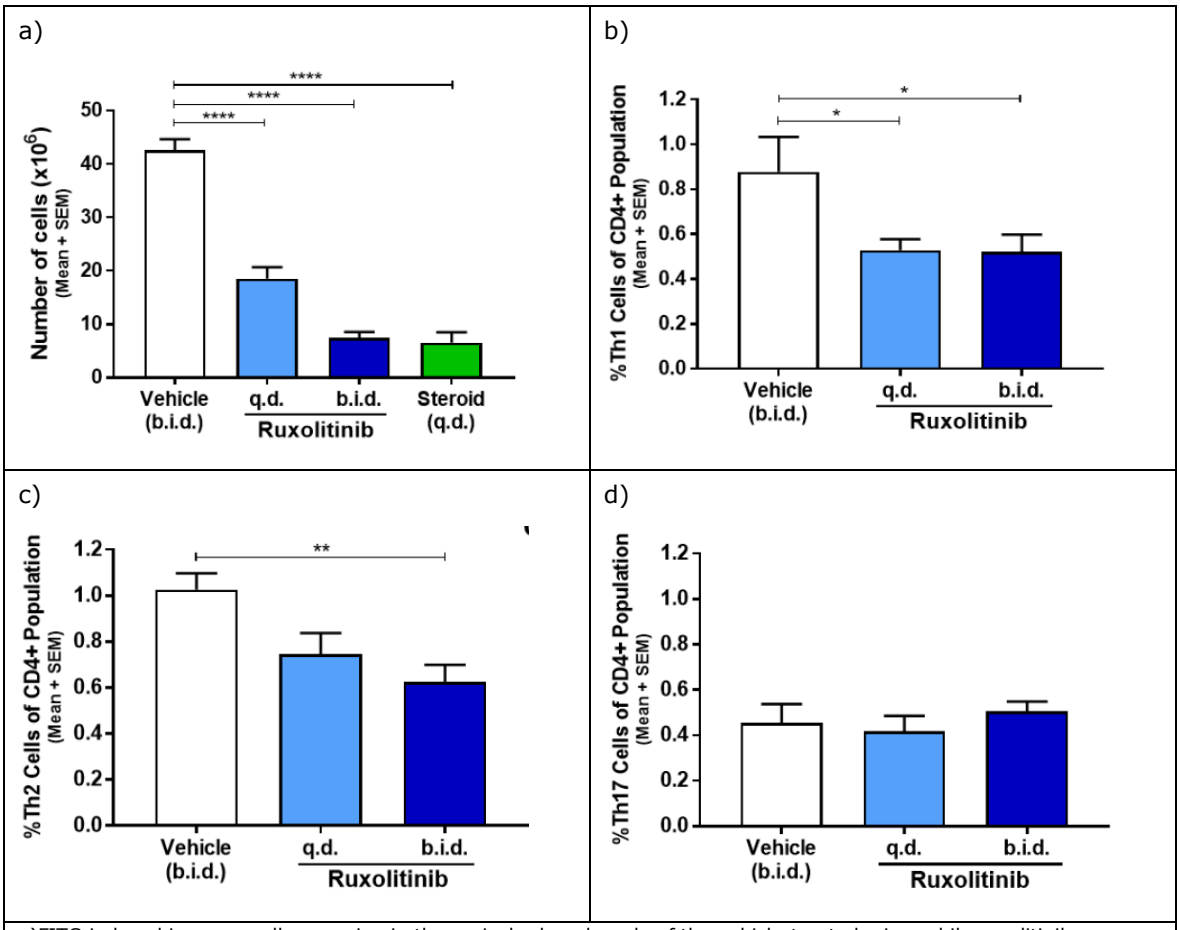


Multiple cytokines, including IL-6, CXCL10, and IL-8 were significantly increased following the treatment of conditioned media. Importantly, ruxolitinib ameliorated this inflammatory response at the 1 µM and 100 nM concentrations tested.
Legend:
- No activated media: No drug No T cell
- Activated media: No drug
- Activated media: INCB018424 1.0 µM
- Activated media: INCB018424 0.1 µM

Literature data on a mouse model of vitiligo confirm the role of cytotoxic CD8+ T cells in promoting the elimination of melanocytes and the implication of IFN-γ signalling through JAKs which appears to be necessary for depigmentation in vitiligo and show a potency of oral ruxolitinib to reverse inflammatory condition in vitiligo. In addition, autoreactive tissue resident T cells secreting IFN-γ have been described in lesional vitiligo skin of mouse model and these cells could be responsible for disease relapse (Azzolino et al, 2021).

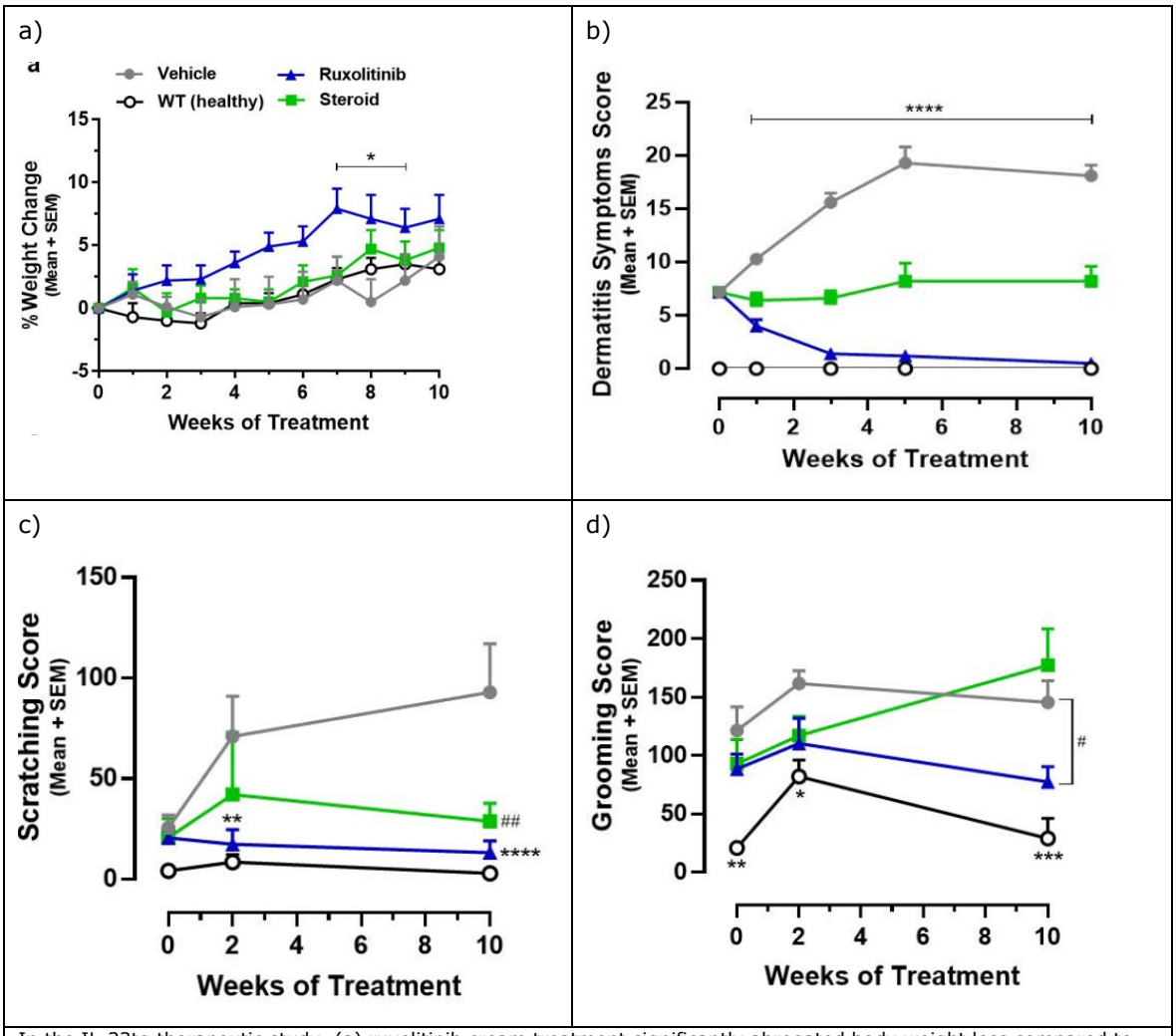
In vivo studies conducted by the applicant evaluated the pharmacological activity of topically applied ruxolitinib in mouse models relevant to the pathogenesis of dermatological conditions other than vitiligo (i.e. thymic stromal lymphopoietin (TSLP)-induced acute dermatitis mouse model, a fluorescein isothiocyanate (FITC)- induced chronic dermatitis mouse model, spontaneous IL-33 transgenic mouse dermatitis model, IL-23 induced psoriasis mouse model, delayed-type hypersensitivity mouse model). Despite phenotypic differences in the inflammatory mediators responsible for driving disease pathogenesis of aforementioned dermatological conditions, all these models are characterised by increased inflammatory mediators that signal through the JAK-STAT pathway, T-helper and/or T-cytotoxic cells. *In vivo* pharmacology studies showed that ruxolitinib 1.5% topical cream was efficacious in these mouse models. Ruxolitinib downregulated inflammatory pathways which was associated with inhibition of Th1 and Th2 lymphocytes and their related proinflammatory cytokines. It reduced ear swelling, infiltration of T-cells, normalised tissue histology and alleviated pruritic behaviours (Figure 5, Figure 6).

Figure 5: Effect of ruxolitinib cream on T-cell subsets during chronic FITC-induced dermatitis



a)FITC-induced immune cell expansion in the auricular lymph node of the vehicle-treated mice, while ruxolitinib cream dose-dependently inhibited this response ($p < 0.0001$). b)The proportion of Th1 cells (CD8-CD4+IFNγ+) was significantly lower in the ruxolitinib groups ($p < 0.05$) (c) There was a dose-dependent decrease in the proportion of Th2 cells (CD8-CD4+IL4+), with the ruxolitinib BID group significantly lower than the vehicle group ($p < 0.01$). (d) There was no significant difference in the proportion of Th17 cells (CD8-CD4+IL17a+) between groups.

Figure 6: Therapeutic treatment in the IL-33tg spontaneous dermatitis model



In the IL-33tg therapeutic study, (a) ruxolitinib cream treatment significantly abrogated body weight loss compared to the vehicle cream-treated group. (b) Topical application of ruxolitinib significantly resolved dermatitis symptoms, while betamethasone cream only prevented further disease progression over time. Mice in the vehicle group exhibited abnormal (c) scratching and (d) grooming behavior. Therapeutic treatment with ruxolitinib cream significantly reduced both scratching and grooming by Week 24. (a) *p < 0.05, vehicle vs. ruxolitinib. (b)****p < 0.0001, vehicle vs. ruxolitinib. (c) **p < 0.01, ****p < 0.0001, vehicle vs. ruxolitinib. ##p < 0.01, vehicle vs. steroid. (d) *p < 0.05, **p < 0.01, ***p < 0.001, vehicle vs. WT (healthy). #p < 0.05, vehicle vs. ruxolitinib.

As regards ruxolitinib metabolites, human metabolites as well as metabolites from rats, rabbits and dogs were found to be pharmacologically active. The potencies of human metabolites analysed *in vitro* were lower than that of the parent compound in an enzyme assay for JAK1, JAK2 and JAK3 as well as IL-6 dependent INA-6 cell proliferation assay and human whole blood IL-6 activated STAT3 phosphorylation assay. The two major metabolites identified, INCB040920 (M18) and INCB040341 (M16), were ~3-5-fold less potent than the parent in this assay.

2.5.2.2. Secondary pharmacodynamic studies

Ruxolitinib was evaluated against a panel of 30 kinases at 0.2 μM concentration, using the respective Km concentrations of ATP for each individual kinase. Under these conditions, ruxolitinib demonstrated no significant inhibition, with the exception for JAK2 and JAK 3 kinases. In addition, ruxolitinib did not demonstrate significant cross reactivity against tested receptors, channels and transporters at 0.1 and 1 μM.

2.5.2.3. Safety pharmacology programme

Ruxolitinib was also evaluated in a safety pharmacology core battery studies during the MAA of Jakavi (EMEA/H/C/002464): CNS and respiratory studies in the rat, a cardiovascular study in telemeterised conscious dogs, and in an *in vitro* hERG channel assay. There were two treatment-related adverse findings: decreases in minute volume in female rats given a single oral dose of 150 mg/kg (NOAEL 50mg/kg) in a respiratory assessment of ruxolitinib; and decreases in arterial blood pressure along with increases in heart rate in radiotelemetry-implanted conscious dogs dosed 30 mg/kg (NOAEL 10mg/kg). Main findings of adverse events on vital functions in rat and dogs following oral administration of ruxolitinib have been reflected in SmPC, section 5.3. Considering the limited systemic exposure of ruxolitinib following topical administration, the applicant considered that the potential for ruxolitinib to cause adverse alterations in respiratory and cardiovascular systems in humans was very low.

2.5.2.4. Pharmacodynamic drug interactions

No interaction studies have been performed. Due to lack of the drug-drug interaction studies, the concomitant use of ruxolitinib cream and any other drug in the same treatment area is not recommended (see SmPC, section 4.5).

2.5.3. Pharmacokinetics

The pharmacokinetics of ruxolitinib has been studied *in vitro* and *in vivo* in non-clinical models. Information on oral dose as well as after dermal application is provided using mice (CD-1, hairless and transgenic), rats (non-pigmented and pigmented), rabbits, dogs, monkeys and minipigs. The systemic exposure from ruxolitinib 1.5% cream may overlap with that from orally administered ruxolitinib, and therefore, non-clinical information from oral dose as well as after dermal application is considered relevant. Extensive non-clinical information on the absorption, distribution, metabolism and excretion following single oral dose administration of ruxolitinib to various species had already been assessed previously during registration of Jakavi medicinal product, tablets. Repeated dermal dose studies with ruxolitinib were performed in minipigs to evaluate the absorption and distribution of topical formulation. These include previously assessed dermal distribution study with ^{14}C-INCB018424 and new PK study with ruxolitinib for determination of the systemic exposure and skin tissue distribution of ruxolitinib after topical vs. oral administration. Analytical assays that were used to characterise the non-clinical PK and toxicokinetic studies were thoroughly assessed and accepted as part of MAA for Jakavi medicinal product.

Absorption

Following single dermal administration of ruxolitinib, the mean skin flux of ruxolitinib was similar for solubilised and dispersed cream formulations (44 ng/cm^2/h and 50 ng/cm^2/h) with a bioavailability of 1.8% and 3.0%, respectively.

Repeated dose study (4 consecutive days of treatment) was conducted to evaluate the systemic exposure and skin distribution of ruxolitinib following oral vs. topical administration in 4 minipigs (oral 40 mg/kg BID; topical 4.5 mg/cm^2 (1.5%) cream BID applied to 10 % BSA) showed that the average steady state dermis concentration of ruxolitinib after topical administration was 507-fold higher compared to dermis concentrations following oral dosing, while the corresponding ratio for the epidermal sections was 1989- fold. Thus, compared to oral dosing, topical administration delivered ruxolitinib more effectively to the targeted skin layers with a lower systemic exposure as compared to oral administration. At 96 h post-dose, the mean Cmax of oral ruxolitinib and topical ruxolitinib was

153 nM and 4 nM, Tmax 3.3 h and 3.5 h, AUC_{0-12} 1060 nM*h and 35 nM*h, respectively (Table 1). There was a wide range of variation among data in male and female minipigs. In female minipigs (N=2), the plasma AUC and Cmax values following topical administration were 40-50-fold lower than those observed by oral administration, while in male minipigs (N=2), AUC and Cmax were ~20 fold lower after topical administration compared to oral administration. The sample size is considered by the applicant to be too small to draw valid conclusions on potential gender differences in ruxolitinib systemic exposure following topical application in minipigs and to estimate its clinical relevance.

Table 1: Absorption in minipigs after topical vs oral repeated dosing

Study ID	N	Dose	Route	Plasma Cmax [c] (nM)	Plasma AUC_{0-12} [c] (nM*h)	Tmax [c] (h)	Epidermis conc. (nM)	Dermis conc. (nM)
DMB-20.57	2M/2F	40mg/kg BID	oral	153±173	1060±1050	3.3±1.5	574.3[b] 543.3[c]	189.5[b] 61.9[c]
DMB-20.57	2M/2F	4mg/cm^2 BID	topical	3.98±2.4 2.70±1.8[a]	34.6±23	3.5±3.3	1 249 000[b] 973 500[c]	66 400[b] 60 450[c]

a: mean female and male conc at steady state
b: at 74 h
c: at 96 h

Distribution

Distribution studies following topical administration of ruxolitinib were conducted in minipig (N=1) with radiolabelled compound (^{14}C INCB018424). Results of auto-radioluminography showed that after 4 daily dermal doses of 1% [^{14}C]-ruxolitinib cream distribution of radioactivity in skin was generally limited to the upper layers of the tissue. The highest concentration was associated with a pigmented layer of cells found in the epidermis, probably composed of keratinocytes and melanocytes. Lower levels were observed in the epidermis above this layer of cells and in the stratum corneum. Levels in the dermis (below the pigmented layer) and hypodermis (sub-cutis) were below the lower limit of quantitation. These data suggest non-specific melanin binding and necessity for assessment of phototoxicity.

Distribution studies were conducted also in non-pigmented and pigmented rats with radiolabelled compound ^{14}C-ruxolitinib (200 µCi/kg in Sprague-Dawley rats and 100 µCi/kg in Long-Evans rats) administered orally. Distribution was wide and rapid in non-pigmented and pigmented rats with the highest concentrations in the gastrointestinal tract, urinary bladder, renal cortex, renal medulla, liver, aorta, and adrenal gland. In pigmented rats, the highest concentrations of radioactivity were observed in the gastrointestinal tract, followed by urine, bile, uveal tract, liver, renal medulla, renal cortex, skin (pigmented), and kidney. Elimination in pigmented rats was rapid in most tissues (below the limit of quantitation at 24 h), with no matrix or tissue containing detectable levels of ruxolitinib-derived radioactivity by 336 h post-dose. Based on the elimination from skin and uveal tract, ruxolitinib-derived radioactivity was not irreversibly bound to melanin. Penetration of ruxolitinib and ruxolitinib-derived radioactivity into central nervous system tissues was limited (less than 10% of plasma concentration). In pregnant rats that received a single oral dose of 30 mg/50 µCi/kg ^{14}C ruxolitinib, the maximum maternal blood and plasma concentrations were at 1 h post-dose and declined to low levels (approximately 1% of Cmax) by 24 h post-dose. In whole foetuses and all foetal tissues, concentrations of radioactivity by 8 h post-dose were below the quantitation limit or not detectable.

The foetus:maternal plasma concentration ratio and foetal tissue: maternal plasma concentration ratios were less than one for all foetal tissues indicating that foetal exposure was limited.

The plasma protein binding of ruxolitinib was species dependent. Results from oral ^{14}C studies indicated minor to no preferential partitioning of ruxolitinib-derived radioactivity into blood cells of mice, rats, dogs and humans. The mean dermal unbound fractions in minipigs at 74 and 96 hours were 11.2% and 19.4%, respectively.

Metabolism

The *in vitro* metabolism of ruxolitinib was investigated using rat liver microsomes and recombinant rat cytochrome P450 (CYP) enzymes. Ruxolitinib was metabolised by the male rat-specific isozymes CYP2C11, CYP2C13 and CYP3A2, but not the female rat specific CYP2C12 isozyme. Ruxolitinib was also metabolised by isozymes found in both female and male rats including CYP1A2, CYP2C6 and CYP2D1. *In vitro* metabolism studies using recombinant human cytochrome P450s (CYPs) and human liver microsomes in the presence and absence of selective chemical inhibitors show that CYP3A4 is the predominant human CYP isozyme responsible for the metabolism of ruxolitinib and to a lesser extent is metabolised by CYP2C9. The *in vitro* studies in human liver microsomes showed that ruxolitinib and its major human metabolite M18 are not expected to inhibit cytochromes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 and is unlikely to cause clinical drug interactions. Ruxolitinib also appears to have a very low potential to induce CYP1A2, CYP2B6 and CYP3A4 enzymes at clinically relevant concentrations.

The *in vivo* metabolic profile of ruxolitinib was investigated in CbyB6F1HyBrid mice, CD-1 mice, rats, minipigs, rabbits, beagle dogs. In general, the metabolite profiles in non-clinical species and humans were similar and consisted of various hydroxylation and ketone metabolites and subsequent glucuronide conjugates. In mice and dogs that were administered oral ruxolitinib, parent compound was the primary component in circulation, while in rats and rabbits, metabolites are the predominant entities. The primary clearance pathway was via metabolism with the predominant metabolic pathways in mice, rat and dog being mono- and di-oxygenation. In mice, dogs, minipigs there were minimal gender differences in the exposure of ruxolitinib and its metabolites. In general, the metabolite profiles and excretion patterns in non-clinical species were similar to those observed in human. The toxicokinetics of eight metabolites previously observed in human plasma after oral dosing were evaluated in plasma from mice, rats and dogs administered at NOAEL oral doses. The results showed that human metabolites were adequately assessed in the toxicology studies conducted in mice, rats, and dogs.

Excretion

Following a single oral dose of 25 mg/kg ^{14}C-ruxolitinib in bile-cannulated female SD rats, elimination of INCB018424-derived radioactivity occurred via the urine, bile and faeces, accounting for an average of 45%, 40% and 20% of the administered dose, respectively. The excretion was rapid, 40% of administered dose was recovered from urine within 8 h, 37% from bile within 8 h and 19% from faeces within 24 h. The total recovery was 106% of the dose.

Following a single oral dose of 3 mg/kg ^{14}C-ruxolitinib in beagle dogs, routes of excretion and rate of elimination were similar in males and females with 82.4% and 79.7% of the dose excreted within 24 h of dosing, respectively. In males and females, 55% and 58% of the administered doses were recovered from faeces and 34% and 36% were recovered from urine.

After oral administration of 30 mg/kg ^{14}C-ruxolitinib to lactating rats, peak radioactivity concentrations occurred at 1-hour post-dose in plasma and blood and at 2 hours post-dose in milk. The milk:plasma concentration ratios ranged from 4.02 to 24.8 (13.4 based on $AUC_{0-\infty)}$, indicating that ^{14}C-INCB018424-related radioactivity preferentially partitioned into milk of rats. After reaching maximum

concentrations, the radioactivity in blood, plasma, and milk declined through 24 hours. The elimination half-lives of radioactivity in blood, plasma, and milk were similar at 2.22, 2.19, and 2.93 hours, respectively. After reaching peak concentration at 2 hours post-dose, concentrations of radioactivity associated with ^{14}C-INCB018424 in milk declined in parallel with plasma concentrations with no accumulation of radioactivity in the maternal milk indicating that accumulation of radioactivity in the maternal milk is likely to be minimal, according to the applicant.

Pharmacokinetic drug interactions

No interaction studies have been performed. Ruxolitinib interaction with systemic drugs after topical administration would be limited by the limited absorption. In addition, based on the available *in vitro* data, ruxolitinib appeared not to be an inhibitor or inducer of CYP enzymes. Therefore, the effect of ruxolitinib on other drugs via cytochrome P450 enzymes is considered to be unlikely by the applicant.

2.5.4. Toxicology

Ruxolitinib was evaluated for potential toxicity following oral and dermal administration. As systemic exposure from ruxolitinib 1.5% cream may overlap with that from orally administered ruxolitinib, the non-clinical information from oral dosing as well as after dermal application is considered relevant. Extensive non-clinical information on toxicology of ruxolitinib following oral administration had already been assessed and accepted previously during registration of the medicinal product Jakavi tablets (EMEA/H/C/002464). To evaluate the safety profile of ruxolitinib 1.5% cream for treatment of vitiligo, the applicant performed dermal single and repeat dose toxicity studies in mice and Göttingen minipigs, an *in vitro* photoclastogenicity study, a dermal 2-year mouse and an oral 2-year rat carcinogenicity study, and a series of local tolerance studies in mice, rabbit, and hairless albino guinea pigs. For topical studies, the cream formulation used was the same as the clinical ruxolitinib cream formulation. Test articles for all GLP studies were appropriately characterised with respect to identity, strength, purity, and composition.

2.5.4.1. Single dose toxicity

All oral single dose studies were part of the dossier of Jakavi (EMEA/H/C/002464). A dermal single dose study in Göttingen Minipigs was performed to support the ruxolitinib cream formulation.

Ruxolitinib was well tolerated following single oral doses of up to 100 mg/kg in rats and 40 mg/kg in dogs, and in male and female minipigs, dosed topically once with 1.5% cream on 25 cm^2 test area (Table 2).

Table 2: Single dose toxicity studies

Study ID	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
T06-07-01 (non-GLP) TK report: DMB-06.175	Göttingen Minipigs, 1/sex/group	TOPICAL 1.5% cream 4, 8 or 10 mg/cm2 25 cm2 test area Cream formulation same as clinical formulation	NOAEL: concentration: 1.5%, application rate: 10 mg/cm2	Well tolerated at all application rates.

T06-06-06 (non-GLP) TK report: DMB-06.170	Rats Crl:CD (SD)IGS BR, 6/sex/group	ORAL GAVAGE 0, 100, 300, 900 0.1% Tween in 0.5% w/v methylcellulose	NOAEL: 100 mg/kg Lethal dose: F: 300 mg/kg, M: 900 mg/kg	Mortality: ≥ 300 mg/kg (f), 900 mg/kg (m). Individual males at 100 mg/kg and surviving females at 300 mg/kg: lethargy and ventral recumbency.
T06-08-14 (non-GLP) TK report: DMB-06.180	Rats Crl:CD (SD)IGS BR, 6/sex/group	ORAL GAVAGE 0, 50, 100 0.5% w/v methylcellulose	NOEL: 100 mg/kg	Well tolerated.
T06-09-06 (non-GLP) TK report: DMB-06.186	Beagle Dogs, 1/sex/group	ORAL GAVAGE 5, 10, 20, 40 0.5% w/v methylcellulose	NOAEL: 40 mg/kg	Emesis noted at 2 hrs post-dose at 40 mg/kg.

f = female animals; m = male animals; NOEL=No-observed-effect level; NOAEL=No-observed-adverse-effect level

2.5.4.2. Repeat dose toxicity

Oral toxicity studies

The toxicity profile of ruxolitinib following oral administration has been assessed in rats and dogs for up to 6 months and 1 year, respectively, during the MAA procedure of Jakavi (EMEA/H/C/002464). Oral repeat dose toxicity studies are summarised in Table 3.

The most common findings in oral repeat dose studies in mice, rats and dogs were expected based on the pharmacological effects of JAK inhibition: decreases in lymphocytes, eosinophils, reticulocytes, red blood cell count, haemoglobin and haematocrit as well as hypocellularity of the bone marrow and lymphoid organs (spleen, thymus, lymph nodes, GALT). All changes demonstrated varying degrees of reversibility when dosing was discontinued.

In the oral rat 6-month study, a finding not clearly associated with the pharmacology of JAK1/2 inhibition was the minimal adrenal cortical atrophy at the highest dose administered, 60 mg/kg/day, which was not observed in other species.

In the dog, findings not clearly related to pharmacology of ruxolitinib were gastrointestinal (GI) inflammation in the 4-week oral study and prostatic hypoplasia in the 6-month study. GI inflammation was not found in longer studies and is therefore not deemed relevant by the applicant. The prostatic hypoplasia was not accompanied by any changes to testis or spermatogenesis and did not occur in the 12-month study under similar exposures.

Table 3: Oral repeat-dose toxicity studies

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
T08-05-07 (GLP)	CByB6F1 Mouse (Tg.rasH2 WT littermates) 10/sex/group	10, 30, 100, 300, 600 (5 days) and 0, 50, 100, 175, 250, additional 350 (4 weeks) mg/kg/day 0.5% methylcellulose, p/o	5 days, 4 weeks	50 (MTD=250)	≥350 mg/kg/day: deaths, ↓lymphocytes, neutrophils, monocytes, WBC, renal lesions ≥300: severe tox. (hunched, shallow breathing), death ≥175: ↓ spleen weights, nasal cavities inflammation ≥100: ↑ chloride, lymphoid repletion in spleen, hypocellularity of bone marrow ≥10: ↓ spleen M more affected than F
T06-06-12 (non-GLP)	Crl:CD®(SD) BR Rat 6/sex/group	0, 100, 200 (M), 0, 50, 100 (F) mg/kg/day 0.5% methylcellulose, p/o	1 week	50	≥100: ↓ WBC, lymphocytes, spleen, thymus weights; minimal-mild ↓ in cellularity in spleen, thymus, bone marrow, ↑ neutrophils
T06-08-03 (GLP)	Crl:CD®(SD) BR Rat 10/sex/group	0, 15, 50, 100 mg/kg/day 0.5% methylcellulose, p/o	4 weeks	50	≥100: ↓ BW gain, adverse ↓ bone marrow cellularity, ↓ cellularity in spleen and thymus ≥15: mild ↓ bone marrow cellularity
T08-06-02 (GLP)	Crl:CD®(SD) BR Rat 10/sex/group	0, 75, 150, 250 mg/kg/day 0.5% methylcellulose, p/o	13 weeks	Not established	All doses exceeded a maximal tolerated dose (↓ BW, lymphoid depletion at all doses) ≥150: F: heart fibrosis
T07-10-06 (GLP)	Crl:CD®(SD) BR Rat 15F/group	0, 5, 15, 30, 60 mg/kg/day 0.5% methylcellulose, p/o	6 months, 6 week recovery	30mg/kg (M) 60mg/kg (F)	60: red material around mouth, ↓ celull. in spleen, ↓ red cell mass, M: ↓ BW (no recovery), M: adrenal atrophy, F: ↑GGT ≥30: ↓ lymphocytes ≥15: ↑ALP, ↓ spleen and adrenal weights,
T06-09-07 (non-GLP)	Dog (Beagle)	0, 3, 10, 30 mg/kg/day	10 days	10 mg/kg	30: Emesis, swelling in feet, ↓ reticulocyte counts 10 and 30: ↓ lymphocytes in spleen, thymus, lymph nodes, and/or bone marrow
T06-11-03 (GLP)	Dog (Beagle)	0, 3, 10, 20 mg/kg/day	4 weeks	3 mg/kg	20: diarrhoea, lymphoid depletion in GALT, ↓ calcium, ↑ urea (M), ↑ ALP (M), ↓ cellularity in spleen ≥10: ↓ reticulocytes, erythrocytes, haemoglobin, haematocrite, ↓ calcium (F), phosphorus, ↓ marrow cellularity, lymph nodes, GALT, thymus, GI inflammation

T07-10-07 (GLP)	Dog (Beagle)	0, 0.5, 2.5, 5, 10 mg/kg/day	6 months	0.5 mg/kg	10: death (due to respiratory, dermal inflammation), ↓ cellularity in bone marrow, ↓ leukocytes, ↓ haematocrite, reticulocytes (F, M), pappilomas, cists on limbs and face ≥ 5: demodicosis (non-reversible), cage sores, ↓ haematocrite, reticulocytes (M), ↓ lymphocytes, eosinophils, ↑ neutrophiles, monocytes, ↓ albumin, ↑ globulin, ↓ cellularity in GALT, lymph nodes, spleen, thymus, prostate hypoplasia, diestrus ≥ 2.5: demodicosis (reversible)
T08-07-03 (GLP)	Dog (Beagle)	0, 0.75, 1.5, 3, 6 mg/kg/day	12 months	1.5 mg/kg	6: euthanasia (due to demodicosis), ↓ cellularity in bone marrow, ↓ haematocrite, reticulocytes (M), ↓ lymphocytes, ↑ neutrophiles, monocytes, ≥3: demodicosis, pyogranulomatous inflammation of skin, cage sores (partially reversible), ↓ cellularity in lymph nodes, ↓ eosinophils, ↓ cellularity in GALT, lymph nodes (reversible)

Dermal toxicity studies

Repeat dose dermal toxicity studies with ruxolitinib in mice and minipigs, were performed in support of topical formulation. No additional toxicities were identified in dermal studies with ruxolitinib as compared to oral route, as most effects observed were secondary to the pharmacological effect.

To support the study design and dose selection for a dermal carcinogenicity study, the toxicity of ruxolitinib was evaluated in CD-1 mice after dermal application for up to 3 months. The toxicity of ruxolitinib after dermal application was evaluated in Gottingen minipigs for up to 9 months. Doses and study designs for pivotal studies were based on results of preliminary 7-day studies where no evidence of systemic toxicity or significant dermal findings were observed. The cream formulation used in the pivotal GLP studies was the same as the clinical formulation. The excipients contained in the drug product are well known, commonly used in the manufacture of medicinal products intended for cutaneous use and of the Ph. Eur. quality, except for glyceryl stearate SE.

The findings associated with dermal application of ruxolitinib to mice for 28 days were increased neutrophils and monocytes in males administered 1.0% w/w BID to 10% BSA, and increased monocytes in males administered 1.5% w/w BID to 10% BSA. Severe dermal findings leading to euthanasia of one male mouse administered 1.5% BID were considered of uncertain relationship to ruxolitinib by the applicant.

Dermal application of ruxolitinib to mice for 90 consecutive days resulted in reductions of body weight in males administered 1.5% w/w BID to 10% BSA. Decreases in total leukocytes and lymphocyte counts and decreases in erythrocytes and haemoglobin were observed. Absolute lymphocyte count was decreased to 59 – 56% of the respective control group value. Margins (based on unbound AUC) at non-adverse levels were approximately 10-fold in male and 24-fold in female mice relative to systemic exposure observed in patients with vitiligo that applied 1.5% ruxolitinib cream twice daily. Erythrocytes were reduced in both sexes at 1.5% BID, but did not reach statistical significance in the females,

although haematocrit was statistically decreased in the females at 1.5% BID. Haemoglobin was decreased dose-dependently in males and females receiving 1.0% and 1.5% BID. Although these changes appeared to be dose-dependent, values remained within normal ranges and were therefore not considered adverse. One female dosed 1.5% BID was euthanised in extremis due to pulmonary inflammation; the relationship of this single finding to the test article is unclear.

In the 9-month dermal study in minipigs, decreases to 40-60% of the baseline in lymphocytes occurred in all ruxolitinib-treated groups. Because there were no associated microscopic findings of lymphoid depletion, these were considered non-adverse in the absence of any other findings suggestive of systemic toxicity. Dermal findings at the application site, including hyperkeratosis, epidermal hyperplasia, erosions, and ulcerations, were generally mild. Epidermal hyperkeratosis and hyperplasia did not show a clear dose response, whereas erosions and ulcerations were most common in the 1.5% w/w BID applied to 10% BSA group. Hence, the systemic NOAEL was identified as the high dose, 1.5% ruxolitinib cream BID, while the dermal NOAEL was identified as the mid dose, 1.0% cream BID. Systemic ruxolitinib exposures were low, consistent with PK studies in minipigs where bioavailability following dermal application was approximately 3%: 1.5% ruxolitinib when applied dermally twice daily to 10% BSA at an application rate of 10 mg/cm2 was associated with Day 293 AUC0-24 of 167 nM·h in males, and 219 ± 116 nM·h in females. Unbound fraction in minipigs is 10-fold higher than in humans. Consequently, the exposures in minipigs were 3-fold the expected exposure at human therapeutic dosage.

This effect was not observed in the 13-week study, which may indicate that the effect is dependent on the duration of the treatment. Upon CHMP's request, the applicant included this information in section 5.3. of the SmPC.

Table 4: Repeat dose dermal toxicity studies

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
T08-01-14 (non-GLP)	CD-1 mice, 10/sex/group	Vehicle (placebo; XHEG-C); 1.0% w/w (XHEI-C); 1.5% w/w (XHEK-C) Once daily (placebo, 1.0%) Twice daily approximately 7 hr apart (placebo, 1.0%, 1.5%); 10% BSA, 10 mg/cm2	7 days	N/A	No toxicity.
T08-02-08 (GLP)	CD-1 mice, 10 animals/sex/group; additional groups of 44 animals/sex (8/sex in placebo control groups) for TK	Vehicle (placebo; AAP-1C); 1.0% w/w (ACM); 1.5% w/w (ACN) Once daily (placebo, 1.0%) Twice daily 6 hr (±1 hr) apart (placebo, 1.0%, 1.5%); 10% BSA, 10 mg/cm2	28 days	NOAEL: M: 1.0% BID, F: 1.5% BID	1.0% BID: M: ↑ neutrophils and monocytes 1.5% BID: M: ↑ monocytes; 1M euthanasia due to severe dermal findings

T08-04-06 (GLP)	CD-1 mice, 15 animals/sex/group; additional groups of 42 animals/sex (6/sex in placebo control groups) for TK	Vehicle (placebo; AAP-1C); 1.0% w/w (ACM); 1.5% w/w (ACN) Once daily (placebo, 1.0%) Twice daily 6 hr (±1 hr) apart (placebo, 1.0%, 1.5%); 10% BSA, 10 mg/cm2	90 days	NOAEL: M: 1.0% QD, F: 1.0% BID	≥1.0% QD: M: unkempt app., discoloured fur ≥1.0% BID: M: ↓ BW, ↓ lymphocytes, erythrocytes and hemoglobin 1.5% BID: M: ↓ BW, ↓ lymphocytes, erythrocytes and hemoglobin F: ↓ lymphocytes, erythrocytes and hemoglobin; 1F euthanasia in extremis due to pulmonary inflammation
T06-07-01 (non-GLP) TK report: DMB-06.175	Göttingen minipigs, 2M/1F or 1M/2F per group	Vehicle (placebo cream; 678-0710X02), 0.5% w/w (678-0710X03), 1.0% w/w (678-0710X01), 1.5% w/w (678-0711X01) Once daily; 10% BSA, 4 or 10 mg/cm2	7 days	NOAEL: 1.5% QD No observable application rate = 10 mg/cm2	Slight erythema (M, F) and desquamation (M) in control and test groups – vehicle related
T07-11-02 (GLP)	Göttingen minipigs, 1M, 1F per group	Vehicle (placebo cream; AAP-C) 1.5% w/w (AAS-C) Once or twice daily; 10% BSA, 4 or 10 mg/cm2	7 days	NOAEL: 1.5% QD	No article-related observed effects.
T06-09-01 (GLP)	Göttingen minipigs, 5M, 5F or 3M, 3F per group	Vehicle (placebo cream; XHEG-C), 0.5% w/w (XHEH-C), 1.0% w/w (XHEI-C), 1.5% w/w (XHEK-C) Once daily; 10% BSA, 4 mg/cm2	4 weeks (with 4 week recovery)	NOAEL: 1.5% QD	No article-related observed effects.
T07-12-01 (GLP)	Göttingen minipigs, 5M, 5F per group	Vehicle (placebo cream; AAP-1C), 1.0% w/w (ACM), 1.5% w/w (ACN) Once daily (placebo, 1.0%) Twice daily approximately 7 hr apart (placebo, 1.0% 1.5%); 10% BSA, 10 mg/cm2	13 weeks (with 4 week recovery)	NOAEL: 1.5% BID	Control and test: Erythema, Sebaceous Gland Hypertrophy/Hyperplasia (M, F) and desquamation (M) ≥1.0% QD: M,F: stratum corneum expansion
T09-01-01 (GLP)	Göttingen minipigs, 7M, 7F per group	Vehicle (placebo cream; ALX-C), 1.0% w/w (AFA-C, AFA-1C), 1.5% w/w (AFB-C) Once daily (placebo, 1.0%) Twice daily 6 hr (±15 min) apart (placebo, 1.0% 1.5%) 10% BSA, 10 mg/cm2	9 months (with 6 week recovery)	1.5% BID	Control and test: M,F: epidermal hyperkeratosis ≥1.5% BID: F: ↓ lymphocytes, M,F: mild skin ulcerations ≥1.0% QD: M: ↓ lymphocytes, mild skin hyperplasia, erosions

BSA = Body surface area

2.5.4.3. Genotoxicity

Ruxolitinib was negative in the Ames assay, in the *in vitro* chromosomal aberrations test with cultured human blood and the *in vivo* rat bone marrow micronucleus assay but was positive for inducing chromosomal aberrations in CHO cells with UV exposure (Table 5).

Although the *in vitro* photoclastogenicity assay may be oversensitive (and is therefore not recommended for regulatory purposes), ruxolitinib is known to absorb UV light, which may be of concern. However, the photoclastogenicity would stem from the generation of reactive oxygen species due to photoinstability, and the applicant has shown that UV or visible light absorption does not lead to significant photodegradation of ruxolitinib. The photoirritation and photoallergy test results showed no adverse effects of ruxolitinib in albino hairless guinea pigs. Furthermore, apart from some irritation under occlusive application, no adverse dermal findings consistent with photoreactivity, phototoxicity or photoallergy have been observed in clinical studies under exaggerated conditions (INCB 18424-104, INCB 18424- 105, INCB 18424-106, INCB 18424- 107, INCB 18424-108).

Although photoclastogenicity cannot be definitively excluded, results of photostability, nonclinical *in vivo* phototoxicity studies and clinical dermal safety studies indicate that ruxolitinib is not photoreactive.

Table 5: Genotoxicity studies

Type of test/study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results Positive/negative/equivocal**
Gene mutations in bacteria T06-01-03	Salmonella TA98, TA100	1.5, 5.0, 15, 50, 150, 500, 1500, 5000 µg/plate ± S9 48-72 hours	Negative
Salmonella-Escherichia coli Mammalian-Microsome Reverse Mutation Assay T06-08-01	Salmonella TA98, TA100, TA1535, TA1537, E. coli WP2uvrA	33.3, 100, 333, 1000, 2500, 5000 µL/mL ± S9 48-56 hours	Cytotoxic Effects: TA100 at 5000µg/plate ±S9 Genotoxic Effects: Not genotoxic
Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes T06-08-02	Peripheral human lymphocytes	-S9: 10, 20, 50, 65 µL/mL +S9: 10, 20, 50, 95 µL/mL 3 hours +S9, 22 hours –S9 treatment with harvest ≈22 hours from treatment start	Negative
Photoclastogenicity T08-02-11	Chinese Hamster Ovary (CHO) (CHO-WBL) Cells	1.79, 5.0, 10, 20, 28.6, 30, 60, 80, 120, 160, 200 µg/mL 3h treatment, harvest 20 h from treatment start	Cytotoxic Effects: Reduction in mitotic index > 30µg/mL Genotoxic Effects: Chromosome aberrations in the presence of UV light at 28.6, 30, and 60µg/mL; negative in absence of UV light.
In Vivo Rat Bone Marrow Micronucleus Assay T06-10-02	Rat polychromatic erythrocytes in bone marrow	Single dose: 62.5, 125, 250 mg/kg Sampling at 24 and 48 h 5M/5F/dose	Cytotoxic to bone marrow at 48 hrs in 250 mg/kg males. Genotoxic Effects: Negative. No significant increase in incidence of micronucleated polychromatic erythrocytes.

2.5.4.4. Carcinogenicity

Ruxolitinib was evaluated for potential carcinogenicity following oral administration in rats for 2 years and Tg.rasH2 mice for 6 months, and following dermal administration of ruxolitinib cream to CD-1 mice

for 2 years (Table 6). The Tg.rasH2 mice for 6 months study has already been assessed as part of Jakavi registrational procedure (EMEA/H/C/002464).

There were some neoplastic findings in the 2-year mice dermal carcinogenicity study. In males, there was a statistically significant increase in the incidence (dose dependence) of adenoma in the kidneys when compared to placebo control, but not when compared to untreated control. There was a statistically significant increase in the incidence of malignant lymphoma when compared to untreated control, but not when compared to placebo control. There was also a statistically significant increase in the incidence of malignant lymphoma when comparing the high dose level with untreated control (15 males vs. 3 males in groups of 60). In females, there was a statistically significant increase in the incidence of systemic hemangiosarcoma when comparing the low dose level with placebo control (11 females vs. 2 females in groups of 60), but not when comparing mid or high dose level with either control groups.

Exposure levels achieved with topical application of 1.5% QD in 2-year mice carcinogenicity study were 0.064 and 0.073 µM·h (M, F, unbound), which is 3.0-3.5-fold the exposure expected in humans after dermal use of ruxolitinib.

Due to the absence of statistical significance when comparing to both control groups and absence of a dose-response with hemangiosarcoma in females, these statistically significant variations were considered by the applicant to be incidental changes unrelated to test article administration. Although these results are seemingly inconsistent, a comparison with historical data for CD-1 mice would have been beneficial. There are some indications that JAK inhibitors may cause malignancies when taken orally in clinical use and the exposure after topical administration is overlapping with exposure after oral administration, therefore, the applicant was asked to further discuss the occurrence of kidney adenoma, malignant lymphoma and haemangiosarcoma. As noted by the applicant, in oral studies there was no increase in these, or related tumours in rats, and no ruxolitinib-related neoplasia in Tg.rasH2 mice despite achieving 10-fold (rat) and 30-fold (Tg.rasH2 mouse) higher exposures than in the dermal mouse study.

In dermal mouse study, although there was a statistically significant trend in the incidence of adenoma in the kidneys in males when compared to placebo control, there were no statistically significant differences in pairwise comparisons with the placebo control, and a similar trend was not observed when compared to the untreated control. The incidence in high dose males was similar to that in the untreated control, suggesting this reflected background variability. There were also no findings of kidney adenoma in females.

The haemangiosarcoma incidence in low dose (0.5%) female mice was significant when compared to the placebo control, but not when compared to the untreated control. No statistically significant differences were found in male groups compared with untreated or placebo control. This can be explained with the incidence of haemangiosarcoma in the placebo control females being notably lower than in untreated controls and in the placebo control males. Further, the incidence of this finding was similar in males and females across all treated groups with no dose-response. Therefore, the increased incidence of haemangiosarcoma in low dose females relative to the placebo control group can be explained by intergroup variability and the low incidence in the placebo control group and cannot be attributed to ruxolitinib cream.

Lymphoma is a common background tumour in CD-1 mice. There was a statistically significant increasing trend in the incidence of lymphoma in males when compared to untreated control, but not when compared with placebo control. There was a statistically significant higher incidence of the tumour when comparing the high dose level with untreated control. Among the unscheduled deaths in males for which lymphoma was the cause of death, there were no apparent trends in the days of death, suggesting no difference in onset or progression of lymphoma in these groups that may suggest

an effect of ruxolitinib cream. There was no evidence of an increase in lymphoma in female mice, and the incidence in both female control groups were notably higher than in male control groups. Collectively, these results indicate that the higher incidence of malignant lymphoma in high dose males is most likely due to intergroup variability in the incidence of this common tumour and was not associated with administration of ruxolitinib cream.

Common neoplasms observed in the rats in the 2-year rat oral carcinogenicity study were consistent with spontaneous neoplasms in aging laboratory rats and were not related to administration of ruxolitinib. Exposure levels achieved at 60 mg/kg in present study were 0.538 and 4.27 µM·h (M, F, unbound), which is 4.7-37.1-fold the exposure expected in humans after dermal use of ruxolitinib. The lower exposure in males may be due to faster metabolism in males of ruxolitinib in this species, therefore the margin of exposure may be underestimated.

No malignancies were detected in the 6-month Tg.rasH2 mice carcinogenicity study. Exposure levels achieved at 125 mg/kg were 3.32 and 3.82 µM·h (M, F, unbound), which is 158-182-fold the exposure expected in humans after dermal use of ruxolitinib.

The applicant considered that non-clinical data do not suggest that ruxolitinib cream is carcinogenic in animals.

Table 6: Carcinogenicity studies

Study ID /GLP	**Dose/Route**	**Exposure (AUC-24 (µM·h))**		**Major findings**
2-year dermal carcinogenicity study in CD-1 mice T09-02-02 (GLP)	0.5%, 1, 1.5% QD cream 100 µL/dose dermal 60 animals/sex/group TK: 42 animals/sex	M	2.37	None
		F	2.70	
2-year oral (gavage) carcinogenicity study in rats T09-01-02 (GLP)	10, 20, and 60 mg/kg in 0.5% methylcellulose 65 animals/sex/group TK: 10 animals/sex	M	2.99	60: ↓ BW(F), yellow material around mouth (M, F), urogenital area (F), spleen lymphoid depletion All doses: ↓ BW (M)
		F	23.7	
26-Week oral repeated Dose Oral carcinogenicity study in Tg.rasH2 mice T09-02-03 (GLP)	15, 45, and 125 mg/kg in 0.5% methylcellulose 25 animals/sex /group Urethane (poz.contr.)-3x1000mg/kg i.p.: 25 animals/sex TK: 44 animals/sex	M	67.8	125: ↓ BW gain (M) ≥45: food consumption (F) All doses: ↓ BW(F), food consumption (M), nasal cavity inflammation
		F	78.0	

2.5.4.5. Reproductive and developmental toxicity

Reproductive and developmental studies were presented during the marketing authorisation procedure for ruxolitinib tablets Jakavi (EMEA/H/C/002464). Studies performed with oral ruxolitinib administration are described in the Table 7 below.

In a fertility study in rats, oral ruxolitinib had no effects on male fertility or on oestrus cycling, mating or fertility indices in females. However, an increase in post-implantation loss was observed at 30 and 60 mg/kg per day.

In embryofoetal development studies in rats and rabbits, increased resorptions and decreased foetal weight were observed at maternally toxic doses (≥ 30 mg/kg/day). In rabbits, an increased number of malformations were noted in animals treated with ruxolitinib, but not in the control group. Hydrocephaly was noted in one foetus and umbilical hernias were noted in two foetuses from separate litters from dams given 60 mg/kg/day, which was associated with maternal toxicity. An unossified pubis was also noted in one foetus at this high dose. Incidental skeletal malformations included fused ribs in one 10 mg/kg/day foetus, fused thoracic centra in two 10 mg/kg/day foetuses from one litter and fused ribs and thoracic centrum in one 30 mg/kg/day foetus.

In rat, the exposure at NOAEL (30 mg/kg per day) was approximately 25.5-fold of that in vitiligo patients during clinical trials. At NOAEL (30 mg/kg per day) the exposure in rabbit was only 0.42-fold of that in vitiligo patients during clinical trials. In rabbits, low plasma ruxolitinib exposure was attributed to extensive metabolism to active metabolites. Thus, plasma ruxolitinib levels may not reflect the level of pharmacologic activity in rabbits.

Following maternal oral administration during gestation and lactation in rats in the pre- and postnatal study, ruxolitinib had no effect on postnatal survival, developmental milestones, behavioural or reproductive function in offspring. Birth weight was slightly lower, and a transient decrease in postnatal body weight gain during the early lactation period was observed at 30 mg/kg per day.

Orally administered ruxolitinib to juvenile rats beginning on Day 7, 14 or 21 postpartum caused reductions in body weight gain and effects on bone measures. These findings were more severe in males than in females, and when dosing was initiated at an earlier age. The relationship of these findings to ruxolitinib pharmacology, and translation to humans is unclear, however the rat may not be a representative model for this effect. The difference is that the juvenile rat skeleton is predominantly a modelling skeleton, while in humans remodelling is more important in bone formation, because the average bone tissue age in a 20-year growth period in humans exceeds the osteocyte-life span.

The juvenile animal toxicity study results elicited a safety concern for the use of ruxolitinib in paediatric subjects. Effects on bone growth were observed at exposures approximately 22-fold (start of dosing at PND7) and 35-fold (start of dosing at PND21) of those in vitiligo patients during clinical trials. Also, none of the effects on the bone seen in the juvenile animal study was seen in adolescent rats and dogs in repeat dose toxicity studies.

Animal data suggest that ruxolitinib is preferentially partitioned into milk. In the rat study with 14C-INCB018424, the milk:plasma concentration ratios ranged from 4.02 to 24.8 (13.4-fold, based on AUC0-∞) (DMB-10.50.1). As the data on juvenile toxicity indicate possible bone development effects in early postnatal development, and the treatment can be postponed, it was decided that ruxolitinib cream should be contraindicated during breastfeeding and treatment must be discontinued approximately four weeks before the beginning of breastfeeding. The applicant has agreed to update the SmPC section 4.6 accordingly.

Table 7: Reproductive and developmental toxicity studies

Study type/ Study ID / GLP	**Species; Number Female/ group**	**Route & dose (mg/kg)**	**Dosing period**	**Major findings**	**NOAEL (mg/kg) & AUC**
Fertility and early embryonic development T09-06-01 **GLP**	Rat/Crl:CD (SD) 22/group/sex	Oral gavage 0, 10, 30, 60	M: 10 weeks F: 21 days (through G7)	≥ 30: F_0: postimplantation loss, ↓ litter size ≥ 10: F_0: M: ↓ BW	60 mg/kg: Reproductive performance and fertility in F_0, both sexes 10 mg/kg: F_0 males and F_1 litters

					0.28 µM·h **(13.4 X safety margin)**
Embryo-foetal dose range finder **T07-10-14** **GLP**	Rat/Crl:CD (SD) 6/group Additional 27F	Oral gavage 0, 15, 30, <u>60</u>, 120	G7-G20	120: maternal tox, resorptions ≥60: ↓ foetal BW	60 mg/kg (F_0 dams, F_1 litters)
Embryo-foetal definitive **T07-12-04**	Rat/Crl:CD (SD) 25/group	Oral gavage 0, 15, <u>30,</u> 60	G7-G20	60: mortality ≥30: ↓ foetal BW	30 mg/kg (F_0 dams, F_1 litters) **0.53 µM·h (26x safety margin)**
Single Dose PK/PD in pregnant rabbits T08-06-11 **Non_GLP**	Rabbit (NZW) 2 animals/group	Oral gavage 10, 30, <u>60</u>	1 day (G13 or G14)[(a)]	N/A	N/A
Embryo-foetal dose range finder **T07-10-13** **GLP**	Rabbit (NZW) 6(+3)/group	Oral gavage 0, 10, 25, <u>50</u>, 100	G8-G21 (G8-G14)	100: postimplantation loss, ↓ uterine weight ≥25: ↓ fetal BW	25 mg/kg (F_0 dams, F_1 litters)
Embryo-foetal definitive **T07-12-05** **GLP**	Rabbit (NZW) 20/group TK: 3/group	Oral gavage 0, 10, <u>30,</u> 60	G8-G21	60: mortality, late postimplantation loss, ↓ foetal BW	30 mg/kg (F_0 dams, F_1 litters) **0.009 µM·h (0.4x safety margin**)
Pre- and post-natal development study **T10-02-03** **GLP**	Rat/Crl:CD (SD) 25/group TK:6/group	Oral gavage 0, 5, 15, <u>30</u>	G6-L20	30: ↑ gestation time, ↓ implantation sites, ↓ size of litter, ↓ live pups/litter, ↓ birth BW and weight gain	30 mg/kg **0.6 µM·h (28.6x safety margin)**
Juvenile Animals range-finder **T16-09-09** **non-GLP**	Rat/Crl:CD (SD) 12/sex/group TK: 8/sex/group	Oral gavage 0, 5, 15, 30, 50, 75	7pp-41pp	≥30: from day 12PP euthanized early due to radiographic findings, bone fracture, callus, or physeal degeneration/necrosis ≥ 15: radiographic findings of bones	5 mg/kg
Juvenile Animals definitive **GLP**	Rat/Crl:CD (SD) 24/sex/group TK: 20/group Fertility:20/sex/group	Oral gavage 0, 1.5, 5, 15	7pp, 14pp, 21pp – 63pp	15: ↓ BW (F) ≥ 5: ↓ BW (M) Haematology and bone findings dependent on start of dosing (see text below)	7pp: 5 mg/kg **M: 0.48 µM·h** **F: 0.46 µM·h** **(22.5x safety margin)** 21pp: 15 mg/kg **M: 0.788 µM·h** **F: 0.67 µM·h** **(34.8x safety margin)**

NOAEL (No-Observed-Adverse-Effect-Level) is underlined

G - gestation day

L - lactation day

2.5.4.6. Toxicokinetic data

Adequate safety margins were achieved during oral repeat dosing of ruxolitinib in rat and dog (Table 8).

Ruxolitinib exposures in dermal repeated dose toxicity studies at the NOAEL in mice (1.0% QD) and minipigs (1.5% BID), were 9.3 – 24-fold (mouse) and 2.6 – 3.4-fold (minipig), respectively, the expected exposure (steady-state AUC0-24, unbound) at the human therapeutic dosage.

The *ex vivo* fraction unbound in plasma is 4.9% in Tg.rasH2 mice, 2.7% in CD-1 mice, 18% in rats, 13% in rabbits, 9.7% in beagle dogs, and 33% in Gottingen minipigs. *In vitro* fraction unbound in human plasma is 3.3%.

Table 8: Summary of toxicokinetics

Study	Sex	NOAEL (mg/kg per day)	AUC0-24 (µM·h)		Safety Margin vs. INCB 18424-306/307[a]	
			Total	Unbound[b]	Total	Unbound
Repeat-Dose Toxicology						
6-month oral rat **T07-10-06**	M	30	0.662	0.119	1.04[d]	5.67[d]
	F	60[c]	25.8	4.64	40.4	221
52-week oral dog **T08-07-03**	M	1.5	2.36	0.229	3.70	10.9
	F	1.5	2.57	0.249	4.03	11.9
3-month mouse – topical **T08-04-06**	M	1.0% QD	7.24	0.195	11.3	9.29
	F	1.0% BID	18.7	0.505	29.3	24.0
9-month minipig – topical **T09-01-01**	M	1.5% BID[c]	0.167	0.055	0.26	2.62
	F	1.5% BID[c]	0.219	0.072	0.34	3.43
Reproductive and Developmental Toxicology						
Fertility and Early Embryo Development – rat **T09-06-01**	M	60c	1.32[e]	0.238	2.07[d]	11.3[d]
	F	60[cf]	25.8[e]	4.64	40.4	221
		10[f]	1.56[g]	0.281	2.45	13.4
Embryofoetal Development – rat **T07-12-04**	F	30	2.98	0.536	4.67	25.5
Embryofoetal Development – rabbit **T07-12-05**	F	30	0.068	0.009	0.10[d]	0.42[d]
Pre/Postnatal Development – rat **T10-02-03**	F	30c	3.34	0.60	5.24	28.6
Juvenile Rat **(Day 7 pp initiation)** **T17-11-14**	M	5	2.66	0.48	4.17	22.9
	F	5	2.57	0.46	4.03	21.9
Juvenile Rat **(Day 21 pp initiation)** **T17-11-14**	M	15	4.38	0.788	6.87	37.5
	F	15	3.73	0.671	5.85	32.0

Carcinogenicity						
104-week mouse – topical **T09-02-02**	M	1.5% QD[c]	2.37	0.064	3.71	3.05
	F	1.5% QD[c]	2.70	0.073	4.23	3.48
104-week rat – oral **T09-01-02**	M	60c	2.99	0.538	4.69	25.6
	F	60c	23.7	4.27	37.1	203
6-month Tg.rasH2 mouse **T09-02-03**	M	125[c]	67.8	3.32	106	158
	F	125[c]	78.0	3.82	122	182

[a] Safety margins were calculated as the multiple of $AUC_{0\text{-}24h}$ at the NOAEL relative to steady state $AUC_{0\text{-}24h}$ in vitiligo patients that applied 1.5% ruxolitinib$_{cream}$ BID to up to 10% BSA in INCB 18424-306 and INCB 18424-307, calculated as Css (geometric mean; 26.6 nM, average of 24 and 40 week) × 24. (638 nM·h total; 21 nM·h unbound) (Module 2.7.2.2.3.2.2).

[b] The ex vivo fraction unbound in plasma is 4.9% in Tg.rasH2 mice, 2.7% in CD-1 mice, 18% in rats, 13% in rabbits, 9.7% in beagle dogs, and 33% in Gottingen minipigs. In vitro fraction unbound in human plasma is 3.3%.

[c] Highest dose tested

[d] Ruxolitinib exposure in male rats and rabbits is not reflective of total pharmacologic activity because of extensive metabolism to active metabolites. Thus,safety margins for pharmacology-driven effects are likely underestimated.

[e] Toxicokinetics were not included in the fertility study. AUC from 60 mg/kg per day in 6-month study in rats.

[f] NOAEL was 60 mg/kg per day female reproductive function and 10 mg/kg per day for early embryonic toxicity

[g] Toxicokinetics were not included in the fertility study. AUC estimated from exposure at 15 mg/kg per day in the 4-week study in rats.

2.5.4.7. Local tolerance

The cream formulation was mildly to slightly irritating to the skin and eye in rabbits. Ruxolitinib was not phototoxic, no dermal sensitiser, and had no photoallergy potential (Table 9).

Table 9: Local tolerance studies

Study Type	Route of Administration	Test System	Major findings
Local Lymph Node Study (dermal hypersensitivity) **T06-09-02 (GLP)**	Topical CBA/J mice	0, 0.625, 2.5, 10% 25 µL/ear	SI: 0.4, 0.6, and 0.4 (at 0.625, 2.5, and 10% (w/w) respectively) SI≤3 means positive result
Primary Dermal Irritation Cream formulation **T06-09-03 (GLP)**	Topical New Zealand White Rabbit	0, 0.5, 1.0, 1.5% 0.06 g	Erythema and slower resolution of erythema (8 vs.4 days) Slightly irritating, non-corrosive
Primary Eye Irritation Cream formulation **T06-09-04 (GLP)**	Ocular New Zealand White Rabbit	0, 0.5, 1.0, 1.5% 0.1 mL	Minimally irritant and non-corrosive
Irritation and Phototoxicity Cream formulation **T06-09-05 (GLP)**	Topical Crl:IAF(HA)-hr guinea pigs	0, 0.5, 1.0, 1.5% 0.05 g single application for 2h, radiation for 2.25h, 3d observation	No phototoxicity.
Dermal Hypersensitivity and Photoallergy Cream formulation **T08-01-06 (GLP)**	Topical Crl:IAF(HA)-hr guinea pigs	0, 1.0, 1.5% 0.05 g	No contact hypersensitivity or photoallergy.

		induction of contact hypersensitivity and photoallergy (FCA) single application for 2h, ± radiation for 2.25h, repeated on d3, 5, 8, 10, 12 challenge on d22	

2.5.4.8. Other toxicity studies

- ***Impurities***

Drug process starting materials, intermediates, and impurities were evaluated in a series of *in silico* platforms, and if they were predicted mutagenic, they were further evaluated in *in vitro* Ames test (TA98, TA100, TA1535, TA97a, and TA102).

The *Salmonella typhimurium* strains were chosen according to the ICHS2(R1) guideline and Ames tests gave no positive result.

Upon CHMP's request, another 19 potential impurities were evaluated using Derek Nexus (v 6.1.0) and Sarah Nexus (v 3.1.0). 17 structures were assigned as ICH M7 Class 5 based on absence of a structural alert and will be treated as non-mutagenic impurities. Two structures, MS 305 and INCB042043, were positive in both Derek and Sarah with an alerting structure of potential alkylating agent and assigned ICH M7 Class 3. For all batches of ruxolitinib phosphate drug substance tested, the two impurities were not detected at or above the method detection limit of 1 ppm. Thus, the potential exposure is below the acceptable threshold of toxicological concern (TTC) for mutagenic impurities based on maximum recommended use. Therefore, none of these compounds needed to be further tested for mutagenicity.

2.5.5. Ecotoxicity/environmental risk assessment

A full Phase I, Phase IIA and partial Phase IIB assessment was performed. All ERA studies were conducted in compliance with GLP.

The mean log K_{OW} (log Dow) octanol-water partition coefficient of ruxolitinib phosphate was determined to be 2.3 to 2.6 (pH 4); 2.3 to 2.4 (pH 7) and 2.5 to 3.0 (pH 9). Mean values from all three assays are below the criteria for the evaluation of secondary poisoning, hence tier B for secondary poisoning was not triggered. Ruxolitinib is not a persistent, bio-accumulative and toxic (PBT) substance since the octanol-water distribution coefficient (log D_{OW}) is <4.5.

Ruxolitinib is not readily biodegradable. In water-sediment systems, ^{14}Cruxolitinib dissipates from the water phase mainly via binding to sediment (bound residues) and the formation of a major transformation product (TP1) and a number of minor transformation products.

Koc in three soils and both sludges was <10,000 mL/g, therefore, ^{14}Cruxolitinib phosphate will not strongly adsorb to activated sludge or soil. According to the McCall classification scale, ^{14}Cruxolitinib phosphate can be classified (based on K_{OC}) as having immobility in the soils.

The DT_{50} value for ^{14}Cruxolitinib phosphate in the total water/sediment test system for Taunton River and Weweantic River aerobic and test systems were determined to be 418 and 761 days at 12 °C, respectively. The total system half-life (DT_{50}) at 12 °C ranged from 344 to 527 days; based on DT_{50} >180 days, ruxolitinib is very persistent (vP) in aquatic systems according to the OECD 308 study. Also, in the water-sediment study, > 10% of the radioactivity was present in the sediment within 14

days. Hence, the applicant performed the Phase II Tier B OECD 218 study in sediment dwelling midge Chironimus riparius (see Table 10).

$PEC_{surfacewater}$ of 0.43 µg/L was calculated using the default F_{PEN} of 0.01, which is acceptable for this marketing application.

The PNECs for surface water, groundwater, microorganisms in a sewage treatment plant, and sediments were 30.4 µg/L, 61.5 µg/L, 1139 µg/L, and 3.63 mg/kg dw, respectively.

RCR (PEC/PNEC) for surface water, groundwater, microorganisms, and sediments were all below the respective trigger values, therefore no adverse environmental effects to the aquatic environment are anticipated as a consequence of therapeutic use of ruxolitinib phosphate cream (1.5%) for the topical treatment of vitiligo in patients 12 years of age and older.

Table 10: Summary of main study results

Substance (INN/Invented Name): ruxolitinib phosphate			
CAS-number (if available): 1092939-17-7			
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH 4= 2.3-2.6 pH 7= 2.3-2.4 pH 9= 2.5-3.0	Not a Potential PBT (log D_{OW} < 4.5)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Water Solubility OECD 105		pH 5= 16.4 g/L pH 7= 15.7 g/L pH 9= 17.8 g/L	Very soluble (solubility > 10000 mg/L)
Bioaccumulation OECD107	log K_{ow}	2.5-3	< 4.5, potentially not B
	BCF	N/A	log K_{ow} <3
Persistence OECD 308	DT_{50} or ready biodegradability	DT50, whole system = 344 – 527 d (12°C) DT50, sediment = 418 - 761 days (12°C)	vP (> 180 d (12 °C))
Toxicity	NOEC algae NOEC daphnia NOEC fish	0.40 mg/L 0.81 mg/L 0.42 mg/L	Not Toxic
PBT-statement:	The compound is not considered as PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default	0.43	µg/L	> 0.01 threshold YES Default F_{PEN} used
Other concerns (e.g. chemical class)	N/A		No additional concern
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	SOILS: K_d= 45.3, 61.4 and 91.9 L/kg (adsorption) K_d= 62.2, 87.1 and 138 L/kg (for desorption) K_{oc} = 1510, 2419 and 6821 L/kg (adsorption) K_{oc} = 2073 and 9678 L/kg (desorption) SLUDGE: K_d= 108 and 155 L/kg (adsorption) K_d= 105 and 154 L/kg (desorption) K_{oc} = 254 and 384 L/kg (adsorption) K_{oc} = 246 and 382 L/kg (for desorption)	Koc < 10,000 L/kg, Kd < 3700 L/kg, IIB terrestrial studies not triggered

Ready Biodegradability Test	OECD 301B	<60% by day 28			Not readily biodegradable
Aerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 3.5-5.8 days (20 °C) $DT_{50, sediment}$ = 196-357 days (20 °C) $DT_{50, whole\ system}$ = 162-248 days (20 °C) $DT_{50, whole\ system}$ = 344-527 days (12 °C) % shifting to sediment: 80% AR Ultimate biodegradation <1% $^{14}CO_2$ recovered TP1>10% AR: TP 1 (max.15.3% d 14): 3-[4-(§-chloro-7H-pyrrolo[2,3-d] pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-cyclopentylpropanenitrile where the value of § could be 2, 5, or 6.			Sediment: sandy loam/sand (USDA) Ruxolitinib is very persistent (trigger value of 180 days). Chironomus test triggered. TP1 proposed chemical name.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test *Raphidocelis subcapitata*	OECD 201	EC_{50} NOEC	6.9 (growth) 3.1 (biomass) <u>0.40</u> (growth) 0.98 (biomass)	mg/L	Measured concentrations: 0.40, 0.98, 2.6, 7.0, 17, 41 mg/L
Daphnia sp. Reproduction Test *Daphnia magna*	OECD 211	EC_{50} NOEC	>1.9 (empirical) 0.81	mg/L	Measured concentrations: 0.13, 0.31, 0.81, 1.9, 5.1 mg /L
Fish, Early Life Stage Toxicity Test *Fathead Minnow*	OECD 210	LOEC NOEC	0.81 0.42	mg/L	Measured concentrations: 0.10, 0.21, 0.42, 0.81, 1.7 mg/L
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50} NOEC	462 (empirical) 15	mg/L	Nominal concentrations: 5, 15, 45, 135, 405 mg/L
Phase IIb Effect studies					
Sediment-water toxicity *Chironomus riparius*	OECD 218	LOEC NOEC $NOEC_{OC10\%}$	>420 (emergence) 210 (developmental rate) 420 (emergence) <u>110</u> (developmental rate) 363.25	mg/kg	Measured concentrations: 25, 55, 110, 210, 420 mg/kg (dw) Normalised to 10% organic carbon content

2.5.6. Discussion on non-clinical aspects

Ruxolitinib phosphate is a topical formulation that proposed for the treatment of non-segmental vitiligo. The potency of ruxolitinib to inhibit Janus kinases (JAK), that mediate the signalling of several cytokines and growth factors that are important for haematopoiesis and immune function, has already been described in the literature. Extensive non-clinical information on the pharmacological activity of ruxolitinib evaluated *in vitro* as well as *in vivo* following orally administration has already been assessed previously during the evaluation of Jakavi (EMEA/H/C/002464), tablets. These studies were deemed acceptable.

Pharmacology

Submitted *in vitro* enzyme and cellular studies indicate that ruxolitinib is a selective inhibitor of JAK 1 and JAK 2 kinases. The primary human metabolites exhibit similar potency compared to ruxolitinib in the enzyme and cellular assays. Based on the *in vitro* results, no secondary pharmacodynamic action is expected due to binding to non-specific receptors/kinases. New *in vitro* and *in vivo* studies submitted with the present application showed that ruxolitinib can reduce the levels of cytokines (IFNγ, IL-2, CXCL10 and Granzyme B) derived from *in vitro* activated CD8+ T cells and consequently normalise melanocyte proliferation and inflammatory response in CD8+ - conditioned media.

In vivo, using mouse models of dermatitis driven by the JAK-STAT signalling pathway, topical administration of ruxolitinib cream significantly decreased expression of inflammatory cytokines in the skin, reduced dermatitis symptoms, reduced infiltration of Th1 and Th2 cells, normalised tissue histology and alleviated pruritic behaviour. Ruxolitinib was also evaluated in a safety pharmacology core battery studies during the MAA of Jakavi (EMEA/H/C/002464). Main findings of adverse events on vital functions (i.e., a significant decrease in minute volume in high dose rat females and lower values for arterial blood pressure in adult male conscious radiotelemetry-implanted Beagle dogs) following oral administration of ruxolitinib were not considered clinically relevant by the CHMP due to a large safety margin.

Overall, the design, methods and conduct of *in vitro* and *in vivo* pharmacology studies are considered appropriate regarding the studies objectives. The selection of the *in vitro* cell culture model including melanocytes and CD8+ T cells is considered suitable to demonstrate the potency of ruxolitinib cream. The selected *in vivo* animal models in combination with *in vitro* test systems and literature data are considered relevant to draw valid conclusions on pharmacological activity of ruxolitinib for the intended therapeutic use in vitiligo. Upon CHMP's request, the applicant submitted data showing that, in contrast to the significant effects of ruxolitinib on proliferation in IL-2 activated T cells, up to 10 mM of ruxolitinib showed no effect on the survival of naïve T cells cultured without cytokine stimulation, which supported the selective role of ruxolitinib. In addition, the applicant submitted previously published work by Fridman et al 2011 in support to ruxolitinib potency to inhibit cytokine stimulated pSTAT3. In addition, the applicant provided a justification for conducting initial non-clinical studies in human test system and across species using STAT3 phosphorylation as a surrogate PD readout which is accepted. The applicant updated the report of *in vitro* experiments utilising human lymphocytes and melanocytes in support to the mechanism of action of ruxolitinib in vitiligo disease. The update provided involved the data for the third dose (0.01 µM). Based on the observed effects of ruxolitinib under selected *in vitro* conditions, the pharmacodynamic "proof of concept" for vitiligo condition is considered to be demonstrated. Updated information on mechanism of action in section 5.1 of SmPC is considered sufficient.

Pharmacokinetics

The pharmacokinetics of ruxolitinib has been studied *in vitro* and *in vivo*. Information on oral dose as well as after dermal application was provided using mice (CD-1, hairless and transgenic), rats (non-pigmented and pigmented), rabbits, dogs, monkeys and minipigs. Extensive non-clinical information on the absorption, distribution, metabolism and excretion following single oral dose administration of ruxolitinib to various species had already been assessed previously during the iMAA of Jakavi, tablets (Procedure No. EMEA/H/C/002464). These studies were deemed acceptable. In addition, dermal repeat dose studies with ruxolitinib were evaluated in minipigs as being the most relevant animal model for dermal studies. Following repeat-dose dermal administration of ruxolitinib cream (40 mg/kg, BID), applied to 10% of body surface area, the mean plasma concentration at steady state was low (Css = 2.7 nM). The plasma AUC and Cmax values after four consecutive days of treatment were 30- to 40-fold lower than those observed following oral administration in minipigs (i.e., 3.2% and 2.6 % of oral

dose, respectively). Distribution studies in minipigs following repeat-dose topical administration of ruxolitinib revealed that ruxolitinib was generally limited to the upper layers of the skin. The highest concentration was associated with the pigmented layer in the epidermis. Levels in the dermis and hypodermis were below the limit of quantitation. Thus, compared to oral dosing, topical administration delivered ruxolitinib more effectively to the targeted skin layers while limiting systemic exposure.

Toxicology

The toxicity profile of orally administered ruxolitinib has been assessed during the MAA of Jakavi (EMEA/H/C/002464). These studies were deemed acceptable. As systemic exposure from ruxolitinib 1.5% cream may overlap with that from orally administered ruxolitinib the non-clinical information from oral dosing as well as after dermal application is considered relevant. Single and repeat dose dermal toxicity studies in mice and minipigs, dermal 2-year carcinogenicity study in mice, oral 2-year rat carcinogenicity study and local tolerance studies with ruxolitinib were performed in support of topical formulation. No additional toxicities were identified in dermal studies with ruxolitinib as compared to oral route, as most effects observed were secondary to the pharmacological effect: reductions in lymphocytes, eosinophils, reticulocytes, red blood cell count, haemoglobin and haematocrit as well as hypocellularity of the bone marrow and lymphoid organs (spleen, thymus, lymph nodes, Peyer's plate). All changes demonstrated varying degrees of reversibility when dosing was discontinued.

Dermal repeat dose studies revealed systemic immunosuppressive effects in mice. Decreased peripheral lymphocyte counts were noted at all doses in minipigs in the 9-month study, which could indicate a systemic effect of ruxolitinib. This effect was not observed in the 13-week study, which may indicate that the effect is dependent on the duration of the treatment. The more prominent systemic effects seen in mice may be related to higher exposures achieved in mice in comparison to minipigs. However, minipigs are considered to be a more representative animal model as the skin of mice is thinner than that of pigs (and humans).

Ruxolitinib exposures in dermal repeated dose toxicity studies at the NOAEL in mice (1.0% QD) and minipigs (1.5% BID), were 9.3 – 24-fold (mouse) and 2.6 – 3.4-fold (minipig) the expected exposure (steady-state AUC0-24, unbound) at the human therapeutic dose. Due to the low safety margins and upon request from the CHMP, immunosuppressive effect was included in the SmPC section 5.3.

Ruxolitinib was negative in the Ames assay, in an *in vitro* chromosomal aberrations test with cultured human blood and in the *in vivo* rat bone marrow micronucleus assay but was positive for inducing chromosomal aberrations in CHO cells with UV exposure. Although photoclastogenicity cannot be definitively excluded, results of photostability testing, nonclinical *in vivo* phototoxicity studies and clinical dermal safety studies indicate that ruxolitinib is not photoreactive. Therefore, the CHMP considered that no additional precautions are necessary for ruxolitinib in the non-segmental vitiligo indication.

Oral administration of ruxolitinib for 2 years in Sprague-Dawley rats and for 6 months in Tg.rasH2 mice did not show any carcinogenic potential. Dermal 2-year carcinogenicity study in mice showed carcinogenic potential of ruxolitinib, as there may be an increase incidence of lymphoma and kidney adenomas in male mice and haemangiosarcoma in female mice. The results were inconsistent, nevertheless, upon CHMP's request, the applicant thoroughly assessed these findings.

The applicant has submitted an additional assessment of the malignancies observed in carcinogenicity studies. As noted by the applicant, in oral studies there was no increase in these, or related tumours in rats, and no ruxolitinib-related neoplasia were observed in Tg.rasH2 mice despite achieving 10-fold (rat) and 30-fold (Tg.rasH2 mouse) higher exposures than in the dermal mouse study.

In dermal mouse study, although there was a statistically significant trend in the incidence of adenoma in the kidneys in males when compared to placebo control, there were no statistically significant differences in pairwise comparisons with the placebo control, and a similar trend was not observed when compared to the untreated control. The incidence in high dose males was similar to that in the untreated control, suggesting this reflected background variability. There were also no findings of kidney adenoma in females.

The haemangiosarcoma incidence in low dose (0.5%) female mice was significant when compared to the placebo control, but not when compared to the untreated control. No statistically significant differences were found in male groups compared with untreated or placebo control. This can be explained by the incidence of haemangiosarcoma in the placebo control females being notably lower than in untreated controls and in the placebo control males. Further, the incidence of this finding was similar in males and females across all treated groups with no dose-response. Therefore, the increased incidence of haemangiosarcoma in low dose females relative to the placebo control group can be explained by intergroup variability and the low incidence in the placebo control group and thus cannot be attributed to ruxolitinib cream.

Lymphoma is a common background tumour in CD-1 mice. There was a statistically significant increasing trend in the incidence of lymphoma in males when compared to untreated control, but not when compared with placebo control. There was a statistically significant higher incidence of the tumour when comparing the high dose level with untreated control. Among the unscheduled deaths in males for which lymphoma was the cause of death, there were no apparent trends in the days of death, suggesting no difference in onset or progression of lymphoma in these groups that may suggest an effect of ruxolitinib cream. There was no evidence of an increase in lymphoma in female mice, and the incidence in both female control groups was notably higher than in male control groups. Collectively, these results indicate that the higher incidence of malignant lymphoma in high dose males is most likely due to intergroup variability in the incidence of this common tumour and was not associated with administration of ruxolitinib cream.

Overall, the non-clinical data do not suggest that ruxolitinib cream is carcinogenic in animals.

In the fertility study in rats, oral ruxolitinib had no effects on male fertility or on oestrus cycling, mating or fertility indices in females. However, an increase in post-implantation loss was observed at 30 and 60 mg/kg per day. In embryofoetal development studies in rats and rabbits, increased resorptions and decreased foetal weight were observed at maternally toxic doses. Sporadic malformations in rabbits were observed at all doses. Following maternal oral administration during gestation and lactation in rats in the pre- and postnatal study, ruxolitinib had no effect on postnatal survival, developmental milestones, behavioural or reproductive function in offspring. Birth weight was slightly lower, and a transient decrease in postnatal body weight gain during the early lactation period were observed at 30 mg/kg per day. This information has been adequately reflected in SmPC section 5.3.

Considering the safety margins in rat and rabbit reproductive toxicity studies and the fact that other JAKi (e.g., Jakavi) are contraindicated during pregnancy and lactation, the applicant was requested to discuss whether ruxolitinib cream should also be contraindicated during pregnancy and lactation**.** The applicant initially did not consider that contraindication of Opzelura in pregnancy and lactation was warranted and has submitted an additional argumentation in support of their position, though no new data was presented. However, reproductive and developmental toxicity studies with other JAK inhibitors have demonstrated risk to female fertility and teratogenicity. Foetal findings following maternal JAK inhibitor administration have included weight changes, external and visceral effects, and skeletal malformations such as fused ribs, vertebral anomalies, and misshapen and/or shortened limbs. Such effects coincide with the identified role of the JAK–STAT pathway in bone morphogenesis in

knockout animal studies (Damerau et al., 2020). Effects of JAK inhibition on female fertility have been characterised by decreased pregnancy rate and corpora lutea and increased pre- and post-implantation loss and resorptions (Hardwick et al., 2022). Furthermore, although embryotoxicity was observed at maternally toxic doses, it cannot be assumed that developmental toxicity was necessarily secondary to maternal toxicity, unless such a relationship would be demonstrated.

It is acknowledged that the rabbit ruxolitinib exposure levels might not be representative of total pharmacologic activity due to extensive metabolism to active metabolites, and the safety margins for pharmacology-driven effects might be underestimated. However, an increased number of malformations were noted in rabbits treated with ruxolitinib but not in the control group. More importantly, some malformations with unknown causality were observed in dose groups, which were not associated with maternal toxicity.

Since there is limited evidence from developmental rat and rabbit studies, but there is a proven developmental risk across the class of JAK inhibitors, the conclusions from the non-clinical data point to a relevant risk. 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 on developing foetus cannot be entirely excluded. Considering that the treatment of vitiligo can be postponed until the end of pregnancy, the applicant contraindicated the use of Ruxolitinib cream during pregnancy (see SmPC section 4.3).

Orally administered ruxolitinib to juvenile rats beginning on Day 7, 14 or 21 post-partum caused significant bone toxicity. These findings were more severe in males than in females, and when dosing was initiated at an earlier age. This information has been included in SmPC section 5.3. This may be partly due to the toxicokinetic (TK) profile in juvenile rats: systemic exposure to ruxolitinib decreased markedly with the increase of age, which was more evident in males. The published literature suggests several potential relationships between specific JAK-STAT signalling and bone metabolism, but how these individual actions relate to a coordinated effect of JAK inhibition on bone dynamics is currently not known. The relationship of the findings in rat to ruxolitinib pharmacology, and translation to humans is unclear, however the rat may not be an adequate representative model for this effect. The juvenile rat skeleton is predominantly a modelling skeleton, while the remodelling is more important in human bone formation, because the average bone tissue age in a 20-year growth period in humans exceeds the osteocyte-life span. Furthermore, no effects on the bone formation were reported in the pivotal repeat-dose toxicology studies, where the ages of animals at the initiation (7 weeks of age for rats in the 6-month study, 4-5 months of age for dogs in the 12-month study, and 4 months of age for minipigs in the 9-month study) were generally equivalent to the human adolescent phase. Therefore, from a non-clinical perspective on bone formation, the use of ruxolitinib from the age of 12 could be supported. Nevertheless, potential effects on bone development in adolescents from age 12 need to be evaluated from a clinical viewpoint, see clinical safety section.

Since animal data suggest that ruxolitinib is preferentially partitioned into milk and that data on juvenile toxicity indicate possible bone development effects in early postnatal development, the applicant contraindicated the use of ruxolitinib cream during breastfeeding (see SmPC section 4.3).

The cream formulation used in the pivotal GLP studies was the same as the clinical formulation. The excipients contained in the drug product are well known, commonly used in the manufacture of medicinal products intended for cutaneous use and of the Ph. Eur. quality, except for glyceryl stearate SE. The chosen excipients are acceptable for the adult population. Their potential impact in the paediatric population has been sufficiently discussed (see section 2.4 on Quality).

The cream formulation was mildly to slightly irritating to the skin and eye in rabbits in local toxicity studies. Ruxolitinib was not phototoxic, or a dermal sensitiser and had no photoallergy potential.

Drug process starting materials, intermediates, and impurities were evaluated in a series of *in silico* platforms, and if they were predicted mutagenic, they were further evaluated *in vitro* Ames test (TA98, TA100, TA1535, TA97a, and TA102). No impurity was recognised as mutagenic.

ERA

Ruxolitinib phosphate is not a PBT substance. Considering the above data, ruxolitinib phosphate is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

In conclusion, the applicant provided a comprehensive evaluation of pharmacologic, pharmacokinetic and toxicologic properties of ruxolitinib. Studies in animal have shown reproductive and skeletal toxicities. The impact on bone development is further discussed in the clinical safety section. Ruxolitnib is contraindicated in pregnancy and breast-feeding. Women of reproductive potential should be advised to use effective contraception during treatment and for 1 month following the final dose of ruxolitinib. Overall, ruxolitinib cream is therefore considered approvable from a non-clinical point.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen[1]	Number of Participants (PK Population)	Healthy Participants or Diagnosis of Participants	Duration of Treatment	Study Status
INCB 18424-211	Efficacy	Phase 2, randomized, double-blind, and vehicle-controlled study	VC period (Day 1-Week 24): • Vehicle BID • Ruxolitinib 0.15% QD • Ruxolitinib 0.5% QD • Ruxolitinib 1.5% QD • Ruxolitinib 1.5% BID Continued DB period (Weeks 24 to 52): • Ruxolitinib 0.15% QD • Ruxolitinib 0.5% QD • Ruxolitinib 1.5% QD • Ruxolitinib 1.5% BID Open-label period (Weeks 52 to 104): • Ruxolitinib 1.5% BID	149	Adult men and women with vitiligo who have depigmented areas including at least 0.5% of the total BSA of the face and at least 3% of the total BSA on nonfacial areas	VC period: 24 weeks Continued DB period: 24 weeks OLE period: 104 weeks	Completed
INCB 18424-306	Efficacy	Phase 3, randomized, double-blind, vehicle-controlled study	DB period: • Vehicle BID • Ruxolitinib 1.5% BID TE period: • Ruxolitinib 1.5% BID	DB period: 214 TE period: 147	Adolescent and adults with nonsegmental vitiligo with depigmented areas including ≥ 0.5% BSA on the face, ≥ 0.5 F-VASI, ≥ 3% BSA on nonfacial areas, ≥ 3 T-VASI, and total body vitiligo area (facial and nonfacial) not exceeding 10% BSA	VC period: 24 weeks TE period: 28 weeks	Completed
INCB 18424-307	Efficacy	Phase 3, randomized, double-blind, vehicle-controlled study	DB period: • Vehicle BID • Ruxolitinib 1.5% BID TE period: • Ruxolitinib 1.5% BID	DB period: 215 TE period: 143	Adolescent and adults with nonsegmental vitiligo with depigmented area including ≥ 0.5% BSA on the face, ≥ 0.5 F-VASI, ≥ 3% BSA on nonfacial areas, ≥ 3 T-VASI, and total body vitiligo area (facial and nonfacial) not exceeding 10% BSA	VC period: 24 weeks TE period: 28 weeks	Completed

Route of administration used in studies was topical.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Methods

LC-MS/MS methods were used for the analysis of ruxolitinib concentrations in human plasma. Four methods were used, and they were validated at Incyte Corporation (Wilmington, DE), ABC Laboratories (Columbia, MO), and Frontage Laboratories (Exton, PA). Cross validation has been performed between the methods GLP-015 and GLP-018 and between the methods GLP-015 and BTM-2217.

Dose-concentration analysis was performed using linear regression. Age and body surface area were significant predictors of Css. The analyses were performed adequately. Parameters were estimated with acceptable precision (RSE 5.8 – 36%).

Absorption

Bioavailability

Plasma PK information obtained by NCA was available from one phase 1 clinical study (INCB 18424-103) and 1 Phase 2 study (INCB 18424-202).

The pharmacokinetics of Opzelura were investigated in 429 subjects with vitiligo aged 12 years and older (12.6% were 12-17 years of age) with a mean ± STD BSA involvement of 7.31 ± 2.02% (range 3.2% to 10.0%). Subjects applied approximately 1.58 mg/cm2 of Opzelura (dose range was approximately 0.18 grams to 8.4 grams of Opzelura per application) to the same skin areas twice daily for 24 weeks.

The PK of ruxolitinib 1.5% cream was investigated in a maximal use study (study INCB 18424-103) from 40 adult and adolescent participants (aged ≥ 12 years) with atopic dermatitis (AD) with a mean ± STD body surface area (BSA) involvement of 37.5 ± 16.1% (range: 25%-90%). In this study, participants applied approximately 1.5 mg/cm^2 of ruxolitinib 1.5% cream (dose range was approximately 1.2 g to 37.6 g per application) BID to all affected areas identified at baseline for 28 days. Blood samples were collected pre-application and at 1, 2, 4 and 12 post-doses on day 1 and day 28. On day 15, samples were collected pre-application and 1-hour post-dose.

Study INCB 18424-202 was a dose-escalation study. Ruxolitinib 1.0% or 1.5% cream was applied (approximately 1 to 2 mg/cm^2) to participants with active, stable, plaque psoriasis involving 2% to 20% BSA, for 28 days. Participants were randomized to the following 5 cohorts: Cohort A (1.5% BID, 2%-7% BSA), Cohort B (1.5% BID, 8%-13% BSA), Cohort C (1.5% QD, 14%-20% BSA), Cohort D (1.0% BID, 14%-20% BSA), and Cohort E (1.5% BID, 14%-20% BSA). Blood samples were collected pre-application and approximately 1-hour post-application on days 1, 8, 15, and 22, pre-application on day 4 and pre-dose and at 1.5, 3, 6-, 9-, 24-, and 48-hours post-dose on day 28.

The mean serial profiles of the plasma ruxolitinib concentrations on day 28 were almost flat (see Figure 7) with the mean peak/trough ratio of approximately 1.6 to 3.2. The applicant was of the view that the observed long $t_{½}$ for the topical formulation (as shown in Table 12) is due to the slow absorption rate of topical formulation and reflects the drug absorption rate rather than the drug elimination rate. Throughout the interval between applications of ruxolitinib cream, the mean concentrations were well-below the whole blood ruxolitinib IC_{50} for JAK2 inhibition (281 nM), a level which the applicant considers clinically relevant for systemic pharmacological effects on bone marrow (Quintas-Cardama et al 2010). This concentration is based on whole blood, but in vitro blood partitioning studies indicated no preferential partitioning of ruxolitinib-related radioactivity into blood cells (EPAR Jakavi). In study

INCB 18424-103, mean relative bioavailability was 2.5% and ranged from 0.027% (subject with 29% BSA affected) to 19.0% (subject with 90% BSA affected). In study INCB 18424-202, the mean systemic bioavailability was 3.8%, 4.1%, 3.4%, 3.9%, and 5.2%, respectively, for Cohorts A-E.

A summary of mean steady-state concentrations of ruxolitinib and bioavailability in study INCB 18424-103 (Css is calculated as average of plasma concentrations on days 15 and 28) is shown in Table 11. The C_{max}, t_{max}, C_{min}, AUC, C_{max}/C_{min} ratio, and $t_{½}$ at steady state after topical applications of ruxolitinib cream are summarized in Table 12.

Table 11: Summary of Steady-State Concentration (on day 15 and 28 combined) of Ruxolitinib and Bioavailability of Topical Ruxolitinib in Study INCB 18424-103

Strata	**N**	**%BSA Affected at Baseline (%)**	**C_{ss} (nM)**	**Bioavailability (%)**
Overall	40	37.5 ± 16.1 (30.9)	104 ± 309 (26.5)	2.54 ± 3.56 (1.71)
12-15 years	14	30.1 ± 4.64 (29.5)	43.8 ± 67.7 (21.1)	1.84 ± 2.31 (0.915)
16-17 years	7	35.1 ± 10.1 (31.5)	20.2 ± 23.0 (14.1)	1.91 ± 1.65 (1.79)
≥ 18 years	19	43.9 ± 20.7 (32.8)	179 ± 438 (39.7)	3.30 ± 4.64 (1.99)
≥ 25% and < 40% BSA	28	29.2 ± 2.60 (29.5)	30.9 ± 32.8 (16.0)	1.49 ± 1.31 (1.29)
≥ 40% BSA	12	57.0 ± 17.8 (45.5)	274 ± 539 (86.6)	5.00 ± 5.60 (2.42)

Note: Summary values are presented as mean ± STD (geometric mean) for C_{ss} and mean ± STD (median) for %BSA and bioavailability.

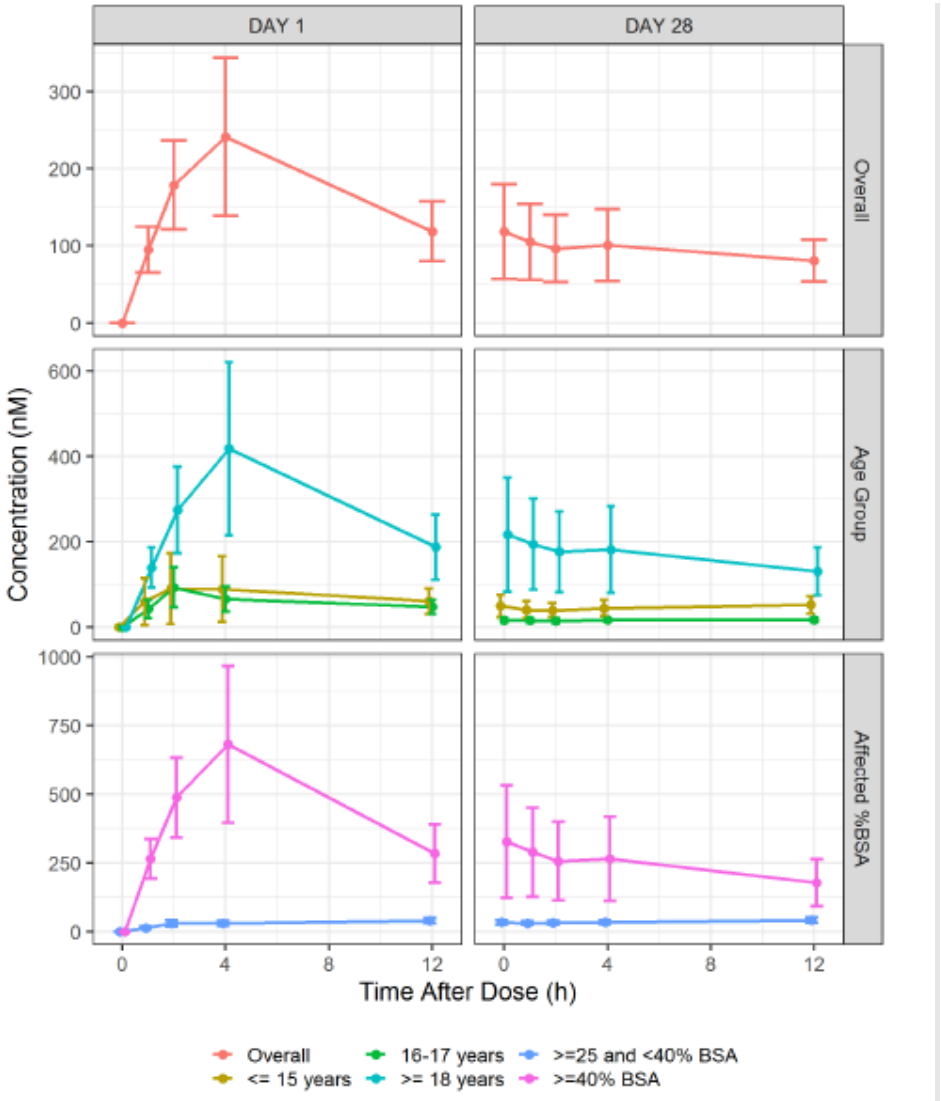
Table 12: Steady state Ruxolitinib Plasma Pharmacokinetic Parameters from noncompartmental analysis after topical administration (Studies INCB 18424-103 and INCB 18424-202)

Study	Formulation	N	C_{max} (nM)	t_{max} (h)	C_{min} (nM)	C_{max}/C_{min} Ratio	AUC_{tau} (h·nM)	$t_{½}$ (h)
INCB 18424-202 (Cohort A, 2%-7% BSA)	1.5% BID	5	10.4 ± 4.39 (9.49)	3.00 (1.50, 9.00)	5.37 ± 1.71 (5.15)	1.98 ± 0.947 (1.84)	93.5 ± 33.4 (88.2)	205 ± 274 (114)
INCB 18424-202 (Cohort B, 8%-13% BSA)	1.5% BID	5	38.6 ± 27.3 (32.8)	1.50 (0.00, 6.00)	21.1 ± 10.5 (19.3)	1.73 ± 0.355 (1.70)	346 ± 208 (306)	88.4 ± 82.6 (66.7)
INCB 18424-202 (Cohort C, 14%-20% BSA)	1.5% QD	5	34.2 ± 23.2 (26.9)	3.00 (0.00, 24.00)	18.4 ± 10.2 (15.7)	1.80 ± 0.709 (1.71)	603 ± 349 (500)	42.4, 38.7
INCB 18424-202 (Cohort D, 14%-20% BSA)	1.0% BID	5	39.8 ± 24.6 (33.9)	3.00 (0.00, 9.00)	25.6 ± 14.0 (22.0)	1.56 ± 0.292 (1.54)	407 ± 259 (336)	69.3, 55.9
INCB 18424-202 (Cohort E, 14%-20% BSA)	1.5% BID	5	83.6 ± 110 (50.2)	3.0 (0.00, 9.00)	34.7 ± 31.8 (26.2)	1.98 ± 0.638 (1.92)	653 ± 711 (445)	79.8 ± 25.5 (76.9)
INCB 18424-103 (all)	1.5% BID	38	137 ± 377 (43.9)	4.00 (0.0, 12.0)	62.6 ± 165 (NC)	2.72 ± 1.91 (2.32) [n = 33]	1120 ± 2930 (349)	116 ± 251 (32.5) [n = 9]
INCB 18424-103 * subgroup (12-15 years)	1.5% BID	14	66.2 ± 93.3 (38.7)	12.0 (0.0, 12.0)	32.8 ± 64.5 (NC)	3.20 ± 2.39 (2.64) [n = 11]	555 ± 863 (287)	266 ± 442 (45.2) [n = 3]
INCB 18424-103 subgroup (16-17 years)	1.5% BID	7	24.5 ± 12.9 (22.5)	1.00 (0.0, 12.0)	11.0 ± 12.2 (NC)	2.90 ± 1.59 (2.58) [n = 6]	196 ± 149 (160)	13.3, 23.3
INCB 18424-103 subgroup (≥ 18 years)	1.5% BID	17	242 ± 548 (64.3)	4.00 (0.0, 12.0)	108 ± 235 (NC)	2.32 ± 1.66 (2.03) [n = 16]	1970 ± 4230 (566)	51.3 ± 49.0 (34.5) [n = 4]
INCB 18424-103 subgroup (≥ 25 and < 40% BSA)	1.5% BID	27	49.2 ± 51.2 (30.3)	4.00 (0.0, 12.0)	23.5 ± 29.3 (NC)	2.80 ± 1.89 (2.39) [n = 23]	427 ± 499 (237)	159 ± 305 (40.1) [n = 6]
INCB 18424-103 subgroup (≥ 40% BSA)	1.5% BID	11	353 ± 669 (109)	1.00 (0.0, 12.0)	159 ± 290 (NC)	2.55 ± 2.05 (2.15) [n = 10]	2830 ± 5170 (904)	28.0 ± 26.0 (21.4) [n = 3]

N = number of participants; n = number of observations.
Note: Summary values are presented as mean ± STD (geometric mean) except for t_{max} in median (min, max) if n > 2; otherwise, individual values are presented. * Surface treated in the age groups (%BSA) is indicated in Table 11

Plasma concentration-time profiles following application of ruxolitinib 1.5% cream on day 1 and day 28 are shown in Figure 7.

Figure 7: Ruxolitinib plasma concentration (mean ± SE) over time on Day 1 and Day 28 (Linear Plot) (Study INCB 18424-103)



Comparisons of steady-state plasma ruxolitinib concentrations between topical application of ruxolitinib cream and oral ruxolitinib dosing have been made. The applicant compared the ruxolitinib mean steady-state daily through concentration (Css) for 1.5% BID topical administration in participants with vitiligo (in Phase 3 studies arithmetic mean 56.9 nM, geometric mean 27.4 nM) with a Cavg,ss which is calculated as 218 nM from AUCss,0-12h = 2610 h*nM (geometric mean) in an oral study in healthy adult volunteers (DMB-08.84 in study INCB-132) following 15 mg BID PO administration. This was the lowest dose level from which steady-state serial PK data were available from healthy participants. On the other hand, the lowest dose level in oral ruxolitinib drug label is 5 mg BID, for which there are no observed data at steady state from healthy participants. Nonetheless, the Cavg,ss following 5 mg BID PO administration is expected to be approximately 73 nM based on dose proportionality. The arithmetic mean and median Css in a subgroup of 215 participants with vitiligo in Phase 3 studies in the top 50% (ie, above the median Css of 35.75 nM) are 99.2 and 83.5 nM for 1.5% BID, respectively. Therefore, there is an overlap between the plasma exposure in the top 50% of participants with vitiligo treated with ruxolitinib 1.5% cream BID in Phase 3 studies and the expected plasma exposure of the lowest approved oral dose of 5 mg ruxolitinib BID in healthy participants (study DMB-21.53).

Following application of ruxolitinib 1.5% cream for 28 days in patients with atopic dermatitis to all affected areas (affected BSA 25 - 90%), mean relative bioavailability was 2.5%, ranging 0.027% to

19% (subjects with 29% and 90% BSA treated respectively). Mean C_{max} and C_{min} at steady state in this study were 49 nM and 24 nM at 25-40% BSA and 353 nM and 159 nM at ≥40% BSA. In patients with psoriasis (affected BSA 2 – 20%), mean C_{max} ranged 10 – 84 nM and mean C_{min} ranged 5.4 – 35 nM. Based on the cohort means, C_{max}, C_{min} and AUC_{tau} appear to increase with increasing treated BSA. Plasma concentrations in patients with AD were lower on day 28 than on day 1. Concentrations were higher in adult subjects compared to subjects < 18 years old and higher in subjects with ≥ 40% BSA treated compared to subjects with 25 – 40% BSA treated. Median Tmax ranged 1.5 – 12 h. Overall median Tmax was 3 – 4 h. Mean (arithmetic) half-life ranged 13 to 266 h; geometric mean half-life ranged 21 to 114 h. According to the applicant, the fairly long half-life likely mostly reflected the slow absorption with a flip-flop effect, since oral elimination half-life was approximately 3 h.

Bioequivalence

Formulations used in the clinical studies contain 0.15%, 0.5%, 0.75%, 1.0%, and 1.5% w/w ruxolitinib base and equal amounts of excipients. The mean bioavailability of ruxolitinib cream was generally low, in the range of 1.5 to 15%. The data indicated no clear effect of frequency of application or formulation strength on bioavailability.

In vitiligo patients in the Phase 3 studies treated with Ruxolitinib Cream 1.5% on maximally 10% BSA, mean Cmin was 56.9 nM (geometric mean 27.4 nM) and bioavailability was estimated to be 9.72% (geometric mean 8.42%).

Average trough values and bioavailability after use of ruxolitinib cream 1.5% on maximally 10% of BSA in vitiligo patients (studies INCB 18424-306 and INCB 18424-307) are shown in Table 13.

Table 13: Summary of baseline population characteristics and ruxolitinib steady-state pharmacokinetic parameters by geographic region, skin type, and age group in phase 3 vitiligo studies (studies INCB 18424-306 and INCB 18424-307)

Groups		**N**	**BSA (m^2)**	**% BSA (%)**	**C_{ss} (nM)[(a)]**	**Bioavailability (%)**
All participants		429	1.88 ± 0.253 (1.86, 13.6)	7.31 ± 2.02 (7.00, 31.2)	56.9 ± 62.6 (27.4, 282)	9.72 ± 8.14 (5.78, 205)
Region	Europe	142	1.82 ± 0.261 (1.8, 14.4)	7.28 ± 1.91 (7.01, 29)	63.2 ± 71.3 (30.9, 263)	10.8 ± 8.56 (6.97, 167)
	North America	287	1.91 ± 0.245 (1.89, 12.9)	7.32 ± 2.07 (6.99, 32.3)	53.8 ± 57.7 (25.8, 291)	9.20 ± 7.88 (5.27, 223)
Skin type	Type I or II	134	1.88 ± 0.254 (1.86, 13.6)	7.24 ± 2.11 (6.9, 32.9)	60.7 ± 61.8 (29.7, 268)	10.4 ± 7.42 (6.62, 200)
	Type III, IV, V, or VI	295	1.88 ± 0.254 (1.86, 13.6)	7.34 ± 1.98 (7.04, 30.5)	55.2 ± 63.0 (26.4, 288)	9.40 ± 8.43 (5.44, 207)
Age	12 to < 18 years	54	1.67 ± 0.266 (1.65, 15.7)	7.30 ± 2.20 (6.93, 34.9)	32.4 ± 43.1 (12.4, 371)	7.71 ± 7.99 (3.62, 304)
	18 to < 65 years	347	1.91 ± 0.242 (1.89, 12.6)	7.28 ± 1.98 (6.99, 30.4)	59.9 ± 64.7 (29.7, 268)	9.84 ± 8.12 (5.99, 195)
	≥ 65 years	28	1.92 ± 0.186 (1.91, 9.33)	7.62 ± 2.13 (7.26, 34.6)	66.6 ± 59.0 (46.2, 116)	12.2 ± 8.06 (9.21, 116)

[a] C_{ss} is the average concentration of Weeks 4 and 24 for individual participants.

Note: Values are presented in the format of mean ± STD (geometric mean, GCV%).

Distribution

Based on an *in vitro* study, ruxolitinib is 97% bound to human plasma proteins, mostly to albumin. The apparent volume of distribution after oral administration in myelofibrosis patients at steady state was 53-65 litres. For the cream, volume of distribution is not reported.

Elimination

Following topical administration of ruxolitinib, the parent compound was predominant in plasma. Also 5 major metabolites were found in plasma, M18, M27, M11, M8 and M7, at amounts comprising up to 24% of parent compound in plasma. These metabolites had also been found after oral administration of ruxolitinib. Considering the limited bioavailability following topical administration when the cream is applied to maximally 10% BSA as recommended in the SmPC, and the limited contribution of the metabolites to the PD activity (15 – 18%), no significant pharmacological activity is expected from the metabolites. Genetic polymorphism can be considered not relevant for ruxolitinib metabolism. Ruxolitinib is not metabolised by CYP2D6 or CYP2C19. CYP2C9 plays a role in ruxolitinib metabolism, but only to a minor extent, but may become important in case CYP3A4 is blocked.

Following a single oral dose of ^{14}C-ruxolitinib in healthy adult participants, elimination was predominately through metabolism with 74% of radioactivity excreted in urine and 22% excreted via faeces. Unchanged drug accounted for less than 1% of the excreted total radioactivity. Oral clearance has been estimated to be approximately 19 L/h. Excretion was not investigated following topical administration. According to the applicant, the excretion pathways are however not expected to be different from those after oral administration.

Mean (arithmetic) half-life ranged 13 to 266 h; geometric mean half-life ranged 21 to 114 h. The fairly long half-life likely mostly reflects the slow absorption, since oral elimination half-life was approximately 3 h.

Dose proportionality and time dependencies

Linear regression indicated a dose-proportional increase of Css with ruxolitinib dose. This was confirmed by the results from the Phase 2 study in vitiligo patients, where Ctrough increased with increasing strength and frequency of dosing and approximately similar treated BSA. Also, Ctrough increased with treated BSA, when the dose was the same.

In the Phase 3 studies in vitiligo patients, trough values were similar from week 4 to week 40 and in Phase 3 studies in patients with atopic dermatitis, trough values were similar from week 2 to week 8, indicating that steady state occurred at week 2 or earlier.

Intra- and inter-individual variability

Inter-individual variability in average trough concentrations of ruxolitinib is high, with CV% of 100 – 200%. The intra-individual variability, expressed as the coefficient of variation, was estimated as 157%. This was similar to the inter-individual variability, which is as expected considering the variation in the exact amount of cream used and the exact area of treated skin.

Special populations

No studies have been performed with ruxolitinib cream in patients with renal or hepatic impairment. No dose adjustment is necessary in patients with mild to severe renal impairment, based upon estimated pharmacological activity adjusted AUC of ruxolitinib and metabolites (up to a 31% increase). In patients with end stage renal disease, this exposure increased almost 2-fold. As a precautionary measure it is advised that ruxolitinib 1.5% cream should not be used by patients with end stage renal disease, due to lack of data regarding the safety (see SmPC section 4.2).

In patients with hepatic impairment, formation of metabolites as percentage of parent compound was not higher than in case of normal liver function. There was no relationship between the increase in AUC and the severity of the hepatic impairment and therefore no dose adjustment is necessary in case of hepatic impairment.

Gender, race and skin type (pale and fair skin vs darker types of skin) were no significant predictors of PK variability.

Age was a significant predictor of PK variability. Css was predicted to be 36% lower in subjects aged 18 years and 28% higher in subjects aged 62 years, compared to subjects aged 40 years. Considering the limited absolute exposure, the small difference in absolute Css between the groups 18 – 65 years and ≥ 65 years (arithmetic mean 59.9 nM, and 66.6 nM resp.), and the high inter-individual variability (> 100%), are considered not clinically relevant.

The exposure is somewhat lower in adolescents than in adults. The applicant ascribed this to the relatively lower daily ruxolitinib dose used in adolescents.

BSA was a significant predictor of PK variability. However, the effect of BSA can be considered not clinically relevant, considering the limited absolute exposure and the high inter-individual variability (> 100%).

Pharmacokinetic interaction studies

Based on *in vivo* interaction studies with oral ruxolitinib, maximally a doubling of AUC can be expected when a potent CYP3A4 inhibitor is co-administered. In section 4.5 of the SmPC it is mentioned that the plasma AUC is approximately doubled with co administration of a potent inhibitor of CYP3A4 while only a modest increase was seen with co-administration of a moderate CYP3A4 inhibitor.

No interaction studies have been performed with topically administered ruxolitinib. The potential for interactions with ruxolitinib is considered to be low because of the limited systemic exposure following topical administration. Ruxolitinib has not been evaluated in combination with other cutaneous medicinal products; therefore, co-application on the same skin areas is not recommended.

Pharmacokinetics using human biomaterials

Ruxolitinib is not a substrate for P-gp. Ruxolitinib and its metabolite M18 did not inhibit P-gp at clinically relevant concentrations. Ruxolitinib and M18 also did not inhibit the transporters BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, and OAT3 at clinically relevant concentrations.

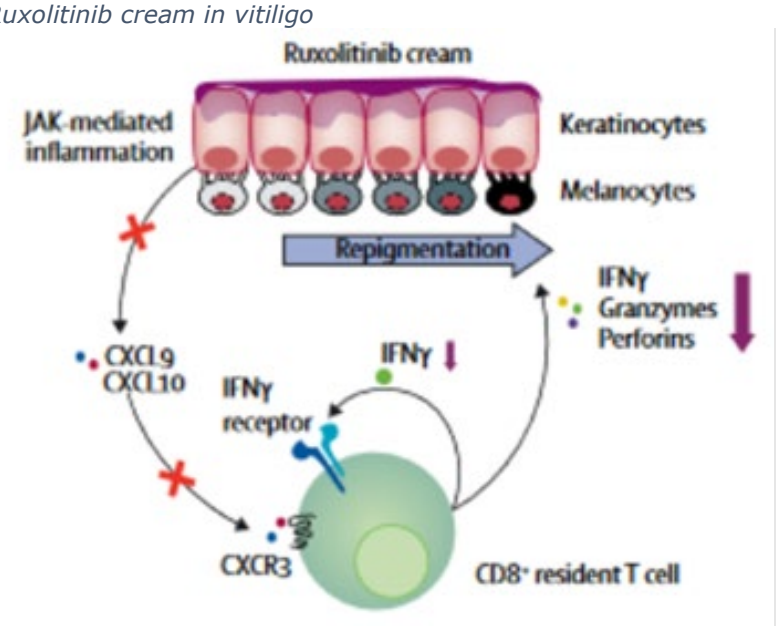
Ruxolitinib inhibited CYP3A4 *in vitro* with an IC_{50} of 8.8 µM. Ruxolitinib did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 to a significant extent. Ruxolitinib was not an inducer of CYP1A2, CYP2B6, or CYP3A4 enzymes at clinically relevant concentrations.

2.6.2.2. Pharmacodynamics

Mechanism of action

Ruxolitinib is a Janus Kinase (JAK) inhibitor with selectivity for the JAK1 and JAK2 isoforms. Intracellular JAK signalling 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, such as CXCL10. Downstream signalling of IFNγ is JAK1/2 dependent and treatment with ruxolitinib reduces CXCL10 levels in vitiligo patients (see below figure).

Figure 8: Ruxolitinib cream in vitiligo



Primary and Secondary pharmacology

Data from three clinical studies (NCBI 18424-211, -306, and -307) in participants with vitiligo were used for the exploration of pharmacodynamics (PD). According to the applicant, the pathophysiology of vitiligo as an auto-immune disorder supports the relevance of JAK inhibition in the treatment of this disorder through repigmentation.

Primary pharmacodynamics of ruxolitinib is well known from its developmental programme based on its oral formulation (Jakavi, ruxolitinib tablets). DDI and genetic differences in the response on treatment with topical ruxolitinib were thus not performed by the applicant given the low systemic exposure.

Studies on secondary pharmacodynamics revealed no PK/PD association between Css and haemoglobin, but there seemed to be an inverse PK-PD relationship for neutrophils as the lowest counts were observed at the highest quartile of Css levels. In addition, there were a few subjects (two in phase 2 and two in phase 3 studies) with grades 2 or 3 decrease in neutrophils, who appear to have higher Css (higher than 100 nM). No change was observed in mean platelet volume. A slight increase in platelet count was observed in subjects in the highest Css quartile (higher than 85 nM). This effect is opposite to the effect on platelets with oral ruxolitinib, where decreases in platelets were observed.

Relationship between plasm concentration and effect

PK/PD relationship – biomarkers

CXCL9, CXCL 10, and INFy are acknowledged biomarkers for inflammatory disease. INFy in blood of participants with vitiligo was absent / low in over 70% of the participant and no treatment effect was found for this biomarker. This might be caused by the large part of participants with stable disease (45%). For CXCL10 a decrease was observed with increased duration of treatment.

PK/PD relationship – clinical outcomes

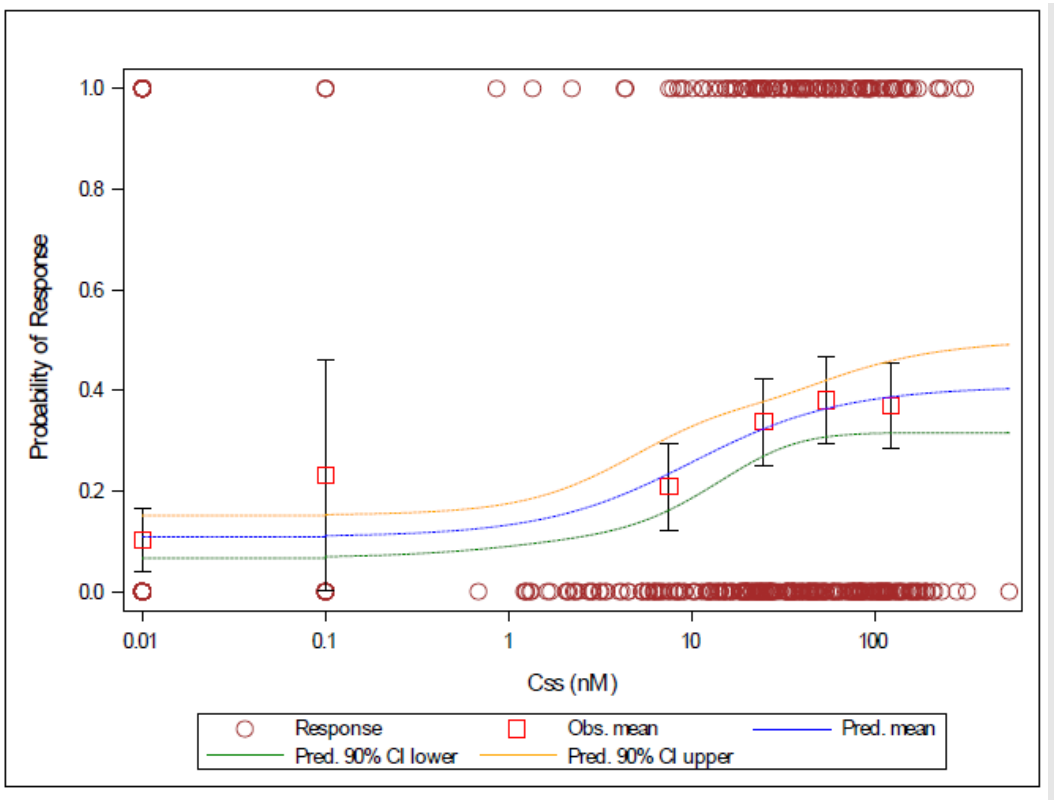
Ruxolitinib phosphate is a selective JAK1/JAK2 inhibitor. In response to stimulation by cytokines such as Interleukin 6 (IL-6), JAKs are responsible for phosphorylation of the STAT3 transcription factor. IL-6 induced phosphorylation of STAT3 can thus be used as a pharmacodynamic marker for JAK inhibition. Inhibition was defined as IC50 (inhibitory concentration at 50% inhibition) of ruxolitinib. The IC50 was determined in a number of clinical studies.

Clinical studies were performed at different sites according to the study protocol of studies INCB 18424-131, -132, -135, -137, and –142, in healthy participants. Blood samples were drawn from healthy subjects at various times after receiving ruxolitinib and the levels of pSTAT3 in response to ex vivo IL-6 stimulation were measured using a pSTAT3-specific ELISA.

PK-PD data were available from 72 healthy volunteers from studies INCB 18424-131 (single dose) and -132 (multiple dose).

The study population in the concentration-response analyses regarding efficacy consisted of 557 participants with evaluable efficacy responses and evaluable Css.

Figure 9: F-VASI75: Exploratory graphical analysis of responses at week 24 versus Css during the double-blind, vehicle-controlled period in pooled phase 3 Css — PK/PD population of F-VASI75



Race (others vs white) was identified as a significant predictor of the F-VASI75 (≥ 75% Improvement From Baseline in the Face Vitiligo Area Scoring Index) responses.

The final logit-Emax model of F-VASI75 included an intercept, an Emax term of the effect of Css, and a binary covariate predictor: race (others vs white). The model parameter estimates and the estimated odds ratios for ruxolitinib concentrations in plasma as well as covariate predictors are presented in Table 14. The maximum odds ratio for achieving Emax was estimated as 6.08.

Plasma concentrations and F-VASI75

The final logit-Emax model of F-VASI75 included an intercept, an Emax term of the effect of Css, and a binary covariate predictor (race; Others vs White). The odds ratio for race was 2.28 (90% CI: 1.51, 3.45), implicating that the odds for participants of non-White to achieve F-VASI75 responses at Week 24 was 128% higher than for White participants. The estimated Emax by Css on the logit of the probability of achieving F-VASI75 at Week 24 was estimated at 1.80 (90% CI: 1.30, 2.31), corresponding to a maximum odds ratio of 6.08 (90% CI: 3.68, 10.0) that could be attributed to Css.

The odds ratio for Css at 7.70 nM, the estimated EC50, vs 0 nM (ie, vehicle-treated or ruxolitinib cream-treated but nonmeasurable concentration in plasma) would be 2.47 (90% CI: 1.92, 3.17).

Table 14: F-VASI75 logit-Emax model parameter estimates and odds ratios

Parameter	Estimate	RSE (%)	p-value	90% CI	
Intercept	−2.29	10.3	< 0.0001	−2.68	−1.90
E_{max}	1.80	16.9	< 0.0001	1.30	2.31
EC_{50} (nM)	7.70	62.4	0.1095	−0.215	15.6
Coefficient on race (Others vs White)	0.826	30.3	0.001	0.414	1.24
Odds Ratio	**Estimate**		**90% CI**		
C_{ss} (increase from 0 to infinity)	6.08		3.68	10.0	
C_{ss} (increase from 0 to EC_{50})	2.47		1.92	3.17	
Race (Others vs White)	2.28		1.51	3.45	

Note: %RSE = SE / abs(Estimate) * 100 (%).

Similar results were obtained in the analysis of F-VASI50. Race (others vs white) and ethnicity (others vs Hispanic or Latino) were identified as significant predictors of the F-VASI50 responses (see Table 15).

Table 15: F-VASI50 Logit-Emax model parameter estimates

Parameter	Estimate	RSE (%)	p-value	90% CI	
Intercept	−0.993	24.7	< 0.0001	−1.40	−0.589
E_{max}	1.90	13.7	< 0.0001	1.47	2.33
EC_{50} (nM)	6.14	60.2	0.0973	0.0484	12.2
Coefficient on race (Others vs White)	0.775	31.4	0.0015	0.374	1.17
Coefficient on ethnicity (Others vs Hispanic or Latino)	−0.651	34.7	0.0041	−1.02	−0.279
Odds Ratio	**Estimate**		**90% CI**		
C_{ss} (increase from 0 to infinity)	6.68		4.35	10.3	
C_{ss} (increase from 0 to EC_{50})	2.59		2.09	3.20	
Race (Others vs White)	2.17		1.45	3.24	
Ethnicity (Others vs Hispanic or Latino)	0.521		0.359	0.757	

Note: %RSE = SE / abs(Estimate) * 100 (%).

Table 16 shows the estimated parameters for the analysis of VNS45. The baseline total body vitiligo area scoring index (T-VASI) was the only significant predictor on VNS45 responses.

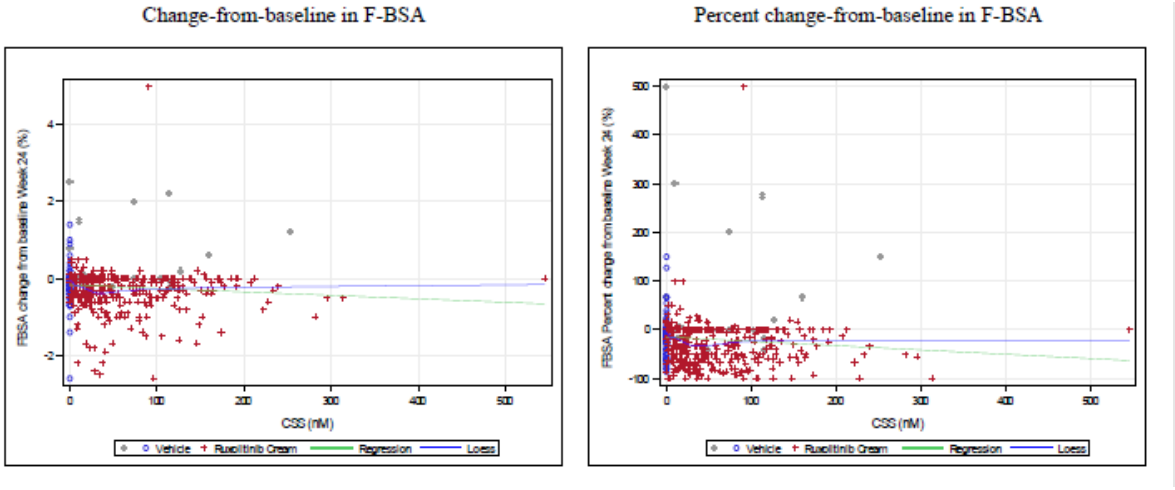
Table 16: VNS45 Logit-Emax model parameter estimates

Parameter	Estimate	RSE (%)	p-value	90% CI	
Intercept	−1.97	24.3	< 0.0001	−2.75	−1.18
E_{max}	2.29	17.2	< 0.0001	1.64	2.93
EC_{50} (nM)	9.27	64.7	0.123	−0.617	19.2
Coefficient on baseline T-VASI score	−0.143	42.4	0.0187	−0.243	−0.0431
Odds Ratio	**Estimate**		**90% CI**		
C_{ss} (increase from 0 to infinity)	9.84		5.15	18.8	
C_{ss} (increase from 0 to EC_{50})	3.14		2.27	4.34	
Baseline T-VASI score (1-point increase)	0.867		0.784	0.958	

Note: %RSE = SE / abs(Estimate) * 100 (%).

The figures below show the relationship between F-BSA in week 24 and Css. No relationship was found between plasma ruxolitinib Css and changes in F-BSA in week 24.

Figure 10: F-BSA: Exploratory graphical analysis of changes in F-BSA at week 24 versus plasma ruxolitinib Css



Co-variates

The final logit-Emax model Binary covariate predictor was race (other versus white).

Dose-response relationships

Relations between plasma ruxolitinib Css and clinical efficacy (in terms of F-VASI75, F-VASI5-, and VNS score or 5 after 24 weeks of treatment) were characterised using a generalised non-linear logit-Emax model framework. Estimated plasma eC50 were all low (6-10 nM). Imputed EC90 values were 69.2 nM (F-VASI75), 55.3 nM (F-VASI50), and 83.4 nM (VNS score 4 or 5); all in the range of the 64th – 75th percentile of plasma ruxolitinib Css in the two pivotal studies. The probabilities of efficacy responses enter the plateau as the plasma ruxolitinib Css exceeds EC90, which are less than 30% of the whole blood ruxolitinib IC50 for JAK2 inhibition (i.e., 281 nM). Percentage of change in F-BSA at week 24 was not statistically associated with plasma ruxolitinib Css.

A significant relationship was observed between plasma ruxolitinib Css and the possibility of achieving 75% improvement in the F-VASI, 50% improvement in the T-VASI or improvement indicated by participants as 4 or 5 (VNS 4-5). These associations suggest that topical ruxolitinib not only has a local

effect but also result in a non-negligible, relevant systemic exposure (see section 2.6.3 below where this is further discussed).

2.6.3. Discussion on clinical pharmacology

This application concerns a cream containing ruxolitinib phosphate (INCB018424) (15 mg/g), proposed for the treatment of non-segmental vitiligo with facial involvement in adults and adolescents from 12 years of age. Ruxolitinib is an inhibitor of JAKs (Janus kinases) with selectivity for JAK1 and JAK2. Ruxolitinib is already registered for oral use (Jakavi, EMEA/H/C/002464).

The cream is recommended to be applied to affected skin areas to a maximum of 10% of body surface area twice daily.

The developmental programme of ruxolitinib phosphate cream consisted of one Phase 2 and two Phase 3 studies in patients with vitiligo, two Phase 1, one Phase 2 and two Phase 3 studies in patients with atopic dermatitis, and four Phase 2 studies in patients with plaque psoriasis and alopecia areata, comprising both adult participants and adolescents. Oral studies which were part of the MAA dossier for Jakavi have also been provided. In addition, the relationship between dose and plasma concentrations was analysed to characterise this relationship and to identify the impact of intrinsic and extrinsic factors on this relationship.

Pharmacokinetics

Methods

The medium QC samples were not at 30 – 50% of the calibration range, as recommended in the Guideline on Bioanalytical Method Validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2), but at 5% and 80%, corresponding to 50 nM and 40 nM respectively (methods GLP-015 and GLP-018) and 7% (method BTM-2217), corresponding to 49 nM. However, since most average steady state concentrations were lower than or around 50 nM, with peaks higher than 100 nM being mostly incidental, this was considered acceptable by the CHMP.

Calibration and QC samples in the clinical studies complied with the criteria of the Guideline on Bioanalytical Method Validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2). Incurred sample reanalysis (ISR) was performed in studies INCB 18424-102, INCB 18424-103, INCB 18424-211, INCB 18424-303 and INCB 18424-304 and was considered adequate. ISR results for studies INCB 18424-306 and INCB 18424-307 have been submitted upon CHMP's request and were considered adequate. The longest sample storage times were within the established long-term stability for ruxolitinib (672 days at -70 °C), except in study INCB 18424-102 where the longest sample storage time was 878 days. Additional long-term stability data have been provided upon CHMP's request. Long-term stability of ruxolitinib has been established for 991 days at -70 °C. The maximal storage time was within the established stability in all studies.

PK data analysis

The methods for pharmacokinetic data analysis are acceptable. The analyses were performed adequately and the parameters were estimated with acceptable precision (RSE 5.8 – 36%).

Absorption

In vitiligo patients treated with ruxolitinib cream 1.5% on maximally 10% BSA in the Phase 3 studies INCB 18424-306 and INCB 18424-307, mean Css was 56.9 nM (geometric mean 27.4 nM) and bioavailability was estimated to be 9.72% (geometric mean 8.42%). The overall mean trough concentration in vitiligo patients when ruxolitinib cream 1.5% was used on maximally 10% BSA is

comparable to the trough concentration when using the 15 mg bid oral dose of ruxolitinib (geometric mean 31.5 nM, arithmetic mean 37.2 nM) and the geometric AUC_{0-12h} in psoriasis patients treated on 8-13% BSA (306 nM.h) is about 12% AUC_{0-12h} at a 15 mg bid oral dose (2610 nM.h). Compared to a 5 mg oral dose, the relative estimated steady state Cmax, AUC and Cmin after application of the 1.5% cream b.i.d. to about 10% surface is about 15, 35 and 184%, respectively. Based on the above data, lower exposure levels are thus observed after application of the cream and higher concentrations will only occur at the end of the dosing interval in the low concentration range (over about 3 h considering the estimated Cmin value of 19.3 nM after application of the cream, 10.5 nM after oral administration and the elimination half-lives). Upon CHMP's request, the applicant also discussed the potential impact on clinical safety. The CHMP agreed that the update of the safety data did not point to ADRs of a systemic nature, and that application to a BSA up to 20% did not lead to apparent safety issues. There also was no recognizable relation between exposure and safety, notably occurrence of infections or instances of neutropenia. There however were concerns raised regarding the occurrence of NMSC that may have a local component, and bone safety upon long term exposure in adolescents. This is further discussed in section 2.6.9.

Formulations used in the clinical studies contained 0.15%, 0.5%, 0.75%, 1.0%, and 1.5% w/w ruxolitinib base and equal amounts of excipients. Mean relative bioavailability in the studies ranged 1.5 – 15%. The data indicate no clear effect of frequency of application or formulation strength on bioavailability. The calculation of the bioavailability may however not have been very accurate, because it was based on the average dose per subject. The dose per treatment was not actually measured. Ctrough appears to be higher at higher strength and at BID compared to QD application.

Distribution

Based on an *in vitro* study (study DMB-07.11), ruxolitinib is 97% bound to human plasma proteins, mostly to albumin. The apparent volume of distribution after oral administration in myelofibrosis patients at steady state was 53-65 litres. For the cream, volume of distribution was not reported.

Elimination

Excretion was not investigated following topical administration in vitiligo patients. The excretion pathways are however not expected to be different from those after oral administration.

The mean elimination half-life of orally administered ruxolitinib is approximately 3 hours. The mean apparent terminal half-life of ruxolitinib following topical application of Opzelura was estimated in 9 adult and adolescent patients with $\geq$ 25% BSA involvement with atopic dermatitis and is approximately 116 hours, reflecting, according to the applicant, the slow drug absorption rate rather than the drug elimination rate.

Following topical administration of ruxolitinib, the parent compound was predominant in plasma. Also 5 major metabolites were found in plasma, M18, M27, M11, M8 and M7, at amounts comprising up to 24% of parent compound in plasma. Considering the limited bioavailability following topical administration when the cream is applied to maximally 10% BSA as recommended in the SmPC, and the limited contribution of the metabolites to the PD activity (15 – 18%), no significant pharmacological activity is expected from the metabolites.

Genetic polymorphism can be considered not relevant for ruxolitinib metabolism. Ruxolitinib is not metabolized by CYP2D6 or CYP2C19. CYP2C9 plays a minor role in ruxolitinib metabolism, which may become important in case CYP3A4 is blocked.

Dose proportionality and time dependency

Linear regression indicated a dose-proportional increase of Css with ruxolitinib dose. This was confirmed by the results from study INCB 18424-211, where Css increased with increasing strength

and frequency of dosing and approximately similar treated BSA. Also, Css increased with treated BSA, when dose was the same.

In studies INCB 18424-306 and INCB 18424-307, trough values were similar from week 4 to week 40 and in studies INCB 18424-303 and INCB 18424-304, trough values were similar from week 2 to week 8, indicating that steady state occurs in week 2 or earlier.

Upon CHMP's request, information regarding intra-individual variability was provided by the applicant. The intra-individual variability, expressed as the coefficient of variation, was estimated as 157%. This was similar to the inter-individual variability, which is as expected considering the variation in the exact amount of cream used and the exact area of treated skin treated.

Special populations

For oral ruxolitinib, it is recommended either to reduce the starting dose in patients with severe renal impairment by 50%, or to reduce the starting dose to 5 mg BID. This is due to an increase of exposure to, primarily, mono-oxygenated metabolites. There are no human safety data on the higher metabolite exposures. These metabolites are also formed when ruxolitinib cream is used. When ruxolitinib 1.5% cream is used on maximally 10% BSA, the exposure based on the pharmacological activity adjusted AUC of ruxolitinib plus the metabolites increases up to maximally 1.3-fold in case of severe renal impairment and up to 2-fold in case of end stage renal disease (ESRD). Since the exposure may be twice as high or higher in patients with ESRD, in particular if more than 10% BSA would be treated, as a precautionary measure it was advised that ruxolitinib 1.5% cream should not be used by patients with end stage renal disease, due to lack of data regarding the safety. This has been added to section 4.2 of the SmPC.

In case of hepatic impairment, $AUC_{0\text{-}inf}$ of orally administered ruxolitinib was increased by up to maximally 87%, though there was no relationship between the increase in AUC and the severity of the hepatic impairment (increase in AUC was 87%, 28% and 65% in patients with mild, moderate and severe hepatic impairment respectively). Considering the fact that there was no clear relationship between severity of hepatic impairment and the increase in AUC, a dosing advice for patients with hepatic impairment was considered not necessary. This information has been adequately reflected in SmPC section 4.2.

The PK of ruxolitinib was not significantly affected by gender, race and skin type. No clinically relevant effect on the PK of ruxolitinib is expected regarding age $\geq$ 65 years compared to 18-65 years and body surface area (see SmPC section 4.2). Further, no relevant impact of skin thickness on ruxolitinib exposure is expected as the efficacy of ruxolitinib cream on vitiligo is not dependent on ruxolitinib systemic exposure.

The exposure was somewhat lower in adolescents than in adults. This is likely caused by the smaller treated lesion area and the smaller amount of cream applied per unit area in adolescents compared to adults.

Based on *in vivo* interaction studies with oral ruxolitinib, maximally a doubling of AUC can be expected when a potent CYP3A4 inhibitor is co-administered. In section 4.5 of the SmPC it is mentioned that the plasma AUC is approximately doubled with co administration of a potent inhibitor of CYP3A4 while only a modest increase was seen with co-administration of a moderate CYP3A4 inhibitor. This is agreed.

Pharmacodynamics

The pathophysiology of vitiligo as an auto-immune disorder supports the relevance of JAK inhibition in the treatment of this disorder through re-pigmentation.

The primary pharmacodynamics of ruxolitinib, a potent JAK1/2 inhibitor, is well known from studies with oral application. Systemic exposure is lower with topical application when compared to oral administration. As JAK inhibitors are known for haematological effects, secondary pharmacology was evaluated for topical ruxolitinib and haematological parameters. There was no relevant effect on haemoglobin levels, and also no clear trend on neutrophils. The use of high dose oral ruxolitinib (Jakavi) was characterised with myelosuppression and lower platelets counts, while in contrast, another JAK1/2 inhibitor was associated with modest increments in platelet counts and VTE when given at relatively low oral doses in diverse auto-immune disorders (e.g., rheumatoid arthritis and atopic dermatitis).

No pharmacodynamic DDI or genetic differences in the response on topical ruxolitinib were investigated, and this is accepted as the cream is recommended to be applied without any further topical treatments.

INFy values in blood was absent / low in over 70% of the participants which might be caused by the large part of participants with stable disease (45%). INFy is assumed to play a pivotal role in the pathophysiology of vitiligo and treatment outcome with ruxolitinib, but vitiligo being a peripheral, local (skin) disease, serum INFy may not necessarily be detected nor related to treatment response. The finding that CXCL10, another biomarker for vitiligo which is associated with INFy, correlated with the VASI and treatment response, was therefore considered satisfactory.

A significant relationship was observed between plasma concentrations and the possibility of achieving 75% improvement in the F-VASI, 50% improvement in the T-VASI, or improvement indicated by participants as 4 or 5 (VNS 4-5). These associations suggested that topical ruxolitinib not only has a local effect but also results in a non-negligible, relevant systemic exposure. The applicant was therefore requested to discuss whether there indeed was systemic exposure and whether this systemic exposure was relevant in terms of efficacy and safety.

Based on the data of study 211, the applicant argued that the treatment effect is primarily related to the amount of BSA that is treated. Study participants who had > 20% BSA affected did not show evidence of repigmentation in areas that were not treated with ruxolitinib cream, which would have been expected in case of systemic action of ruxolitinib. Also, serum CXCL10 levels were reduced after treatment, but were not correlated with systemic exposure (Css). It is agreed that these correlations are low/absent and likely determined by outliers (although performing correlation after stratification of one of the bivariates is not endorsed).

Further evidence comes from the non-clinical studies in mini pigs, showing that topical ruxolitinib primarily reached the dermis and epidermis (site of action), much more than reaching the blood stream. Given the above, it is a likely possibility that the correlations that were detected between efficacy responses (F-VASI75, T-VASI50, and VNS scores of 4 or 5) and steady-state plasma ruxolitinib trough concentrations in the Phase 2 and 3 vitiligo studies, were based on the amount of BSA treated, but not a result of systemic exposure to ruxolitinib.

The applicant chose infections and neutropenia as variables to evaluate the relation between systemic exposure to ruxolitinib and safety. It is agreed that these two parameters are a priori relevant representations of the concept of safety, because of the proposed mechanism of action of ruxolitinib (JAK inhibition). The applicant has analysed plasma concentrations of ruxolitinib, stratified by presence or absence of infections. According to the results including the 52-week follow-up data (pool 4), the Css (medians) was similar in patients with (32 nM) and without (31 nM) infection, which was corroborated by similarity of P25 – P75 and the geometrical means. It is therefore considered that there is no obvious relation between the occurrence of infections and level of systemic exposure. The applicant also assessed whether there was a relation between systemic exposure and a certain pattern of infections, which was not found, as might be expected. The incidence of neutropenia was low (the

most frequently occurring cytopenia, see section 2.6.9), which is reassuring, but also precludes a meaningful analysis of the relation of neutropenia with systemic exposure.

Overall, the CHMP considered that the systemic exposure that followed topical application of ruxolitinib does not correlate with efficacy and is not related to the occurrence of infections.

Race was a covariate on the relationship between Css and and the chance of achieving 75% improvement in the F-VASI75 and 50% improvement in the F-VASI50, predicting lower responses for non-white patients. This is however not due to a difference in PK, as there was no difference in Css between subjects with light skin (types I and II) and subjects with darker types of skin. In contrast, according to the subgroup analyses of clinical responder rates in the pivotal trials, ruxolitinib cream appeared to be similarly effective in all subgroups for race, although confidence intervals were wide for non-caucasian subgroups (see Ancillary analyses, section 2.6.5.2). Due to low patient numbers of subjects with race other than white no definitive conclusions can be drawn. Remarkably, there was no significant relationship between Css and the continuous parameter F-BSA (percent change from baseline in total affected facial area at week 24).

2.6.4. Conclusions on clinical pharmacology

Overall, the pharmacokinetics of topically applied ruxolitinib have been adequately characterised. Due to lack of data regarding the safety and as a precautionary measure, SmPC sections 4.2 and 5.2 were updated to advise HCPs that ruxolitinib 1.5% cream should not be used by patients with end stage renal disease.

2.6.5. Clinical efficacy

The applicant has performed one phase 2 study for dose-finding (INCB 18424-**211**) and two phase 3 studies (INCB 18424**-306 and -307**) in patients with vitiligo, and both studies were completed. A maintenance – withdrawal study comprising participants who completed study 306 or 307, had recently been initiated (INCB 18424**-308**) (Table 17); final data are expected in the first half of 2023 (also see section 2.7).

The study population of the pivotal studies 306 and 307 included adolescents (12 – 17 years of age) and adults, with non-segmental vitiligo involving up to 10% of the total body surface area (BSA) and with at least some facial involvement (see inclusion criteria). A single dose regimen of ruxolitinib cream (1.5% BID) was included in the pivotal studies; it was the highest dose regimen in the dose-finding study. It was planned that ~10% of patients would be adolescents. PK data were also available from adolescents with atopic dermatitis in studies INCB 18424-102 and INCB 18424-103 (see section on pharmacokinetics). No further studies in special populations had been performed.

Table 17: Main clinical studies in the clinical programme for vitiligo

Study Identifier Report Location Study Status Type of Report	Study Objective(s)	Study Design and Type of Control	Test Product(s) Dose Regimen(s) Route of Administration	Duration of Treatment	Diagnosis of Participants Sex (M/F) Median Age (Range)	Participants Planned/ Participants Enrolled	Efficacy Endpoints
INCB 18424-**211**	Efficacy, safety, and PK	Phase 2, randomized, double-blind, vehicle-controlled, dose-ranging study	Vehicle-controlled period: Vehicle BID Ruxolitinib 0.15% QD Ruxolitinib 0.5% QD Ruxolitinib 1.5% QD Ruxolitinib 1.5% BID Continued double-blind period: Ruxolitinib 0.15% QD Ruxolitinib 0.5% QD Ruxolitinib 1.5% QD Ruxolitinib 1.5% BID Open label extension period: Ruxolitinib 1.5% BID	Vehicle-controlled period: 24 weeks Continued double-blind period: 28 weeks Open-label extension period: 104 weeks	Adults with vitiligo with depigmented areas including ≥ 0.5% F-BSA and ≥ 3% T-BSA on nonfacial areas 73/84 49.0 years (18-73 years)	157	Primary: Proportion of participants treated with ruxolitinib cream reaching FVASI50 at Week 24 compared with participants treated with vehicle cream Key secondary: Proportion of participants reaching F-PhGVA of clear or almost clear at Week 24 Proportion of participants reaching T-VASI50 at Week 52

Study Identifier Report Location Study Status Type of Report	Study Objective(s)	Study Design and Type of Control	Test Product(s) Dose Regimen(s) Route of Administration	Duration of Treatment	Diagnosis of Participants Sex (M/F) Median Age (Range)	Participants Planned/ Participants Enrolled	Efficacy Endpoints
INCB 18424-**306**	Efficacy, safety, and PK	Phase 3, randomized, double-blind, vehicle-controlled study	Double-blind period: Vehicle BID Ruxolitinib 1.5% BID Treatment-extension period: Ruxolitinib 1.5% BID	Double-blind period: 24 weeks Treatment-extension period: 28 weeks	Adolescents and adults with nonsegmental vitiligo with depigmented areas including ≥ 0.5% FBSA, ≥ 0.5 FVASI, ≥ 3% BSA on nonfacial areas, ≥ 3 TVASI, and total body vitiligo area (facial and nonfacial) not exceeding 10% 144/186 39.0 years (1279 years)	330	Primary: Proportion of participants reaching FVASI75 at Week 24 Key secondary: 1. Proportion of participants reaching F-VASI50 at Week 24 1. Proportion of participants reaching F-VASI90 at Week 24 2. Proportion of participants reaching T-VASI50 at Week 24 3. Proportion of participants reaching a VNS of "4 – A lot less noticeable" or "5 – No longer noticeable" at Week 24 4. Percentage change from baseline in F-BSA at Week 24
INCB 18424-**307**	Efficacy, safety, and PK	Phase 3, randomized, double-blind, vehicle-	Double-blind period: Vehicle BID Ruxolitinib 1.5% BID Treatment-extension period:	Double-blind period: 24 weeks	Adolescents and adults with nonsegmental vitiligo with depigmented areas including ≥ 0.5% FBSA,	344	Primary: Proportion of participants reaching FVASI75 at Week 24 Key secondary:

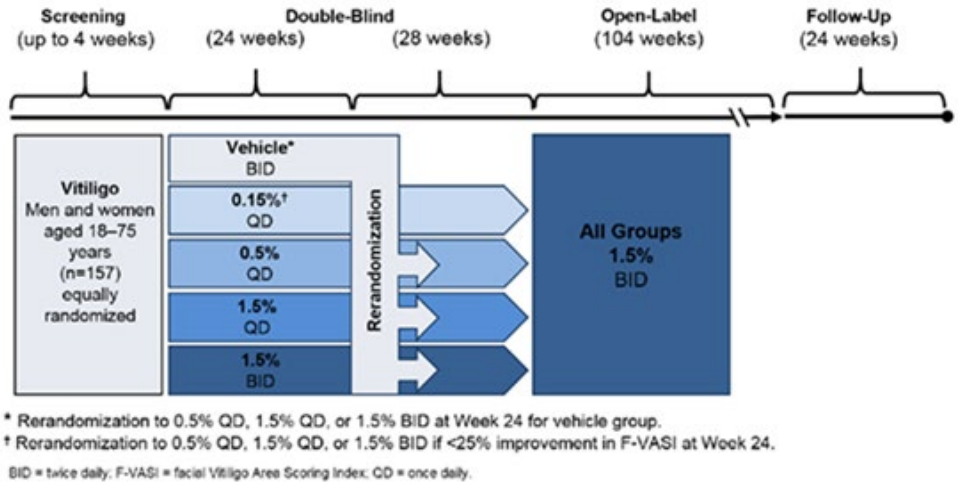
		controlled study	Ruxolitinib 1.5% BID	Treatment-extension period: 28 weeks	≥ 0.5 FVASI, ≥ 3% BSA on nonfacial areas, ≥ 3 TVASI, and total body vitiligo area (facial and nonfacial) not exceeding 10% 172/172 38.0 years (1277 years)		1. Proportion of participants reaching F-VASI50 at Week 24 2. Proportion of participants reaching F-VASI90 at Week 24 3. Proportion of participants reaching T-VASI50 at Week 24 4. Proportion of participants reaching a VNS of "4 – A lot less noticeable" or "5 – No longer noticeable" at Week 24 5. Percentage change from baseline in F-BSA at Week 24

Study Identifier **Report Location** **Study Status** **Type of Report**	**Study Objective(s)**	**Study Design and Type of Control**	**Test Product(s)** **Dose Regimen(s)** **Route of Administration**	**Duration of Treatment**	**Diagnosis of Participants** **Sex (M/F)** **Median Age (Range)**	**Participants Planned/ Participants Enrolled**	**Efficacy Endpoints**
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	Efficacy and safety	Phase 3, randomized, double-blind, vehicle controlled treatment withdrawal and extension study	Cohort A (F-VASI90 fulfilled): - Vehicle BID - Ruxolitinib 1.5% BID (1:1) Cohort B (F-VASI90 not fulfilled): - Ruxolitinib 1.5% BID	52 weeks of treatment extension, following study 306 or 307	Participants originated from parent studies 306 and 307; i.e. comprising adolescents and adults with nonsegmental vitiligo with depigmented areas including ≥ 0.5% FBSA, ≥ 0.5 FVASI, ≥ 3% BSA on nonfacial areas, ≥ 3 TVASI, and total body vitiligo area (facial and nonfacial) not exceeding 10%	Participants who successfully completed either of the studies 306 or 307 and tolerated ruxolitinib without safety issues and with good compliance for continuation were considered eligible	Primary: In cohort A: Time to relapse (defined as < F-VASI75) Key secondary: In Cohort A: • Time to maintain ≥ F-VASI90 response.

2.6.5.1. Dose response study

Study INCB 18424-**211** was a phase 2, randomized study designed as a proof-of-concept and dose-ranging study, including PK assessments, with an open-label extension to 104 weeks to evaluate long-term efficacy and safety of ruxolitinib cream in subjects with segmental or non-segmental vitiligo. A total of 157 adult patients with segmental or non-segmental vitiligo were randomized (1:1:1:1:1) to one of the five 24-week dosing regimens (ruxolitinib 0.15% QD, 0.5% QD, 1.5% QD, 1.5% BID, and vehicle). Participants on the three highest dosing regimens continued up to week 52, thereafter all participants could continue with the highest dosing regimen (1.5% BID). Application of the cream was limited to 20% of the total BSA. The primary endpoint was the proportion of participants who reached F-VASI50 at week 24; the F-VASI75 was secondary endpoint (Figure 11).

Figure 11: Design of dose-ranging study (INCB 18424-211)



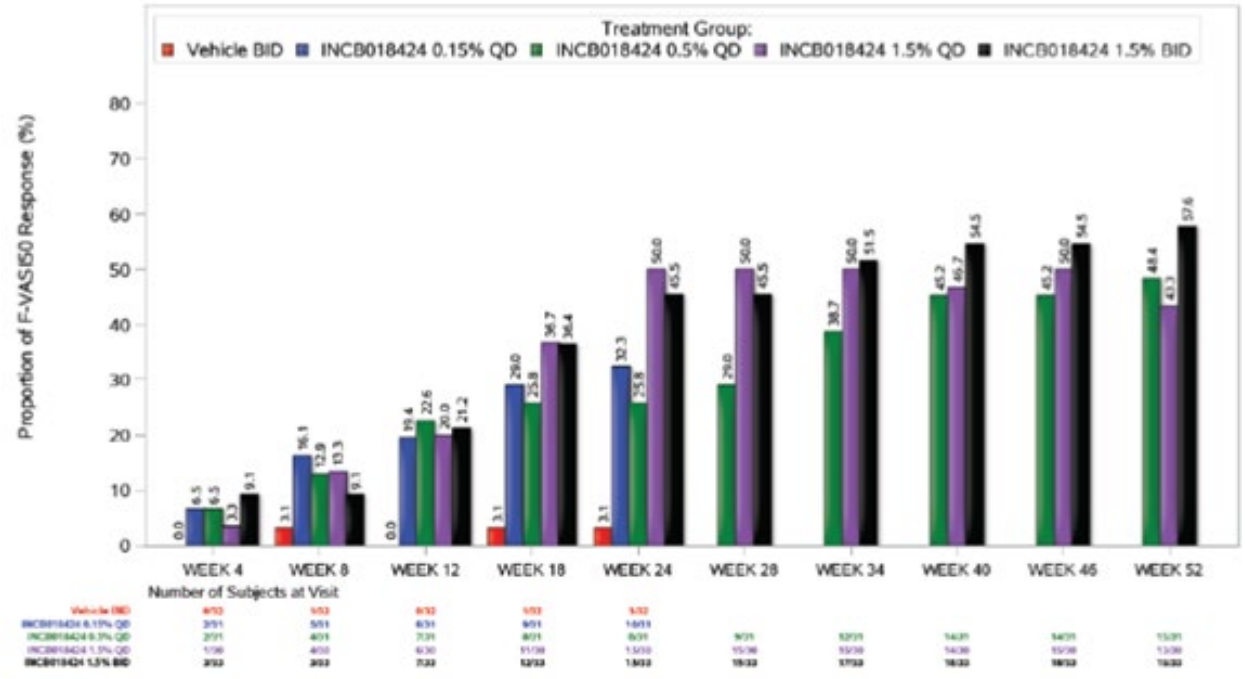
Results showed superiority of ruxolitinib versus vehicle for each of the 4 dosing regimens, with the highest percentages responders in the 1.5% QD and BID groups (Table 18). Based on these 24-week results, the 1.5% QD dosing regimen was initially selected by the applicant for the confirmatory studies and this was endorsed in the 2019 CHMP Scientific Advice (EMEA/H/SA/1155/3/2019/III), considering the lower systemic exposure with the QD regimen compared to the 1.5% BID regimen. However, based on the 52-week results at the F-VASI75 with 58% responders in the 1.5% BID group versus 43% responders in the 1.5% QD group (Figure 12), the applicant ultimately selected the 1.5% BID regimen as the single dose of ruxolitinib cream to be tested in the confirmatory studies. Given the largest proportions of responders in F-VASI75 for the 1.5% BID dose at week 24 and beyond and given that the F-VASI75 is more stringent than the F-VASI50, this choice can be understood. Further, in the 2019 CHMP Scientific Advice (EMEA/H/SA/1155/3/2019/III), the applicant was recommended to favor the F-VASI75 over the F-VASI50 as primary endpoint for the confirmatory trials.

Table 18: Proportions of participants reaching F-VASI50 at week 24 (primary outcome)

	Vehicle	**Ruxolitinib 0.15% QD**	**Ruxolitinib 1.0% QD**	**Ruxolitinib 1.5% QD**	**Ruxolitinib 1.5% BID**
F-VASI50 wk 24 n (%)	1 (3.1%)	10 (32.3%)	8 (25.8%)	15 (50%)	15 (45.5%)
OR		13.8	10.3	28.5	24.7
95% CI		1.7 – 640.9	1.24 – 487.3	3.7 – 1305.2	3.3 – 1121.4
p-value		0.0057	0.0243	< 0.0001	< 0.0001

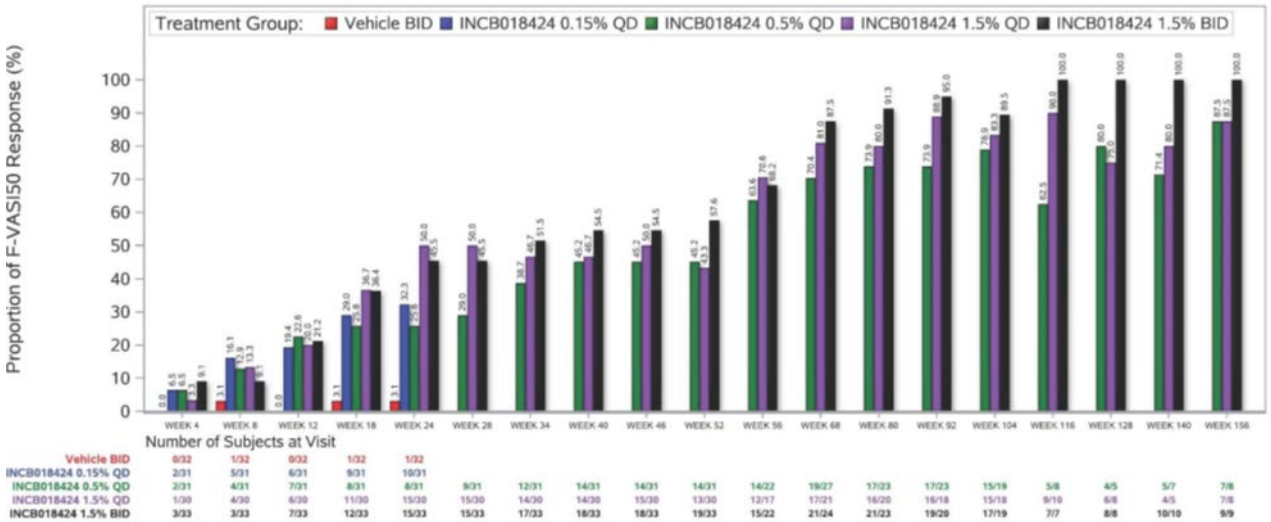
The bar chart with proportions of F-VASI50 responders over time until week 52, showed numerical superiority of all ruxolitinib dosing groups versus vehicle from week 8 (Figure 12). After week 24, in the continued double-blind period, the treatment effect appeared to increase further for the 0.5% QD group and seemed to plateau for the 1.5% QD and BID dosing regimens.

Figure 12: The proportions F-VASI50 responders by treatment group up to week 52



Proportions of participants reaching the **F-VASI75** over time are shown below (Figure 13). Participants in the vehicle group did not achieve this endpoint. The largest proportions were observed for ruxolitinib 1.5% BID with 30% at week 24 and 52% at week 52; for ruxolitinib 1.5% QD these proportions were 17% and 30%.

Figure 13: Proportions of participants reaching F-VASI75 by treatment group up to week 156



2.6.5.2. Main studies

The main studies that provided efficacy data were:

Title of study

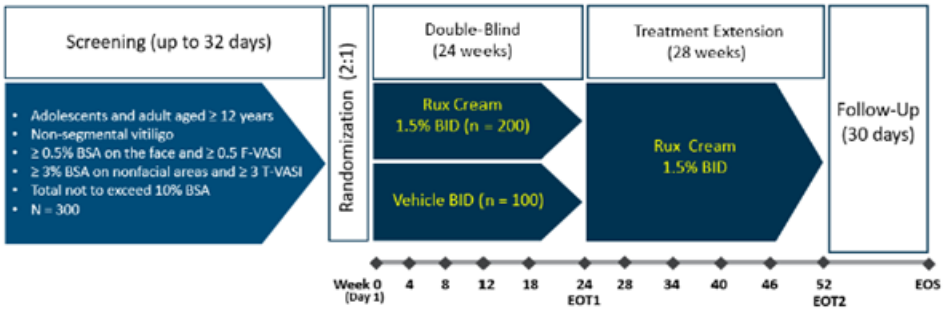
Study INCB 18424-306: A Phase 3, double-blind, randomised, vehicle-controlled, efficacy and safety study of ruxolitinib cream followed by an extension period in participants with vitiligo (TRuE-V1).

Study INCB 18424-307: A Phase 3, double-blind, randomised, vehicle-controlled, efficacy and safety study of ruxolitinib cream followed by an extension period in participants with vitiligo (TRuE-V1/2).

These pivotal studies were identical in design and therefore are presented together (Figure 14).

The two trials had a screening period of up to 32 days, followed by a randomised, vehicle-controlled period of 24 weeks, and a subsequent treatment extension phase of 28 weeks during which all participants received ruxolitinib 1.5% BID. Follow-up was determined at 30 days.

Figure 14: Design of the studies INCB 18424-306 and -307



BID = twice daily; BSA = body surface area; F-VASI = Face Vitiligo Area Scoring Index; Rux = ruxolitinib; T-VASI = total body Vitiligo Area Scoring Index.

Methods

- **Study Participants**

Participants in study INCB 18424-306 were recruited at 45 sites (in Bulgaria, Canada, Germany, Italy, Poland, Spain, and the United States of America) and those in study -307 at 49 sites (in Bulgaria, Canada, France, Germany, Netherlands, Poland, and the United States of America).

Main **inclusion criteria** were:

- Adolescents and adults ≥ 12 years of age, with BMI 17-40;
- Clinical diagnosis of non-segmental vitiligo with depigmented area including ≥ 0.5% BSA on the face, ≥ 0.5 F-VASI, ≥ 3% BSA on non-facial areas, ≥ 3 T-VASI, and total body vitiligo area (facial and non-facial) not exceeding 10% BSA.
- Willingness to discontinue all agents used to treat vitiligo from screening through the final safety follow-up visit.

Main **exclusion criteria** were:

- Absence of pigmented hair within any of the vitiligo areas on the face;
- Other forms of vitiligo or other skin depigmentation disorders;

- The use of depigmentation treatments (eg, monobenzone) for past treatment of vitiligo or other pigmented areas;
- Concurrent conditions and history of cardiovascular disease (uncontrolled cardiac disease or hypertension; history of thrombosis), malignant disease, (metastatic) malignant disease, liver disease, alcoholism or drug addiction;
- The use of the following treatments within the indicated washout period before baseline:
    - 1 week: topical drugs when used on the vitiligo areas;
    - 4 weeks: melanocyte-stimulating agents, immunomodulating systemic medications, any other systemic therapies that could increase the skin sensitivity to UV/visible light or impact skin pigmentation; or those who received live vaccine;
    - 8 weeks: laser or any kind of phototherapy;
    - 5 half-lives or 12 weeks: biologicals, investigational, or experimental therapy or procedures for vitiligo;
- Previous treatment with JAK inhibitors (systemic or topical);
- Clinically significant abnormal laboratory values for haemoglobin, liver enzymes, creatinine clearance < 30 ml/min, significant abnormal TSH / fT4 at screening, and / or positive HIV antibody test; and
- Pregnant or lactating participants, or those considering pregnancy.

- **Treatments**

Study treatment

In the double-blind period, participants were treated with either **ruxolitinib cream 1.5% BID** or **vehicle cream BID**. Study medication was provided by the sponsor in tubes of 60 grams. Participants were instructed to apply the cream as a thin film at depigmented areas which were identified at baseline up to 10% BSA, and to use no more than one tube of 60 grams a week. Treatment of up to 10% BSA was chosen as it was considered most appropriate for long-term, continuous treatment of vitiligo; applying a topical treatment BID to an area greater than 10% BSA was assumed to be difficult and impractical for most patients. Treatment had to be continued even if (partial or full) re-pigmentation was achieved. In case of expansion of existing areas of vitiligo treatment was allowed to be extended (up to a maximum of 10% BSA) to these areas as well, after evaluation at the clinic. Applications were documented in diaries by the participant and study tubes were weighted before and after application. Compliance was then determined by the number of actual versus anticipated number of applications, which had to be within 70% to 130% of the prescribed number of applications.

Discontinuation

According to the guidelines for interruption and restarting of study drug in the protocol, treatment with the study drug was interrupted in case of ALAT / ASAT > 3 times the upper limits, any Grade 3 or higher abnormality in lab, any Grade 4 or higher abnormality or ASAT / ALAT > 5 times upper limits of normal.

Permanent discontinuation of the study drug was required in case of unacceptable severity of an AE possibly related to study drug, including worsening of vitiligo that required treatment with a prohibited concomitant drug. Pregnancy as well as non-compliance (under certain circumstances) were reasons to discontinue a participant from the study.

Concomitant treatment

Participants were allowed to use bland emollients or camouflage makeups and sunscreens at least 2 hours after study drug application. Over the counter products were allowed until 7 days before baseline visit unless deemed acceptable by the investigator. Prescription medication was allowed until 7 days prior to baseline visit. Treatment for dermatological diseases other than vitiligo was allowed on areas not concurrently treated for vitiligo if it involved < 10% of the BSA outside the areas treated for vitiligo (including topical steroids for a maximum of seven days and calcineurin inhibitors). Oral steroids for other conditions such as exacerbations of asthma were acceptable for no longer than seven days.

Rescue treatment

No rescue medication was foreseen in the protocol. Participants were not allowed to use any other treatments for vitiligo at any time during the study. If the worsening of vitiligo required treatment with prohibited medication, the study treatment had to be discontinued.

- **Objectives**

Primary objective of studies INCB 18424-306 and -307 was to evaluate the efficacy of ruxolitinib cream 1.5% BID in participants with vitiligo versus vehicle cream BID after 24 weeks of treatment, defined as the percentage of participants achieving the F-VASI75. Secondary objectives were to evaluate efficacy, safety, and tolerability after 24 and 52 weeks of treatment of ruxolitinib cream 1.5% BID versus vehicle cream BID as well as the study of biomarkers in blood.

- **Outcomes/endpoints**

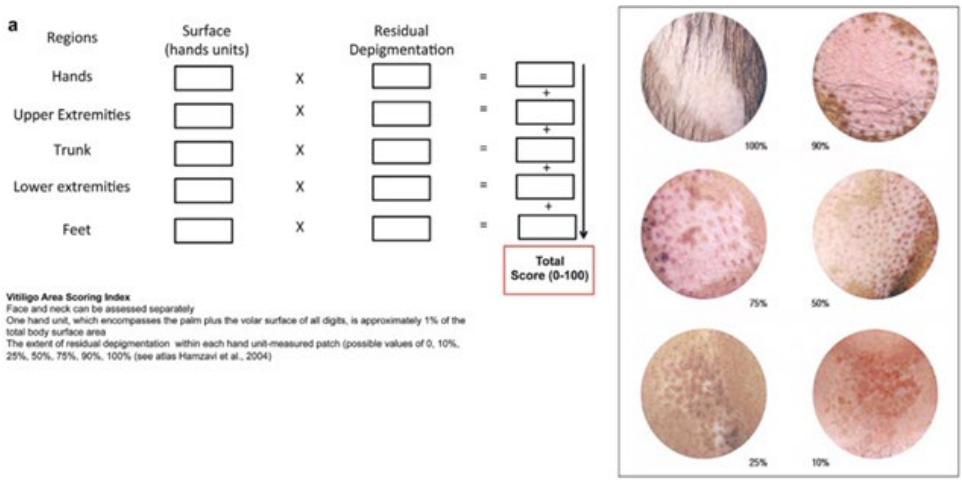
Primary outcome

The primary outcome was the proportion of participants reaching at least 75% improvement in facial depigmentation from baseline on the Vitiligo Area Scoring Index (**F-VASI75**) at week 24.

The VASI is a validated physician-based tool for the quantification of depigmentation in vitiligo, analogous to the PASI which is used in psoriasis. It is based on a composite estimate of the overall body surface area (BSA) of vitiligo patches and the degree of re-pigmentation within these patches over time. The degree of depigmentation for each vitiligo site (hands, upper extremities, trunk, lower extremities, and feet) is determined and estimated to the nearest percentage (i.e. 0%, 10%, 25%, 50%, 75%, 90%, 100%) (Figure 15). The VASI is then calculated with the following formula:

VASI = Σ [hand units] x [residual depigmentation] all body sites

Figure 15: Components of the Vitiligo Area Scoring Index (VASI) and reference pictures



The F-VASI was developed by the applicant for the purpose of the pivotal studies. The percentage of vitiligo involvement in the face (% BSA) was calculated for 3 sites of the face (area on the forehead to the original hairline, on the cheek to the jawline vertically to the jawline, and laterally from the corner of the mouth to the tragus). Of note, the face did not include the lips, scalp, ears or neck, but included the nose and eyelids. For each of the three sites, the degree of depigmentation was determined (in %). The F-VASI was calculated by multiplying the values assessed for the vitiligo involvement by percentage of affected skin and summing the values of these sites (range 0 – 3). No additional studies on the psychometric properties of the F-VASI (and the T-VASI, see below) were performed.

Key secondary outcomes

Key secondary endpoints were tested sequentially only if the null hypothesis for the primary endpoint was rejected.

- **F-VASI50** at week 24: The proportion of participants reaching at least 50% improvement in facial depigmentation from baseline on the facial VASI.
- **F-VASI90** at week 24: The proportion of participants reaching at least 90% improvement in facial depigmentation from baseline on the facial VASI.
- **T-VASI50** at week 24: The proportion of participants reaching at least 50% improvement in facial depigmentation from baseline on the total-body VASI. The T-VASI was defined by the applicant and consisted of the traditional VASI with 1 additional body area, which is the face/neck. For the T-VASI, the percentage of vitiligo involvement was estimated in hand units (% BSA) as described above, by the same investigator during the study, for six body regions (the head / neck, hands, upper extremities excluding the hands, the trunk, lower extremities excluding the feet, and feet). Of note, the original VASI comprises the same body regions, except for the head / neck. The degree of depigmentation for each vitiligo site is determined and estimated to the nearest percentage (i.e. 0%, 10%0, 25%, 50%, 75%, 90%, 100%). The T-VASI is calculated by multiplying the values assessed for the vitiligo involvement by the percentage of affected skin for each body site and summing the values of each body site together (range 0 – 100): VASI = Σ [hand units] x [residual depigmentation] all body sites.
- **Vitiligo Noticeable Scale (VNS) response** at week 24: The proportion of patients with a score of 4 (a lot less noticeable depigmentation) or 5 (depigmentation no longer noticeable) in the Vitiligo Noticeability Scale (VNS). The VNS is a patient - reported measure of vitiligo treatment success, which has a 5-point scale. Psychometric properties were condidered sufficient (Batchelor et al 2016). The facial photograph taken at baseline was shown to the participants for reference and a mirror was provided to the participants to assess the vitiligo on their face. The participant was asked to respond to the following query: 'Compared with before treatment, how noticeable is the vitiligo now?'. The responses options were: (1) More noticeable, (2) As noticeable, (3) Slightly less noticeable, (4) A lot less noticeable, and (5) No longer noticeable. VNS scores of 4 or 5 were interpreted as representing treatment success.
- Percent change from baseline in **F-BSA.**

Other secondary endpoints

All other secondary outcomes, not being regarded as 'key secondary', were summarised using descriptive statistics, no statistical hypothesis testing was planned to be performed. These outcomes included:

- Percentages change from baseline: F-VASI, T-VASI, Facial and Total body Physician Global Vitiligo Assessment (**F- and T-PhGVA**), and **T-BSA**.

- Patient-reported outcomes: **Color-matching question**, Facial and Total body Patient Global Impression of Change-Vitiligo (**F- and T-PaGIC**).
- Other endpoints: (Children's) Dermatology Life Quality Index (**(C)DLQI**), Hospital Anxiety and Depression Scale (**HADS**), **WHO-5**, the Treatment Satisfaction Questionnaire for Medication (**TSQM**), and the Vitiligo-specific Quality-of-life instrument (**VitiQoL)**.

- **Sample size**

The sample size was calculated to provide at least 85% power to detect a difference between the 1.5% BID with vehicle BID in primary and key secondary endpoints and was calculated based on response rates observed in study INCB 18424-211 (response rate F-VASI75 in ruxolitinib group 20% versus 5% in vehicle group). The Fisher's exact test with a 2-sided alpha of 0.05 was used. At least 300 were anticipated to be included in each pivotal trial; adolescents had to make up at least 10% of the study population.

- **Randomisation and Blinding (masking)**

The participants were randomised in a 2:1 ratio to ruxolitinib 1.5% BID or vehicle BID, stratified by baseline skin type (Fitzpatrick scale Type I and II vs Type III, IV, V, and VI) and region (North America or Europe). Sponsor, investigators, and participants were blinded for treatment allocation. Investigators and participants kept blinding until the end of the study (week 52). Unblinding during the study was only allowed in case of a medical emergency; the participant was then withdrawn from study treatment.

- **Statistical methods**

The COVID-19 pandemic impacted on clinical study participation, which led to both increased discontinuations and missed efficacy assessments. To minimise potential bias from missing values and impact on study interpretation, the sponsor considered the following changes to the protocol-defined analyses, which were specified in the Statistical Analysis Plan:

- The FAS was planned to replace the ITT population in the evaluation of efficacy for the 24-week, double-blind period. However, based on feedback from the FDA, the primary population for efficacy analyses was changed back to the ITT population after unblinding.
- Multiple imputation was used to replace NRI as the primary method for handling missing values in the analyses of the primary and key secondary endpoints.

The **ITT population** included all randomised participants. Treatment groups for this population were defined according to the treatment assignment at randomisation. The ITT population was used for the analyses of efficacy and summaries of demographics, baseline characteristics, and participant disposition. The PP population included all participants in the ITT population excluding participants with important protocol deviations.

The FAS population included all participants in the ITT population that have baseline and any postbaseline assessments.

The **primary endpoint analysis** was performed using exact logistic regression and tested the primary alternative hypothesis (superiority of ruxolitinib cream vs vehicle) at Week 24. This model included the treatment group and stratification factors of skin type (Fitzpatrick scale Type I and II or Type III, IV, V, and VI) and geographic region (North America or Europe). The unadjusted p-value between the 1.5% BID group versus vehicle was compared at 2-sided $\alpha = 0.05$ level. Odds ratio and 95% CIs in response rates (ruxolitinib cream vs vehicle) at Week 24 were also computed. The primary endpoint was also examined for the PP population using the same model as the primary analysis.

Missing data for the F-VASI assessment at a given visit in the double-blind period was handled using multiple imputation under the missing-at-random assumption. For multiple imputation, a fully conditional specification method that assumed the existence of a joint distribution for all variables was used to impute the numerical score.

Sensitivity analyses performed on the primary endpoint are:

- Non-responder imputation. Participants who are missing postbaseline values were defined as non-responders.
- Last observed non-missing post-baseline value was used to fill in missing values at Week 24.
- A tipping point sensitivity analysis was conducted to examine the potential effects of missing data. The missing F-VASI75 response at Week 24 in each treatment group was replaced by a range of values from the most conservative case (all missing is non-response) to the most aggressive case (all missing is response).

Key secondary efficacy endpoint analyses for *binary outcomes* (F-VASI50/90, T-VASI50, and VNS response) were performed using similar methods to those specified in the analysis of the primary endpoint. For the *continuous outcome* (the percent change from baseline in F-BSA at Week 24) an ANCOVA model was used with treatment group, stratification factors, and baseline value as covariates.

A **gatekeeping testing strategy for the primary and key secondary analyses** was implemented to control the overall Type I error rate, 2-sided $\alpha = 0.05$. These endpoints were tested in a fixed sequence at 2-sided $\alpha = 0.05$ level in the following order: F-VASI75, F-VASI50, F-VASI90, T-VASI50, VNS and F-BSA, all at Week 24. The endpoint was tested only if the null hypothesis for the primary endpoint (and the secondary endpoints in previous steps) was rejected.

For *continuous* **secondary efficacy endpoints**, a mixed-effect model with repeated measurements was fit for the comparisons between 1.5% BID cream group and vehicle cream group. For *categorical* secondary endpoints, a similar exact logistic regression models as specified in the primary and key secondary analysis was used if applicable.

Subgroup analyses on response rate differences for the primary endpoint were performed for the following participant characteristics and baseline variables:

- Skin type (Fitzpatrick scale Type I and II vs Type III, IV, V, VI)
- Age (12 to 17, ≥ 18 to 64, ≥ 65 years; ≤ 40, > 40 years)
- Region (North America, Europe)
- Sex (Male, Female)
- Race
- F-BSA (<1.5, ≥1.5)

Furthermore, separate analyses were performed for the primary and key secondary outcomes in *adolescents compared to adults* as to provide evidence for inclusion of this subgroup in the indication.

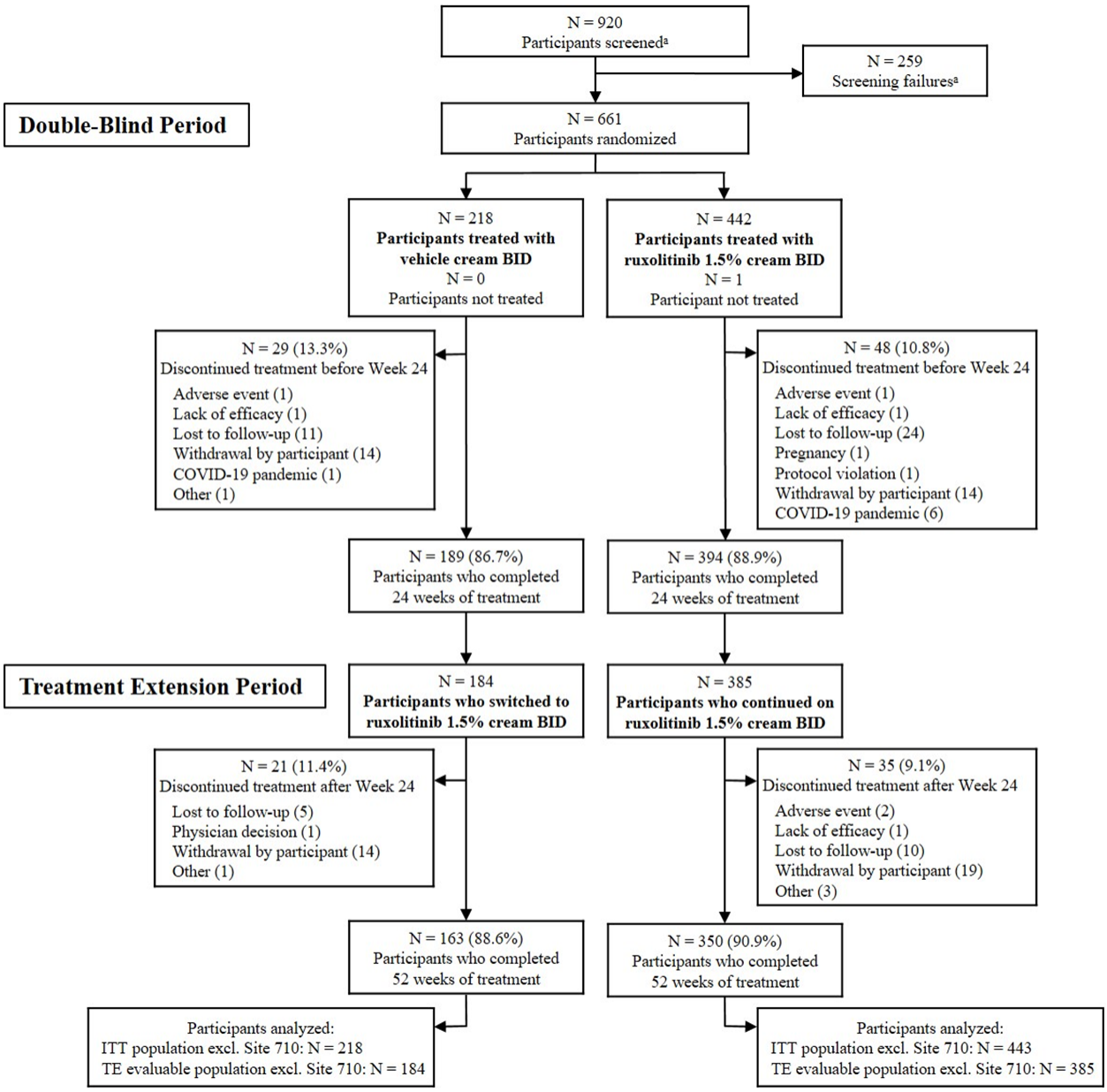
No formal interim analysis was planned in these studies.

Results

- **Participant flow**

Participant flow for both studies is shown in Figure 16 below.

Figure 16: Participant flow in pooled studies INCB 18424-306 and -307



Abbreviations: BID = twice daily; ITT = intent-to-treat; PP = per protocol; TE = treatment extension.

Note 1: Data from participants screened and enrolled at Site 710 in Study INCB 18424-307 were excluded.

Note 2: A total of 661 participants were randomized in Studies INCB 18424-306 (N = 330) and INCB 18424-307 (N = 331) to the vehicle cream or ruxolitinib 1.5% cream BID during the 24-week double-blind vehicle-controlled period (ITT Pooled Population). All but 1 of these participants applied study drug at least once during the double-blind period, 583 participants (88.2%) completed treatment through Week 24, and 569 of these participants continued into the TE period. A total of 513 participants (90.2%) of the participants who continued into the TE period completed treatment through Week 52. Reasons for discontinuation during the double-blind and TE periods were most commonly lost to follow-up or withdraw by the participant with no meaningful differences in incidences between the treatment groups or studies. a Data on file.

The ITT population consisted of 661 participants; participants (n = 13) from study site 710 were excluded from the study due to non-compliance with the protocol and concerns with data quality. Of

the 661 participants randomised, 660 (99.8%) applied ruxolitinib 1.5% BID at least once, and 583 (88.2%) completed the double-blind period. Study discontinuation was similar between treatment arms and studies.

A total of 569 participants (n = 283 in study INCB 18424-306 and n = 286 in study INCB 18424-307) applied ruxolitinib 1.5% BID at least once in the treatment extension period; 513 participants (90.2%) completed treatment through week 52 (n = 256 in study 306 and n = 257 in study 307).

- **Recruitment**

Study INCB 18424-306 started collecting data on September 20 in 2019, and study INCB 18424-307 started collecting on October 3, 2019. Both studies were completed in the first quarter of 2022.

- **Conduct of the study**

The applicant stated that all studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and in compliance with the International Council on Harmonisation Good Clinical Practices Guidelines. The studies were performed in accordance with applicable laws and country-specific regulations in which the studies were conducted.

The protocol was amended at three time-points (October 31, 2019; December 12, 2019; February 21, 2020). The first amendment mainly aimed at incorporating revisions requested by the Voluntary Harmonisation Procedure (VHP).

Relevant issues in the amendments were:

- The addition of (the option for participation in the sub-study involving) exit interview at week 24 and 52.
- Removal of the statement that hormonal contraception may be susceptible to interaction with the investigational product which may reduce the efficacy of the contraception method, was described as this was considered specific for oral ruxolitinib rather than topical since the systemic exposure was considered to be low.
- A change in the description of how to handle participants not meeting the eligibility criteria, which was changed from ‘may discontinue’ to 'must discontinue'.
- Revision of the per protocol population and clarification of the primary analysis.
- Revision of the key secondary endpoints and an update of the analysis plan
- Removal of stratification criteria by age and adding stratification by region.
- Addition of an exclusion criterion, i.e., exclusion of other forms of vitiligo to the population section.

Most amendments were considered minor by the applicant. The replacement of stratification criteria by age with stratification by region was not considered to have had a negative impact on the study results by the applicant.

Following an audit, the data of site 710 were excluded from the efficacy analyses. This decision was due to one critical finding (informed consent) and two major findings (source documents and organisation and personnel). The analyses were repeated with the centre excluded, and the main analyses with and without the centre were comparable.

- **Baseline data**

Demographic variables were balanced between the two studies, as well as between the vehicle and the ruxolitinib groups. Mean (sd) age of the pooled population (comprising studies 306 and 307) was

40 (15) years, ranging from 12 to 79 years. Adolescents between 12 - 18 years of age represented 10.9% (n = 72) of the pooled population; those aged 65 years or older represented 6.8% (n = 45). A total of 54% (n = 354) was female and most participants had Fitzpatrick skin type II, III, or IV (89%, n = 590). Mean (sd) body mass index was 27 (5.2). Most participants (82%, n = 542) were of white race; black and African Americans were represented by 4.7% (n = 31) of the participants.

Medical history was also balanced between the two studies, as well as between the vehicle and the ruxolitinib groups (Table 19). Mean (sd) years since diagnosis was 15 (12) years with a range from 0 to 60.5 years. In 63% (n = 419) the diagnosis was set during adulthood and in 74% (n = 486) the disease was stable. Total percentage of affected body surface area was on average (sd) 7.4% (2.0).

Baseline **disease characteristics** were overall balanced between the two studies, as well as between the vehicle and the ruxolitinib groups (Table 19). The median (range) F-VASI at baseline was 0.70 (0.4 – 3.0) in both treatment groups over the two studies. The average (range) facial BSA was 1% (0.5% - 3.0%). Median T-VASI at baseline was about 6.7 over the two studies, and the average (range) total BSA affected by vitiligo was 7% (3% - 10%). Thirty-eight percent of all participants was treatment-naïve; phototherapy and topical calcineurin inhibitors were the most common prior therapies (32% of the participants), followed by topical corticosteroids (28%).

Table 19: Baseline medical history and disease characteristics (studies INCB 18424-306 and -307)

Variable	Study INCB 18424-306			Study INCB 18424-307			Pooled Population		
	Vehicle Cream BID (N = 109)	Ruxolitinib 1.5% Cream BID (N = 221)	Total (N = 330)	Vehicle Cream BID (N = 109)	Ruxolitinib 1.5% Cream BID (N = 222)	Total (N = 331)	Vehicle Cream BID (N = 218)	Ruxolitinib 1.5% Cream BID (N = 443)	Total (N = 661)
Years since initial diagnosis of vitiligo									
n	109	221	330	109	222	331	218	443	661
Mean (STD)	13.18 (10.042)	13.85 (11.664)	13.63 (11.143)	16.36 (11.762)	15.46 (11.943)	15.76 (11.873)	14.77 (11.027)	14.66 (11.819)	14.69 (11.555)
Median	11.96	10.60	11.08	14.87	12.28	12.95	12.15	11.62	11.96
Min, max	0.1, 47.5	0.0, 60.5	0.0, 60.5	0.0, 59.5	0.0, 50.3	0.0, 59.5	0.0, 59.5	0.0, 60.5	0.0, 60.5
Vitiligo diagnosed in childhood, n (%)									
No	75 (68.8)	149 (67.4)	224 (67.9)	66 (60.6)	129 (58.1)	195 (58.9)	141 (64.7)	278 (62.8)	419 (63.4)
Yes	34 (31.2)	72 (32.6)	106 (32.1)	43 (39.4)	93 (41.9)	136 (41.1)	77 (35.3)	165 (37.2)	242 (36.6)
Age at diagnosis, n (%)									
0-5 years	7 (6.4)	5 (2.3)	12 (3.6)	7 (6.4)	16 (7.2)	23 (6.9)	14 (6.4)	21 (4.7)	35 (5.3)
6-11 years	12 (11.0)	40 (18.1)	52 (15.8)	14 (12.8)	48 (21.6)	62 (18.7)	26 (11.9)	88 (19.9)	114 (17.2)
12-17 years	15 (13.8)	27 (12.2)	42 (12.7)	22 (20.2)	29 (13.1)	51 (15.4)	37 (17.0)	56 (12.6)	93 (14.1)
Disease status, n (%)									
Stable	80 (73.4)	165 (74.7)	245 (74.2)	82 (75.2)	159 (71.6)	241 (72.8)	162 (74.3)	324 (73.1)	486 (73.5)
Progressive	29 (26.6)	56 (25.3)	85 (25.8)	27 (24.8)	63 (28.4)	90 (27.2)	56 (25.7)	119 (26.9)	175 (26.5)
Other autoimmune disorders, n (%)									
No	91 (83.5)	168 (76.0)	259 (78.5)	91 (83.5)	186 (83.8)	277 (83.7)	182 (83.5)	354 (79.9)	536 (81.1)
Yes	18 (16.5)	53 (24.0)	71 (21.5)	18 (16.5)	36 (16.2)	54 (16.3)	36 (16.5)	89 (20.1)	125 (18.9)
F-VASI score									
n	109	221	330	109	222	331	218	443	661
Mean (STD)	0.999 (0.5942)	0.932 (0.5813)	0.954 (0.5855)	0.834 (0.5342)	0.898 (0.5256)	0.877 (0.5285)	0.917 (0.5698)	0.915 (0.5537)	0.915 (0.5586)
Median	0.740	0.690	0.700	0.600	0.700	0.680	0.690	0.700	0.700
Min, max	0.50, 2.70	0.40, 3.00	0.40, 3.00	0.50, 3.00	0.45, 3.00	0.45, 3.00	0.50, 3.00	0.40, 3.00	0.40, 3.00
F-BSA involvement (% of the total body)									
n	109	221	330	109	222	331	218	443	661
Mean (STD)	1.15 (0.710)	1.05 (0.692)	1.09 (0.698)	0.92 (0.582)	0.98 (0.571)	0.96 (0.575)	1.04 (0.658)	1.02 (0.635)	1.02 (0.642)
Median	0.90	0.80	0.80	0.70	0.80	0.80	0.80	0.80	0.80
Min, max	0.5, 3.0	0.5, 3.0	0.5, 3.0	0.5, 3.0	0.5, 3.0	0.5, 3.0	0.5, 3.0	0.5, 3.0	0.5, 3.0

Variable	Study INCB 18424-306			Study INCB 18424-307			Pooled Population		
	Vehicle Cream BID (N = 109)	Ruxolitinib 1.5% Cream BID (N = 221)	Total (N = 330)	Vehicle Cream BID (N = 109)	Ruxolitinib 1.5% Cream BID (N = 222)	Total (N = 331)	Vehicle Cream BID (N = 218)	Ruxolitinib 1.5% Cream BID (N = 443)	Total (N = 661)
Categorical summary of F-BSA involvement, n (%)									
< 1.5%	86 (78.9)	172 (77.8)	258 (78.2)	93 (85.3)	183 (82.4)	276 (83.4)	179 (82.1)	355 (80.1)	534 (80.8)
≥ 1.5%	23 (21.1)	49 (22.2)	72 (21.8)	16 (14.7)	39 (17.6)	55 (16.6)	39 (17.9)	88 (19.9)	127 (19.2)
T-VASI score									
n	109	221	330	109	222	331	218	443	661
Mean (STD)	6.424 (1.9241)	6.489 (2.0228)	6.467 (1.9881)	6.979 (2.1953)	6.790 (2.0435)	6.852 (2.0933)	6.702 (2.0781)	6.640 (2.0365)	6.660 (2.0490)
Median	6.250	6.380	6.340	7.290	7.125	7.170	6.780	6.770	6.770
Min, max	3.06, 10.00	3.01, 10.00	3.01, 10.00	3.10, 10.00	3.00, 10.00	3.00, 10.00	3.06, 10.00	3.00, 10.00	3.00, 10.00
T-BSA involvement (% of the total body)									
n	109	221	330	109	222	331	218	443	661
Mean (STD)	7.22 (2.008)	7.28 (2.033)	7.26 (2.022)	7.66 (2.040)	7.38 (2.025)	7.47 (2.031)	7.44 (2.031)	7.33 (2.027)	7.37 (2.028)
Median	7.30	7.70	7.60	8.30	7.70	8.00	7.70	7.70	7.70
Min, max	3.7, 10.0	3.2, 10.0	3.2, 10.0	3.6, 10.1	3.5, 10.0	3.5, 10.1	3.6, 10.1	3.2, 10.0	3.2, 10.1
Vitiligo in genital area, n (%)									
No	48 (44.0)	99 (44.8)	147 (44.5)	53 (48.6)	107 (48.2)	160 (48.3)	101 (46.3)	206 (46.5)	307 (46.4)
Yes	61 (56.0)	122 (55.2)	183 (55.5)	56 (51.4)	115 (51.8)	171 (51.7)	117 (53.7)	237 (53.5)	354 (53.6)
Prior therapy given for vitiligo, n (%)									
No	48 (44.0)	90 (40.7)	138 (41.8)	34 (31.2)	81 (36.5)	115 (34.7)	82 (37.6)	171 (38.6)	253 (38.3)
Yes	61 (56.0)	131 (59.3)	192 (58.2)	75 (68.8)	141 (63.5)	216 (65.3)	136 (62.4)	272 (61.4)	408 (61.7)
Topical corticosteroids	28 (25.7)	67 (30.3)	95 (28.8)	28 (25.7)	65 (29.3)	93 (28.1)	56 (25.7)	132 (29.8)	188 (28.4)
Vit D derivatives	2 (1.8)	4 (1.8)	6 (1.8)	1 (0.9)	0	1 (0.3)	3 (1.4)	4 (0.9)	7 (1.1)
Topical calcineurin inhibitors	31 (28.4)	72 (32.6)	103 (31.2)	37 (33.9)	74 (33.3)	111 (33.5)	68 (31.2)	146 (33.0)	214 (32.4)
Phototherapy	31 (28.4)	61 (27.6)	92 (27.9)	45 (41.3)	76 (34.2)	121 (36.6)	76 (34.9)	137 (30.9)	213 (32.2)
NB-UVB	20 (18.3)	41 (18.6)	61 (18.5)	26 (23.9)	52 (23.4)	78 (23.6)	46 (21.1)	93 (21.0)	139 (21.0)
Others									
PUVA	4 (3.7)	8 (3.6)	12 (3.6)	8 (7.3)	14 (6.3)	22 (6.6)	12 (5.5)	22 (5.0)	34 (5.1)
Excimer laser	8 (7.3)	18 (8.1)	26 (7.9)	14 (12.8)	16 (7.2)	30 (9.1)	22 (10.1)	34 (7.7)	56 (8.5)
Other	2 (1.8)	1 (0.5)	3 (0.9)	1 (0.9)	5 (2.3)	6 (1.8)	3 (1.4)	6 (1.4)	9 (1.4)

Variable	Study INCB 18424-306			Study INCB 18424-307			Pooled Population		
	Vehicle Cream BID (N = 109)	Ruxolitinib 1.5% Cream BID (N = 221)	Total (N = 330)	Vehicle Cream BID (N = 109)	Ruxolitinib 1.5% Cream BID (N = 222)	Total (N = 331)	Vehicle Cream BID (N = 218)	Ruxolitinib 1.5% Cream BID (N = 443)	Total (N = 661)
Prior therapy given for vitiligo, n (%) (continued)									
Surgical techniques	0	0	0	0	1 (0.5)	1 (0.3)	0	1 (0.2)	1 (0.2)
Other therapy									
Oral steroid	2 (1.8)	5 (2.3)	7 (2.1)	0	5 (2.3)	5 (1.5)	2 (0.9)	10 (2.3)	12 (1.8)
Other	7 (6.4)	18 (8.1)	25 (7.6)	13 (11.9)	23 (10.4)	36 (10.9)	20 (9.2)	41 (9.3)	61 (9.2)
History of acne vulgaris, n (%)									
No	84 (77.1)	180 (81.4)	264 (80.0)	87 (79.8)	167 (75.2)	254 (76.7)	171 (78.4)	347 (78.3)	518 (78.4)
Yes	25 (22.9)	41 (18.6)	66 (20.0)	22 (20.2)	55 (24.8)	77 (23.3)	47 (21.6)	96 (21.7)	143 (21.6)
Currently have acne vulgaris on the face, n (%)									
No	102 (93.6)	204 (92.3)	306 (92.7)	105 (96.3)	204 (91.9)	309 (93.4)	207 (95.0)	408 (92.1)	615 (93.0)
Yes	7 (6.4)	17 (7.7)	24 (7.3)	4 (3.7)	18 (8.1)	22 (6.6)	11 (5.0)	35 (7.9)	46 (7.0)

Note: Data from participants enrolled at Site 710 in Study INCB 18424-307 were excluded.

Study drug exposure

Duration of treatment in days, the median weight of study drug applied in grams, and the median total weight of study drug applied in grams during the double-blind period were numerically comparable between the two studies and between the vehicle and ruxolitinib groups (Table 20).

Table 20: Study drug exposure during the double-blind period (studies INCB 18424-306 and -307)

	Study INCB 18424-306			**Study INCB 18424-307**		
	Vehicle BID (n = 109)	**Ruxolitinib 1.5% BID (n = 221)**	**Total (n = 330)**	**Vehicle BID (n = 115)**	**Ruxolitinib 1.5% BID (n = 228)**	**Total (n = 343)**
Duration of treatment during DB period (days)						
Mean (sd)	152.7 (42.6)	160.0 (32.3)	**157.6 (36.1)**	160.3 (35.0)	157.9 (37.5)	**158.7 (36.6)**
Median (min – max)	168.0 (1.0 - 200.0)	168.0 (1.0 - 237.0)	**168.0 (1.0 - 237.0)**	168.0 (4.0 - 248.0)	168.0 (1.0 - 220.0)	**168.0 (1.0 - 248.0)**
Average weight of study drug applied during DB period (grams)						
Mean (sd)	9.3 (32.2)	5.8 (16.6)	**7.0 (23.0)**	5. 1 (6.3)	8.9 (31.4)	**7.6 (25.9)**
Median (min – max)	3.5 (0.3 - 236.3)	4.2 (0.4 - 237.1)	**4.0 (0.3 - 237.1)**	4.4 (0.5 - 59.3)	4.0 (0.4 - 237.0)	**4.2 (0.4 - 237.0)**
Total weight of study drug applied during DB period (grams)						
Mean (sd)	597.0 (349.5)	691.1 (370.0)	**659.9 (365.5)**	685.6 (360.8	674.2 (396.1)	**678.0 (384.1)**
Median (min - max)	535.0 (23.0 - 1418.4)	632.5 (61.0 - 1434.6)	**607.0 (23.0 - 1434.6)**	674.6 (77.1 - 1517.1)	579.0 (11.2 - 1442.7)	**618.8 (11.2 - 1517.1)**

Compliance to application of ruxolitinib / vehicle was high for both groups in both studies (Table 21).

Table 21: Compliance to application of vehicle / ruxolitinib BID (studies INCB 18424-306 and -307)

	Study NCBI 18424-306		**Study NCBI 18424-307**	
	Vehicle BID	**Ruxolitinib 1.5% BID**	**Vehicle BID**	**Ruxolitinib 1.5% BID**
0 – 60%	0	0	0	0
> 60 - ≤ 80%	1 (0.9%)	6 (2.7%)	3 (2.6%)	3 (1.3%)
> 80%	108 (99.1%)	215 (97.3%)	112 (97.4%)	225 (98.7%)

Concomitant medication

Concomitant medication was taken by 74% (in study INCB 18424-306) and 72% (in study INCB 18424-307) of the participants during the double-blind period, without notable differences between the vehicle and ruxolitinib groups. By WHO drug class, most commonly used medications were thyroid hormones (19.1% in study 306 and 14.6% in study 307), priopionic acids derivates (14.8% and 9.6%), (multi)vitamins (7.9% and 7.9%). HMG Co-A reductase inhibitors (8.2% and 6.4%), and anilides (7.3% and 12.8%). Most commonly used medications by WHO term were ibuprofen (10.9% in study 306 and 7.3% in study 307), levothyroxine (sodium) (17.9% and 14.3%), and paracetamol (5.2% and 9.3%). These concomitant medications were in line with the protocol. Data from study site 710 are still included in this section.

- **Numbers analysed**

Data from the intention to treat (ITT) population constituted the primary analysis set. It consisted of n = 109 and n = 221 (100%) participants in the vehicle and ruxolitinib groups respectively for study 306, and n = 109 (100%) and n = 222 (100%) respectively for study 307 (numbers without study site 710). The per protocol population included randomised participants who were considered to be sufficiently compliant with the protocol. For study 306 it included the same numbers as the ITT population for both treatment groups study (n = 221 (100%) and n = 109 (100%); for study 307

these numbers were lower, i.e., 99/109 (91%) and 203/222 (91%) respectively (numbers without study site 710).

For study 306, 90 participants in the vehicle group entered the treatment extension (TE) phase from whom 82 (91%) completed the 52-weeks of treatment; for ruxolitinib 193 participants entered the TE phase and 174 (90%) completed treatment. For study 307, 102 participants in the vehicle group entered the TE phase from whom 81 (83%) completed the 52-weeks of treatment; for ruxolitinib 206 participants entered the TE phase and 182 (92%) completed treatment.

- **Outcomes and estimation**

Primary outcome

In both studies, the primary endpoint was met. The proportion of participants reaching F-VASI75 at 24 weeks (primary outcome), was significantly higher in the ruxolitinib 1.5% BID group versus the vehicle BID group in both pivotal studies. In the pooled data of both studies, the average proportion of responders in the ruxolitinib group was 31% compared to 9.6% in the vehicle group with a response rate difference of 21% ($p < 0.0001$) (Table 22). Pre-planned sensitivity analyses using NRI and using LOCF yielded comparable results; post hoc analyses of the primary endpoint including data from site 710 yielded similar results as well. As early as week 12, a treatment effect of ruxolitinib in F-VASI75 appeared, and the proportions of participants reaching F-VASI75 continued to increase until weeks 42/46 and then the effect seems to flatten (Figure 17).

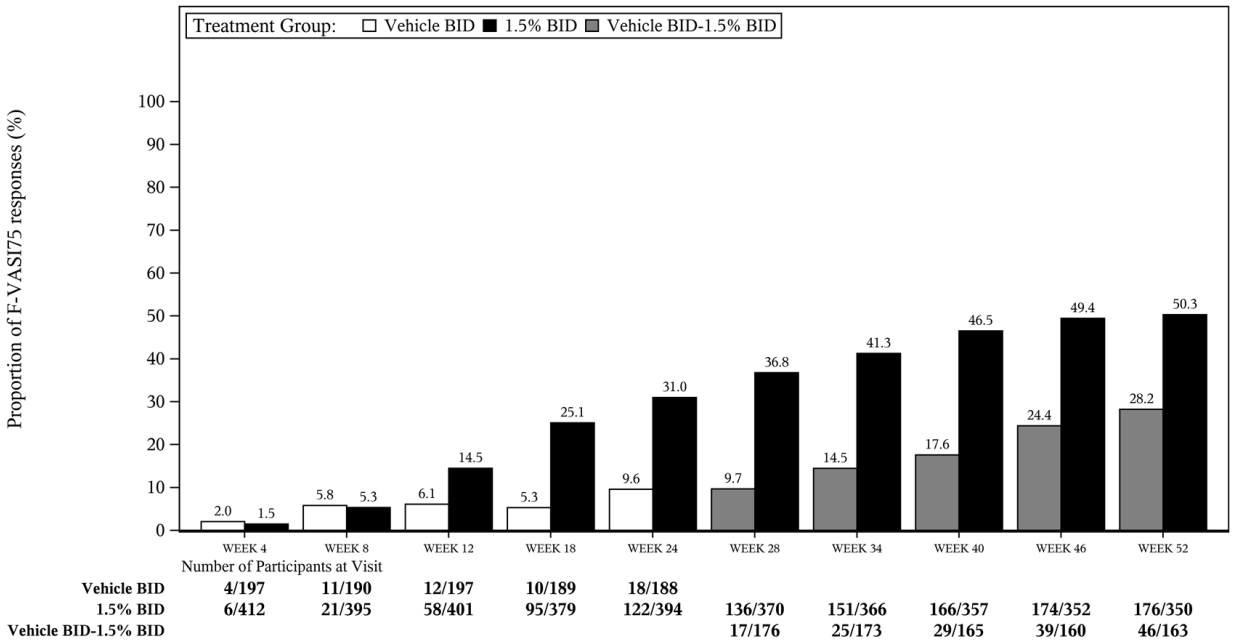
For details on the results in adolescents, it is referred to the section on subgroup analyses.

Table 22: Results for the F-VASI75 at week 24 (studies INCB 18424-306 and -307)

	Study INCB 18424-306		Study INCB 18424-307		Pooled Analysis	
Endpoint	**Vehicle Cream BID (N = 109)**	**Ruxolitinib 1.5% Cream BID (N = 221)**	**Vehicle Cream BID (N = 109)**	**Ruxolitinib 1.5% Cream BID (N = 222)**	**Vehicle Cream BID (N = 218)**	**Ruxolitinib 1.5% Cream BID (N = 443)**
Multiple imputation[a]						
Estimated F-VASI75 response rate (%) (SE)	7.4 (2.65)	29.8 (3.21)	11.4 (3.20)	30.9 (3.27)	9.6 (2.17)	30.7 (2.29)
Response rate difference (SE)[b]	—	22.3 (4.15)	—	19.5 (4.56)	—	21.1 (3.18)
95% CI	—	(14.214, 30.471)	—	(10.537, 28.420)	—	(14.853, 27.342)
Active treatment vs vehicle						
Odds ratio (95% CI)[c]	—	5.28 (2.341, 11.903)	—	3.45 (1.737, 6.835)	—	4.17 (2.434, 7.142)
p-value	—	< 0.0001	—	0.0004	—	< 0.0001
NRI[d]						
F-VASI75 response rate (%) (SE)	6.4 (2.35)	27.1 (2.99)	10.1 (2.89)	27.9 (3.01)	8.3 (1.86)	27.5 (2.12)
Response rate difference (SE)[e]	—	20.7 (3.80)	—	17.8 (4.17)	—	19.3 (2.82)
Active treatment vs vehicle						
Odds ratio (95% CI)[c]	—	5.43 (2.353, 14.655)	—	3.42 (1.683,7.546)	—	4.21 (2.461, 7.570)
p-value	—	< 0.0001	—	0.0002	—	< 0.0001
LOCF[f]						
Estimated F-VASI75 response rate (%) (SE)	7.0 (2.55)	28.5 (3.09)	11.4 (3.10)	29.4 (3.14)	9.3 (2.03)	28.9 (2.20)
Response rate difference (SE)[e]	—	21.5 (4.00)	—	18.0 (4.41)	—	19.7 (2.99)
Active treatment vs vehicle						
Odds ratio (95% CI)[c]	—	5.25 (2.272, 14.189)	—	3.18 (1.593, 6.833)	—	3.96 (2.334, 7.032)
p-value	—	< 0.0001	—	0.0004	—	< 0.0001

Note: Data from study site 710 were excluded.

Figure 17: Proportions of participants reaching F-VASI75 during the double-blind period (ITT Population); pooled data from studies INCB 18424-306 and -307



Note: Data from study site 710 were excluded.

Key secondary outcomes

The findings for the key secondary outcomes were in line with the primary outcome: all met statistical significance in both studies, favoring ruxolitinib 1.5% BID over vehicle BID at 24 weeks of treatment. The treatment effects (ruxolitinib versus vehicle) were numerically quite similar for the two pivotal studies (Table 23). Presented data are updated, excluding those from participants from study site 710.

In the pooled results, 51.7% of the participants in the ruxolitinib 1.5% BID group and 19.6% in the vehicle group achieved at least 50% repigmentation after 24 weeks of treatment (**F-VASI50**), with a response rate difference of 32.2% (p<0.0001) (Table 23, Figure 18).

Almost complete repigmentation (**F-VASI90**) was reached in 16% in the ruxolitinib group versus 1.9% in the vehicle group after 24 weeks of treatment, with a response rate difference of 14.2% (p < 0.0001) (Table 23, Figure 19).

Proportions of participants reaching at least 50% repigmentation of the total body after 24 weeks (**T-VASI50**) were 21.9% in participants on ruxolitinib versus 5.8% of the participants in the vehicle group, with a response rate difference of 16.1% (p<0.0001) (Table 23, Figure 20).

The proportion of patients who scored their vitiligo (**VNS**) as 'a lot less noticeable' or 'no longer noticeable' after 24 weeks was larger in the group of participants treated with ruxolitinib (22.5%) as compared to those treated with vehicle (4.2%), with a treatment effect of 18.3% (p<0.0001) (Table 23, Figure 21).

The percent change in **F-BSA** at week 24 was significantly higher in the ruxolitinib 1.5% BID group versus vehicle BID (LSM difference -20.0 (sd 3.17)) with a 95% CI of -26.22 - -13.77 (p<0.0001) (Table 23, Figure 22).

Sensitivity analysis yielded comparable results as compared to the primary analyses of the key secondary outcomes; post hoc analyses *including* data from site 710 yielded similar results as well.

Table 23: Summary of results for the key secondary endpoints

Endpoint	Study INCB 18424-306		Study INCB 18424-307		Pooled Analysis	
	Vehicle BID (N = 109)	**Ruxolitinib 1.5% BID (N = 221)**	**Vehicle BID (N = 109)**	**Ruxolitinib 1.5% BID (N = 222)**	**Vehicle BID (N = 218)**	**Ruxolitinib 1.5% BID (N = 443)**
Estimated F-VASI50 response rate (%) (SE) at Week 24	16.9 (3.89)	51.2 (3.46)	20.9 (4.06)	51.4 (3.50)	19.6 (2.89)	51.7 (2.46)
Response rate difference (SE)[a]	—	34.2 (5.18)	—	30.6 (5.36)	—	32.2 (3.83)
95% CI	—	(24.092, 44.408)	—	(20.048, 41.061)	—	(24.646, 39.672)
Active treatment vs vehicle						
Odds ratio (95% CI)[b]	—	5.18 (2.831, 9.482)	—	3.99 (2.296, 6.949)	—	4.40 (2.918, 6.647)
p-value	—	< 0.0001	—	< 0.0001	—	< 0.0001
Estimated F-VASI90 response rate (%) (SE) at Week 24	2.2 (1.51)	15.3 (2.50)	1.3 (1.25)	16.3 (2.62)	1.9 (1.01)	16.0 (1.83)
Response rate difference (SE)[a]	—	13.2 (2.89)	—	15.0 (2.92)	—	14.2 (2.09)
95% CI	—	(7.497, 18.839)	—	(9.250, 20.702)	—	(10.080, 18.274)
Active treatment vs vehicle						
Odds ratio (95% CI)[b]	—	8.49 (1.997, 36.048)	—	15.29 (2.150, 108.739)	—	10.33 (3.310, 32.210)
p-value	—	0.0038	—	0.0065	—	< 0.0001
Estimated T-VASI50 response rate (%) (SE) at Week 24	5.1 (2.34)	20.6 (2.76)	6.8 (2.50)	23.9 (2.97)	5.8 (1.64)	21.9 (2.04)
Response rate difference (SE)[a]	—	15.5 (3.63)	—	17.1 (3.87)	—	16.1 (2.62)
95% CI	—	(8.339, 22.592)	—	(9.538, 24.721)	—	(10.910, 21.200)
Active treatment vs vehicle						
Odds ratio (95% CI)[b]	—	4.93 (1.795, 13.566)	—	4.29 (1.865, 9.853)	—	4.55 (2.419, 8.577)
p-value	—	0.0020	—	0.0006	—	< 0.0001
Estimated VNS scores of 4 or 5 response rate (%) (SE) at Week 24	3.3 (1.85)	24.5 (3.03)	4.9 (2.17)	20.5 (2.85)	4.2 (1.45)	22.5 (2.09)
Response rate difference (SE)[a]	—	21.2 (3.54)	—	15.5 (3.58)	—	18.3 (2.53)
95% CI	—	(14.271, 28.143)	—	(8.515, 22.561)	—	(13.317, 23.246)
Active treatment vs vehicle						
Odds ratio (95% CI)[b]	—	9.53 (2.900, 31.290)	—	4.86 (1.851, 12.755)	—	6.52 (3.114, 13.667)
p-value	—	0.0002	—	0.0013	—	< 0.0001
Percent change from baseline in F-BSA score at Week 24						
ANCOVA[c]						
LSM (SE)	−9.5 (3.25)	−28.9 (2.22)	−7.0 (3.82)	−26.4 (2.57)	−7.9 (2.63)	−27.8 (1.75)
95% CI	(−15.90, −3.17)	(−33.23, −24.53)	(−14.45, 0.53)	(−31.45, −21.39)	(−13.02, −2.69)	(−31.29, −24.41)
Active treatment vs vehicle						
LSM difference (SE)	—	−19.3 (3.93)	—	−19.5 (4.59)	—	−20.0 (3.17)
95% CI	—	(−27.05, −11.64)	—	(−28.46, −10.45)	—	(−26.22, −13.77)
Between-group p-value	—	< 0.0001	—	< 0.0001	—	< 0.0001

Note: Multiple imputation: missing VASI scores and F-BSA were imputed by fully conditional specification. The multiple imputation method uses treatment and observed stratification factors as predicators.

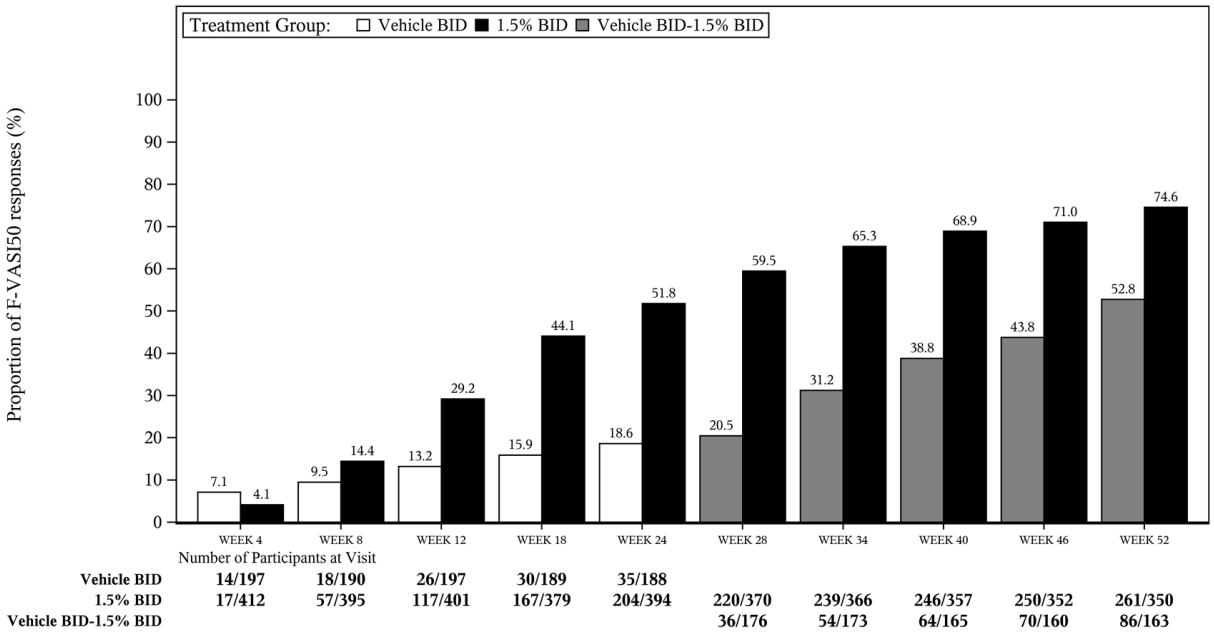
Note: P-values from exact logistic regression: [response at Week 24 = treatment + stratification factors (Fitzpatrick skin type I and II vs Fitzpatrick skin type III, IV, V, and VI, Region North America/Europe)].
Note: Data from study site 710 were excluded.

a p < 0.0001, ruxolitinib vs vehicle.

b p < 0.01 ruxolitinib vs vehicle.

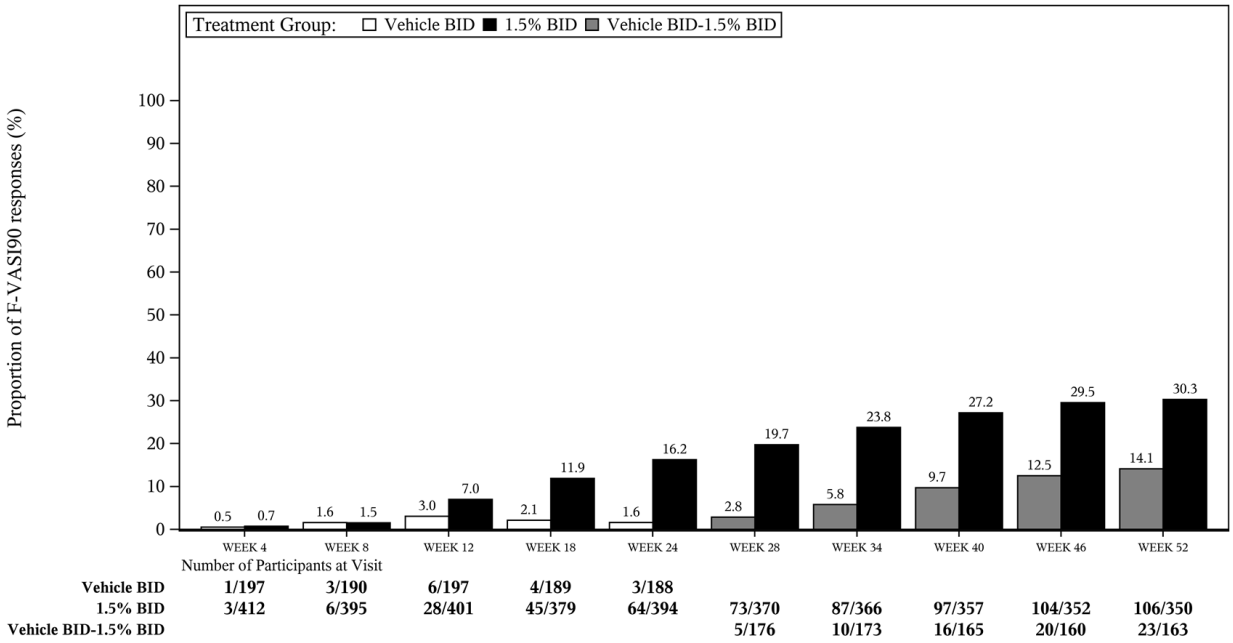
c p = 0.0159 ruxolitinib vs vehicle.

Figure 18: Proportions of participants Reaching F-VASI50 during the double-blind period (ITT Population); pooled data from studies INCB 18424- 306 and -307



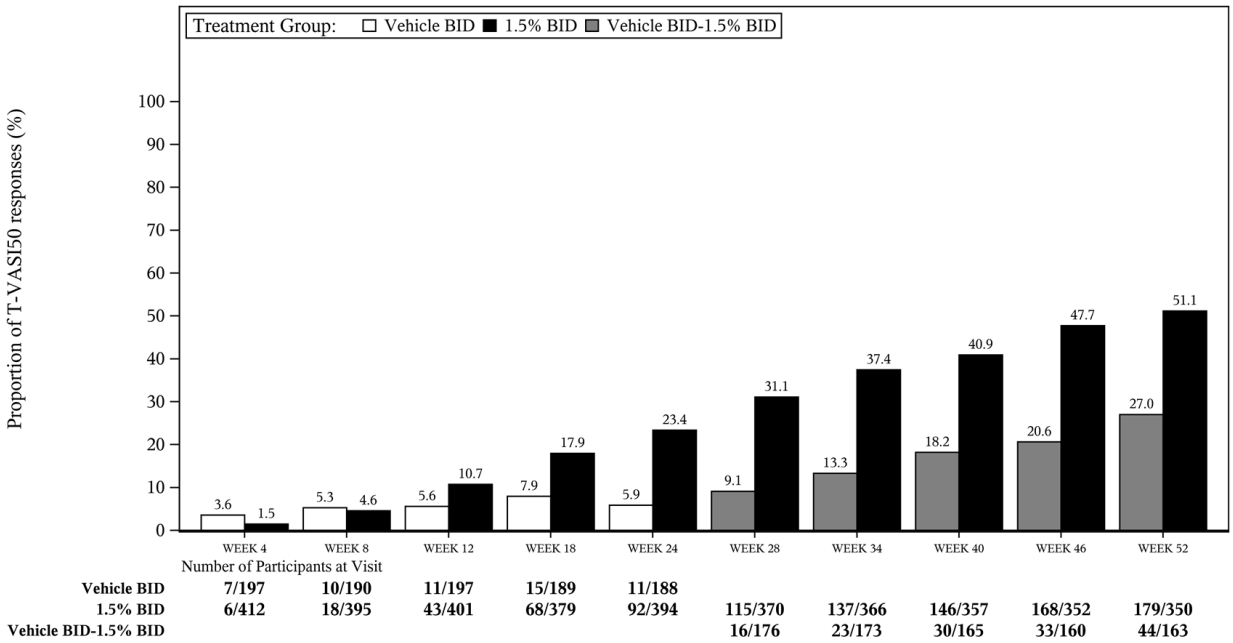
Note: Data from study site 710 were excluded.

Figure 19: Proportions of participants reaching F-VASI90 during the double-blind period (ITT Population); pooled data from studies INCB 18424- 306 and -307



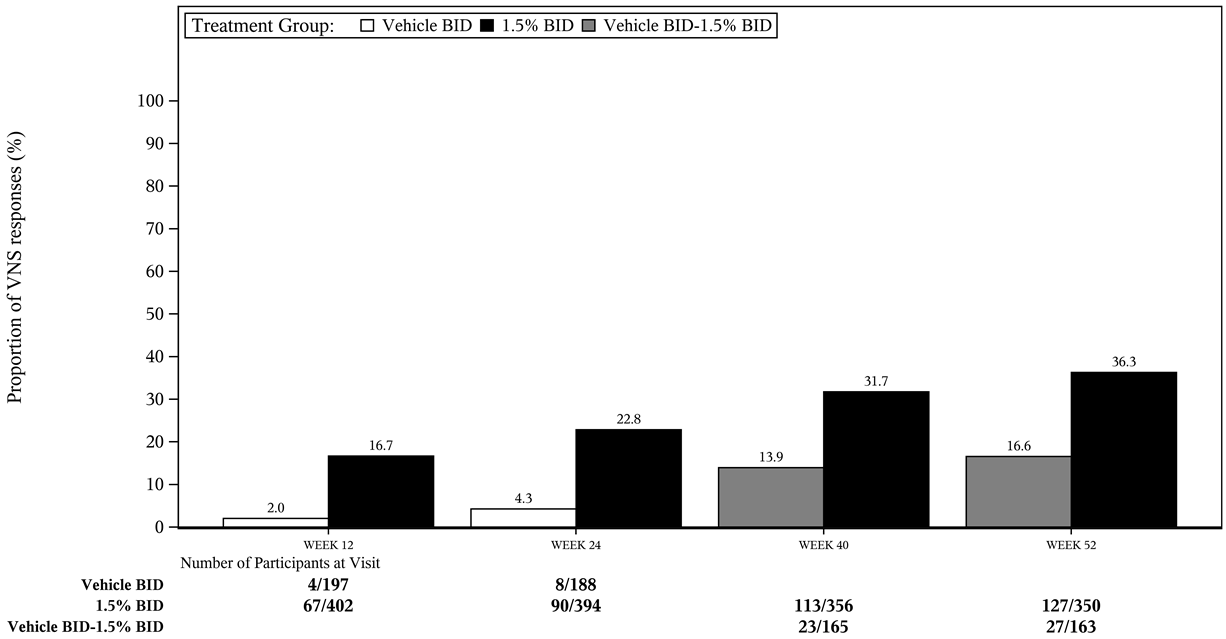
Note: Data from study site 710 were excluded.

Figure 20: Proportions of participants reaching T-VASI50 during the double-blind period (ITT Population); pooled data from studies INCB 18424- 306 and -307



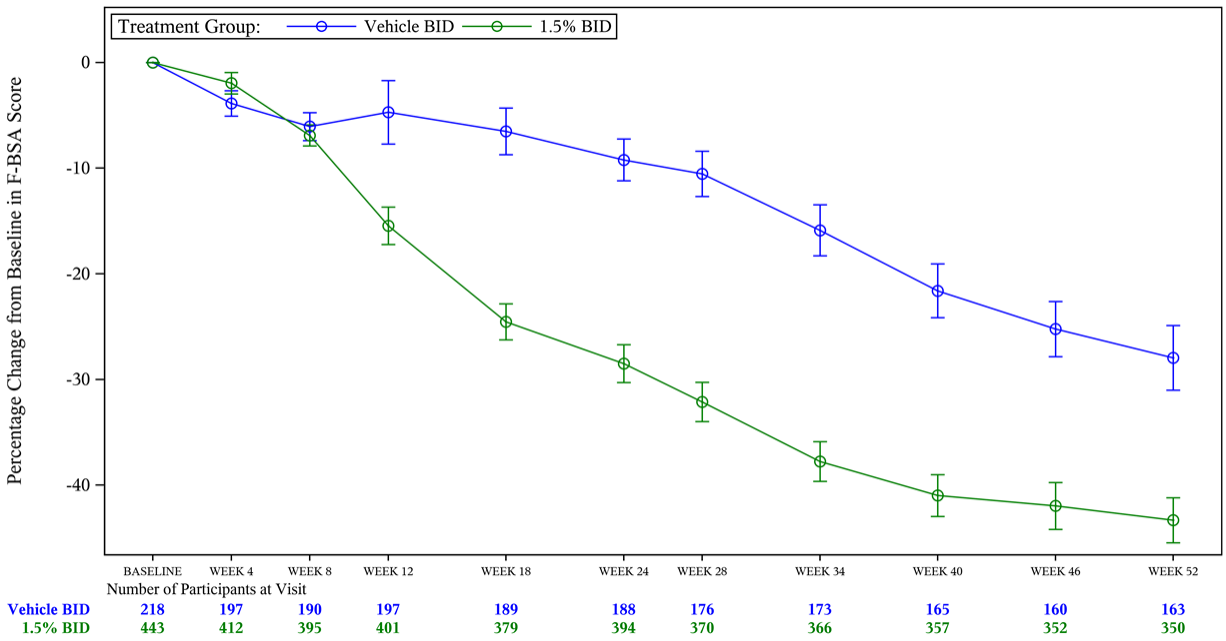
Note: Data from study site 710 were excluded.

Figure 21: Proportions of participants reaching VNS score 4 or 5 during the double-blind period (ITT Population); pooled data from studies INCB 18424-306 and -307



Note: Data from study site 710 were excluded.

Figure 22: Mean (± SE) percent change from baseline in F-BSA Score during the double blind period (ITT population); pooled data from studies INCB 18424-306 and -307

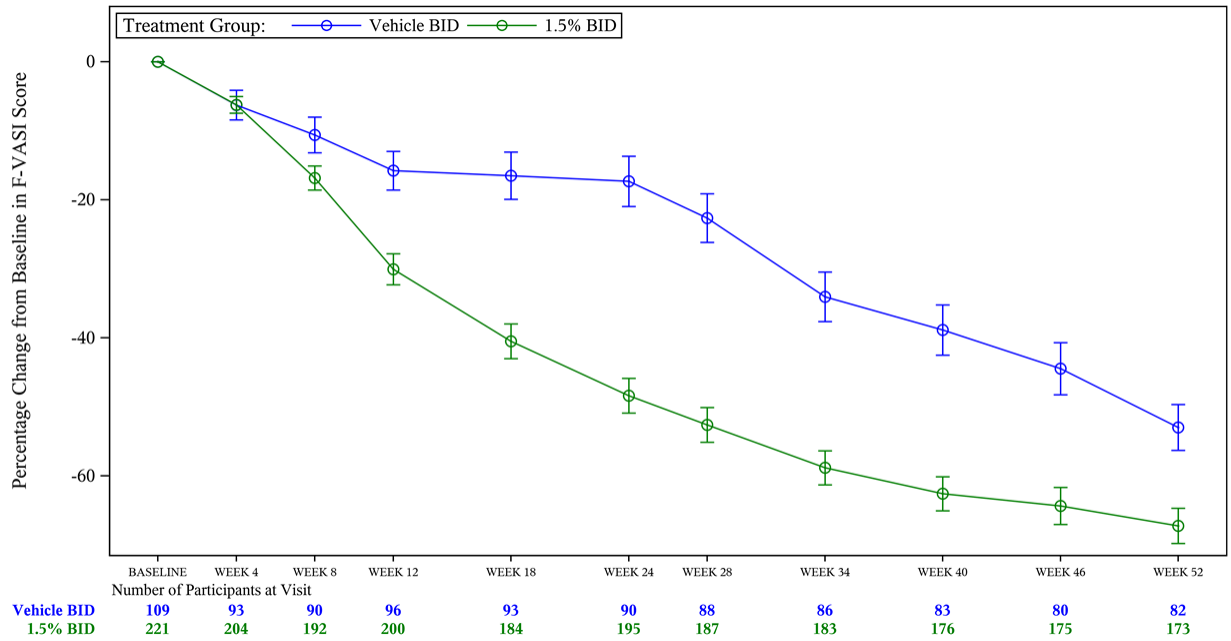


Note 1: Data from participants enrolled at Site 710 in Study INCB 18424-307 were excluded.
Note 2: All participants applied ruxolitinib 1.5% cream BID after Week 24.

Other secondary outcomes

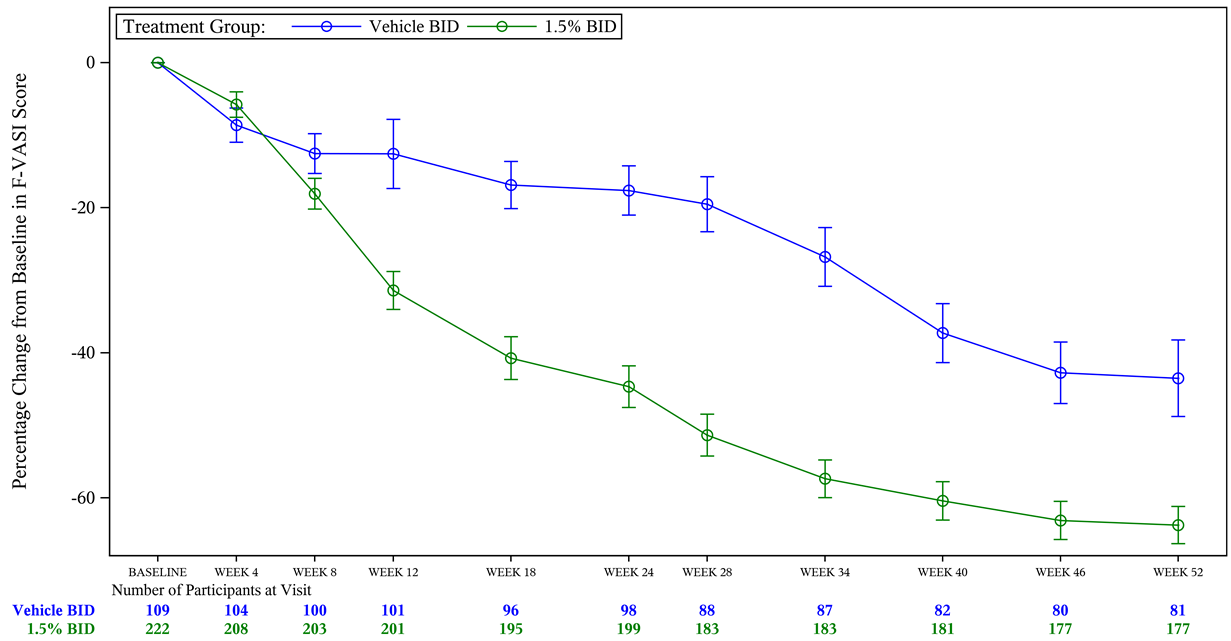
Proportions of patients reaching the F-VASI75, F-VASI50, F-VASI90, T-VASI50, VNS score 4 or 5, and **changes in F-BSA, F-VASI, and T-VASI** during both the double-blind 24 weeks period as well as during the treatment extension phase up to 52 weeks are presented in the below figures. Generally, a differentiation between the treatment responses for the vehicle and ruxolitinib groups emerges at about 12 weeks, and the responses further improve until week 52. A trend was suggested towards flattening of the response after week 40/46 especially for the facial endpoints (F-VASI). Those starting ruxolitinib after initial treatment with vehicle showed an expected catch up in treatment responses.

Figure 23: Mean (SE) percent change from baseline in F-VASI score of study INCB 18424- 306



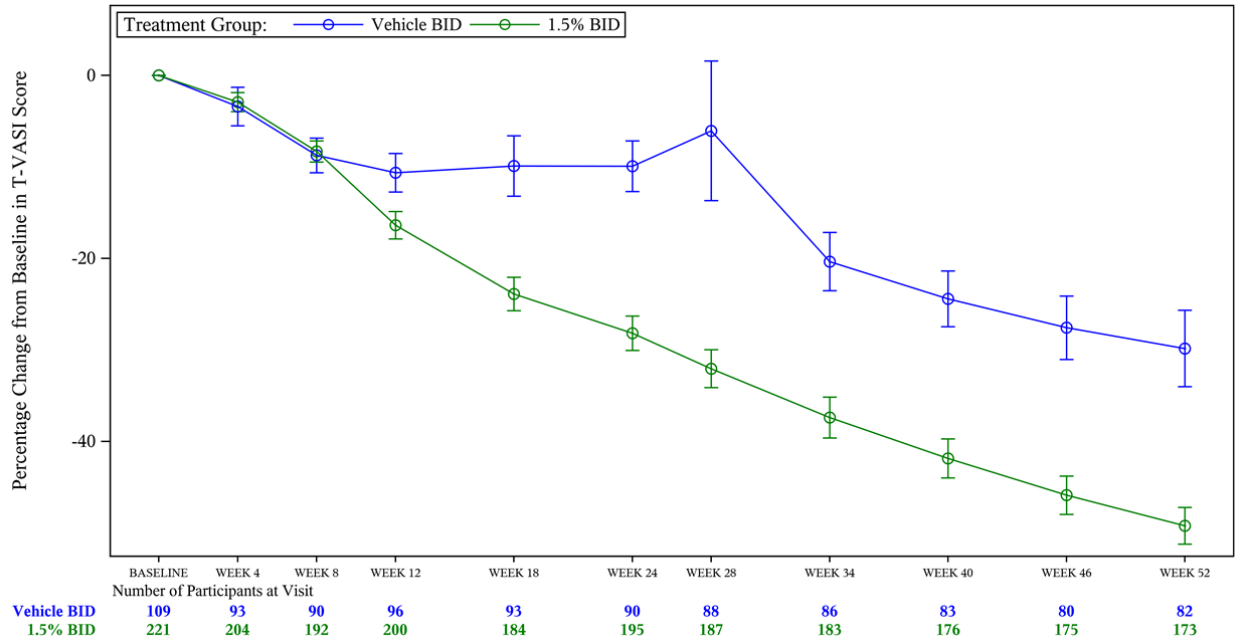
Note: Data from study site 710 were excluded.

Figure 24: Mean (SE) percent change from baseline in F-VASI score of study INCB 18424-307



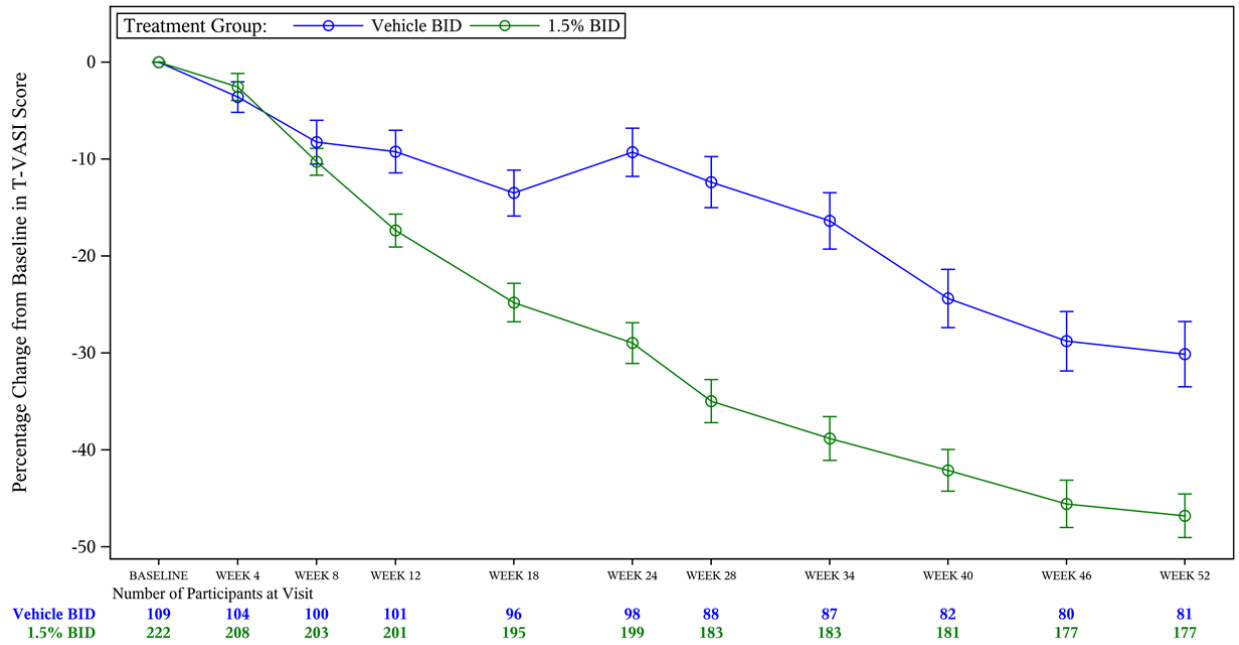
Note: Data from study site 710 were excluded.

Figure 25: Mean (SE) percent change from baseline in T-VASI score of study INCB 18424-306



Note: Data from study site 710 were excluded.

Figure 26: Mean (SE) percent change from baseline in T-VASI score of study INCB 18424-307



Note: Data from study site 710 were excluded.

These findings were confirmed by the **shift summary data** on the maintenance of response for the **F-VASI** and the **T-VASI** as calculated with the completed dataset (see Table 24 and Table 25). For the F-VASI less than 15% of the participants *deteriorated* one or more categories at week 52 compared to week 24; between 50-68% of the participants *improved* at least one category between week 24 and 52. For the T-VASI less than 26% of the participants *deteriorated* one or more categories at week 52

compared to week 24; between 35-56% of the participants *improved* at least one category between week 24 and 52.

Table 24: Shift summary of maintenance of response on the F-VASI over time (pooled data)

Response at Week 24		Response at Week 52					
Value	n (%)	< F-VASI25	F-VASI25 to < F-VASI50	F-VASI50 to < F-VASI75	F-VASI75 to < F-VASI90	F-VASI90	Missing
Pooled analysis							
< F-VASI25	131 (33.2)	47 (35.9)	21 (16.0)	30 (22.9)	7 (5.3)	8 (6.1)	18 (13.7)
F-VASI25 to < F-VASI50	59 (15.0)	0	9 (15.3)	21 (35.6)	12 (20.3)	4 (6.8)	13 (22.0)
F-VASI50 to < F-VASI75	82 (20.8)	1 (1.2)	8 (9.8)	26 (31.7)	22 (26.8)	19 (23.2)	6 (7.3)
F-VASI75 to < F-VASI90	58 (14.7)	0	2 (3.4)	7 (12.1)	22 (37.9)	26 (44.8)	1 (1.7)
F-VASI90	64 (16.2)	1 (1.6)	0	1 (1.6)	7 (10.9)	49 (76.6)	6 (9.4)

Note: Data from participants enrolled at Site 710 in Study INCB 18424-307 were excluded.

Table 25: Shift summary of maintenance of response on the T-VASI over time (pooled data)

Response at Week 24		Response at Week 52					
Value	n (%)	< T-VASI 25	T-VASI25 to < T-VASI50	T-VASI50 to < T-VASI75	T-VASI75 to < T-VASI90	T-VASI90	Missing
< T-VASI25	198 (50.3)	75 (37.9)	58 (29.3)	33 (16.7)	6 (3.0)	1 (0.5)	25 (12.6)
T-VASI25 to < T-VASI50	104 (26.4)	4 (3.8)	29 (27.9)	46 (44.2)	11 (10.6)	1 (1.0)	13 (12.5)
T-VASI50 to < T-VASI75	66 (16.8)	0	3 (4.5)	24 (36.4)	28 (42.4)	5 (7.6)	6 (9.1)
T-VASI75 to < T-VASI90	23 (5.8)	1 (4.3)	1 (4.3)	4 (17.4)	9 (39.1)	8 (34.8)	0
T-VASI90	3 (0.8)	0	0	0	0	3 (100.0)	0

Note: Data from participants enrolled at Site 710 in Study INCB 18424-307 were excluded.

Updated results for the other secondary endpoints physician and patient assessments of improvement of vitiligo (**F-PhGVA, T-PhGVA, F-PaGIC-V, T-PaGIC-V, and Color-matching question**) until week 52 are presented in Table 26. These endpoints were not included in the multiple-testing procedure; thus p-values are nominal. Overall, improvements were seen at week 24 compared to baseline, with some further improvement until week 52; a catch up was observed for those initially assigned to vehicle starting ruxolitinib after 24 weeks.

Table 26: Physician and patient assessments of improvement of vitiligo at weeks 12, 24, 40, and 52 for studies INCB 18424-306 and –307 (ITT population)

	Study INCB 18424-306		Study INCB 18424-307	
Endpoint Timepoint, n/N (%)	Vehicle BID (N = 109)	Ruxolitinib 1.5% BID (N = 221)	Vehicle BID (N = 109)	Ruxolitinib 1.5% BID (N = 222)
F-PhGVA score of clear (0) or almost clear (1)				
Week 12	12/95 (12.6)	35/199 (17.6)	6/97 (6.2)	39/197 (19.8)
Week 24	11/90 (12.2)	52/193 (26.9)	6/98 (6.1)	67/194 (34.5)
p-value	—	0.0060	—	< 0.0001
Week 40	20/80 (25.0)	68/176 (38.6)	15/81 (18.5)	75/179 (41.9)
Week 52	22/82 (26.8)	75/172 (43.6)	23/81 (28.4)	74/176 (42.0)
T-PhGVA score of clear (0) or almost clear (1)				
Week 12	4/95 (4.2)	6/199 (3.0)	3/97 (3.1)	9/197 (4.6)
Week 24	3/90 (3.3)	13/193 (6.7)	0/98 (0)	18/194 (9.3)
p-value	—	0.3765	—	0.0006
Week 40	5/80 (6.3)	12/176 (6.8)	1/81 (1.2)	22/179 (12.3)
Week 52	9/82 (11.0)	18/172 (10.5)	5/81 (6.2)	19/176 (10.8)
F-PaGIC-V score of very much improved (1) or much improved (2)				
Week 12	5/96 (5.2)	59/200 (29.5)	8/100 (8.0)	65/202 (32.2)
Week 24	7/90 (7.8)	88/195 (45.1)	8/98 (8.2)	80/199 (40.2)

Endpoint Timepoint, n/N (%)	Study INCB 18424-306		Study INCB 18424-307	
	Vehicle BID (N = 109)	Ruxolitinib 1.5% BID (N = 221)	Vehicle BID (N = 109)	Ruxolitinib 1.5% BID (N = 222)
p-value	—	< 0.0001	—	< 0.0001
Week 40	25/83 (30.1)	92/176 (52.3)	29/82 (35.4)	87/180 (48.3)
Week 52	31/82 (37.8)	96/173 (55.5)	31/81 (38.3)	90/177 (50.8)
T-PaGIC-V score of very much improved (1) or much improved (2)				
Week 12	5/96 (5.2)	41/200 (20.5)	7/101 (6.9)	42/202 (20.8)
Week 24	3/90 (3.3)	59/195(30.3)	6/98 (6.1)	59/199 (29.6)
p-value	—	< 0.0001	—	< 0.0001
Week 40	13/83 (15.7)	71/176 (40.3)	20/82 (24.4)	66/180 (36.7)
Week 52	22/82 (26.8)	81/173 (46.8)	17/81 (21.0)	71/177 (40.1)
Color-matching question score of excellent (1), very good (2), or good (3)				
Week 12	47/96 (49.0)	122/200 (61.0)	44/101 (43.6)	129/202 (63.9)
Week 24	39/90 (43.3)	150/195 (76.9)	28/98 (28.6)	140/199 (70.4)
p-value	—	< 0.0001	—	< 0.0001
Week 40	56/83 (67.5)	145/176 (82.4)	50/82 (61.0)	133/180 (73.9)
Week 52	55/82 (67.1)	138/173 (79.8)	52/81 (64.2)	135/177 (76.3)

Note: Data from study site 710 were excluded.

No changes in the Dermatology Life Quality Index **(DLQI)** and the Children's Dermatology Life Quality Index **(CDLQI)** were observed over time. Updated scores at the **VitiQol**, (subscales of the) Treatment Satisfaction Questionnaire for Medication **(TSQM),** the **WHO-5,** and the (subscales of the) Anxiety and Depression Scale **(HADS)** are presented in Table 27. Except for better treatment satisfaction in the ruxolitinib group than the vehicle group (TSQM subscales) no differences were seen between the two groups over time.

Table 27: Summary of other secondary endpoints for studies INCB 18424-306 and -307 (ITT population) (updated, including week 40-52 data)

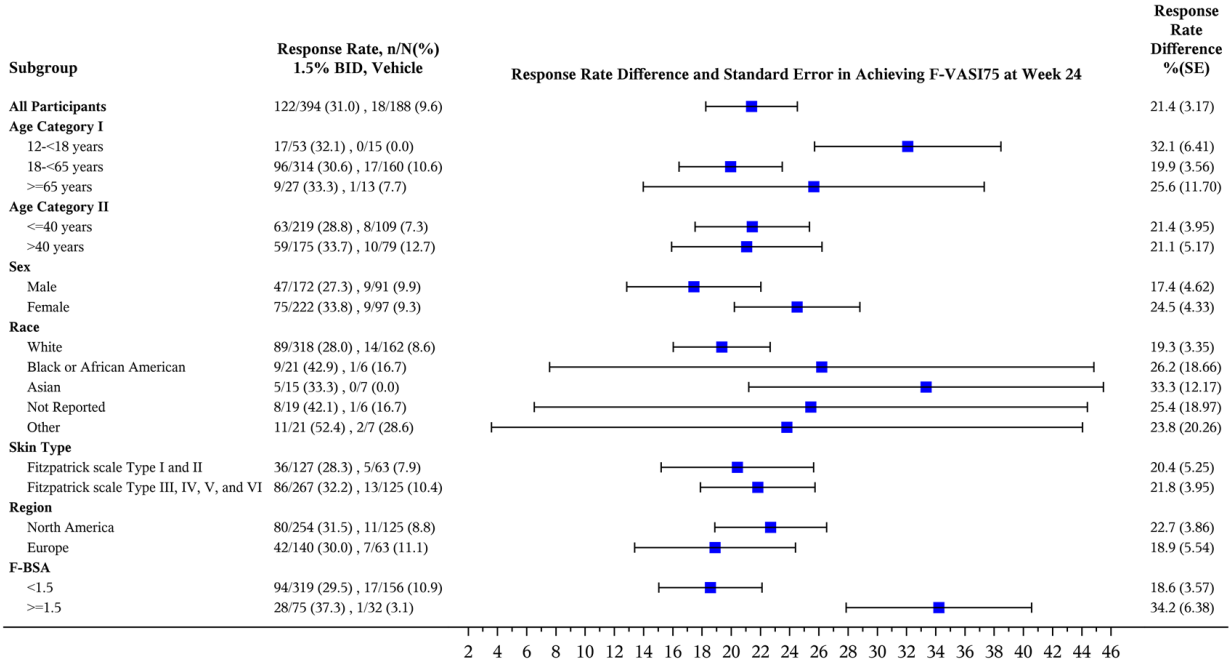
Endpoint Timepoint, Mean (STD)	Study INCB 18424-306		Study INCB 18424-307	
	Vehicle BID (N = 109)	Ruxolitinib 1.5% BID (N = 221)	Vehicle BID (N = 109)	Ruxolitinib 1.5% BID (N = 222)
VitiQoL total score				
Baseline	36.63 (23.229)	36.32 (22.254)	41.61 (24.634)	36.48 (24.300)
Week 12	33.01 (22.876)	32.97 (21.619)	39.44 (23.065)	32.73 (23.452)
Week 24	32.34 (22.818)	30.17 (21.780)	38.93 (24.192)	31.18 (22.660)
Between-group p-value	—	0.8976	—	0.0915
Week 40	31.04 (22.820)	28.42 (22.082)	36.91 (24.900)	29.21 (23.278)
Week 52	31.59 (21.094)	27.35 (22.015)	35.93 (24.481)	29.98 (21.792)
TSQM overall satisfaction score				
Week 12	52.37 (.240)	64.32 (21.957)	53.03 (23.064)	63.83 (22.881)
Week 24	51.79 (25.120)	66.28 (21.560)	49.06 (22.655)	61.03 (24.016)
Between-group p-value	—	< 0.0001	—	< 0.0001
Week 40	62.28 (23.821)	70.64 (19.508)	58.94 (22.668)	66.73 (22.578)
Week 52	65.48 (20.681)	69.78 (19.182)	62.11 (23.267)	65.71 (22.497)
TSQM effectiveness score				
Week 12	43.39 (20.280)	56.89 (21.137)	44.22 (21.102)	55.97 (22.111)
Week 24	42.22 (21.457)	59.03 (21.567)	39.74 (19.513)	53.49 (22.860)
Between-group p-value	—	< 0.0001	—	< 0.0001
Week 40	55.22 (18.103)	64.08 (18.724)	52.03 (20.088)	59.72 (21.213)
Week 52	56.10 (18.776)	63.39 (17.629)	51.23 (19.124)	58.69 (19.478)
TSQM convenience score				
Week 12	66.61 (16.156)	69.75 (17.209)	67.68 (17.431)	67.99 (18.071)
Week 24	65.56 (14.644)	69.32 (17.553)	64.91 (17.083)	67.03 (16.761)
Between-group p-value	—	0.0943	—	0.2262
Week 40	68.34 (16.863)	69.98 (18.075)	65.11 (16.454)	67.56 (18.063)
Week 52	68.29 (17.687)	69.20 (17.440)	66.53 (20.146)	65.60 (18.193)
WHO-5 total score				
Baseline	16.40 (4.587)	17.04 (4.548)	16.58 (5.114)	16.42 (4.551)
Week 12	16.97 (4.842)	17.10 (5.171)	15.79 (5.164)	16.57 (4.527)
Week 24	16.31 (4.796)	16.98 (5.213)	16.16 (5.246)	15.93 (4.469)
Between-group p-value	—	0.7596	—	0.9285
Week 40	17.04 (5.209)	17.65 (5.140)	16.22 (5.289)	16.61 (4.510)
Week 52	16.94 (4.793)	17.90 (4.901)	16.54 (5.003)	16.44 (5.036)
HADS total score of depression				
Baseline	3.63 (3.718)	3.39 (3.223)	3.71 (3.258)	3.72 (3.113)
Week 24	3.57 (2.907)	3.14 (3.022)	3.78 (3.229)	3.73 (3.016)
Between-group p-value	—	0.2715	—	0.7398
Week 52	3.65 (3.515)	3.10 (3.032)	3.67 (3.248)	3.83 (3.326)
HADS total score of anxiety				
Baseline	6.56 (3.438)	6.66 (3.621)	6.77 (4.153)	6.67 (3.655)
Week 24	6.09 (3.625)	5.83 (3.721)	6.57 (3.520)	6.43 (3.193)
Between-group p-value	—	0.6350	—	0.7486
Week 52	6.05 (3.566)	5.72 (3.893)	6.04 (3.426)	6.38 (3.554)

- **Ancillary analyses**

Subgroup analyses

Response rate differences for the F-VASI75 at week 24 were in favor of ruxolitinib as compared to vehicle in all predefined subgroups. Subgroups for race, except white race, were too small to draw conclusions (Figure 27).

Figure 27: Forest plot of response rate difference in proportion of participants reaching F-VASI75 at week 24 (ITT population, pooled data from INCB 18424-306 and -307)



Note: Data from participants enrolled at Site 710 in Study INCB 18424-307 were excluded.

Subgroup analyses were also performed (ad hoc) for the F-VASI75 at week 24 by disease status and prior therapy showed numerically comparable response rates for the subgroups, all favoring ruxolitinib 1.5% BID versus vehicle BID (Table 28).

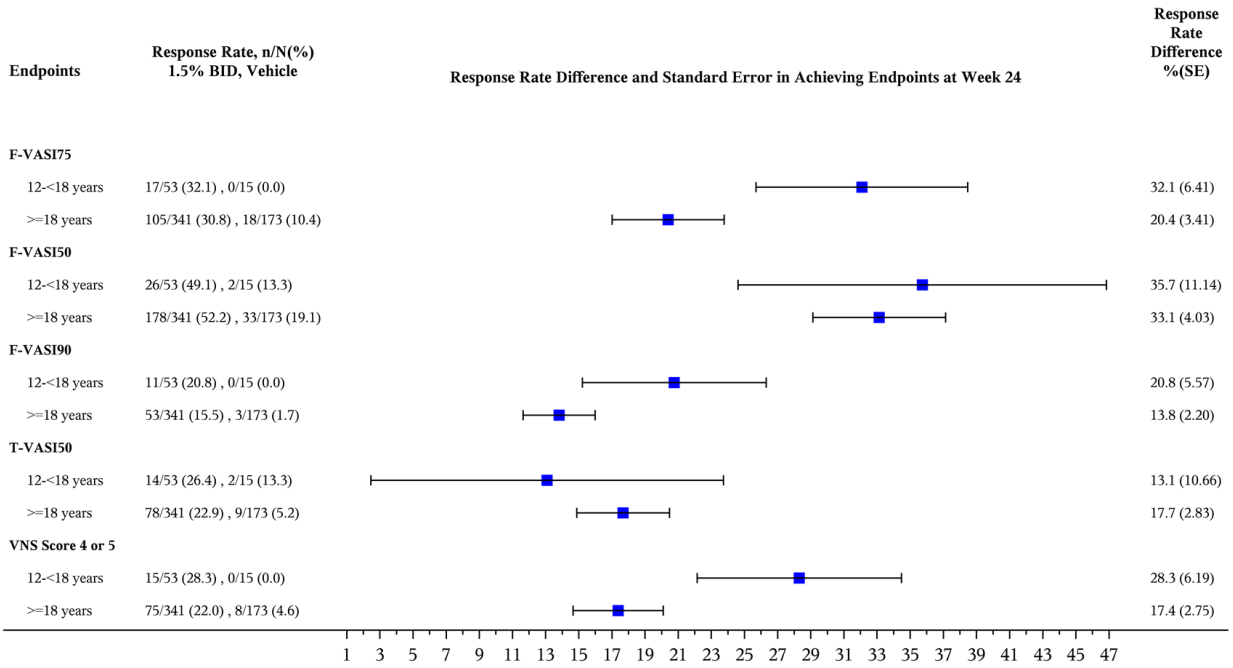
Table 28: Ad hoc subgroup analysis for the F-VASI75 at week 24 by disease status and prior therapy (ITT population, pooled data from INCB 18424-306 and -307)

Subgroup	**Vehicle Cream BID**	**Ruxolitinib 1.5% Cream BID**
All participants, n/N (%)	**18/188 (9.6)**	**122/394 (31.0)**
Response rate difference (SE)	**—**	**21.4 (3.17)**
Baseline disease status		
Stable disease, n/N (%)	11/141 (7.8)	87/287 (30.3)
Response rate difference (SE)	—	25.5 (3.53)
Progressive disease, n/N (%)	7/47 (14.9)	35/107 (32.7)
Response rate difference (SE)	—	17.8 (6.89)
Prior vitiligo therapy		
Topical corticosteroids, n/N (%)	4/44 (9.1)	39/120 (32.5)
Response rate difference (SE)	—	23.4 (6.09)
Topical calcineurin inhibitors, n/N (%)	4/62 (6.5)	44/136 (32.4)
Response rate difference (SE)	—	25.9 (5.08)
Phototherapy, n/N (%)	5/64 (7.8)	43/126 (34.1)
Response rate difference (SE)	—	26.3 (5.39)

Note: Data from participants enrolled at Site 710 in Study INCB 18424-307 were excluded.

Additional ad hoc subgroup analyses for adolescents were performed for the primary and secondary endpoints (see Figure 28). Those assigned to the ruxolitinib 1.5% BID group showed better outcome compared to those assigned to the vehicle group; response rate differences were in line with, or even more favorable, compared to those in adults.

Figure 28: Forest plot of response rate differences for the primary and secondary endpoints by age category, pooled data from INCB 18424-306 and -307)



Note: Data from participants enrolled at Site 710 in Study INCB 18424-307 were excluded.

- **Summary of main efficacy results**

The following Table 29 and Table 30 summarise the efficacy results from the two main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 29: Summary of efficacy for study INCB 18424-306

Title: **A Phase 3, Double-Blind, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream Followed by an Extension Period in Participants With Vitiligo**			
Study identifier	INCB 18424-**306**		
Design	A randomized (1:2), vehicle-controlled, double-blind trial with a double-blind period of 24 weeks followed by a treatment-extended (ruxolitinib cream 1.5% BID) period of 28 weeks		
	Duration of main phase: Duration of un-in phase: Duration of extension phase:		24 weeks (double-blind (DB) period) n.a. 28 weeks (treatment-extension (TE) period)
Hypothesis	Superiority		
Treatments groups	Vehicle BID		N = 109
	Ruxolitinib 1.5% BID		N = 221
	Ruxolitinib 1.5% BID in treatment extension phase		*N = 283*
Relevant endpoints and definitions	Primary endpoint	F-VASI75	Proportion of participants achieving F-VASI75 at week 24
	Secondary endpoints	F-VASI90	Proportion of participants achieving F-VASI90 at week 24
		T-VASI50	Proportion of participants achieving T-VASI50 at week 24
		VNS score 4 or 5	Proportion of participants achieving VNS score 4 or 5 at week 24
Database lock	Date for data cut-off: March 18, 2021		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT population at week 24		
	Treatment group	**Vehicle BID**	**Ruxolitinib 1.5% BID**
	Number of subject s	109	221

Descriptive statistics and estimate variability	F-VASI75 *Estimated response rate in % (SE)*	7.4% (2.65)	29.8% (3.21)
	F-VASI90 *Estimated response rate in % (SE)*	2.2% (1.51)	15.3% (2.50)
	T-VASI50 *Estimated response rate in % (SE)*	5.1% (2.34)	20.6% (2.76)
	VNS score 4 or 5 *Estimated response rate in % (SE)*	3.3% (1.85)	24.5% (3.03)
Effect estimate per comparison	**Primary outcome** F-VASI75	**Ruxolitinib 1.5% BID *versus* Vehicle BID**	
		Odds Ratio	5.28
		Confidence interval	2.341 – 11.903
		P-value	< 0.0001
	Key secondary endpoint F-VASI90		
		Odds Ratio	8.49
		Confidence interval	1.997 – 36.048
		P-value	0.0038
	Key secondary endpoint T-VASI50		
		Odds Ratio	4.93
		Confidence interval	1.795 – 13.566
		P-value	0.0020
	Key secondary endpoint VNS score 4 or 5		
		Odds Ratio	9.53
		Confidence interval	2.900 – 31.290
		P-value	0.0002
Notes	A statistically significantly higher proportion of participants reached primary and key secondary endpoints F-VASI75, F-VASI90, T-VASI50, and score 4 or 5 for VNS in the ruxolitinib group versus the vehicle group.		

Table 30: Summary of efficacy for study INCB 18424-307

Title: **A Phase 3, Double-Blind, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream Followed by an Extension Period in Participants With Vitiligo**			
Study identifier	INCB 18424-**307**		
Design	A randomized (1:2), vehicle-controlled, double-blind trial with the double-blind period of 24 weeks followed by a treatment-extended (ruxolitinib cream 1.5% BID) period of 28 weeks		
	Duration of double-blind period: Duration of run-in phase: Duration of extension period:		24 weeks (double-blind (DB) period) n.a. 28 weeks (treatment-extension (TE) period)
Hypothesis	Superiority		
Treatments groups	Vehicle BID		N = 109
	Ruxolitinib 1.5% BID		N = 222
	Ruxolitinib 1.5% BID in treatment extension phase		*N = 286*
Relevant endpoints and definitions	Primary endpoint	F-VASI75	Proportion of participants achieving F-VASI75 at week 24
	Secondary endpoints	F-VASI90	Proportion of participants achieving F-VASI90 at week 24
		T-VASI50	Proportion of participants achieving T-VASI50 at week 24
		VNS score 4 or 5	Proportion of participants achieving VNS score 4 or 5 at week 24
Database lock	Date for data cut-off was March 18, 2021		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT population at week 24		
Descriptive statistics and estimate variability	Treatment group	**Vehicle cream BID**	**Ruxolitinib cream 1.5% BID**
	Number of subject s	109	222
	F-VASI75 *Estimated response rate in % (SE)*	11.4% (3.20)	30.9% (3.27)
	F-VASI90 *Estimated response rate in % (SE)*	1.3% (1.25)	16.3% (2.62)
	T-VASI50 *Estimated response rate in % (SE)*	6.8% (2.50)	23.9% (2.97)
	VNS score 4 or 5 *Estimated response rate in % (SE)*	4.9% (2.17)	20.5% (2.85)
Effect estimate per comparison	**Primary outcome** F-VASI75	**Ruxolitinib 1.5% BID *versus* Vehicle BID**	
		Odds Ratio	3.45
		Confidence interval	1.737 – 6.835
		P-value	0.0004
	Key secondary endpoint		

	F-VASI90	Odds Ratio	15.29
		Confidence interval	2.150 – 108.739
		P-value	0.0065
	Key secondary endpoint T-VASI50		
		Odds Ratio	4.29
		Confidence interval	1.865 – 9.853
		P-value	0.0006
	Key secondary endpoint VNS score 4 or 5		
		Odds Ratio	4.86
		Confidence interval	1.851 – 12.755
		P-value	0.0013
Notes	A statistically significantly higher proportion of participants reached primary and key secondary endpoints F-VASI75, F-VASI90, T-VASI50, and score 4 or 5 for VNS in the ruxolitinib group versus the vehicle group.		

Note: Data from participants enrolled at Site 710 in Study INCB 18424-307 were excluded.

2.6.5.3. Clinical studies in special populations

No separate clinical studies in special populations with vitiligo were performed. Subgroup analysis for adolescents was performed for the primary outcome measure only, as described in the section on subgroups above. Adolescents between 12 - 18 years of age represented 10.9% (n = 72) of the pooled population; those aged 65 years or older represented 6.8% (n = 45).

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Pooled analyses were performed for the two pivotal studies. These data are integrated in the section of main studies and in the section on subgroup analysis. Data on response shifts are presented below.

In the pooled study data, there were 350 participants with F-VASI data at weeks 24 and 52. Among the 133 (33%) participants who had less than 25% repigmentation (<F-VASI25) at week 24, approximately 58% improved in F-VASI response, with 13% reaching F VASI75 at week 52 (Table 31). Among participants with <T VASI25 at week 24, approximately 57% improved in T-VASI response, with 23% reaching T VASI50 at week 52 (Table 32). Of the participants with an F-VASI<25% or a T-VASI<25% at week 52, about 50% showed improvements up to week 68 but few patients reached F-VASI75 or T-VASI75 (Table 33 and Table 34).

Table 31: Shift summary of maintenance response on F-VASI (ITT population) from week 24 to week 52 (pooled data from participants in the ruxolitinib 1.5% cream BID group in studies INCB18424-306 and INCB 18424-307)

Response at Week 24		Response at Week 52						
Value	n (%)	< F-VASI25	F-VASI25 to < F-VASI50	F-VASI50 to < F-VASI75	F-VASI75 to < F-VASI90	F-VASI90	Missing	
Pooled analysis								
< F-VASI25	131 (33.2)	47 (35.9)	21 (16.0)	30 (22.9)	7 (5.3)	8 (6.1)	18 (13.7)	
F-VASI25 to < F-VASI50	59 (15.0)	0	9 (15.3)	21 (35.6)	12 (20.3)	4 (6.8)	13 (22.0)	
F-VASI50 to < F-VASI75	82 (20.8)	1 (1.2)	8 (9.8)	26 (31.7)	22 (26.8)	19 (23.2)	6 (7.3)	
F-VASI75 to < F-VASI90	58 (14.7)	0	2 (3.4)	7 (12.1)	22 (37.9)	26 (44.8)	1 (1.7)	
F-VASI90	64 (16.2)	1 (1.6)	0	1 (1.6)	7 (10.9)	49 (76.6)	6 (9.4)	

Note 1: Data from participants enrolled at Site 710 in Study INCB 18424-307 were excluded.
Note 2: The analysis was conducted in the ITT population for participants in the ruxolitinib 1.5% cream BID group with nonmissing F-VASI scores at Week 24.

Table 32: Shift summary of maintenance response on T-VASI (ITT pooled population with nonmissing T-VASI Score at week 24 in the ruxolitinib 1.5% cream BID treatment group)

Response at Week 24		Response at Week 52					
Value	n (%)	< T-VASI25	T-VASI25 to < T-VASI50	T-VASI50 to < T-VASI75	T-VASI75 to < T-VASI90	T-VASI90	Missing
< T-VASI25	198 (50.3)	75 (37.9)	58 (29.3)	33 (16.7)	6 (3.0)	1 (0.5)	25 (12.6)
T-VASI25 to < T-VASI50	104 (26.4)	4 (3.8)	29 (27.9)	46 (44.2)	11 (10.6)	1 (1.0)	13 (12.5)
T-VASI50 to < T-VASI75	66 (16.8)	0	3 (4.5)	24 (36.4)	28 (42.4)	5 (7.6)	6 (9.1)
T-VASI75 to < T-VASI90	23 (5.8)	1 (4.3)	1 (4.3)	4 (17.4)	9 (39.1)	8 (34.8)	0
T-VASI90	3 (0.8)	0	0	0	0	3 (100.0)	0

Note: Data from participants enrolled at Site 710 in Study INCB 18424-307 were excluded.

Table 33: Shift Summary of F-VASI Response From Week 52 to Week 68 (FAS Cohort B)

Response at Week 52		Response at Week 68					
Value	n (%)	< F-VASI25	F-VASI25 to < F-VASI50	F-VASI50 to < F-VASI75	F-VASI75 to < F-VASI90	F-VASI90	Missing
< F-VASI25	41 (18.6)	19 (46.3)	9 (22.0)	2 (4.9)	1 (2.4)	3 (7.3)	7 (17.1)
F-VASI25 to < F-VASI50	35 (15.8)	2 (5.7)	11 (31.4)	12 (34.3)	4 (11.4)	3 (8.6)	3 (8.6)
F-VASI50 to < F-VASI75	77 (34.8)	1 (1.3)	3 (3.9)	41 (53.2)	20 (26.0)	10 (13.0)	2 (2.6)
F-VASI75 to < F-VASI90	63 (28.5)	2 (3.2)	0	4 (6.3)	30 (47.6)	25 (39.7)	2 (3.2)
F-VASI90	5 (2.3)	0	0	0	0	4 (80.0)	1 (20.0)

Note: The analysis population consisted of the FAS (participants initially randomized to ruxolitinib 1.5% cream BID in the parent studies [INCB 18424-306 and -307] who applied at least 1 dose of study drug in Study INCB 18424-308 Cohort B) with nonmissing F-VASI scores at Week 52. Data from participants enrolled at Site 710 in parent Study INCB 18424-307 were excluded.

Table 34: Shift summary of T-VASI response from week 52 to week 68 (FAS cohort B)

Response at Week 52		Response at Week 68					
Value	n (%)	< T-VASI25	T-VASI25 to < T-VASI50	T-VASI50 to < T-VASI75	T-VASI75 to < T-VASI90	T-VASI90	Missing
< T-VASI25	66 (29.9)	38 (57.6)	17 (25.8)	3 (4.5)	1 (1.5)	0	7 (10.6)
T-VASI25 to < T-VASI50	61 (27.6)	4 (6.6)	32 (52.5)	18 (29.5)	3 (4.9)	0	4 (6.6)
T-VASI50 to < T-VASI75	67 (30.3)	1 (1.5)	2 (3.0)	43 (64.2)	17 (25.4)	2 (3.0)	2 (3.0)
T-VASI75 to < T-VASI90	22 (10.0)	1 (4.5)	0	2 (9.1)	16 (72.7)	2 (9.1)	1 (4.5)
T-VASI90	5 (2.3)	0	0	0	0	4 (80.0)	1 (20.0)

Note: The analysis population consisted of the FAS (participants initially randomized to ruxolitinib 1.5% cream BID in the parent studies [INCB 18424-306 and -307] who applied at least 1 dose of study drug in Study INCB 18424-308 Cohort B) with nonmissing T-VASI scores at Week 52. Data from participants enrolled at Site 710 in parent Study INCB 18424-307 were excluded.

2.6.5.6. Supportive studies

Study NCBI 18424-308

Data of study NCBI 18424-308, the treatment extension study, was considered supportive for the long-term efficacy of ruxolitinib 1.5% BID. Study 308 is still ongoing and data from cohort A will remain blinded until the study is completed by all participants. Preliminary data from cohort B were provided, including participants who had not reached the F-VASI 90 at week 52 in studies INCB 18424-306 or INCB 18424-307 and continued the use of ruxolitinib 1.5% BID. At time of data cut off all participants in cohort B had completed 68 weeks of treatment. Proportions of participants reaching the F-VASI75, the F-VASI90, and the T-VASI50 are provided in the below figures. According to the applicant, these preliminary data support continuous improvement in repigmentation, also after 52 weeks use of ruxolitinib 1.5% BID.

Data on rebound is to be expected from cohort A from study 308 in the first half of 2023.

Figure 29: Proportion of participants reaching F-VASI75 in study 308 (cohort B)

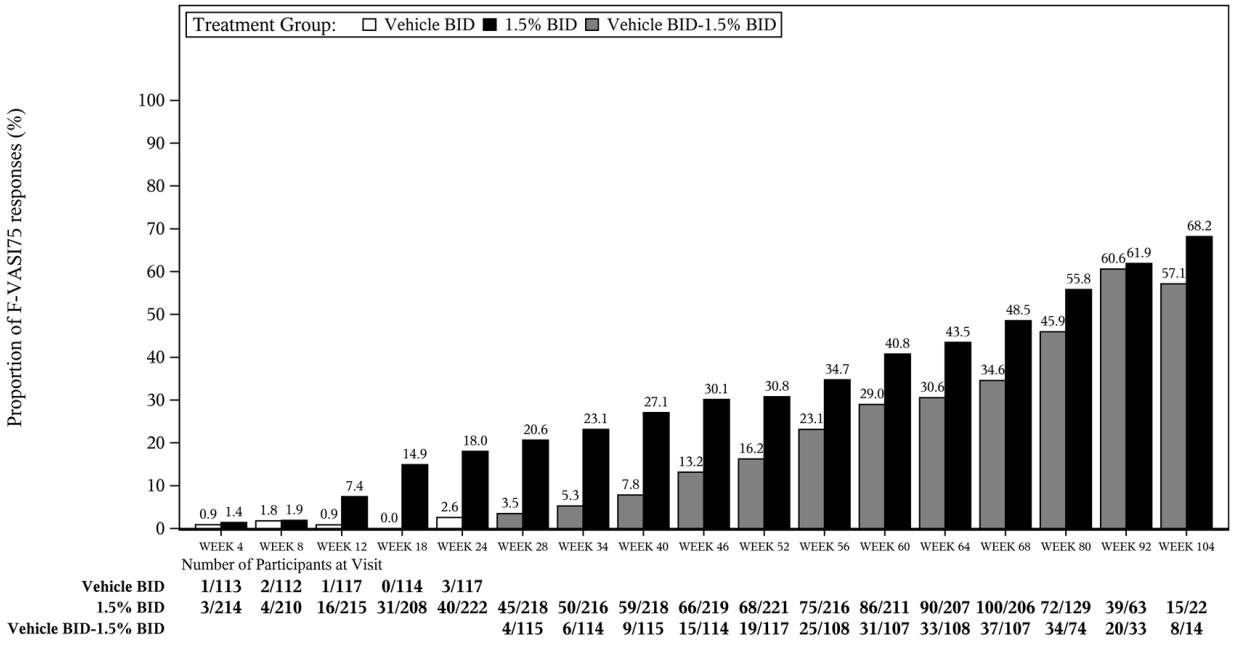


Figure 30: Proportion of participants reaching F-VASI90 in study 308 (cohort B)

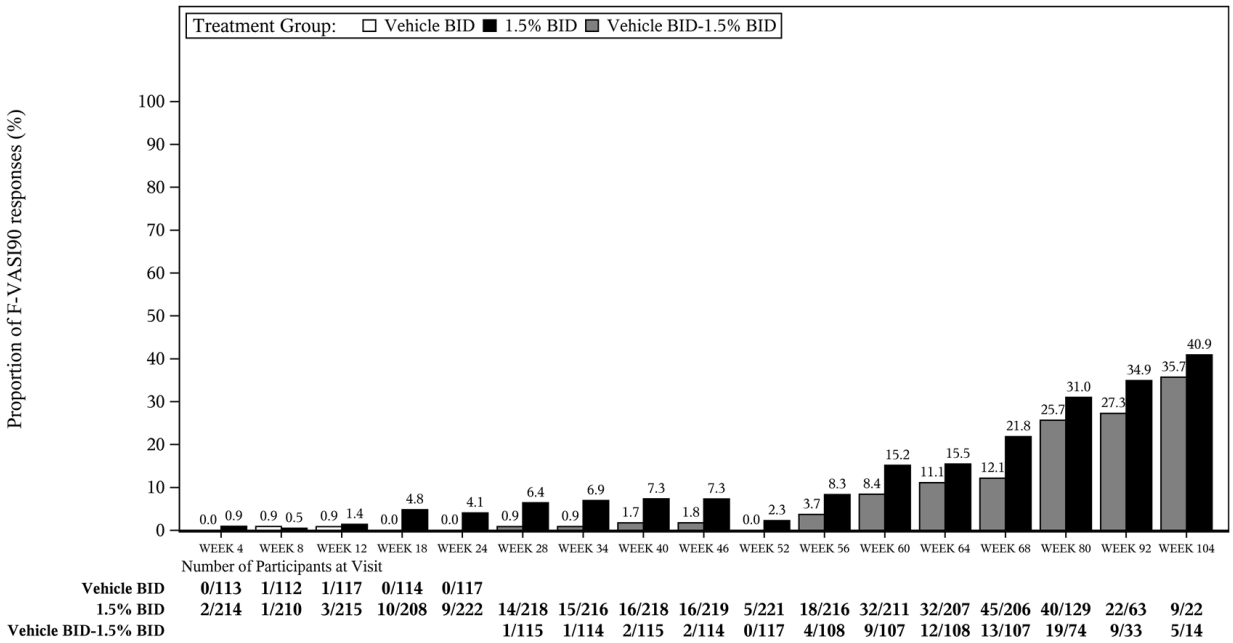
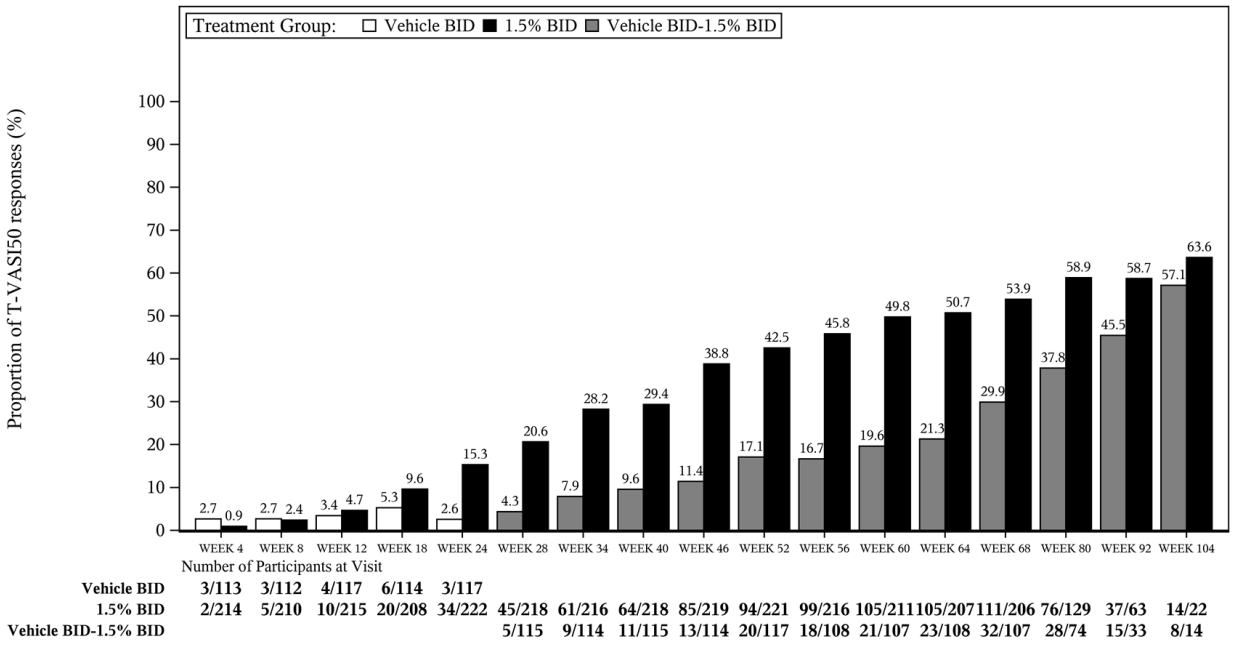


Figure 31: Proportion of participants reaching T-VASI50 in study 308 (cohort B)



Shift summary data for maintenance of response on the F-VASI and the T-VASI between week 52 and week 68 were in line with those found for between week 24 and week 52.

Study INCB 18424-211

Data of study INCB 18424-211 was considered supportive for the long-term efficacy of ruxolitinib 1.5% BID as during the initial application no long-term data beyond 24 weeks was available for studies INCB 18424-306 and -307. Upon CHMP's request, data of studies 306 and 307 were submitted by the

applicant. The numbers in study 211 on ruxolitinib 1.5% BID are low, the supportive value of study 211 mainly concerns the data on rebound effects after treatment discontinuation rather than for long-term clinical efficacy.

Rebound was defined as an F-VASI score during the follow-up period of ≥ 25% than the F-VASI score at baseline (n = 70). None of the participants (except a single participant with segmental vitiligo) met this definition. More data on rebound is to be expected from study 308 (cohort A) in the first half of 2023.

Exit interviews and associations between clinical outcomes

Exit interviews were performed in participants who finished the pivotal studies. The interviews aimed, amongst others, at confirming the threshold of clinical meaningful improvement in the F-VASI, and to identify thresholds for meaningful change in the T-VASI and the VNS. Thirty-six participants were interviewed on their interpretation of meaningful changes at the F-VASI, T-VASI, and VNS scores. The previously set threshold for **meaningful improvement** at the F-VASI at 75% was supported by the results of the interviews. Similarly, the threshold for meaningful improvement at the T-VASI was 50% and for the VNS this was 3-5. However, number of patients involved was limited.

The study of **associations** between different outcome measures at baseline of the two pivotal studies were performed to support their respective validity. Correlations were calculated between the F-VASI and the F-PhGVA (r = 0.310, n = 648), and between the T-VASI and the T-PhGVA (r = 0.339, n = 648), but not between the VNS and any other outcome measure.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The developmental programme of topical ruxolitinib was broad and included clinical studies in vitiligo, but also in atopic dermatitis, plaque psoriasis, and alopecia areata (see section 2.6 for an overview). For vitiligo, one phase 2 study (INCB 18424-**211**) was performed for dose finding and long-term efficacy and safety. Based on the results of this study, ruxolitinib 1.5% BID (the highest dose evaluated) was used for the subsequent two identically designed pivotal phase 3 studies (INCB 18424-**306** and -**307**) on efficacy and safety of ruxolitinib in patients with non-segmental vitiligo (NSV). The studies were all completed. Data from the maintenance and withdrawal study (INCB 18424-**308**) are expected in the first half of 2023 and will be submitted for review.

Main studies

Studies INCB 18424-306 and INCB 18424-307 were the pivotal, identical phase 3 studies comparing ruxolitinib 1.5% BID with vehicle cream BID in participants with NSV. These studies were completed during the current procedure. Supportive studies were study INCB18424-308 (treatment maintenance and withdrawal study) which is still ongoing, and dose-finding study INCB 18424-211 (completed). The comparator chosen in the pivotal studies was vehicle cream and this is acceptable since other available therapies are not well established.

The (identical) design of the two pivotal studies was adequate and followed the study objectives. There are no specific guidelines on the design of studies for vitiligo, but Scientific Advice of the CHMP was sought in March 2019 (EMEA/H/SA/1155/3/2019/III). In this CHMP SA, a double-blind period of >24 weeks was recommended because 24 weeks was considered potentially too short to reach (full) re-pigmentation. Upon CHMP's request, the applicant provided complete data up to week 52 for each of the primary and (key) secondary endpoints for the two pivotal studies, and additionally provided supportive, preliminary long-term data up to week 68 from study INCB 18424-308. This follow-up is

considered sufficiently long for an adequate benefit-risk assessment for efficacy (and safety) of ruxolitinib 1.5% BID. Data on maintenance (but not withdrawal) from study 308 were preliminary and not complete, but this was considered not required for the current application. The final results will be submitted for review once available (i.e. in the first half of 2023).

Study participants

The in- and exclusion criteria were in line with the target population as defined in the proposed indication, i.e. "*treatment of non-segmental vitiligo with facial involvement in adults and adolescents from 12 years of age*". The inclusion criteria defined an eligible population with a relatively mild phenotype of NSV; the total body surface area (BSA) affected by vitiligo (facial and non-facial) should not be exceeding 10%. This 10% corresponded to the maximum % BSA to be treated in the pivotal studies 306 and 307. In study 211, patients with more extensive disease were included as well. Response rates in study 211 was similar to the response rates seen in the pivotal trials and so was the safety patterns. Specifically, in those participants who presented with > 20% BSA, but who were only permitted to treat up to 20% BSA, the response rates for F-VASI50 and F-VASI75 and the safety profile were similar to those who presented with ≤ 20% BSA affected. Nevertheless, in the absence of long-term safety data, the CHMP agreed that the maximum BSA to be treated (10%) should be included in SmPC section 4.2. In addition, a warning in SmPC section 4.4 was added to reflect that in the absence of long-term safety data the skin area to be treated should be as limited as possible and not exceed the recommended posology for vitiligo (see also safety discussion). Another aspect in the proposed indication concerned '*…vitiligo with* ***facial involvement****…*'; participants in the two pivotal studies were selected accordingly. However, it is unclear if and why facial involvement will be necessary for patients to be eligible for treatment with ruxolitinib 1.5% BID, when authorised. The CHMP acknowledged that it is likely the most debilitating manifestation of the disease, but whether treatment should be confined to patients with facial involvement for efficacy reasons could be questioned. Nevertheless, this issue was not further pursued by the CHMP, and the proposed indication was thus considered acceptable.

Treatment-naïve as well as participants who achieved previous treatment were included in the pivotal studies. The proposed indication does not incorporate a treatment-line, in line with the CHMP Scientific Advice received. This can be accepted as results indicated there was no relevant heterogeneity in results across lines of treatment. Furthermore, there are no available authorised treatments in vitiligo and for none of the alternative treatments, efficacy has been established in randomised trials.

Study treatments

Participants were treated with either vehicle cream BID or ruxolitinib cream 1.5% BID. Topical treatment inherently introduced dosing and compliance issues, but reasonable effort was made to evaluate these aspects. Compliance was defined as 70%-130% of the expected number of applications to be reached.

The ruxolitinib dosing regimen was defined as 1.5% BID to be applied on up to 10% BSA. There were two points of discussion arising with this choice: 1) BID versus QD, and 2) the limit of 10% BSA.

Ad 1) During the CHMP SA of 2019, the 1.5% QD regimen was selected, based on the F-VASI50 at week 24 in study 211 as well as anticipated lower systemic exposure. The 1.5% BID regimen was however selected for the pivotal studies 306 and 307, based on the F-VASI75 at 52 weeks in study 211. This is understood as the largest responses in F-VASI75 were indeed seen with the 1.5% BID dose at week 24 and beyond, and the F-VASI75 is more stringent than the F-VASI50. Although the BID regimen is associated with a higher level of (systemic) exposure as compared to QD, this exposure is still considered to be low and did not result in new or more severe safety issues compared to what had been observed for the 1.5% QD regimen.

Ad 2) In study 211 the maximum area to be treated was 20% BSA, but this was reduced to 10% BSA in the pivotal studies and this threshold was also reflected in the proposed posology in SmPC section 4.2. The 10% BSA was chosen as application to a larger area would become impractical and thus to improve treatment compliance and to decrease patient burden. Furthermore, the applicant highlighted that this 10% BSA was a common threshold described in several guidelines on topical therapy for vitiligo. As the hands and face, usually the most visible body areas in Europe, together form ~10% BSA, treatment up to 10% BSA was ultimately considered as clinically relevant for the treatment of vitiligo by the CHMP. See also section on study participants above.

Outcomes

The endpoints chosen in the pivotal studies 306 and 307 were discussed in the 2019 CHMP Scientific Advice and covered in the literature and are thus considered acceptable by the CHMP.

Primary outcome was the proportion of participants reaching at least 75% facial repigmentation at 24 weeks (F-VASI75). Key secondary outcomes were proportions of participants reaching the F-VASI50, F-VASI90, the T-VASI50, and VNS score 4 or 5, and the percentage of change of F-BSA, at week 24. The F-VASI75, the T-VASI 50, and the VNS were considered the most relevant outcomes for this application.

The F- and the T-VASI were based on the validated, original VASI, and adjusted for the purpose of the pivotal studies. As the F- and T-VASI are fundamentally overlapping with the original VASI, it seemed justified to assume that their psychometric properties are likely to approach those of the original VASI. The PhGVA and PaGIC were similarly adjusted (F-PhGVA, T-PhGVA, F-PaGIC-V, T-PaGIC-V); although no comprehensive data on psychometric properties were available for these supportive endpoints, these endpoints were indeed not among the primary or key secondary outcomes and were face valid and easy to understand for participants. Additional data on psychometric properties were thus considered not warranted.

Sample size, randomisation, and blinding

Sample size calculations were based on treatment effects observed in study 211 which is justified. The randomisation and blinding procedures were considered acceptable.

Statistical analyses

The COVID-19 pandemic impacted study participants and conduct. Therefore, the applicant decided to define the FAS as efficacy population in the SAP rather than the protocol defined ITT population. After unblinding, the population was changed back to ITT based on FDA feedback. The change was made after unblinding, however since the results were similar between the analysis using FAS and the ITT population, the post-hoc change did not have an impact on the primary analyses.

The definition of the analysis populations was standard. The primary endpoint was analysed using exact logistic regression including the stratification factors used at randomisation. Missing primary endpoint data were handled using multiple imputation, assuming missing at random. This is acceptable and the impact on the results was adequately tested in sensitivity analyses (non-response imputation, LOCF imputation and a tipping point analysis).

Key secondary endpoints were analysed using similar methods as for the primary endpoint, other secondary endpoints were analysed as appropriate. Multiplicity across the primary and key secondary endpoints was handled by a sequential testing strategy, to control the overall type I error rate and is considered acceptable.

Conduct of the study

Although there were several protocol amendments, these did not affect the conduct and outcome of the pivotal studies. The protocol amendment in which the exclusion criterion 'other forms than nonsegmental vitiligo' was introduced, appeared to be a textual one and did not have impact on the actual selection of participants: only participants with NSV were included in the studies.

Three investigator inspections and 5 site audits were reported by the applicant. The three clinical investigator inspections did not lead to remarkable GCP findings. Based on the audit of study site 710 (included in study INCB 18424-307), it was decided to exclude all participants from the analyses due to 1 critical finding (informed consent) and two major findings (source documents and organisation and personnel). Other GCP inspections were not performed. This is accepted.

Efficacy data and additional analyses

Study population

Demographic characteristics were well balanced between the vehicle and the ruxolitinib groups, as well as between the two pivotal studies. Adolescents comprised about 10% of the study sample. The group of participants aged 65 years or older comprised 6.8% in total. Females were slightly overrepresented.

Non-white participants (18%) were underrepresented compared to the incidence of vitiligo in this population. It was hypothesised that a satisfactory re-pigmentation result may be more difficult to reach in those with a non-white skin type. The subgroup analysis for the F-VASI75 stratified by skin type I-II versus III – VI did not reveal differences in outcome, suggesting that for both white and non-white skin the response rates were comparable although the heterogeneity within the subgroups was large. Also, when stratified by race no clear differences in outcome were seen, but the numbers in the non-white subgroups were small. Altogether, the subgroup analyses did not suggest a trend towards between-group differences. This issue was therefore not further pursued by the CHMP.

Completion

A total of 674 participants was included in the pivotal studies. Data from participants from study site 710 were ultimately excluded from the analyses (n = 13; see section on conduct of the study above); data from 661 participants were eligible for the analyses (218 in vehicle and 443 in ruxolitinib 1.5% BID groups respectively). The numbers (13% - 11%) and reasons of discontinuation or withdrawal before week 24 were similar between vehicle and ruxolitinib groups and both studies. Up to week 52, 163 (88.6%) and 350 (90.9%) of the participants in the vehicle and the ruxolitinib 1.5% BID groups completed the study. Reasons for discontinuation (withdrawal by participant and lost to follow up) were comparable between the two groups. Numbers analysed in the ITT population did not substantially differ across treatments groups and studies.

Adherence and drug exposure

Median duration of treatment was 168 days during the double-blind period, with an average total amount of study drug applied of 678 grams. Drug exposure was comparable between the two studies and between the vehicle and ruxolitinib group. Compliance of > 80% of the drug applications was achieved in > 89.7%, irrespective of treatment group or study. There were few protocol violations due to non-adherence. Adherence and study drug exposure were presented for the population including those from study site 710 because the patients are part of the safety data.

Concomitant medication

Concomitant medication was taken by about 70% of the participants during the double-blind period in both studies, without differences between the vehicle and ruxolitinib group. It is unlikely that the use of concomitant medication has affected the outcome of the pivotal studies.

Combination therapy

As ruxolitinib cream has not been evaluated in combination with other medicinal products used to treat vitiligo, SmPC section 4.5 was updated to reflect that co-application on the same skin areas is not recommended. In addition, limited data are available on the use of phototherapy in combination with ruxolitinib cream from study 211. The applicant highlighted that a study was ongoing to examine the impact of concomitant UV treatment; the SmPC will be updated in a future variation, if considered appropriate.

Emollients and Sunscreen

Upon CHMP's request, SmPC section 4.5 was updated to include recommendations on the concomitant use of emollients and sunscreen.

Treatment effects

In both pivotal studies, the primary endpoint was met. The proportion of participants reaching F-VASI75 at 24 weeks was significantly higher in the ruxolitinib 1.5 % BID group versus the vehicle BID group (30% versus 7.4% and 31% versus 11.4% respectively in studies 306 and 307).

Higher proportions of participants treated with ruxolitinib 1.5% BID versus vehicle BID reached the *primary outcome* (F-VASI75 at week 24): 31% versus 9.6% respectively using pooled data, and this difference was statistically significant in both studies. The robustness of the findings was supported by sensitivity analyses. Analyses with and without the data from study site 710 yielded comparable outcome (see below).

Data from *key secondary outcomes (F-VASI50, F-VASI90, T-VASI50, Vitiligo Noticeability Scale score 4 or 5, F-BSA at week 24)* were in line with the primary outcome. In the pooled results, 52% of the participants in the ruxolitinib 1.5% BID group and 21% in the vehicle group reached at least 50% repigmentation after 24 weeks of treatment (F-VASI50), with a response rate difference of 31% ($p<0.0001$). Almost complete repigmentation (F-VASI90) was reached in 16% in the ruxolitinib group versus 1.9% in the vehicle group after 24 weeks of treatment, with a response rate difference of 14% ($p = 0.0001$). Proportions of participants reaching at least 50% repigmentation of the total body after 24 weeks (T-VASI50) were 22% in participants on ruxolitinib versus 6% of the participants in the vehicle group, with a response rate difference of 16% ($p<0.0001$). The proportion of patients who scored their vitiligo (VNS) as 'a lot less noticeable' or 'no longer noticeable' after 24 weeks was larger in the group of participants treated with ruxolitinib (23%) as compared to those treated with vehicle (4.2%), with a treatment effect of 18% ($p<0.0001$). The percent change in F-BSA at week 24 was significantly higher in the ruxolitinib 1.5% BID group versus vehicle BID (LSM difference -20.0 (sd 3.2)) with a 95% CI of -26.2 - -13.8 ($p<0.0001$). Results showed to be robust in the sensitivity analyses.

Altogether, data from pivotal studies 306 and 307 included 661 patients up to week 52, excluding those of 13 patients from site 710 where major protocol violations were observed. The impact of these 13 excluded subjects was marginal: at week 24, the re-calculated estimated F-VASI75 response rate without the 13 subjects from site 710 was not different from the estimated F-VAS75 previously reported including those subjects (30.7% versus 30.1% for ruxolitinib 1.5% BID, with response rate differences of 21.1% versus 19.3%). For the key secondary outcomes (F-VASI50, F-VASI90, T-VASI50 and the VNS score 4 or 5 at week 24) similar results were found, concluding that the data of these 13 subjects did not affect interpretation of the results.

Other *outcome secondary outcomes* generally supported these findings, but there were no statistically significant between-group differences in changes in quality of life (DLQI/CDLQI, WHO-5 and VitiQol) and anxiety/depression (HADS) possibly due to low baseline scores.

Onset of effect and long-term treatment effect

Visual inspection of the effects of ruxolitinib 1.5% BID over time as compared to vehicle BID showed that the treatment effect of ruxolitinib can be observed from week 12, however this was not formally tested. Long-term data until week 52 (pivotal trials 306 and 307) and beyond (preliminary data cohort B study 308; participants in this cohort had < F-VASI90 at Week 52 in the Phase 3 studies and continued on open-label ruxolitinib 1.5% cream BID up to Week 104) showed that repigmentation continues after week 24. Further improvement is seen for the primary and key secondary outcome measures until week 52, about 50% showed improvements up to week 68 but few patients reached F-VASI75 or T-VASI75. In general, the response to treatment in vitiligo took more time than in other inflammatory diseases, due to the lag-time in the regeneration following a reduction of the inflammatory process. The data showed that patients who did not have a response by week 24 may get a response before week 52, and that patients who did not have response by week 52 however have little chance to get a response later. Considering the low systemic exposure, a 52-week cut-off for non-response in case of vitiligo is considered appropriate. This information has been adequately reflected in the SmPC section 4.2.

Maintenance of effect and treatment withdrawal

Data on withdrawal of treatment will come from cohort A (including participants who had reached the F-VASI90 at week 52 and were randomised into treatment continuation or discontinuation) from study INCB 18424-308 which is currently ongoing. Data are expected to be available in the first half of 2023.

Further, data on rebound after treatment withdrawal were derived by post hoc analyses of data from study 211 including 70 participants who discontinued ruxolitinib (independent of dose) during the open label extension period. None (except one participant with segmental vitiligo) met the definition of rebound (F-VASI score during follow-up of at least 25% higher than the F-VASI at baseline). It is therefore considered unlikely that treatment discontinuation will trigger a rebound effect. Given the available data, this conclusion is endorsed. Nevertheless, definite data are expected after completion of study 308.

The applicant will submit a type II variation to implement these results in the SmPC after the data become available. This is accepted.

Adolescents

Adolescents (12 - 18 years) are included in the proposed indication and comprised about 10% (n=72) of the total study population. Subgroup analyses for the F-VASI75 as well as for the key secondary outcomes showed comparable percentages responders in the ruxolitinib group compared to vehicle at week 24. This, supported by the assumed similar pathophysiological mechanism of vitiligo in adolescents compared to adults and comparable systemic ruxolitinib exposure between adolescents and adults, confirmed the efficacy of ruxolitinib 1.5% BID in adolescents. Together with a similar safety profile (see clinical safety section) the inclusion of adolescents in the therapeutic indication SmPC section 4.1 is considered to be well justified and thus acceptable by the CHMP.

Subgroups

Subgroup analyses were performed for the primary endpoint only. The effect on the F-VASI75 at week 24 (primary outcome) was overall robust across the predefined subgroups. Although response rate differences were larger in adolescents versus those aged 18-65 years, and in participants with an F-BSA of at least 1.5% versus < 1.5% at baseline, contrast was mainly ascribed to lower response rates in the vehicle group. The sample size of the subgroup adults > 65 years of age was rather small which affects robustness of the findings. The SmPC section 4.2 has been revised to inform HCPs that a

limited number of patients aged 65 years and above have been enrolled in the clinical studies with ruxolitnib cream in vitiligo to determine whether they respond differently from younger subjects.

Supportive studies and pooled data

Supportive data with regard to long-term treatment (up to 104 weeks) for the F-VASI75, F-VASI90, and T-VASI50 of ruxolitinib 1.5% BID were derived from studies INCB 18424-308 and study INCB 18424-211. Study 308 also provided supportive data on treatment withdrawal and rebound effects (see section on treatment withdrawal above).

Exit interviews and analyses on associations between outcomes from studies 306 and 307 were provided as supplementary supportive data. The thresholds for meaningful improvement at the F-VASI, T-VASI, and VNS were confirmed with the exit interviews. However, number of patients involved was small which limit the interpretation of these results.

2.6.7. Conclusions on the clinical efficacy

In the two confirmatory studies in adolescent and adult participants with non-segmental vitiligo treated with ruxolitinib 1.5% BID, the primary outcome was met. The results were supported by the sensitivity analyses and each of the key secondary outcomes, most notably the F-VASI90, the T-VASI50, and the Vitiligo Noticeability Scale (VNS). Treatment with ruxolitinib 1.5% BID for 24 weeks resulted in 21% and 16% more participants having repigmentation of the skin of the face (F-VASI75, primary outcome) and of the skin in the total body (T-VASI50) respectively, as compared to vehicle. The 75% repigmentation of the skin of the face is considered a clinically relevant magnitude of change and this was supported by treatment effects seen in the patient-reported VNS. Data beyond week 24 confirm further improvement of treatment response (rates) between weeks 24 and 52; but patients with less than 25% repigmentation by week 52 are unlikely to show clinically meaningful improvement thereafter.

Adolescents are included in the proposed indication but comprise only 10% (n=72 in total) of the study population in the pivotal studies. Subgroup analyses consistently showed comparable treatment responses for the primary and key secondary endpoints in adolescents compared to adults. These findings, together with the similar pathophysiology and comparable systemic ruxolitinib exposure between adolescents and adults, justify the inclusion of adolescents in the indication.

Overall, the following proposed therapeutic indication is considered acceptable: *'Opzelura is indicated for the treatment of non-segmental vitiligo with facial involvement in adults and adolescents from 12 years of age.'* In line with the inclusion criteria, ruxolitinib cream should be applied to depigmented skin areas up to a maximum of 10 % of body surface area (see section 4.2 of the SmPC).

2.6.8. Clinical safety

The ruxolitinib cream clinical development programme included 18 studies: four studies in participants with vitiligo and nine studies in participants with other inflammatory skin diseases (5 studies in atopic dermatitis, 3 studies in psoriasis, 1 study in alopecia areata), and five skin safety studies in healthy participants.

The main clinical studies that provide safety data for the current application are the 'phase 2' dose-ranging study (INCB 18424-**211**), and the two identically designed 'phase 3' confirmatory studies (INCB 18424-**306** and -**307**) in adolescents (10%) and adults. All three studies have been completed. Final data for the treatment-extension period (up to week 52) of studies 306 and 307 were made available in the first round of the procedure upon CHMP's request.

The date of completion of the 'phase 2' study was September 8, 2021, when all participants had either completed the 52-week double-blind period and the 104-week open label extension period (the Week 156 visit) or discontinued early. The dates of completion of the 'phase 3' studies were October 21, 2021, and October 1, 2021, when all participants had completed the 24-week double-blind period and the 28-week treatment extension period or had discontinued early. The treatment extension study in participants with vitiligo (INCB 18424-**308**) of patients who completed studies 306 or 307, is still ongoing. At the time of the cut-off date of January 28, 2022, Cohort A was still blinded. For Cohort B, 36 participants had completed treatment through Week 104, 49 participants had discontinued treatment, and 256 participants were ongoing with treatment in the study. **Adolescents** were included in the two 'phase 3' trials 306 and 307 in Vitiligo (n=72 with n=55 assigned to ruxolitinib 1.5% cream). Adolescents were also included in studies in the atopic dermatitis PK study 102 (n=21 of 71 paediatric subjects were adolescents), maximum use study 103 (n=21), and in 'phase 3' trials 303 and 304 (n=245 with n=72 assigned to ruxolitinib cream 1.5% BID).

2.6.8.1. Patient exposure

The integrated safety database included data from 2620 participants evaluated in 11 studies (INCB 18424-102 (cohorts 1 and 2 only), -201, -202, -203, -204, -206, -211, -303, 304, -306, and -307). A total of 2263 participants applied ruxolitinib 1.5% cream at least once, including 1824 participants in the pooled studies, 41 participants with atopic dermatitis in the maximum use study, and 398 healthy participants in the dermal safety studies.

The primary analysis of the safety of ruxolitinib cream was based on pooled results from the 24-week, double-blind periods of the Phase 3 confirmatory studies (the Phase 3 Vitiligo Vehicle Controlled Population).

Data pools

The Phase 3 Vitiligo Vehicle-Controlled Population includes 673 participants distributed approximately 2:1 between the ruxolitinib 1.5% cream BID and vehicle cream BID treatment groups. All participants had either completed treatment during the 24-week double-blind period (88%) or discontinued early from the study drug (12%).

With the addition of the data of the treatment extension phase, the exposure data consisted of the patients exposed to vehicle cream, who were switched to ruxolitinib cream at week 24, and the patients who were initially randomised to ruxolitinib cream and now continued on ruxolitinib (Table 35). All participants had completed 52 weeks of exposure to ruxolitinib or vehicle followed by ruxolitinib (83%), or had discontinued early (17%).

Table 35: Summary of exposure (phase 3 vitiligo vehicle-controlled population)

Variable	Vehicle Cream BID (N = 224)	Ruxolitinib 1.5% Cream BID (N = 449)	Total (N = 673)
Duration of treatment (days)			
Mean (STD)	156.80 (38.888)	158.94 (34.974)	158.22 (36.309)
Median	168.00	168.00	168.00
Min, max	1.0, 248.0	1.0, 237.0	1.0, 248.0
Categorical summary of duration of treatment (weeks, mean [STD])			
< 8 weeks	11 (4.9)	16 (3.6)	27 (4.0)
≥ 8 to < 16 weeks	12 (5.4)	19 (4.2)	31 (4.6)
≥ 16 to < 24 weeks	23 (10.3)	62 (13.8)	85 (12.6)
≥ 24 weeks	178 (79.5)	352 (78.4)	530 (78.8)
Total weight of medication applied (g)			
Mean (STD)	642.23 (357.348)	682.54 (383.105)	669.13 (374.945)
Median	591.05	609.10	607.80
Min, max	23.0, 1517.1	11.2, 1442.7	11.2, 1517.1
Average weight of medication applied daily (g)			
Mean (STD)	7.12 (22.957)	7.36 (25.230)	7.28 (24.480)
Median	3.81	4.07	4.03
Min, max	0.3, 236.3	0.4, 237.1	0.3, 237.1

The Phase 2/3 Vitiligo Population included 830 participants from studies 211, 306 and 307. At the time of the data cut-off, 256 participants (31%) were ongoing on treatment in the Phase 3 vitiligo treatment extension study (308) study, 299 participants (36%) had completed treatment, and 275 participants (33%) had discontinued study drug early. Among the 767 participants who applied ruxolitinib 1.5% cream BID in the Phase 2/3 Vitiligo Population, 546 participants (71%) were treated with ruxolitinib 1.5% cream BID for ≥ 52 weeks.

Ruxolitinib cream was also evaluated in other disease than vitiligo, i.e. atopic dermatitis, psoriasis, and alopecia areata. The All Ruxolitinib Cream Population included 2579 participants. Across the 1750 participants who applied ruxolitinib 1.5% cream BID at least once in the All Ruxolitinib Cream Population, 828 participants were treated with ruxolitinib 1.5% cream BID for ≥ 52 weeks, and 76 participants were treated with ruxolitinib 1.5% cream BID for ≥ 104 weeks. Ruxolitinib cream exposure was 1462,9 Patient Years of exposure for the ruxolitinib 1.5% cream BID treatment group.

Peadiatric population

About 10% of all patients in the 'phase 3' vitiligo studies were adolescents, 55/449 (12%) were allocated to ruxolitinib cream 1.5% BID. In the 'phase 2' study no adolescents were included.

2.6.8.2. Adverse events

Summary of Adverse Events

In the **pooled vehicle-controlled** vitiligo data, the overall incidences of TEAEs and treatment related TEAEs were higher in the ruxolitinib 1.5% cream BID treatment group (48% and 15%, respectively) versus the vehicle cream BID treatment group (35% and 7.6%, respectively); (see Table 36). A total of 67 (15%) of the participants in the ruxolitinib group reported 'Application Site Reactions', versus 13 (5.8%) in the vehicle group. Few participants had Grade 3 or higher TEAEs, serious TEAEs, or TEAEs leading to study drug discontinuation or interruption, no participant had a TEAE with a fatal outcome; there were no differences between the ruxolitinib and the vehicle groups for these outcomes.

In **adolescents**, the overall incidence of TEAEs and treatment-related TEAEs were also higher in the ruxolitinib 1.5% cream BID treatment group (56% and 16%, respectively) versus the vehicle cream BID treatment group (35% and 0%, respectively). In the ruxolitinib group there were more patients with an 'Application Site Reaction' than with vehicle (18% versus 0, respectively). Few participants had Grade 3 or higher TEAEs/serious TEAEs, and in the ruxolitinib group there were no TEAEs leading to study drug discontinuation or interruption. No participant had a TEAE with a fatal outcome.

Table 36: Overall summary of treatment-emergent adverse events (phase 3 vitiligo vehicle-controlled population)

Category, n (%)	Vehicle Cream BID (N = 224)	Ruxolitinib 1.5% Cream BID (N = 449)
Participants who had a TEAE	79 (35.3)	214 (47.7)
Participants who had a treatment-related TEAE	17 (7.6)	66 (14.7)
Participants who had a Grade 3 or higher severity TEAE	4 (1.8)	10 (2.2)
Participants who had a treatment-related Grade 3 or higher severity TEAE	0	0
Participants who had a serious TEAE	1 (0.4)	8 (1.8)
Participants who had a treatment-related serious TEAE	0	0
Participants who had a TEAE with a fatal outcome	0	0
Participants who had an ASR	13 (5.8)	67 (14.9)
Participants who had a TEAE leading to study drug interruption	4 (1.8)	6 (1.3)
Participants who had a TEAE leading to study drug discontinuation	1 (0.4)	2 (0.4)

In the **pooled treatment extension phase**, the proportion of patients with at least 1 TEAE was 37% in the patients who switched from vehicle to ruxolitinib, similar to the 36% in the vehicle period, and was 59% in the group of patients who continued ruxolitinib (Table 37). The proportion of patients with a SEA or a Grade>3 TEAE, or TEAEs leading to dose discontinuation or interruption were similar in the vehicle and vehicle switch to ruxolitinib groups, and approximately double in the group continuing ruxolitinib. The proportion of patients with an 'Application Site Reaction' was highest in the group who continued ruxolitinib. Overall, low proportions of participants had Grade 3 or higher TEAEs, serious TEAEs, or TEAEs leading to study drug discontinuation or interruption (except for vehicle cream), and no participant had a TEAE with a fatal outcome.

Table 37: Overall summary of treatment-emergent adverse events (phase 3 vitiligo vehicle controlled and treatment extension period, up to week 52).

Variable	Treatment Group: Vehicle BID (N=224)	Vehicle to 1.5% BID (N=188)	1.5% BID to 1.5% BID (N=449)	1.5% BID Total (N=637)
Participants who had a TEAE	81(36.2)	69(36.7)	263(58.6)	332(52.1)
Participants who had a treatment-related TEAE	16(7.1)	11(5.9)	76(16.9)	87(13.7)
Participants who had a serious TEAE	1(0.4)	3(1.6)	11(2.4)	14(2.2)
Participants who had a grade 3 or higher TEAE	3(1.3)	3(1.6)	16(3.6)	19(3.0)
Participants who had a fatal TEAE	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Participants who had an ASR	14(6.3)	12(6.4)	78(17.4)	90(14.1)
Participants who had adverse event leading discontinuation of study drug	1(0.4)	0(0.0)	3(0.7)	3(0.5)
Participants who had adverse event leading to dose interruption	4(1.8)	2(1.1)	10(2.2)	12(1.9)
Participants who had grade 3 or higher treatment-related adverse events	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Participants who had treatment-related serious adverse events	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Exposure-adjusted IR of TEAEs - n (Per 100 PY)[1]	81(84.2)	69(73.2)	263(66.3)	332(67.6)
Exposure-adjusted IR of ASRs - n (Per 100 PY)[1]	14(14.6)	12(12.7)	78(19.7)	90(18.3)

PROGRAM/OUTPUT:T_AE4/T_3_2_1_4_AE1_4 DATE(TIME): 28MAR22(11:33)

Abbreviations: ASR = Application Site Reaction.
Pool 4 includes data from all periods of the Phase 3 vitiligo studies (306/307) for participants who applied study drug at least once.
AE summary only includes AEs from Phase 3 studies 306 and 307.
TEAE: Any AE reported for the first time or worsening of a pre-existing event after first application of study drug.
Treatment-Related TEAEs: treatment-emergent adverse events judged as related by the investigator or with a missing causality.
Note [1]: Exposure-adjusted IR is the number of participants with the event per 100 person-years of exposure.
MedDRA Version: 23.1

Common Adverse Events

In the **pooled vehicle-controlled** vitiligo data, the treatment-emergent AEs were most frequently reported in the following SOCs: 'infections and infestations' (21.8% in the ruxolitinib 1.5% cream BID treatment group vs 16.5% in the vehicle cream BID treatment group), 'general disorders and administration site conditions' (16.5% vs 6.7%, respectively), 'gastrointestinal disorders' (5.3% vs 2.7%, respectively), and 'skin and subcutaneous tissue disorders' (4.2% vs 5.4%, respectively). Within each of these SOCs, TEAEs were largely Grade 1 or 2 in severity and nonserious. Further, Treatment-emergent AEs were more frequently reported in the ruxolitinib 1.5% cream BID treatment group as compared to the vehicle cream BID treatment group, in the following SOCs: 'investigations' (4.7% vs 1.8%, respectively), 'respiratory disorders' (3.3% vs 1.8%, respectively).

Treatment-emergent AEs occurring in ≥ 1% of participants in the vehicle and the ruxolitinib groups are summarised in Table 38. Application site acne was the most common TEAE among participants who applied ruxolitinib 1.5% cream BID and was reported in more participants than in the vehicle group (5.8% in the ruxolitinib 1.5% cream BID treatment group vs 0.9% in the vehicle cream BID treatment group). Of the other common events, 'application site pruritus' and 'nasopharyngitis' were reported more frequently for the ruxolitinib 1.5% cream BID treatment group compared with the vehicle cream treatment group (≥2.0% higher incidence). 'Headache', 'influenza', 'pyrexia', 'urinary tract infection', and 'increased ALT' were numerically more frequent with ruxolitinib as compared to vehicle (Table 38).

In **adolescents**, the most frequently occurring TEAEs (≥2%) with higher incidence in the ruxolitinib group as compared to the vehicle group, were: 'nasopharyngitis', 'covid-19', 'headache', 'application site acne', 'application site pruritis', 'acne', 'application site erythema', 'vomiting'.

Table 38: Summary of treatment-emergent adverse events occurring in ≥ 1% of participants in Any Treatment Group (Phase 3 Vitiligo Vehicle-Controlled Population)

MedDRA PT, n (%)	Vehicle Cream BID (N = 224)	Ruxolitinib 1.5% Cream BID (N = 449)
Participants with any TEAE	*79 (35.3)*	*214 (47.7)*
Application site acne	2 (0.9)	26 (5.8)
Application site pruritus	6 (2.7)	23 (5.1)
Nasopharyngitis	5 (2.2)	19 (4.2)
Headache	6 (2.7)	17 (3.8)
COVID-19	6 (2.7)	13 (2.9)
Upper respiratory tract infection	5 (2.2)	13 (2.9)
Sinusitis	5 (2.2)	10 (2.2)
Application site erythema	1 (0.4)	7 (1.6)
Application site rash	2 (0.9)	7 (1.6)
Influenza	1 (0.4)	6 (1.3)
Pyrexia	0	6 (1.3)
Urinary tract infection	1 (0.4)	6 (1.3)
Alanine aminotransferase increased	1 (0.4)	5 (1.1)
Oral herpes	3 (1.3)	5 (1.1)
Arthralgia	3 (1.3)	3 (0.7)
Pharyngitis streptococcal	3 (1.3)	0

The occurrence of common TEAEs in the **pooled treatment extension phase** and the **pooled phase 2/3** vitiligo studies were quite similar to each other. The pooled phase 2/3 data are presented below, for comprehensiveness (Table 39). Relatively common (>2%) TEAEs in participants in the ruxolitinib 1.5% cream BID treatment group included 'COVID-19', 'nasopharyngitis', 'acne', 'application site pruritus', 'upper respiratory tract infection', 'application site acne', 'headache', 'sinusitis', 'pruritus', 'urinary tract infection', 'hypertension', 'influenza', and 'oral herpes'. Events of 'COVID-19', 'nasopharyngitis', 'acne', 'upper respiratory tract infection', 'application site acne', and 'hypertension' were reported more frequently for the ruxolitinib 1.5% cream BID treatment group compared with the vehicle cream treatment group (≥ 2.0% higher incidence). The common TEAEs in the pooled phase 2/3 data were also apparent in the vehicle-controlled data.

Table 39: Summary of treatment-emergent adverse events occurring in ⩾ 1% of participants in any treatment group (Phase 2/3 vitiligo population)

MedDRA PT, n (%)/Study Size– and Exposure-Adjusted IR per 100 PY	Vehicle Cream BID (N = 256)	Ruxolitinib Cream Regimen				Ruxolitinib Cream Total[a] (N = 789)
		0.15% QD (N = 31)	0.5% QD (N = 45)	1.5% QD (N = 44)	1.5% BID (N = 767)	
Participants with any TEAE	103 (40.2)/ 103.6	20 (64.5)/ 29.8	33 (73.3)/ 24.0	29 (65.9)/ 24.5	463 (60.4)/ 50.5	493 (62.5)/ 49.7
COVID-19	7 (2.7)/5.4	0	0	0	68 (8.9)/7.0	68 (8.6)/7.0
Nasopharyngitis	9 (3.5)/12.0	4 (12.9)/6.0	5 (11.1)/3.6	5 (11.4)/4.2	43 (5.6)/4.6	55 (7.0)/5.5
Acne	2 (0.8)/2.8	4 (12.9)/6.0	5 (11.1)/3.6	4 (9.1)/3.4	36 (4.7)/4.1	48 (6.1)/4.7
Application site pruritus	9 (3.5)/10.7	6 (19.4)/9.0	3 (6.7)/2.2	3 (6.8)/2.5	30 (3.9)/3.1	41 (5.2)/4.1
Upper respiratory tract infection	5 (2.0)/3.9	1 (3.2)/1.5	5 (11.1)/3.6	1 (2.3)/0.8	31 (4.0)/3.4	37 (4.7)/3.7
Application site acne[b]	3 (1.2)/2.2	0	0	0	35 (4.6)/3.6	35 (4.4)/3.6
Headache	9 (3.5)/10.6	1 (3.2)/1.5	0	3 (6.8)/2.5	31 (4.0)/3.3	35 (4.4)/3.5
Sinusitis	6 (2.3)/5.8	2 (6.5)/3.0	1 (2.2)/0.7	2 (4.5)/1.7	26 (3.4)/3.0	29 (3.7)/2.9
Pruritus	6 (2.3)/8.4	1 (3.2)/1.5	5 (11.1)/3.6	5 (11.4)/4.2	10 (1.3)/1.2	20 (2.5)/1.9
Urinary tract infection	1 (0.4)/0.8	1 (3.2)/1.5	0	3 (6.8)/2.5	15 (2.0)/1.6	19 (2.4)/1.9
Hypertension	0	0	2 (4.4)/1.5	1 (2.3)/0.8	15 (2.0)/1.7	18 (2.3)/1.8
Influenza	1 (0.4)/0.8	1 (3.2)/1.5	2 (4.4)/1.5	2 (4.5)/1.7	12 (1.6)/1.4	17 (2.2)/1.7
Oral herpes	3 (1.2)/2.3	2 (6.5)/3.0	1 (2.2)/0.7	1 (2.3)/0.8	14 (1.8)/1.6	17 (2.2)/1.7
Cough	1 (0.4)/0.8	0	2 (4.4)/1.5	1 (2.3)/0.8	12 (1.6)/1.4	15 (1.9)/1.5
Diarrhoea	1 (0.4)/2.0	1 (3.2)/1.5	0	2 (4.5)/1.7	12 (1.6)/1.3	15 (1.9)/1.5
Application site erythema	2 (0.8)/2.8	2 (6.5)/3.0	0	3 (6.8)/2.5	9 (1.2)/1.0	14 (1.8)/1.4
Arthralgia	4 (1.6)/4.3	1 (3.2)/1.5	1 (2.2)/0.7	1 (2.3)/0.8	11 (1.4)/1.2	14 (1.8)/1.4
Bronchitis	1 (0.4)/0.8	5 (16.1)/7.5	0	1 (2.3)/0.8	10 (1.3)/1.2	14 (1.8)/1.4
Oropharyngeal pain	1 (0.4)/0.7	1 (3.2)/1.5	0	1 (2.3)/0.8	11 (1.4)/1.2	13 (1.6)/1.3
Ear infection	0	0	0	1 (2.3)/0.8	11 (1.4)/1.3	12 (1.5)/1.2
Application site exfoliation	1 (0.4)/0.7	2 (6.5)/3.0	0	1 (2.3)/0.8	8 (1.0)/0.9	11 (1.4)/1.1
Application site rash	2 (0.8)/1.5	1 (3.2)/1.5	0	0	10 (1.3)/1.0	11 (1.4)/1.1
Nausea	1 (0.4)/0.8	2 (6.5)/3.0	2 (4.4)/1.5	1 (2.3)/0.8	7 (0.9)/0.7	11 (1.4)/1.1
Pyrexia	0	0	0	0	11 (1.4)/1.2	11 (1.4)/1.1
Alanine aminotransferase increased	1 (0.4)/0.8	0	0	0	10 (1.3)/1.0	10 (1.3)/1.0
Application site dermatitis	0	0	0	0	10 (1.3)/1.0	10 (1.3)/1.0
Dermatitis contact	3 (1.2)/6.1	0	1 (2.2)/0.7	2 (4.5)/1.7	7 (0.9)/0.8	10 (1.3)/1.0
Folliculitis	1 (0.4)/0.7	1 (3.2)/1.5	0	0	9 (1.2)/1.0	10 (1.3)/1.0
Procedural pain	0	0	0	1 (2.3)/0.8	9 (1.2)/1.0	10 (1.3)/1.0

Toothache	1 (0.4)/0.7	0	0	1 (2.3)/0.8	9 (1.2)/0.9	10 (1.3)/1.0
Depression	0	0	1 (2.2)/0.7	0	8 (1.0)/0.9	9 (1.1)/0.9
Fatigue	1 (0.4)/0.7	0	1 (2.2)/0.7	1 (2.3)/0.8	7 (0.9)/0.8	9 (1.1)/0.9
Gastritis	0	0	0	0	9 (1.2)/1.0	9 (1.1)/0.9
Influenza like illness	1 (0.4)/2.0	0	2 (4.4)/1.5	0	7 (0.9)/0.8	9 (1.1)/0.9
Nasal congestion	0	0	2 (4.4)/1.5	2 (4.5)/1.7	5 (0.7)/0.5	9 (1.1)/0.9
Viral infection	1 (0.4)/0.7	0	0	0	9 (1.2)/1.0	9 (1.1)/0.9
Anxiety	0	0	0	0	8 (1.0)/0.9	8 (1.0)/0.8
Dermatitis acneiform	1 (0.4)/0.7	0	1 (2.2)/0.7	1 (2.3)/0.8	6 (0.8)/0.7	8 (1.0)/0.8
Gastroenteritis	2 (0.8)/2.8	0	0	1 (2.3)/0.8	7 (0.9)/0.7	8 (1.0)/0.8
Hypercholesterolaemia	0	0	0	0	8 (1.0)/0.9	8 (1.0)/0.8
Skin papilloma	1 (0.4)/0.7	0	1 (2.2)/0.7	1 (2.3)/0.8	6 (0.8)/0.7	8 (1.0)/0.8

[a] Participants who switched to another treatment during the study were only counted once in total.

[b] During the Phase 3 studies, sites were specifically instructed to capture "Application site acne" if acne was present only where vehicle or ruxolitinib cream had been applied; however, in the Phase 2 study, these events were generally captured under the broader term "acne."

The occurrence of **Covid-19** was similar in the vehicle and ruxolitinib groups in the vehicle-controlled phase and was quite similar in the pooled phase2/3 data, with a IR of 5.0/100PY for vehicle and 7.0/100PY for ruxolitinib 1.5% BID (Table 39), where there also was longer follow-up and a shift in calendar time for ruxolitinib 1.5% cream. The occurrence of **Application site reactions** (ASR) in the pooled phase 3 vitiligo data was 14.9% in the ruxolitinib 1.5% cream BID treatment group and 5.8% in the vehicle cream BID treatment group. All of the events were nonserious, Grade 1 or 2 in severity, and, with the exception of 1 event of application site rash, none led to discontinuation of the study drug. The majority of ASR events resolved without interruption of the study drug and did not recur, except for acne. Application site acne (4.9% in the ruxolitinib 1.5% cream BID treatment group vs 0.9% in the vehicle cream BID group) and application site pruritus (4.7% vs 2.7%, respectively) were the most common events. Also, application site erythema, -rash, and -dermatitis occurred more frequently with ruxolitinib cream. Application site acne typically did not recover/resolve but did not lead to study drug discontinuation. Only one event of application site acne led to study drug interruption.

With the update of the 52-week data, the occurrences (IR) of application site reactions, other than application site acne, where numerically similar in the vehicle group and vehicle to ruxolitinib group (observation periods) and the group who continued on ruxolitinib (Table 40).

Table 40: Summary of application site reactions (Phase 3 vitiligo 52-week population)

MedDRA Preferred Term, n (%)/Exposure-Adjusted IR Per 100 PY	Vehicle Cream BID[a] (N = 224)	Vehicle Cream BID to Ruxolitinib 1.5% Cream BID[b] (N = 188)	Ruxolitinib 1.5% Cream BID to Ruxolitinib 1.5% Cream BID[c] (N = 449)	Ruxolitinib 1.5% Cream BID Total (N = 637)
Any application site TEAE	*14 (6.3)/14.6*	*12 (6.4)/12.7*	*78 (17.4)/19.7*	*90 (14.1)/18.3*
Application site acne	3 (1.3)/3.1	5 (2.7)/5.3	29 (6.5)/7.3	34 (5.3)/6.9
Application site pruritus	6 (2.7)/6.2	1 (0.5)/1.1	24 (5.3)/6.1	25 (3.9)/5.1
Application site dermatitis	0	0	10 (2.2)/2.5	10 (1.6)/2.0
Application site rash	2 (0.9)/2.1	1 (0.5)/1.1	9 (2.0)/2.3	10 (1.6)/2.0
Application site erythema	1 (0.4)/1.0	1 (0.5)/1.1	7 (1.6)/1.8	8 (1.3)/1.6
Application site exfoliation	1 (0.4)/1.0	1 (0.5).1.1	5 (1.1)/1.3	6 (0.9)/1.2
Application site dryness	1 (0.4)/1.0	1 (0.5)/1.1	4 (0.9)/1.0	5 (0.8)/1.0
Application site pain	0	0	5 (1.1)/1.3	5 (0.8)/1.0
Application site discolouration	0	1 (0.5)/1.1	3 (0.7)/0.8	4 (0.6)/0.8
Application site folliculitis	0	0	4 (0.9)/1.0	4 (0.6)/0.8
Application site eczema	0	1 (0.5)/1.1	2 (0.4)/0.5	3 (0.5)/0.6
Application site irritation	1 (0.4)/1.0	0	2 (0.4)/0.5	2 (0.3)/0.4
Application site papules	1 (0.4)/1.0	1 (0.5)/1.1	1 (0.2)/0.3	2 (0.3)/0.4
Application site bruise	0	0	1 (0.2)/0.3	1 (0.2)/0.2
Application site paraesthesia	1 (0.4)/1.0	0	1 (0.2)/0.3	1 (0.2)/0.2
Application site urticaria	0	0	1 (0.2)/0.3	1 (0.2)/0.2

a Treatment-emergent AEs that occurred during the 24-week, double-blind, vehicle-controlled treatment period are summarized for participants who applied vehicle cream BID.
b Treatment-emergent AEs that occurred during the 28-week treatment-extension period are summarized for participants who crossed over to treatment with ruxolitinib 1.5% cream BID.
c Treatment-emergent AEs that occurred during the 52-week study are summarized for participants who applied ruxolitinib 1.5% cream BID throughout the study.

In **adolescents**, a higher percentage in the ruxolitinib 1.5% cream BID group had ASR TEAEs compared to older age groups, in the vehicle cream BID group no ASRs occurred (Table 41). Of the 10 adolescent participants who had ASR TEAEs in the ruxolitinib 1.5% cream BID treatment group, 3 had application site acne and 3 had application site pruritus. With the updated safety data, the occurrences of ASR in the adolescent participants on ruxolitinib (7% for switch group and 20% for maintenance) were similar to the occurrences in adults (6% and 17%), while the types of application site reactions were similar.

Table 41: Summary of application site reaction TEAEs by age group (Phase 3 vitiligo vehicle-controlled population)

Age group, n/N (%)	Vehicle Cream BID	Ruxolitinib 1.5% BID
12 to < 18 years	0/17	10/55 (18.2)
18 to < 65 years	10/191 (5.2)	53/366 (14.5)
≥ 65 years	3/16 (18.8)	4/28 (14.3)

Dermal safety studies

The safety of ruxolitinib 1.5% cream BID under **maximum use conditions** was evaluated in study INCB 18424-**103**. This study was conducted in adolescent and adult participants with atopic

dermatitis; the same formulation, dosage form, strength, and dosing frequency were used for this study as was used in the vitiligo programme. A higher percentage of affected BSA was treated in this study (at least 25%) than in the Phase 3 vitiligo studies (up to 10%). Thirteen participants (32%) experienced ≥ 1 TEAE. Of these, 4 participants experienced 6 treatment-related TEAEs (dyspnea, neutropenia, haemoglobin decreased, AST increased [2 occurrences], and ALT increased). No ASR TEAEs were reported in the study.

Study INCB 18424-**104** was a randomised, evaluator-blinded, within-participant comparison study to evaluate the **skin irritation potential** of ruxolitinib 1.5% cream in healthy adult participants with Fitzpatrick skin types I through IV, using a cumulative irritation patch test design. Forty-four participants were enrolled in the study and 39 participants completed the study. No participants discontinued the patch applications due to irritation. The mean irritation score for ruxolitinib 1.5% cream (0.458) was statistically significantly higher than mean scores for vehicle cream (0.082, $p < 0.001$) and 0.9% saline (0.111, $p < 0.001$) and statistically significantly lower than the mean score for 0.2% Sodium lauryl sulfate (2.479, $p < 0.001$).

Study INCB 18424-**105** was a randomised, double-blind, within participant comparison study to evaluate the **photoallergic potential** of ruxolitinib 1.5% cream in healthy adult participants with Fitzpatrick skin types I through III. In the study, application to healthy skin was followed by light exposure. Sixty participants were enrolled in the study and 52 participants completed the study. During the induction phase, a statistically significant difference was seen with the vehicle cream irradiated sites showing a higher irritation score than the ruxolitinib 1.5% cream irradiated sites; there were no dermal responses in ruxolitinib cream nor vehicle if non-irradiated.

Study INCB 18424-**106** was a single-centre, randomised, controlled, evaluator-blinded, within participant comparison study to evaluate the **sensitisation potential** of ruxolitinib 1.5% cream in healthy adult participants with Fitzpatrick skin types I through IV. Two hundred forty-four participants were enrolled in the study and 214 participants completed the study. For ruxolitinib 1.5% cream, none of the participants showed irritation scores of 1, 2, or 3 during the challenge phase of this study. While 0.9% saline had a higher irritation score than ruxolitinib 1.5% cream and vehicle cream, none of the 3 tested products were classified as causing more than mild skin irritation.

Study INCB 18424-**107** was a single centre, randomised, double blind, controlled, within participant comparison study to evaluate the **phototoxicity potential** of ruxolitinib 1.5% cream in healthy adult participants with Fitzpatrick skin types I through III. Thirty-two participants were enrolled in the study and 31 participants completed the study. All 3 irradiated sites (ruxolitinib 1.5% cream, vehicle cream, and untreated) had higher irritation scores than the nonirradiated sites (ruxolitinib 1.5% cream and vehicle cream) but based on the data these were considered related to the light application itself and not due to phototoxicity.

Adverse drug reactions

The applicant did propose 'Application site acne' to be included as ADR in section 4.8 of the SmPC, as many of the application site acne apparently did not resolve. See 2.6.9 on clinical safety for further discussion on ADRs.

2.6.8.3. Serious adverse event/deaths/other significant events

In the **pooled vehicle-controlled** vitiligo data, SAEs were more frequent in the ruxolitinib cream group as compared to the vehicle group (Table 42). No serious TEAEs occurred in >1 participant in any treatment group, and no serious TEAE was considered related to the study drug by the investigator. No deaths occurred.

Table 42: Summary of serious treatment-emergent adverse events (Phase 3 vitiligo vehicle-controlled population)

MedDRA PT, n (%)	Vehicle Cream BID (N = 224)	Ruxolitinib 1.5% Cream BID (N = 449)
Participants with any serious TEAE	*1 (0.4)*	*8 (1.8)*
Anal fistula	0	1 (0.2)
Appendicitis	0	1 (0.2)
Concussion	0	1 (0.2)
Coronary artery stenosis	0	1 (0.2)
Hepatitis infectious mononucleosis	0	1 (0.2)
Kidney contusion	0	1 (0.2)
Myocarditis	0	1 (0.2)
Ureterolithiasis	0	1 (0.2)
Tibia fracture	1 (0.4)	0

In the **pooled treatment extension data** of the vitiligo phase 3 studies, new serious TEAEs included: 'appendiceal abscess', 'joint dislocation', 'prostate cancer', in the vehicle to ruxolitinib group; 'hypersensitivity', 'rhabdomyolysis', 'papillary thyroid cancer', and 'subacute combined cord degeneration' in the continued ruxolitinib group.

In the **pooled 'All ruxolitinib'** data, a total of 69 participants (2.7%) experienced ≥1 serious TEAE; no serious TEAEs occurred in more than 1 participant in the ruxolitinib 1.5% cream BID group, except 'cholelithiasis'. Except one, no serious TEAE was considered related to the study drug by the investigator. The majority of events were reported as recovered/resolved and did not result in a change in treatment. Serious events occurring in > 1 participant in the ruxolitinib cream total group included 'pneumonia' in 4 participants, ''cholelithiasis in 3 participants, and 'cerebrovascular accident', 'coronary artery occlusion', 'prostate cancer', and 'sepsis' in 2 patients each. All of these events recovered/resolved except for 1 event of 'cerebrovascular accident' (recovering/resolving) and both events of 'prostate cancer' (not recovered/not resolved).

2.6.8.4. Adverse Events of Special Interest

ADRs of JAK inhibitors including oral ruxolitinib were considered as AESIs. Systemic safety considerations with oral ruxolitinib include cytopenias (erythropenia, thrombocytopenia, and neutropenia), risk of infections (e.g., herpes zoster), liver enzyme elevations, and observations of nonmelanoma skin cancers (NMSC). Serious infections, thromboembolic events, MACE, and malignancies are considered a safety concern for oral JAK inhibitors used in chronic inflammatory disorders. An analysis of lipid elevations performed for a previous submission in the US showed a low incidence of elevated lipid events and identified no clinically relevant trends in laboratory values. Therefore, lipids were not measured in the confirmatory Phase 3 vitiligo studies. The applicant considered the likelihood of AEs caused by systemic exposure following topical application of ruxolitinib cream to be low (see Pharmacokinetics and clinical safety sections for discussion).

Cytopenias (erythropenia, thrombocytopenia, neutropenia)

In the pooled phase 3 vitiligo data, the incidences of **erythropenia** TEAEs (0.4% and 0.9% of participants in the vehicle cream BID and ruxolitinib 1.5% cream BID treatment groups, respectively)

and **neutropenia** TEAEs (0.4% and 0%, respectively) were low and similar between the treatment groups (Table 43). There were no events of **thrombocytopenia** in the Phase 3 vitiligo vehicle-controlled population. All TEAEs were nonserious and Grade 1 or 2 in severity.

One participant in the vehicle cream BID group in Study INCB 18424-306 had study drug interrupted after a Grade 2 TEAE of neutrophil count decreased, but the TEAE resolved, and treatment was restarted. All other TEAEs resolved without the need for changes to the study drug.

Table 43: Summary of erythropenia, neutropenia, and thrombocytopenia treatment-emergent adverse events in decreasing order of frequency (Phase 3 vitiligo vehicle-controlled population)

Category MedDRA PT, n (%)	Vehicle Cream BID (N = 224)	Ruxolitinib 1.5% Cream BID (N = 449)
Any erythropenia TEAE	1 (0.4)	4 (0.9)
Haemoglobin decreased	0	2 (0.4)
Anaemia	1 (0.4)	1 (0.2)
Microcytic anaemia	0	1 (0.2)
Any neutropenia TEAE	1 (0.4)	0
Neutrophil count decreased	1 (0.4)	0
Any thrombocytopenia TEAE	0	0

In the All Ruxolitinib Cream Population, the overall incidences of erythropenia, neutropenia, and thrombocytopenia events were low, with 0.9%, 1.4%, and 0.2%, respectively, for the ruxolitinib cream total group. All of these cytopenia events were nonserious and the majority of erythropenia, neutropenia, and thrombocytopenia events resolved with no action taken with the study drug. With inclusion of the data through Week 52 of the phase 3 studies, erythropenia, neutropenia, and thrombocytopenia TEAEs remained infrequent, with no meaningful imbalances in incidences by treatment group.

Herpes zoster and other viral skin infections

In the pooled phase 3 vitiligo data up to week 52, there were two participants with **herpes zoster,** both in the group who continued on ruxolitinib.

Treatment-emergent herpes zoster events (16 events of herpes zoster and 2 events of postherpetic neuralgia) occurred in a total of 15 participants (all of whom applied ruxolitinib) across all studies for all indications in the All Ruxolitinib Cream Population including 2579 participants. All events were Grade 1 or 2 in severity except for 1 TEAE of herpes zoster (Grade 3) that was considered related to the study drug by the investigator. 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 who had postherpetic neuralgia. All participants, with the exception of 1 participant with atopic dermatitis who interrupted study drug due to application site irritation, were able to continue ruxolitinib cream. Plasma ruxolitinib concentrations for participants with available PK concentration values were substantially less than the IC_{50} for JAK2 inhibition in whole blood assays at timepoints prior to the onset of the herpes zoster TEAEs in all cases but one.

The only **viral skin infections** other than herpes zoster, that were identified in the clinical database were herpes simplex (n=9), varicella (n=1), and molluscum contagiosum (n=1). The overall incidence of herpes simplex in the All Ruxolitinib Cream Population was low: 0.5% for the group of patients on ruxolitinib 1.5% cream BID. All events of herpes simplex were Grade 1 or 2 in severity, and all events resolved with no action taken with the study drug except for 1 event that occurred in a participant with atopic dermatitis during the vehicle-controlled period of a Phase 3 study.

Infections and Infestations

In the pooled phase 3 vitiligo data, the most frequently reported (≥ 2%) **infections** for participants who applied ruxolitinib 1.5% cream BID were 'nasopharyngitis', 'COVID-19', 'upper respiratory tract infection', and 'sinusitis' (Table 44). All infections and infestations were Grade 1 or 2 in severity and nonserious with the exception of the following four events: 'appendicitis', 'hepatitis infectious mononucleosis', 'foot infected corn' (not an application site), 'pilonidal cyst' (vehicle group).

Table 44: Summary of treatment-emergent adverse events in the infections and infestations SOC in decreasing order of frequency (phase 3 vitiligo vehicle-controlled population)

.	**Vehicle Cream BID (N = 224)**	**Ruxolitinib 1.5% BID Cream (N = 449)**
Infections and infestations	37 (16.5)	98 (21.8)
Nasopharyngitis	5 (2.2)	19 (4.2)
COVID-19	6 (2.7)	13 (2.9)
Upper respiratory tract infection	5 (2.2)	13 (2.9)
Sinusitis	5 (2.2)	10 (2.2)
Influenza	1 (0.4)	6 (1.3)
Urinary tract infection	1 (0.4)	6 (1.3)
Oral herpes	3 (1.3)	5 (1.1)
Application site folliculitis	0	3 (0.7)
Ear infection	0	3 (0.7)
Gastroenteritis	0	3 (0.7)
Hordeolum	0	3 (0.7)
Rhinitis	1 (0.4)	3 (0.7)
Bacterial vaginosis	0	2 (0.4)
Cystitis	0	2 (0.4)
Folliculitis	1 (0.4)	2 (0.4)
Tooth abscess	0	2 (0.4)
Viral infection	1 (0.4)	2 (0.4)
Vulvovaginal mycotic infection	0	2 (0.4)
Appendicitis	0	1 (0.2)
Body tinea	0	1 (0.2)
Bronchitis	1 (0.4)	1 (0.2)
Conjunctivitis	1 (0.4)	1 (0.2)
Diverticulitis	0	1 (0.2)
Fungal infection	0	1 (0.2)
Fungal skin infection	0	1 (0.2)
Gingivitis	0	1 (0.2)
Helicobacter gastritis	0	1 (0.2)
Hepatitis infectious mononucleosis	0	1 (0.2)
Herpes simplex	0	1 (0.2)
Localised infection	0	1 (0.2)
Otitis externa	0	1 (0.2)
Pharyngitis	1 (0.4)	1 (0.2)
Post procedural infection	0	1 (0.2)

Pulpitis dental	0	1 (0.2)
Suspected COVID-19	1 (0.4)	1 (0.2)
Tinea pedis	0	1 (0.2)
Tonsillitis bacterial	0	1 (0.2)
Tooth infection	1 (0.4)	1 (0.2)
Acute sinusitis	1 (0.4)	0
Labyrinthitis	1 (0.4)	0
Otitis media bacterial	1 (0.4)	0
Pharyngitis streptococcal	3 (1.3)	0
Pilonidal cyst	1 (0.4)	0
Tinea versicolor	1 (0.4)	0

With the update of the 52-week safety data of the vitiligo phase 3 studies, there were no obvious differences in occurrence of infections at the SOC level: the occurrence of infections and infestations (SOC) was 17.4% in the vehicle group over 24 weeks, 15.4% for the period that these patients switched from vehicle to ruxolitinib for 24 weeks, and 29.8% for the patients remaining on ruxolitinib for up to 52 weeks. Among the most frequent infections at the PT level, there were no obvious between-group differences, with probable exception of 'influenza' (Table 45). With the update of safety data, 'Covid-19' became the most frequently occurring infectious TEAE, with no notable differences between groups (3.1% versus 3.2% versus 7.3%) as there is a longer observation period in the ruxolitinib 1.5% maintenance group, n/PY were comparable: 7.3 for vehicle and 7.9 for maintenance with ruxolitinib 1.5% BID.

Table 45: Treatment-emergent adverse events of nasopharyngitis, influenza, and urinary tract infection in the vitiligo studies

	Vehicle Cream BID	**Vehicle Cream BID to Ruxolitinib 1.5% Cream BID**	**Ruxolitinib 1.5% Cream BID**
Week 24 Phase 3 Studies, n (%)	N = 224		N = 449
Nasopharyngitis	5 (2.2)		19 (4.2)
Influenza	1 (0.4)		6 (1.3)
Urinary tract infection	1 (0.4)		6 (1.3)
Week 52 Phase 3 Studies, n (%)		N = 188	N = 449
Nasopharyngitis		5 (2.7)	26 (5.8)
Influenza		0	7 (1.6)
Urinary tract infection		1 (0.5)	9 (2.0)
Phase 2/3 Studies, n (%)/exposure-adjusted IR per 100 PY	N = 256		N = 767
Nasopharyngitis	9 (3.5)/12.0		43 (5.6)/4.6
Influenza	1 (0.4)/0.8		12 (1.6)/1.4
Urinary tract infection	1 (0.4)/0.8		15 (2.0)/1.6

In the All Ruxolitinib Cream Population, infections and infestations were nonserious with the exception of the following 12 events: four cases of 'serious pneumonia'; two cases of 'sepsis'; one case each of 'bronchitis', 'infective cholecystitis', 'chronic tonsillitis', 'tooth infection', and 'diverticulitis'.

Non-melanoma skin neoplasms

In the All Ruxolitinib Cream Population, in total 11 participants had a TEAE of **nonmelanoma skin neoplasms**: 'basal cell carcinoma' in 6 participants, 'squamous cell carcinoma' in 5 participants, and 'Bowen's disease' in 1 participant. In the Phase 2/3 Vitiligo Population, the prevalence of nonmelanoma skin neoplasms was 0.5% (4 of 767) in the ruxolitinib cream treatment group and 0.4% (1 of 256) in the vehicle cream treatment group; 4/5 participants on ruxolitinib had a NMSC on an application site, as had the participant with NMSC in the vehicle group. The occurrence was lower as compared to approximately 5% in the general US population (Stern 2010), while the prevalence 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).

Malignancies

An analysis of **malignancies** in the Phase 3 Vehicle-Controlled Vitiligo Population, Phase 3 safety data up to week 52, and the Phase 2/3 Vitiligo Population showed a low incidence of malignancies in the vitiligo Phase 3 studies, and no significant differences between groups. In the phase 2/3 safety pool, malignancies other than NMSC occurred in 1 participant (0.4%) in the vehicle cream BID group and 10 participants (1.3%) in the ruxolitinib 1.5% cream group. Events identified were: 'breast cancer', 'colon adenoma', 'ovarian cancer', 'haemangioma', 'lipoma', 'melanocytic naevus', 'papillary thyroid cancer', 'pituitary cancer', and 'prostate cancer'.

Arterial and venous thromboembolic events, MACE, and thrombocytosis events

In the All Ruxolitinib Cream Population, a total of 9 participants (3 with vitiligo, 5 with atopic dermatitis, and 1 with psoriasis), all of whom were on a ruxolitinib cream regimen at the time of onset of the event, had at least 1 treatment-emergent thromboembolic event, including VTE and MACE: 'coronary artery occlusion', 'pulmonary embolism (PE)', and 'cerebrovascular accident' in 2 participants each and 'myocardial infarction', 'deep venous thrombosis (DVT)', 'transient ischemic attack', and 'thrombosis' in 1 participant each. Plasma ruxolitinib concentrations in 8 of the 9 participants with thromboembolic events were substantially lower than the IC_{50} for JAK2 inhibition in whole blood assays at all timepoints prior to the onset of the TEAEs.

In the updated safety database of the phase2/3 vitiligo studies, no cases of VTE occurred, but two thromboembolic TEAEs were found ('cardiac ventricular thrombosis' and 'thrombosis') with one MACE. According to the case descriptions, these participants had other risk factors for the event (multiple risk factors for MACE including previous PE and DVT; immobilisation after surgery without anticoagulation).

In the All Ruxolitinib Cream Population, the exposure-adjusted incidence rates of thrombosis (1 event in a participant with vitiligo), DVT (1 event in a participant with atopic dermatitis), and PE (2 events in 2 participants with atopic dermatitis) were 10 per 10,000 PY. These incidence rates are similar to those reported in the general population: 4.5 to 11.7 per 10,000 PY for DVT and 2.9 to 7.8 per 10,000 PY for PE (Alotaibi et al 2016, Heit 2015) and to those reported for participants with vitiligo (Schneeweiss et al 2021). For oral ruxolitinib (Jakavi), no association of arterial and venous thromboembolic events and MACE was observed in the randomised periods of the Phase 3 studies in participants with myelofibrosis and polycythemia vera.

Liver function

Elevations in **liver function** parameters, including ALT and AST, have been observed with oral ruxolitinib treatment (Jakavi SmPC). No participant in any oral ruxolitinib clinical study has met the criteria for Hy's law. In the pooled phase 3 Vitiligo data, raised values of liver function tests were infrequent in both the ruxolitinib cream and vehicle groups in the vehicle-controlled vitiligo data, with increases in ALT occurring in 1.1% of the ruxolitinib cream group, versus 0.4% (n=1) in the vehicle

group (Table 46). Over all indications ('All ruxolitinib cream population'), there were no signals for liver-related investigations, signs or symptoms, as all occurrences of TEAEs were <1%. No TEAEs met the criteria for Hy's law. Also, after inclusion of the data of the maintenance phase in vitiligo to the vehicle-controlled data, there were no consistent patterns of abnormalities in liver function tests, over time.

Table 46: Summary of liver-related investigations, signs and symptoms SMQ treatment-emergent adverse events in decreasing order of frequency (phase 3 vitiligo vehicle-controlled population)

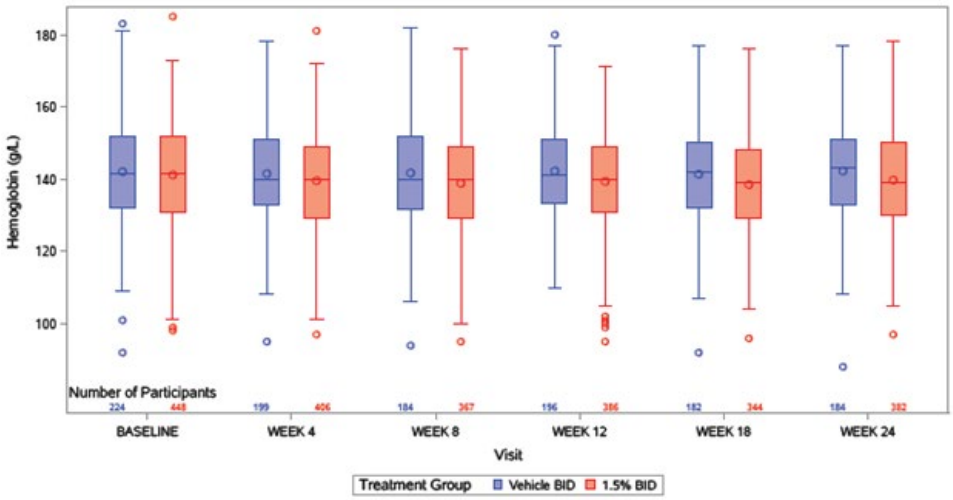
MedDRA PT, n (%)	Vehicle Cream BID (N = 224)	Ruxolitinib 1.5% Cream BID (N = 449)
Any liver-related investigations, signs and symptoms TEAE	*2 (0.9)*	*7 (1.6)*
Alanine aminotransferase increased	1 (0.4)	5 (1.1)
Aspartate aminotransferase increased	2 (0.9)	2 (0.4)
Blood alkaline phosphatase increased	0	1 (0.2)
Transaminases increased	0	1 (0.2)

2.6.8.5. Laboratory findings

Haematology

At all visits through week 24 in the Phase 3 Vitiligo Vehicle-Controlled Population, the mean **haemoglobin** levels were largely overlapping between the vehicle cream BID treatment group and the ruxolitinib 1.5% cream BID treatment group (see Figure 32). There were no apparent trends over time for mean haemoglobin levels, and observed fluctuations were minor and not clinically relevant. With the inclusion of data from the treatment-extension periods of the Phase 3 studies, mean hemoglobin concentrations remained similar between participants who were initially randomised to vehicle and participants who were initially randomised to the ruxolitinib 1.5% cream BID treatment group.

Figure 32: Box plot of haemoglobin levels by visit and treatment group (phase 3 vitiligo vehicle-controlled population)



Note: Mean values are denoted by the larger "o" symbol.

Across all treatment groups, no participants had a postbaseline shift to CTCAE Grade 3 in haemoglobin concentration values (Table 47). Overall, the proportion of postbaseline shifts in haemoglobin concentration CTCAE grade values was small. Three participants in the ruxolitinib 1.5% cream BID treatment group had a Grade 1 to Grade 2 postbaseline shift.

Table 47: Shift summary of haemoglobin concentration values in CTCAE grade to the worst (low) abnormal value (phase 3 vitiligo vehicle-controlled population)

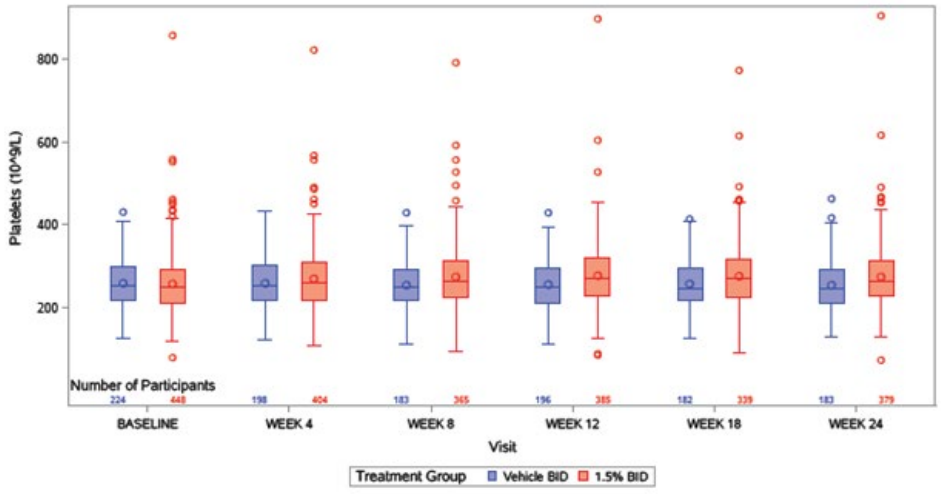
Treatment Group	Baseline[a]		Worst Postbaseline Value[b]				
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Missing
Vehicle cream BID (N = 224)	Grade 0	205 (91.5)	179 (87.3)	16 (7.8)	0	0	10 (4.9)
	Grade 1	18 (8.0)	4 (22.2)	14 (77.8)	0	0	0
	Grade 2	1 (0.4)	0	0	1 (100.0)	0	0
	Grade 3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	224 (100.0)	183 (81.7)	30 (13.4)	1 (0.4)	0	10 (4.5)
Ruxolitinib 1.5% cream BID (N = 449)	Grade 0	418 (93.1)	361 (86.4)	42 (10.0)	1 (0.2)	0	14 (3.3)
	Grade 1	28 (6.2)	1 (3.6)	23 (82.1)	3 (10.7)	0	1 (3.6)
	Grade 2	2 (0.4)	0	0	2 (100.0)	0	0
	Grade 3	0	0	0	0	0	0
	Missing	1 (0.2)	0	0	0	0	1 (100.0)
	Total	449 (100.0)	362 (80.6)	65 (14.5)	6 (1.3)	0	16 (3.6)

a The percentages were calculated using the baseline total as the denominator.

b For each row, the percentages were calculated using the number of participants with given grade at baseline as the denominator; worst value on study is the worst grade observed postbaseline for a given participant.

At all visits through week 24 in the Phase 3 Vitiligo Vehicle-Controlled Population, the mean **platelet levels** were largely similar between the vehicle cream BID treatment group and the ruxolitinib 1.5% cream BID treatment group (see Figure 33). There were outlying mild-moderate *increases* in platelet counts for some participants (n=4), and these were more common for ruxolitinib than for the vehicle control (n=1). With the inclusion of data from the treatment-extension periods of the Phase 3 studies, mean platelet counts remained similar between participants who were initially randomised to vehicle cream and participants who were initially randomised to the ruxolitinib 1.5% cream BID treatment group.

Figure 33: Box plot of platelet counts by visit and treatment group (phase 3 vitiligo vehicle-controlled population)



Note: Mean values are denoted by the larger "o" symbol.

Abnormal platelet count *decreases* by CTCAE grade in the Phase 3 Vitiligo Vehicle-Controlled Population are presented in Table 48. One participant in the ruxolitinib 1.5% cream treatment group had a postbaseline shift from Grade 1 to Grade 2. All other shifts were shifts to at most Grade 1. Most participants with decreased platelet counts at baseline remained at the same grade postbaseline.

Table 48: Shift summary of platelet count values in CTCAE grade to the worst (low) abnormal value (phase 3 vitiligo vehicle-controlled population)

Treatment Group	Baseline[a]		Worst Postbaseline Value[b]					
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Vehicle cream BID (N = 224)	Grade 0	223 (99.6)	212 (95.1)	1 (0.4)	0	0	0	10 (4.5)
	Grade 1	1 (0.4)	0	1 (100.0)	0	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Total	224 (100.0)	212 (94.6)	2 (0.9)	0	0	0	10 (4.5)
Ruxolitinib 1.5% cream BID (N = 449)	Grade 0	443 (98.7)	426 (96.2)	2 (0.5)	0	0	0	15 (3.4)
	Grade 1	5 (1.1)	1 (20.0)	3 (60.0)	1 (20.0)	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	1 (0.2)	0	0	0	0	0	1 (100.0)
	Total	449 (100.0)	427 (95.1)	5 (1.1)	1 (0.2)	0	0	16 (3.6)

[a] The percentages were calculated using the baseline total as the denominator.
[b] For each row, the percentages were calculated using the number of participants with given grade at baseline as the denominator; worst value on study is the worst grade observed postbaseline for a given participant.

At all visits through week 24 in the Phase 3 Vitiligo Vehicle-Controlled Population, mean **neutrophil counts** were similar between the vehicle cream BID treatment group and the ruxolitinib 1.5% cream BID treatment group. There were no apparent trends over time for mean neutrophil counts, and observed fluctuations were minor and not clinically significant. In the long-term safety data of the phase 3 vitiligo population, the occurrence of neutropenia and of erythropenia and thrombocytopenia remained low. This picture did not change when considering the long-term follow-up data of the phase 2/3 pool.

According to the applicant, overall, the proportion of postbaseline decreases in neutrophil count CTCAE grade values was small and similar between the 2 treatment groups (Table 49). The majority of shifts were to Grade 1 or 2 and were not clinically relevant: 1 participant each in the vehicle cream BID and ruxolitinib 1.5% cream BID treatment groups had a Grade 0 to Grade 3 postbaseline decrease in neutrophil count values; the participants had no other abnormal neutrophil values during the study and no TEAEs associated with abnormal neutrophil values.

Table 49: Shift summary of neutrophil count values in CTCAE grade to the worst (low) abnormal value (phase 3 vitiligo vehicle-controlled population)

Treatment Group	Baseline[a]		Worst Postbaseline Value[b]					
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Vehicle cream BID (N = 224)	Grade 0	218 (97.3)	193 (88.5)	10 (4.6)	5 (2.3)	1 (0.5)	0	9 (4.1)
	Grade 1	4 (1.8)	1 (25.0)	0	3 (75.0)	0	0	0
	Grade 2	2 (0.9)	0	0	1 (50.0)	0	0	1 (50.0)
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0

Treatment Group	Baseline[a]		Worst Postbaseline Value[b]					
	Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
	Total	224 (100.0)	194 (86.6)	10 (4.5)	9 (4.0)	1 (0.4)	0	10 (4.5)
Ruxolitinib 1.5% cream BID (N = 449)	Grade 0	432 (96.2)	391 (90.5)	19 (4.4)	6 (1.4)	1 (0.2)	0	15 (3.5)
	Grade 1	10 (2.2)	5 (50.0)	2 (20.0)	3 (30.0)	0	0	0
	Grade 2	5 (1.1)	1 (20.0)	2 (40.0)	2 (40.0)	0	0	0
	Grade 3	1 (0.2)	0	0	0	1 (100.0)	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	1 (0.2)	0	0	0	0	0	1 (100.0)
	Total	449 (100.0)	397 (88.4)	23 (5.1)	11 (2.4)	2 (0.4)	0	16 (3.6)

The percentages were calculated using the baseline total as the denominator.
For each row, the percentages were calculated using the number of participants with given grade at baseline as the denominator; worst value on study is the worst grade observed postbaseline for a given participant.

Across all 3 safety pools, there were no notable differences in the change or percentage change from baseline in leukocyte counts, lymphocyte counts, erythrocyte counts and reticulocyte counts, between the vehicle cream BID treatment group and the ruxolitinib 1.5% cream BID treatment groups through Week 156.

Clinical chemistry

Descriptive statistics for the Phase 3 Vitiligo Vehicle-Controlled Population and treatment extension period up to week 52, the Phase 2/3 Vitiligo Population, and the All Ruxolitinib Population showed no evidence of treatment-related changes in any chemistry values. In addition, there were no consistent patterns of abnormalities in chemistry parameters, including liver and renal function tests, over time.

Vital signs

In each of the Phase 3 studies in participants with vitiligo and the dose-ranging Phase 2 study in participants with vitiligo, the majority of participants had normal vital signs values at baseline and at each visit throughout the double-blind period. There were few alert vital signs, and none were associated with TEAEs. Alert vital signs showed most frequently single instances of high diastolic or high systolic blood pressure and were higher in ruxolitinib cream groups than in the vehicle control group.

2.6.8.6. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.7. Safety in special populations

The possible effect of intrinsic factors, including age, sex, and race, on the safety profile of ruxolitinib cream was evaluated for both of the pooled vitiligo populations (pool 1 and pool 2). An overall summary of TEAEs for participants in the Phase 3 Vitiligo Vehicle-Controlled Population by demographic subgroup is presented in Table 50.

Table 50: Overall summary of treatment-emergent adverse events by demographic characteristic subgroup (phase 3 vitiligo vehicle-controlled population)

Demographic Characteristic	Subgroup	Treatment Group	N	Treatment-Emergent Adverse Events, n (%)						
				All	Treatment-Related	≥ Grade 3	Serious	With Fatal Outcome	Leading to Study Drug Interruption	Leading to Study Drug Discontinuation
Age	12 to < 18 years	Vehicle cream BID	17	6 (35.3)	0	1 (5.9)	0	0	2 (11.8)	0
		Ruxolitinib 1.5% cream BID	55	31 (56.4)	9 (16.4)	0	1 (1.8)	0	0	0
	18 to < 65 years	Vehicle cream BID	191	64 (33.5)	14 (7.3)	3 (1.6)	1 (0.5)	0	2 (1.0)	1 (0.5)
		Ruxolitinib 1.5% cream BID	366	172 (47.0)	53 (14.5)	10 (2.7)	7 (1.9)	0	4 (1.1)	2 (0.5)
	≥ 65 years	Vehicle cream BID	16	9 (56.3)	3 (18.8)	0	0	0	0	0
		Ruxolitinib 1.5% cream BID	28	11 (39.3)	4 (14.3)	0	0	0	2 (7.1)	0
Sex	Male	Vehicle cream BID	114	29 (25.4)	3 (2.6)	1 (0.9)	1 (0.9)	0	3 (2.6)	1 (0.9)
		Ruxolitinib 1.5% cream BID	201	85 (42.3)	20 (10.0)	4 (2.0)	7 (3.5)	0	4 (2.0)	1 (0.5)
	Female	Vehicle cream BID	110	50 (45.5)	14 (12.7)	3 (2.7)	0	0	1 (0.9)	0
		Ruxolitinib 1.5% cream BID	248	129 (52.0)	46 (18.5)	6 (2.4)	1 (0.4)	0	2 (0.8)	1 (0.4)
Race	White	Vehicle cream BID	189	67 (35.4)	14 (7.4)	3 (1.6)	1 (0.5)	0	4 (2.1)	0
		Ruxolitinib 1.5% cream BID	362	174 (48.1)	53 (14.6)	8 (2.2)	6 (1.7)	0	4 (1.1)	2 (0.6)
	Black or African American	Vehicle cream BID	9	1 (11.1)	0	0	0	0	0	0
		Ruxolitinib 1.5% cream BID	23	8 (34.8)	1 (4.3)	0	0	0	0	0
	Asian	Vehicle cream BID	11	0	0	0	0	0	0	0
		Ruxolitinib 1.5% cream BID	17	4 (23.5)	1 (5.9)	0	0	0	1 (5.9)	0
	Not reported	Vehicle cream BID	6	5 (83.3)	1 (16.7)	1 (16.7)	0	0	0	0
		Ruxolitinib 1.5% cream BID	19	17 (89.5)	8 (42.1)	2 (10.5)	2 (10.5)	0	1 (5.3)	0

Demographic Characteristic	Subgroup	Treatment Group	N	Treatment-Emergent Adverse Events, n (%)						
				All	Treatment-Related	≥ Grade 3	Serious	With Fatal Outcome	Leading to Study Drug Interruption	Leading to Study Drug Discontinuation
	Other	Vehicle cream BID	9	6 (66.7)	2 (22.2)	0	0	0	0	1 (11.1)
		Ruxolitinib 1.5% cream BID	28	11 (39.3)	3 (10.7)	0	0	0	0	0

No meaningful differences were observed between the different age subgroups for treatment-related or other TEAE categories. No meaningful differences were observed between the sex and race subgroups for TEAE categories.

Use on areas larger than 10%BSA

In patients with vitiligo, use is restricted to maximal 10% of BSA, according to the posology reflected in SmPC section 4.2. The safety of using ruxolitinib 1.5% cream on larger areas was evaluated in study 211.

The safety data of study 211, comparing ruxolitinib 1.5% BID with vehicle with a controlled phase of 24 weeks, stratified by using ruxolitinib on ⩽10% BSA or >10% BSA, showed that also in patients using ruxolitinib on 10%-20% BSA, ruxolitinib was well tolerated. In that study, there were no clear differences in safety profile between patients using ruxolitinib 1.5% cream on less or more than 10% of BSA regarding occurrence of TEAEs (72% versus 66%), SAEs (0% versus 4%), Grade>3 AEs (2.6% versus 4%); similar proportions of patients had TEAEs leading to drug interruption (10% versus 12%) or discontinuation (2.6% versus 3.3%). However, though based on a small number of patients, all 4 SAEs occurred in the group of patients on ruxolitinib and a BSA>10%: subdural haematoma by external physical influence; Grade 3 seizure; coronary artery occlusion in a participant with history of hypertension and hyperlipidaemia; Grade 3 oesophageal achalasia in a participant with history of dyspepsia. None of these events were designated as treatment-related by the investigator. Except for influenza (4 cases versus 1 case), there were no TEAEs at the PT level that tended to occur more often in patients on ruxolitinib treating a BSA>10%, as compared to patients using ruxolitinib <10% BSA.

Adolescents

In the 'phase 3' vehicle-controlled population, the overall incidence of TEAEs for participants who applied ruxolitinib cream was somewhat higher in adolescents (56.4%) compared with participants in the 18 to < 65 years and ≥ 65 years subgroups (47.0% and 39.3%, respectively).

On PT-level, the incidence of both 'COVID-19' and 'headache' was higher in adolescents (7.3% each) than in participants aged 18 to < 65 years (2.5% and 3.6%, respectively), but the instances of 'application site acne' and 'application site pruritus' were comparable across groups (ranging from 5.5% to 5.7%). 'Nasopharyngitis' in the ruxolitinib 1.5% cream treatment group was also more commonly reported in adolescents (14.5%) versus participants aged 18 to < 65 years (3.0%) and ≥ 65 years (0%). In total there were 13 (24%) instances of 'application site reactions' in adolescents on ruxolitinib 1.5% BID, versus 65 (18%) in adults between 18-65 years of age.

In adolescents continuing ruxolitinib for at least 52 weeks as maintenance, the overall occurrence of TEAS was quite similar (64% versus 58%) as compared to adults. In adolescents, one participant had a SAE and discontinuations due to AEs did not occur. The type and occurrence of the most common TEAEs were considered reasonably similar for adolescents and adults, including 'application site reactions', 'application site acne' and 'pruritis' (Table 51).

In the All ruxolitinib cream population, the proportion of patients with ≥1 TEAE, ≥Grade 3 AEs, SAEs, and AEs leading to study drug interruption or discontinuation, was similar or lower in the 195 adolescent patients on ruxolitinib cream 1.5% BID, as compared to the 1417 adults aged between 18 and 65 on the same regimen.

Table 51: Summary of treatment-emergent adverse events occurring in ≥ 2% of adolescent or adult participants in the ruxolitinib 1.5% cream BID (total) treatment group (phase 3 vitiligo 52-week population)

	Adolescents (12 to < 18 Years)				**Adults (≥18 Years)**			
MedDRA Preferred Term	**Vehicle Cream BID[a] (N = 17)**	**Vehicle Cream BID to Ruxolitinib 1.5% Cream BID[b] (N = 15)**	**Ruxolitinib 1.5% Cream BID to Ruxolitinib 1.5% Cream BID[c] (N = 55)**	**Ruxolitinib 1.5% Cream BID Total (N = 70)**	**Vehicle Cream BID[a] (N = 207)**	**Vehicle Cream BID to Ruxolitinib 1.5% Cream BID[b] (N = 173)**	**Ruxolitinib 1.5% Cream BID to Ruxolitinib 1.5% Cream BID[c] (N = 394)**	**Ruxolitinib 1.5% Cream BID Total (N = 567)**
Participants with any TEAE	*6 (35.3)*	*2 (13.3)*	*35 (63.6)*	*37 (52.9)*	*75 (36.2)*	*67 (38.7)*	*228 (57.9)*	*295 (52.0)*
COVID-19	0	0	5 (9.1)	5 (7.1)	7 (3.4)	6 (3.5)	28 (7.1)	34 (6.0)
Application site acne	0	1 (6.7)	3 (5.5)	4 (5.7)	3 (1.4)	4 (2.3)	26 (6.6)	30 (5.3)
Application site pruritus	0	0	3 (5.5)	3 (4.3)	6 (2.9)	1 (0.6)	21 (5.3)	22 (3.9)
Nasopharyngitis	0	0	9 (16.4)	9 (12.9)	5 (2.4)	5 (2.9)	17 (4.3)	22 (3.9)
Headache	1 (5.9)	0	4 (7.3)	4 (5.7)	5 (2.4)	3 (1.7)	18 (4.6)	21 (3.7)
Upper respiratory tract infection	1 (5.9)	1 (6.7)	1 (1.8)	2 (2.9)	4 (1.9)	4 (2.3)	14 (3.6)	18 (3.2)
Sinusitis	0	0	1 (1.8)	1 (1.4)	5 (2.4)	1 (0.6)	12 (3.0)	13 (2.3)
Application site rash	0	0	2 (3.6)	2 (2.9)	2 (1.0)	1 (0.6)	7 (1.8)	8 (1.4)
Acne	0	0	3 (5.5)	3 (4.3)	1 (0.5)	4 (2.3)	2 (0.5)	6 (1.1)
Application site erythema	0	0	2 (3.6)	2 (2.9)	1 (0.5)	1 (0.6)	5 (1.3)	6 (1.1)
Application site exfoliation	0	1 (6.7)	1 (1.8)	2 (2.9)	1 (0.5)	0	4 (1.0)	4 (0.7)
Vomiting	0	1 (6.7)	2 (3.6)	3 (4.3)	0	0	2 (0.5)	2 (0.4)
Epistaxis	0	0	2 (3.6)	2 (2.9)	0	0	1 (0.3)	1 (0.2)

Pregnancy and lactation

When pregnant rats and rabbits were administered oral ruxolitinib during the period of organogenesis, adverse developmental outcomes occurred at doses associated with maternal toxicity (see non-clinical assessment). 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. Nevertheless, ruxolitinib and/or its metabolites were present in the milk of lactating rats (see non-clinical assessment).

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.

A total of 9 pregnancies and 4 pregnancies of a partner have been reported across the ruxolitinib cream clinical development programme as of the data cutoff dates for the ongoing study. Five pregnancies resulted in a term birth and healthy infant. Two participants had TEAEs of spontaneous abortion (both assessed as unrelated to the study drug by the investigator), and 1 participant had a benign hydatidiform mole (serious TEAE assessed as related to the study drug by the investigator). The outcomes of the remaining five pregnancies that occurred during the trial are unknown.

Liver impairment

In the pivotal studies, patients were excluded if they had current and/or history of liver disease, including known hepatitis B or C, with hepatic or biliary abnormalities. For the posology section in the SmPC, the applicant initially proposed to reflect that *'no studies with ruxolitinib cream 1.5% BID have been performed in hepatically impaired patients. However, due to limited systemic exposure, dosage adjustment is not necessary in patients with hepatic impairment.'*

Renal impairment

In the pivotal studies, patients with severe renal disease (with creatinine clearance < 30 ml/min) or renal disease requiring dialysis were excluded. For the posology section in the SmPC, the applicant initially proposed to reflect that *'No studies with ruxolitinib cream 1.5% have been performed in renally impaired patients. However, due to limited systemic exposure, dosage adjustment is not necessary in patients with renal impairment.'*

Upon CHMP's request, the following information was added to SmPC section 4.2 *'As a precautionary measure, ruxolitinib cream should not be used by patients with end stage renal disease, due to lack of data regarding the safety.'*

2.6.8.8. Immunological events

Since ruxolitinib is a topical cream, the risk of anti-drug antibodies formation is considered negligible.

2.6.8.9. Safety related to drug-drug interactions and other interactions

Ruxolitinib is predominantly cleared by CYP3A4 metabolism. Drug-drug interaction potential for *oral* ruxolitinib was evaluated in dedicated clinical pharmacology studies that included coadministration of strong or moderate CYP3A4 inhibitors or a strong inducer (see Clinical pharmacology section for details). The plasma area under the curve of ruxolitinib was approximately doubled with coadministration of ketoconazole, a potent inhibitor of CYP3A4, while only a modest increase was seen with coadministration of erythromycin, a moderate inhibitor of CYP3A4.

No drug-drug interaction studies of ruxolitinib cream were conducted. However, the potential for drug-drug interactions with ruxolitinib following topical applications of ruxolitinib cream is considered lower

than that of ruxolitinib after oral dosing because systemically absorbed ruxolitinib following topical administration is not subject to first-pass clearance. The applicant argued that concomitant strong CYP3A4 inhibitors are expected to have a lesser impact on plasma concentrations of ruxolitinib, while concomitant strong CYP3A4 inducers are not expected to be of clinical impact since the efficacy of ruxolitinib cream is likely driven by the local actions of ruxolitinib in the skin.

Based on the above, the applicant considered that no adjustment to ruxolitinib cream applications is needed when patients with vitiligo are on a concomitant treatment with a CYP3A4 inhibitor or inducer.

Upon CHMP's request, the following information was added to SmPC section 4.5: *'Ruxolitinib has not been evaluated in combination with other cutaneous medicinal products; therefore, co-application on the same skin areas is not recommended.'* And *'Other topical medicinal products used to treat other conditions on the same skin areas should be applied with a minimum of 2 hours after the application of ruxolitinib cream. This is also applicable to the use of sunscreen or emollients'.*

2.6.8.10. Discontinuation due to adverse events

The overall incidence of TEAEs leading to permanent discontinuation of study drug for participants in the pooled phase 3 vitiligo data was low, with discontinuation reported for 2 participants each in the ruxolitinib 1.5% cream BID (application site rash, fatigue) and vehicle cream BID treatment groups (nausea, headache). All events that led to study drug discontinuation were Grade 1 or 2, and all events were reported as having recovered/resolved.

The overall incidence of TEAEs leading to temporary interruption of study drug for participants in the pooled phase 3 vitiligo data was low, with discontinuation reported for a single participant for any PT in the ruxolitinib 1.5% cream BID and vehicle cream BID groups (Table 52). The majority of events that led to study drug interruption were Grade 1 or 2 with the exception of Grade 3 hepatitis infectious mononucleosis and coronary artery stenosis. All TEAEs leading to study drug interruption were reported as having recovered/resolved except for 1 participant with Grade 2 application site acne (not recovered/not resolved) and 1 participant with Grade 2 elevated blood creatine phosphokinase (recovering/resolving); both participants restarted treatment and were ongoing in the treatment extension period at the time of data cutoff.

Table 52: Summary of treatment-emergent adverse events leading to interruption of study drug (phase 3 vitiligo vehicle-controlled population)

MedDRA PT, n (%)	**Vehicle Cream BID (N = 224)**	**Ruxolitinib 1.5% Cream BID (N = 449)**
Participants with any TEAE leading to interruption of study drug	*4 (1.8)*	*6 (1.3)*
Application site acne	0	1 (0.2)
Coronary artery stenosis	0	1 (0.2)
Cough	0	1 (0.2)
Hepatitis infectious mononucleosis	0	1 (0.2)
Nephrolithiasis	0	1 (0.2)
Pain	0	1 (0.2)
Pyrexia	0	1 (0.2)
Sunburn	0	1 (0.2)
Transaminases increased	0	1 (0.2)
Aspartate aminotransferase increased	1 (0.4)	0

Blood creatine phosphokinase increased	1 (0.4)	0
Blood pressure fluctuation	1 (0.4)	0
Neutrophil count decreased	1 (0.4)	0
Pharyngitis streptococcal	1 (0.4)	0

With the inclusion of the data from the treatment-extension periods of the Phase 3 studies, 1 additional participant who was initially randomised to the ruxolitinib 1.5% cream BID group had a TEAE leading to discontinuation of study drug (application site eczema). There were 6 other participants who had TEAEs leading to interruption of study drug: application site papules and contact dermatitis were reported for 1 participant each of those initially randomised to vehicle cream BID, and application site rash, hypersensitivity, acarodermatitis, and photosensitivity reaction were reported for 1 participant each of those initially randomised to ruxolitinib 1.5% cream BID.

2.6.8.11. Post marketing experience

There is no post-marketing data for ruxolitinib.

2.6.9. Discussion on clinical safety

Safety database

Pool 1 consisted of the data obtained from the Phase 3 studies in vitiligo, where 449 patients were exposed to ruxilitonib 1.5% cream for a period of on average 159 days (i.e. 23 weeks, range 1-237 days), and 224 to placebo-vehicle. Pool 4 consisted of the treatment extension phase of both pivotal studies, 325 (72%) of 449 patients originally allocated to ruxolitinib 1.5% cream BID had at least 52 weeks of exposure, and 166 (88%) of 188 patients who switched from vehicle to ruxolitinib at week 24 had at least 24 to 32 weeks of exposure. The number of patients who were exposed beyond 52 weeks also increased, mainly by participants originally included in the phase 2 study. In the pool of phase2/3 vitiligo trials, there were 546 (71%) of 767 patients exposed more than 52 weeks and of them 76 (10%) were exposed for at least 104 weeks. Together with the safety data of the studies in diseases other than vitiligo, the data set is considered to be sufficiently large to detect relatively common AEs; even though the vehicle-controlled period is limited to 24 weeks in vitiligo and 8 weeks in atopic dermatitis.

Pooled data from 2579 participants of other studies than in vitiligo (atopic dermatitis, psoriasis, alopecia areata) were also used to evaluate adverse events of special interest. Extrapolation to vitiligo was not extensively discussed by the applicant, but overall the approach can be supported by the CHMP. Nevertheless, the larger BSA areas on inflamed or non-intact skin such as in atopic dermatitis trial may provide a more "worse case'" scenario for the systemic effect discussion. However, it is noted that the majority of these studies were also of relatively short in duration (24 weeks), and about 20% provided long term data (52 weeks).

It is considered reasonable to extrapolate the safety data of adults to adolescents, as the safety data of the vehicle-controlled and maintenance phases of the pivotal studies do not point to essential differences between adolescents and adults, nor do the data give rise to safety concerns in adolescents other than in adults. The type and occurrence of the most common TEAEs were considered reasonably similar for adolescents and adults, including application site reactions, application site acne and -pruritis. The higher occurrence of nasopharyngitis in exposed adolescents is not considered a concern. Plasma concentrations of ruxolitinib are lower than in adults (see Pharmacokinetics section), which is supportive for safe use in adolescents.

Target population

The dose of ruxolitinib cream that was studied in the pivotal studies 306 and 307 was limited to ≤10% BSA, as reflected in the posology section of the SmPC section 4.2. According to the applicant, this limitation was included for practical reasons/patient convenience, and in line with general guidance on the BSA to be treated topically in vitiligo. The safety data of study 211, comparing ruxolitinib 1.5% BID with vehicle with a controlled phase of 24 weeks, stratified by using ruxolitinib on ≤10% BSA or >10% BSA, showed that in patients using ruxolitinib on 10%-20% BSA, ruxolitinib was well tolerated. In that study, there were no clear differences in safety profile between patients using ruxolitinib on less or more than 10% of BSA regarding occurrence of TEAEs, SAEs, Grade>3 AEs; similar proportions of patients had TEAEs leading to drug interruption or discontinuation. In addition, the results from the maximum use study, which was performed in patients with atopic dermatitis, did not lead to conclusions that AEs increased with the % BSA treated, although the systemic exposure was higher in patients with a higher % BSA treated; ruxolitinib appeared to be well tolerated at topical administration.

Upon CHMP's request, the applicant also provided a summary of exposure according to baseline total BSA in study INCB 184424-211. Overall, 33 participants with more than 10% BSA were treated with ruxolitinib 1.5% cream BID at least once over the course of study 211 (104 weeks). Taking into account the small number of patients which hampers any robust conclusion on the risk of treating more than 10% BSA, and as long-term safety data are currently limited, a warning in the SmPC highlighting that Opzelura should be used at the lowest skin area necessary and that the posology recommendations should not be exceeded has been included in section 4.4.

In the vitiligo studies, the exclusion criteria included: previous thrombosis/VTE, liver disease, low (<10 g/dl) haemoglobin, moderately raised liver function values (AST or ALT $\geq 2 \times$ ULN, alkaline phosphatase and/or bilirubin > $1.5 \times$ ULN. Recommendations was provided not to use ruxolitinib cream in patients with end-stage renal disease.

Local toxicity studies

From the dermal safety studies that were performed in healthy volunteers, ruxolitinib 1.5% cream was slightly irritating, but there was no evidence that ruxolitinib 1.5% cream did lead to allergic reactions, would induce photosensitisation, or has phototoxic properties.

Adverse Events

In the pooled 'phase 3' data over 24 weeks, there were more patients with at least one TEAE (48% *versus* 35%), and patients with a treatment-related TEAE (15% *versus* 7.6%), for ruxolitinib cream 1.5% BID as compared to vehicle. For both the ruxolitinib cream and vehicle groups, there were few severe AEs (2.2% *versus* 1.8%) or SAEs (1.8% *versus* 0.4%), and discontinuations or interruptions due to AEs were infrequent (0.4% - 1.8%) in both treatment groups.

In the pooled data of the two vehicle-controlled studies up to week 24, in several **SOC** domains the occurrence of AEs was more frequent in ruxolitinib as compared to vehicle: infections and infestations (22% versus 17%); general disorders and administration site conditions (17% versus 6.7%); gastrointestinal disorders (5.3% versus 2.7%), investigations (4.7% versus 1.8%).

When adding the 52-week data including the maintenance period (pool 4), the findings were in line with the safety findings from the vehicle-controlled phase. The occurrence of AEs in the ruxolitinib continuation group increased as compared to the 24-week period, as expected due to the longer period of observation with prolonged treatment. Nevertheless, the pattern and occurrence of AEs was overall similar. In the group who switched from vehicle to ruxolitinib the proportion of patients with at least 1 TEAE was 37%, which became 59% in the patients who remained on ruxolitinib. The numbers of

patients with a SAE were low (1.6% in the switch group and 3.6% in the continuation group) and no fatalities occurred. AEs leading to discontinuation of drug or dose interruption were infrequent (2.2% in the ruxolitinib continuation group).

The **most common TEAEs** (≥1%) that were more frequent in the ruxolitinib group, as compared to vehicle, included application site acne (5.8% versus 0.9%) and application site pruritis (5.1% versus 2.7%), as well as application site erythema or rash and nasopharyngitis (4.2% versus 2.2%). Small numerical differences appeared for upper respiratory tract infection (2.9% versus 2.2%), influenza (1.3% versus 0.4%), urinary tract infection (1.3% versus 0.4%), pyrexia (1.3% versus 0), and headache (3.8% versus 2.7%). Thus, although there was no clear between-group difference for individual infection AEs, at the SOC level there seemed to be more occurrence of infections with ruxolitinib cream, as compared to vehicle (this is further discussed below).

With addition of the 52-week data, Covid-19 was the most common TEAE at the PT level, which can be valued as coinciding with the epidemic. The occurrences of Covid-19 in the vehicle group added to occurrence in the vehicle to ruxolitinib group (observation periods) is not dissimilar from the occurrence of Covid-19 in the treatment continuation group. Likewise, the occurrence (IR) in the pooled phase2/3 population was 5.4/100 PY in the vehicle group and 7.0 /100 PY in the ruxolitinib 1.5% cream BID group. Application site AEs (acne, pruritis, dermatitis, rash), nasopharyngitis and headache, upper respiratory tract infection, sinusitis and urinary tract infection remained the most common (≥2% in any group) AEs.

The applicant did propose 'Application site acne' to be included as an ADR in section 4.8 of the SmPC, which is agreed. Many of the application site acne did not resolve over time, treatment was interrupted due to application site acne in 1 case, the acne did not resolve, and treatment was resumed.

With the update of the 52-week data, for the group of patients who switched from vehicle to ruxolitinib cream, the occurrence of application site reactions other than application site acne, was not notably different as compared to the previous period, when these patients were exposed to vehicle. This is in contrast to the findings of the 24-week data of vehicle against ruxolitinib, where it appeared that application site reactions accumulated in the ruxolitinib group, most notably application site acne, -pruritis, -erythema, -rash, and -dermatitis. In study 211, there was no recognisable trend for higher occurrence of application site pruritis, -erythema, -rash, and -dermatitis, overdose groups, with the exception of application site acne. In the trials in Atopic dermatitis, there was no difference between vehicle and exposed groups regarding the occurrence of application site acne, pruritis, -erythema, -rash, and dermatitis. Overall, there is thus currently insufficient evidence to consider application site pruritis, -erythema, -rash, and -dermatitis as ADRs. In addition, systemic exposure of ruxolitinib cream 1.5% is considered to be low, with a bioavailability of about 10% of oral treatment with a regular 15 mg dose (see discussion in the Pharmacokinetics section).

In the 24-week vehicle-controlled phase, there were several AEs that occurred more frequently with ruxolitinib cream as compared to vehicle cream, most notably: upper respiratory tract infections and urinary tract infections, pyrexia, and increases of liver transaminases. This was unexpected for topical treatment with a relatively low systemic exposure. Based on the week 52 safety data from vitiligo and atopic dermatitis patients, the incidence of pyrexia, and increases of liver transaminases (notably ALT) remained infrequent and no differences suggesting an imbalance over treatment groups were found. Moreover, pyrexia did appear to be associated with other underlying events, and not as isolated events. Overall, there is insufficient evidence to consider pyrexia and increase in liver transaminases as ADR of ruxolitinib cream.

Given the mode of action of ruxolitinib and given its ability to penetrate the skin as needed to exert its intended pharmacological action, it is reassuring that skin infections did not appear as an ADR, in the

24-week vehicle-controlled phase nor in the 52-week maintenance phase. Infections are further discussed in the section below on AESI's.

Serious adverse events and deaths

In the 24-week vehicle-controlled data, the occurrence of SAEs was higher in the ruxolitinib cream 1.5% BID group (n=8, 1.8%) as compared to the vehicle cream group (n=1, 0.4%). Although the occurrence of SAEs in the ruxolitinib group was higher as compared to vehicle, the occurrence of SAEs is considered to be low and all SAEs were single events. There were no SAEs that are labelled as ADRs of *oral* ruxolitinib (Jakavi SmPC). In addition, in the data of trials including other indications ('All ruxolitinib cream data') there was no clear clustering of SAEs. With addition of the 52-week treatment extension period, the numbers of patients with a SAE were low (1.6% in the switch group and 3.6% in the continuation group).

No deaths occurred in the vitiligo programme.

Adverse events of special interest (AESI)

The applicant complied with the recommendation from the 2019 CHMP SA, to consider ADRs of (oral) JAK inhibitors as AESI's, since, based on the knowledge available, the systemic exposure of ruxolitinib cream 1.5% BID was deemed not negligeable. The applicant used the pooled data of the vitiligo 'phase 3' trials, the pooled vitiligo 'phase 2/3 trials' and the integrated ruxolitinib cream database over the diseases studies in the clinical programme, to analyse the occurrence of AESIs.

The occurrence of **cytopenias** (erythropenia, neutropenia, and thrombocytopenia TEAEs) was low, without a clear difference between ruxolitinib cream and vehicle, and the occurrence did not increase with longer exposure. In the long-term safety data of the phase 3 vitiligo population and the pooled phase 2/3 population, there was no tendency for a mean change (decrease) in neutrophil count over time. The number of shifts from baseline in neutrophil count, platelet count, and haemoglobin concentrations, were low and usually Grade 1 or 2 shifts. Overall, there is no evidence to support the inclusion of cytopenias, including neutropenia, as ADRs in the SmPC.

In the pooled 24-week vehicle-controlled data in vitiligo, AEs in the **infections** and infestations SOC were more frequent with ruxolitinib cream as compared to vehicle (22% versus 17%). This could not be attributed to local skin infections and single PTs, such as nasopharyngitis and urinary tract infections. With the update of the safety data of the vitiligo phase 3 studies however, there were no obvious differences in occurrence of infections at the SOC level: the occurrence of infections and infestations (SOC) was 17.4% in the vehicle group over 24 weeks, 15.4% for the period that these patients switched from vehicle to ruxolitinib for 24 weeks, and 29.8% for the patients remaining on ruxolitinib for up to 52 weeks. Also at the PT level, there were no obvious between-group differences, except for influenza. With the update of safety data, Covid-19 became the most frequently occurring infectious TEAE, with no notable differences between groups, while IRs were comparable: 7.3/100PY for vehicle and 7.9/100PY for maintenance with ruxolitinib 1.5% BID. Based on the available evidence, including the follow-up data in vitiligo and the data in atopic dermatitis, there is insufficient evidence to conclude that common infections, notably nasopharyngitis, influenza, urinary tract infections, should be considered as ADR for ruxolitinib 1.5% cream BID. There was a concern about **serious**/severe infections, especially lower respiratory tract infection, even with a low incidence. Indeed, in the Pool 3 ruxolitinib cream total group, there were 14 serious infections including 9 serious infections in ruxolitinib 1.5% cream BID. Among these infections, 4 participants had serious pneumonia (3 of Grade 3 and 1 of Grade 4), and 1 participant had serious bronchitis. Three other patients had Grade $\geq$ 3 bronchitis. However, the current data regarding serious and/or severe infections TEAEs and plasma ruxolitinib levels did not indicate a link between these events and ruxolitinib cream. Therefore, current

data do not support the need to include a specific warning regarding serious infections in the SmPC section 4.4 of ruxolitinib cream.

In the 24-week vehicle-controlled period of the pooled 'phase 3' studies in vitiligo, as well as in the pooled data of all other indications (0.3%), and 52-week follow-up data of the pivotal studies, there were few cases of **herpes simplex** which was the most frequently occurring **viral skin infection**. In the 24-week vehicle-controlled period and in the 52-week follow-up period of the pooled 'phase 3' studies in vitiligo, no participant had developed **herpes zoster**. In the pooled data of all other indications, there were relatively few (n=15, 0.6%) cases of herpes zoster, all except one were grade 1 or 2 in severity and all events resolved without interruption of the study drug. Currently, there are no signals from the performed clinical studies to suspect herpes zoster as an ADR of ruxolitinib cream 1.5% BID.

In the ruxolitinib cream population (pool 3), a total of 10 participants had a TEAE of **non-melanoma skin neoplasms**. In the pooled data of the phase2/phase 3 trials, basal cell carcinoma was most frequent (n=3) of all malignancies reported. There is no established difference between ruxolitinib cream and vehicle. From the available data it does not appear that the frequency of (non-melanoma) skin neoplasms was increased in the treated population. JAK inhibitors have immunomodulatory properties, and ruxolitinib was positive for inducing chromosomal aberrations in CHO cells with UV exposure (see Non-clinical AR). A non-genotoxic carcinogenic effect however was considered unlikely, based on non-clinical data. Nevertheless, in the vitiligo patients on ruxolitinib with NMSC, 4/5 patients had NMSC at an application site (in AD this was the case in 1 of 5). Furthermore, for NMSC to occur at application sites, systemic exposure is not needed. The follow-up of patients treated with ruxolitinib cream was not long enough to discard this risk as NMSC may develop over years and lesions are asymptomatic in their early stages (in the Phase 3 vitiligo studies, there were 325 participants treated with ruxolitinib 1.5% cream BID for 52 to 60 weeks). While for oral ruxolitinib NMSC is included in the SmPC section 4.4, a causal relation between oral ruxolitinib and NMSC has not been established post-marketing (Jakavi SmPC). Furthermore, a warning regarding NMSC is included in SmPC section 4.4 of several JAKi used in chronic inflammatory disorders. Therefore, based on the lack of long-term follow-up, and as NMSC may be caused locally, a warning has been included in SmPC section 4.4; this safety concern was also included as an important potential risk in the RMP and will be followed-up post-approval with a PASS.

Whether the risk of **VTE** and of **MACE**, can be excluded for the general target population could not be established. In the 24-week vehicle-controlled vitiligo data, no cases of VTE occurred, but patients were excluded if they had a history of thrombosis, deep venous thrombosis and pulmonary embolism. VTE is also not described as ADR for oral ruxolitinib (Jakavi SmPC), although it cannot be excluded that the JAK1,2 inhibitors may cause VTE, as reported for other JAKi used in chronic inflammatory disorders, as a class effect. While high doses of oral ruxolitinib rather induces thrombocytopenia, for the low dose topical ruxolitinib cream, individual cases of thrombocytosis were observed. In the integrated clinical data base, the occurrence of VTE and of MACE was infrequent: a total of 9 participants (3 with vitiligo, 5 with atopic dermatitis, and 1 with psoriasis), had at least 1 treatment-emergent thromboembolic AE. In vitiligo this was a pulmonary emboly (PE) in 2 participants and DVT in one participant. In the updated safety database of the phase 2/3 vitiligo studies, no cases of VTE occurred, but two additional thromboembolic TEAEs were found (cardiac ventricular thrombosis and thrombosis). According to the case descriptions, these participants had other risk factors for the event (multiple risk factors for MACE including previous PE and DVT; immobilisation after surgery without anticoagulation). The available clinical evidence available thus far and the relatively low systemic exposure to ruxolitinib upon topical administration (see PK discussion), do not suggest that there is a risk for VTE or MACE due to treatment with ruxolitinib 1.5% cream BID. Consequently, the CHMP was

of the view that the current data do not support the need to include a specific warning regarding VTE and MACE in the SmPC section 4.4 of ruxolitinib cream.

Raised values of **liver function tests** were infrequent in both the ruxolitinib cream and vehicle groups in the vehicle-controlled vitiligo data, with increases in ALT occurring in 1.1% of the ruxolitinib cream group, versus 0.4% (n=1) in the vehicle group. Transaminase increment are a known effect of JAK-inhibitors including oral ruxolitinib, but occurrence with topical ruxolitinib was low. When considering the safety data of the maintenance phase in vitiligo, there were no strong differences between treatment groups in occurrence of ALT increased, nor in the other liver related TEAEs, or levels of transaminases over time. The vehicle-controlled data and the maintenance data in Atopic dermatitis do also not suggest an imbalance in liver-related TEAEs.

In Phase 2 and 3 studies, alert vital signs showed most frequently single instances of high diastolic or high systolic **blood pressure**. TEAE 'Hypertension' had a higher incidence rate (and a higher study size and exposure adjusted IR) reported in Phase 2 and Phase 3 studies (2.0% in ruxolitinib cream total group and 1.7% in ruxolitinib 1.5% BID group, vs 0% in the vehicle control group). In ruxolitinib cream Phase 3 studies, TEAE 'Headache' were more frequent in ruxolitinib 1.5% cream BID group than vehicle control group (3.8% vs 2.7%). With updated data of phase 3 studies at 52 weeks, it was difficult to conclude on causality between ruxolitinib cream and hypertension, and relationship between headache and hypertension events, with so few cases and minor difference between vehicle and ruxolitinib groups. As a result, adding these events as ADRs in the SmPC section 4.8 is currently not considered needed.

Adolescents

The safety data of **adolescents with vitiligo** was limited in number of subjects (n=72 with n=55 on ruxolitinib). In the 'phase 3' vehicle-controlled population, the overall incidence of TEAEs for participants who applied ruxolitinib cream was somewhat higher in adolescents (56.4%) compared with participants in the 18 to < 65 years and ≥ 65 years subgroups (47.0% and 39.3%, respectively). However, in the 'All ruxolitinib cream population' over all four diseases in the clinical programme, the proportion of patients with ≥1 TEAE, ≥Grade 3 AEs, SAEs, and AEs leading to study drug interruption or discontinuation, was similar or lower in the 195 adolescent patients on ruxolitinib cream 1.5% BID, as compared to the 1417 adults aged between 18 and 65 on the same regimen as outlined below. To further support the safety data in adolescents with vitiligo, the applicant submitted safety data of adolescents with atopic dermatitis (AD) in two trials (303 and 304) upon CHMP's request. Adolescents with AD were also included in the maximum use study (103) and in two cohorts of a safety/PK study (102). When comparing the safety results of adolescents with adults in AD, there were no safety concerns: The occurrence of TEAEs, SAEs, ≥Grade3 AEs, and AEs leading to discontinuation or interruption of study drug were all lower in adolescents as compared to adults. The most common (≥2%) AEs were headache, upper respiratory tract infection and nasopharyngitis, without notable differences between adolescents and adults exposed to ruxolitinib 1.5% BID. In the maintenance period from week 8 to week 52, the occurrence of SAEs, ≥3AEs, and AEs leading to discontinuation or interruption of study drug remained low. The maximum use study was performed in adolescents (n=21) and adults, and did not point to safety concerns and no application site reactions were reported. It should however be noted that this a small-sized study. The PK study (102) that was performed in adolescents (n=21) neither pointed to safety concerns regarding the similar occurrence of TEAS over the dose range, and the absence of SAEs and treatment-related Grade≥3 AEs.

Overall, based on the safety data available thus far in NSV (including the 52-week data) and AD, the CHMP considered that there was no difference in the safety profile of ruxolitinib 1.5% BID between adolescents and adults.

However, for some JAK-inhibitors, non-clinical findings pointed to potential adverse effects on bone development and growth and the applicant was requested to discuss the risk associated with potential effects on bone physiology mediated by ruxolitinib in the adolescents and to also discuss the need for further studies to investigate bone safety in adolescents.

The considered that there is currently no signal that ruxolitinib cream could cause detrimental bone effects in adolescents; the risk is considered to be low (see non-clinical section), and this was further strengthened by the low systemic exposure. However, it was highlighted that in humans, where the growth period is longer, tissue renewal (bone remodelling) becomes important already during growth, because the average bone tissue age in a 20-year growth period in humans exceeds the osteocyte-life span, and matrix microdamage may trigger the bone renewal process (remodelling). Hence, the effects of ruxolitinib cream on human bone development may differ from the effect observed in the rat. Furthermore, the lack of understanding of how JAK inhibition affects bone dynamics further complicates translation from the non-clinical finding to the clinic. Considering that in vitiligo Phase 3 studies, only 43 adolescents applied ruxolitinib 1.5% cream BID during at least 52 weeks and that these studies were not designed to identify a specific risk in adolescent population (i.e., clinical data on growth are not available for ruxolitinib cream in vitiligo), the CHMP considered it to be appropriate to address the safety issue of 'impaired bone growth and development if used in paediatric patients < 18 years' as missing information. As a result, in addition to routine pharmacovigilance activities (follow-up in future PSURs), clinical studies INCB 18424-309 and INCB 18424-308 were added as category 3 additional pharmacovigilance activities to further characterise this safety concern (see RMP section).

Special populations

The sample of **elderly** patients (>65 years) with vitiligo in the studies was particularly small (n=44 in the Phase 3 vitiligo studies), which limits the interpretation of safety data in this group. However, it is currently considered that the safety profile of ruxolitinib cream in adults is likely to be similar for the elderly.

There was little information regarding **pregnancy** outcomes when being treated with ruxolitinib cream. Oral use of ruxolitinib (Jakavi) is contraindicated during pregnancy. Since there is limited evidence from developmental rat and rabbit studies, but there is a proven developmental risk in the class of JAK inhibitors and the data for ruxolitinib point to a very low safety margin as compared to the human exposure after dermal application, the CHMP considered that the conclusions from the non-clinical data pointed to a relevant risk. Even when systemic exposure to topical ruxolitinib is lower than for topical ruxolitinib, considering that the treatment of vitiligo can be postponed until the end of pregnancy, ruxolitinib cream was ultimately contraindicated during pregnancy and breastfeeding (see SmPC section 4.3).

It is considered that the systemic exposure to ruxolitinib is low but not negligible (see Pharmacology discussion). As a precautionary measure, since exposure may be twice as high or higher in patients with end-stage renal disease, in particular if more than 10% BSA would be treated, it was indicated in the SmPC section 4.2 that use in patients with end stage renal disease is not recommended due to lack of safety data. There were no clear differences in safety profile between patients using ruxolitinib on ≤ 10% BSA and in patients using ruxolitinib on 10-20% BSA and there was no clear relationship between severity of hepatic impairment and the increase in AUC, a dosing advice for patients with hepatic impairment was thus not considered necessary.

Interactions with co-medication

No drug-drug interaction studies of ruxolitinib cream were conducted. For oral ruxolitinib, it is known that the use of strong CYP3A4 inhibitors nearly doubled the systemic exposure (AUC) to ruxolitinib. A relevant interaction is not deemed excluded for topical ruxolitinib, thus this information was included in

the SmPC section 4.5. As ruxolitinib has not been evaluated in combination with other cutaneous medicinal products; the co-application on the same skin areas is not recommended. SmPC section 4.5 has been updated accordingly. Further, other topical medicinal products used to treat other conditions on the same skin areas should be applied with a minimum of 2 hours after the application of ruxolitinib cream. This is also applicable to the use of sunscreen or emollients (see SmPC section 4.5).

Article 20 referral on JAK inhibitors used in chronic inflammatory disorders

In line with the above, there were no systemic TEAEs that appeared as ADRs for ruxolitinib cream; the only ADR was application site acne. The ocurrence of severe AEs and SAEs were infrequent and was not considered to be treatment-related. Consequently, the class effects identified for oral JAK inhibitors, and thus potentially applicable to ruxolitinib as a substance, are not considered relevant for the current application as the systemic exposure, given the different route of administration of Opzelura (ruxolitinib cream), is considered to be sufficiently low, not to lead to systemic effects including VTE, MACE, malignancy other than NMSC, and serious infections.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The safety profile of ruxolitinib cream is overall acceptable. The findings when adding the 52-week data including the maintenance period (pool 4), were in line with the safety findings from the vehicle-controlled phase. There were no systemic TEAEs that appeared as ADRs for ruxolitinib cream, the only local ADR was application site acne. Given its effects on JAK1/2, the applicability of the class effects considered for approved oral JAK inhibitors to ruxolitinib as a substance was raised. Nevertheless, systemic exposure is considered to be sufficiently low, not to lead to systemic effects including VTE, MACE, malignancy other than NMSC, and serious infections. Consequently, the CHMP was of the view that the current data do not support the need to include specific warnings regarding those class effects in the SmPC of ruxolitinib cream. The occurrence of serious/severe AEs and of temporary or permanent treatment discontinuations due to AEs was infrequent, in both adults and adolescents. The safety profile of ruxolitinib cream in adolescents is supported by the data in adults and the data of adolescents in other studies (e.g. in atopic dermatitis). 'Impaired bone growth and development in paediatric patients <18 years' was included in the RMP as missing information and will be followed-up post-approval. Based on the lack of long-term follow-up and because NMSC can be caused locally, a warning was included in SmPC section 4.4.; this safety concern will also be followed up post-approval with a PASS (category 3, see RMP). Pregnancy and lactation were included as contra-indication in SmPC section 4.3. Women of childbearing potential have to use effective contraception during treatment and for 4 weeks after discontinuation of treatment; and ruxolitinib cream treatment must be discontinued approximately 4 weeks before the beginning of breastfeeding.

2.7. Risk Management Plan

2.7.1. 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

2.7.2. Pharmacovigilance plan

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 INCB 18424-308	To evaluate the duration of clinical response of	Impaired bone growth and development in	Final CSR	June 2023

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Completed	ruxolitinib cream in participants with vitiligo.	paediatric patients < 18 years of age		
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.	June 2024

2.7.3. Risk minimisation measures

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

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

Based on the fact that there is no centrally approved medicinal product available for repigmentation in non-segmental vitiligo, the PRAC is of the opinion that a separate entry in the EURD list for Opzelura is needed, as it cannot follow the already existing entry for ruxolitinib. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request the alignment of the new PSUR cycle with the international birth date (IBD). The IBD is 21.09.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found unacceptable by the QRD Group for the following reasons: in light of the space available on the immediate packaging (including multilingual pack), every effort should be made to print the abbreviation 'EXP' and 'Lot' on the tube label as per legal requirements. The Group also pointed out that the inclusion of CMO number may increase the risk of confusion between the different digits. However, the QRD Group accepted the omission of MAH's full name and address on the tube label; it is replaced with the MAH's logo which contains the MAH name.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication for ruxolitinib cream is "*treatment of non-segmental vitiligo with facial involvement in adults and adolescents from 12 years of age*".

Ruxolitinib phosphate is a potent and selective inhibitor of the JAKs with selectivity for JAK1 and JAK2. In vitiligo, JAK-mediated inflammation upregulates CXCL9 and CXCL10 and herewith stimulates CD8+ T-cells to produce among others interferon gamma (IFNγ) which impairs pigmentation by melanocytes and keratinocytes. Ruxolitinib blocks this JAK-mediated inflammation and as such contributes to re-pigmentation.

The clinical presentation of vitiligo typically involves asymptomatic depigmented patches and macules, without clinical signs of inflammation. The disease has a predilection for the face and areas around the orifices, genitals, and hands. Depigmented areas may show more than one colour shade (trichrome, quadrichrome, pentachrome). Non-segmental vitiligo, which has a symmetrical presentation on left and right body site, and often occurs in skin area's prone to pressure and friction, is the most common form. The clinical course of vitiligo is unpredictable, with stable disease, slow progression over years, and occasional flares.

Vitiligo is a disease with high psychological burden and the ultimate aim of treatment is to reach durable re-pigmentation of depigmented patches or macules, with an acceptable appearance from the patient's perspective.

3.1.2. Available therapies and unmet medical need

In the EU, there are no approved medicinal products for re-pigmentation in vitiligo, and evidence for the effectiveness of drug therapies used off-label is limited. Few randomised and controlled clinical studies have evaluated potential treatments, and interpretation of these studies is hampered by small study sizes as well as heterogeneity of study designs, methodologies, and measures (Eleftheriadou et al 2012, Whitten et al 2016). The current management of vitiligo is empirical and based on 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 topical steroids and calcineurin inhibitors, which are most useful for treating limited disease (typically ≤ 10% BSA is treated). Second-line treatments consist of phototherapy (NB-UVB and PUVA) and systemic steroid treatment, and third-line treatments consist of surgical grafting techniques and depigmenting treatments of neighboring healthy skin. Responses to current treatment options vary and have limited durability. Treatments can also be time-intensive and burdensome to the patient and may produce cosmetically unacceptable results. As a result, there is an unmet need for safe and effective treatment options.

3.1.3. Main clinical studies

The two identical pivotal studies INCB 18424-**306** and INCB 18424-**307** were randomised, double-blind, vehicle-controlled, phase 3 studies in adolescents (12 – 17 years) and adults with non-segmental vitiligo (NSV) up to 10% BSA and at least 0.5% BSA of the face involved. The studies were

completed and provided data up to 52 weeks. In total, 673 participants were randomised (2:1) to ruxolitinib 1.5% BID or vehicle BID during the double-blind period of 24 weeks. About 10% of the included patients were adolescents.

The primary and key secondary endpoints were tested in a fixed sequence at 2-sided α = 0.05 level in the following order: F-VASI75, F-VASI50, F-VASI90, T-VASI50, VNS and F-BSA, all at week 24. Only if the null hypothesis for the primary endpoint (F-VASI75) was rejected, the secondary endpoints were subsequently tested.

The following supportive studies were submitted in support of this application:

Study NCBI 18424-**308**, the treatment extension study, was considered supportive for the long-term efficacy of ruxolitinib 1.5% BID. Study 308 is still ongoing and data from cohort A will remain blinded until the study is completed by all participants. Preliminary data from cohort B were provided, including participants who had not reached the F-VASI 90 at week 52 in studies INCB 18424-306 or INCB 18424-307 and continued the use of ruxolitinib 1.5% BID. At time of data cut off all participants in cohort B had completed 68 weeks of treatment.

In addition, in a dose-finding study INCB 18424-**211**, a total of 157 adult patients with segmental or NSV up to 20% BSA were randomized (1:1:1:1:1) to receive ruxolitinib 0.15% QD, 0.5% QD, 1.5% QD, 1.5% BID, or vehicle for 24 weeks; 89% completed the study.

3.2. Favourable effects

The primary endpoint was met in both pivotal studies. The proportions of participants reaching at least 75% repigmentation in the face (**F-VASI75**) after 24 weeks of treatment were significantly higher in those treated with ruxolitinib 1.5% BID versus vehicle BID ($p < 0.0001$). In the pooled analysis, the estimated F-VASI75 response rate was 30.7% (SE 2.3) in the ruxolitinib 1.5% BID group versus 9.6% (SE 2.2) in the vehicle BID group, with a response rate difference of 21% ($p < 0.0001$). Pre-planned sensitivity analyses yielded comparable results.

In line with the primary endpoint, each of the five key secondary endpoints were met in both pivotal studies, favouring ruxolitinib 1.5% BID over vehicle BID at 24 weeks of treatment. The sensitivity analyses confirmed the robustness of these findings.

- Proportions of participants reaching at least 50% re-pigmentation in the face (**F-VASI50**) after 24 weeks of treatment were significantly higher in those treated with ruxolitinib 1.5% BID versus vehicle BID ($p < 0.0001$). In the pooled analysis the estimated F-VASI50 response rate was 51.7% (SE 2.46) in the ruxolitinib 1.5% BID group versus 19.6% (SE 2.89) in the vehicle BID group, with a response rate difference of 32.2% (SE 3.83).
- Proportions of participants reaching at least 90% re-pigmentation in the face (**F-VASI90**) after 24 weeks of treatment were significantly higher in those treated with ruxolitinib 1.5% BID versus vehicle BID ($p < 0.0001$). In the pooled analysis the estimated F-VASI90 response rate was 16.0% (SE 1.83) in the ruxolitinib 1.5% BID group versus 1.9% (SE 1.01) in the vehicle BID group, with a response rate difference of 14.2 % (SE2.09).
- Proportions of participants reaching at least 50% re-pigmentation in the total body (**T-VASI50**) after 24 weeks of treatment were significantly higher in those treated with ruxolitinib 1.5% BID versus vehicle BID ($p < 0.0001$). In the pooled analysis the estimated T-VASI50 response rate was 21.9% (SE 2.04) in the ruxolitinib 1.5% BID group versus 5.8% (SE 1.64) in the vehicle BID group, with a response rate difference of 16.1% (SE 2.62).
- Proportions of participants reporting a Vitiligo Noticeable Scale (VNS) response score of 4 or 5

(**VNS**) after 24 weeks of treatment were significantly higher in those treated with ruxolitinib 1.5% BID versus vehicle BID ($p < 0.0001$). In the pooled analysis the estimated VNS response rate was 22.5% (SE 2.09) in the ruxolitinib 1.5% BID group versus 4.2% (SE 1.45) in the vehicle BID group, with a response rate difference of 18.3% (SE 2.53).

- The percentage of change from baseline for the **F-BSA** after 24 weeks of treatment was significantly higher in those treated with ruxolitinib 1.5% BID versus vehicle BID (p-value for between-group difference < 0.0001). LSM (SE) for this difference was -20.0 (3.17), with a 95% confidence interval of -26.22 to -13.77.

Among the other secondary outcomes (not corrected for multiple testing), physician and patient assessments of improvement in vitiligo (F-PhGVA, T-PhGVA, Colour-matching question, F-PaGIC-V, T-PaGIC-V) were in line with the findings on primary and key secondary endpoints. Overall satisfaction and effectiveness scored with the Treatment Satisfaction Questionnaire for Vitiligo (TSQM) was also nominally statistically significantly higher in participants treated with ruxolitinib 1.5% BID versus those treated with vehicle BID. It can be understood that the quality-of-life measures did not show treatment effects, as vitiligo does not come with symptoms (pain, itch) like other inflammatory skin conditions. The impact of vitiligo rather concerns self-esteem and social impact.

Adolescents (n = 72) showed equal response rates for the primary and key secondary endpoints (at 24 weeks) when treated with ruxolitinib 1.5% BID compared to adults from 18-65 years of age.

Subgroup analyses for the primary outcome measure showed consistent results across the relevant subgroups.

Maintenance of treatment effect with continued ruxolitinib 1.5% BID exposure was shown for each of the primary and key secondary endpoints until week 52 in the pivotal trials. Preliminary data from study INCB 18424-308 suggested a maintenance of effect, or further improvement of response up to week 68.

Results from the supportive dose finding study 211 showed superiority of ruxolitinib versus vehicle for each of the 4 dosing regimens, with the highest percentages responders in the 1.5% QD and BID groups.

3.3. Uncertainties and limitations about favourable effects

Non-white participants were under-represented in the study population. Nevertheless, based on the comparable response rates across the different race categories as well as the different (Fitzpatrick) skin types, a trend towards between-group differences is not expected. This issue was therefore not further pursued by the CHMP.

Ruxolitinib cream has not been evaluated in combination with other medicinal products used to treat vitiligo; the application of ruxolitinib cream and other medicinal products used to treat vitiligo on the same skin areas was prohibited in the pivotal clinical studies. Consequently, SmPC section 4.5 was revised to highlight that co-application on the same skin areas is not recommended. Furthermore, only limited data are available on the use of phototherapy in combination with ruxolitinib cream (study 211); an additional study is ongoing to examine the impact of concomitant UV treatment. The SmPC will then be updated accordingly in a future variation, if appropriate.

The other (non-key) *secondary outcomes* generally supported the results obtained with the primary and key secondary endpoints, nevertheless there were no significant between-group differences in changes in quality of life (DLQI/CDLQI and VitiQol) and anxiety/depression (HADS) possibly due to low baseline scores.

Patients with less than 25% repigmentation by week 52 are unlikely to show clinically meaningful improvement with prolonged treatment. Therefore, a 52-week cut-off for non-response in case of non-segmental vitiligo was added in SmPC section 4.2.

Additional data on treatment maintenance will come from cohort A from study INCB 18424-308 which is currently ongoing. Final results are expected in the first half of 2032 and will be submitted for assessment once available.

Further, data on rebound after treatment withdrawal were derived from post-hoc analyses of data from study 211 where none (except one participant with segmental vitiligo) met the definition of rebound (F-VASI score during follow-up of at least 25% higher than the F-VASI at baseline). It was therefore considered unlikely by the applicant that treatment discontinuation will trigger a rebound effect. Based on the available data thus far, this conclusion was endorsed by the CHMP. However, definite data are expected from cohort A to be submitted after completion of study 308 in the first half of 2023.

Adolescents (12 - 18 years) are included in the proposed indication and comprised about 10% (n=72) of the total study population. The percentage of adolescents included in the pivotal studies was considered to be rather small. Nevertheless, adolescents showed equal response rates for the primary and key secondary endpoints (at 24 weeks) when treated with ruxolitinib 1.5% BID compared to adults from 18-65 years of age. Given the similar pathophysiological mechanism of vitiligo in adolescents compared to adults and comparable systemic ruxolitinib exposure between adolescents and adults, together with a similar safety profile; the inclusion of adolescents in the therapeutic indication was accepted by the CHMP.

The sample size of the subgroup adults > 65 years of age was rather small which affected robustness of the findings in this sub-population. Consequently, SmPC section 4.2 has been revised upon CHMP's request to inform HCPs that a limited number of patients aged 65 years and above have been enrolled in the clinical studies with ruxolitnib cream in vitiligo to determine whether they respond differently from younger subjects.

3.4. Unfavourable effects

In the vehicle-controlled phase, the overall incidences of TEAEs and treatment-related TEAEs were higher in the ruxolitinib 1.5% BID treatment group (48% and 15%, respectively) versus the vehicle BID treatment group (35% and 7.6%, respectively). Very few participants had AEs leading to study drug discontinuation (0.4%) or temporarily interruption of study drug (1.3%), no participant had a TEAE with a fatal outcome. SAEs were infrequent but occurred more in the ruxolitinib group (1.8%) as compared to the vehicle group (0.4%). None of the serious TEAEs occurred more than once in any treatment group, and no serious TEAE was considered related to the study drug. In adolescents, the overall incidence of TEAEs and treatment related TEAEs were also higher in the ruxolitinib 1.5% cream BID treatment group (56% and 16%, respectively) versus the vehicle cream BID treatment group (35% and 0%, respectively). Overall, the findings when adding the 52-week data including the maintenance period in vitiligo, were in line with the safety findings from the vehicle-controlled phase. The number of AEs in the ruxolitinib continuation group increased as compared to the 24-week period, due to the longer period of observation with prolonged treatment.

At SOC level, treatment-emergent AEs were most frequently reported as: infections and infestations (22% in the ruxolitinib group *versus* 17% in the vehicle group), general disorders and administration site conditions (17% *versus* 6.7%), gastrointestinal disorders (5.3% *versus* 2.7%). In the Pool 3 ruxolitinib cream total group, there were 14 serious infections including 9 serious infections in ruxolitinib 1.5% cream BID. Among these infections, 4 participants had serious pneumonia (3 of Grade 3 and 1 of Grade 4), and 1 participant had serious bronchitis. Three other patients had Grade ≥ 3

bronchitis. With the update of the 52-week safety data of the vitiligo phase 3 studies, there were no obvious differences in occurrence of infections at the SOC level: The occurrence of infections and infestations (SOC) was 17.4% in the vehicle group over 24 weeks, 15.4% for the period that these patients switched from vehicle to ruxolitinib for 24 weeks, and 29.8% for the patients remaining on ruxolitinib for up to 52 weeks. 'Covid-19' became the most frequently occurring infectious TEAE, with no notable differences between groups (3.1% versus 3.2% versus 7.3%) as there is a longer observation period in the ruxolitinib 1.5% maintenance group, n/PY were comparable: 7.3 for vehicle and 7.9 for maintenance with ruxolitinib 1.5% BID.

Common AEs (>1% in either group) that were more frequent in the ruxolitinib group as compared to the vehicle group were: application site acne (5.8% versus 0.9%) and application site pruritis (5.1% versus 2.7%), nasopharyngitis (4.2% versus 2.2%), and headache (3.8% versus 2.7%). Upper respiratory tract infection, application site rash and erythema, influenza, pyrexia, urinary tract infection, and increased ALT were numerically more frequent with ruxolitinib as compared to vehicle, at low frequency (<2%). Application site acne was included as an ADR in SmPC section 4.8 with a frequency 'common'.

In the pooled vehicle-controlled vitiligo data, SAEs were more frequent in the ruxolitinib cream group as compared to the vehicle group (n=8, 1.8% vs n=1, 0.4%). No serious TEAEs occurred in >1 participant in any treatment group, and no serious TEAE was considered related to the study drug by the investigator.

In the All Ruxolitinib Cream Population, in total 11 participants had a TEAE of nonmelanoma skin neoplasms: 'basal cell carcinoma' in 6 participants, 'squamous cell carcinoma' in 5 participants, and 'Bowen's disease' in 1 participant. In the Phase 2/3 Vitiligo Population, the prevalence of nonmelanoma skin neoplasms was 0.5% (4 of 767) in the ruxolitinib cream treatment group and 0.4% (1 of 256) in the vehicle cream treatment group; 4/5 participants on ruxolitinib had a NMSC on an application site, as had the participant with NMSC in the vehicle group.

3.5. Uncertainties and limitations about unfavourable effects

When ruxolitinib is applied on maximally 10% BSA, systemic exposure of ruxolitinib will be below the levels of orally administered ruxolitinib, overlap in plasma levels with oral ruxolitinib at 5 mg BID PO will thus only occur during short periods of time. In the situation where ruxolitinib would be applied on larger surfaces (i.e., > 10% BSA), plasma levels will be higher and therefore the overlap with oral ruxolitinib may become larger. The safety data of study 211 showed that in patients using ruxolitinib on 10%-20% BSA, ruxolitinib cream is also well tolerated. Several AEs occurred more frequently with ruxolitinib cream as compared to vehicle cream such as upper respiratory tract infections and urinary tract infections, pyrexia, and increases of liver transaminases, but robust conclusion on the risk of treating more than 10% BSA could not be drawn due to the small sample (n=33). As long-term safety data are currently limited, a warning not to exceed the posology instructions (up to a maximum of 10% of BSA) and a recommendation to use ruxolitinib cream at the lowest skin area necessary were included in the SmPC section 4.4.

Oral JAK inhibitors are associated with myelosuppression (anaemia, neutropenia), infections, NMSC, VTE (venous thrombotic events), and MACE, amongst others. Inclusion of specific warnings in the SmPC of ruxolitinib cream considering the class effects of JAKis was not considered needed by the CHMP because systemic exposure is considered to be low following topical application of ruxolitinib cream and overlap with systemic exposure following the administration of a potential oral dose of JAKi is considered to be limited. Compared to a 5 mg oral dose, the relative estimated steady state Cmax

and AUC after application of the 1.5% cream b.i.d. to about 10% surface is about 15% and 35%, respectively. In addition, no systemic effects were seen in the data available thus far.

Although NMSC was infrequent, most patients (4/5) with NSV and NMSC had NMSC on an application site. Furthermore, the follow-up of patients treated with ruxolitinib cream was not long enough to discard this risk, as NMSC may develop over years and lesions are asymptomatic in their early stages. Based on the lack of long-term safety follow-up, a warning was included in SmPC section 4.4. In addition, this safety issue will be further followed up post-approval as part of a PASS.

Oral use of ruxolitinib (Jakavi) is contraindicated during pregnancy and lactation. Although there is limited evidence from developmental rat and rabbit studies, there is a proven developmental risk in the class of JAK inhibitors. In addition, considering that the treatment of vitiligo can be postponed until the end of pregnancy, ruxolitinib cream was contraindicated during pregnancy and breast feeding (see SmPC section 4.3). Women of reproductive potential should be advised to use effective contraception during treatment and for 1 month following the final dose of ruxolitinib.

Regarding detrimental bone effects observed in non-clinical data, there is currently no signal that ruxolitinib cream could cause detrimental bone effects in adolescents because the safety margins in the juvenile rat study were 22-38x based on the unbound fraction and detrimental bone effects were only found in very young animals and not in adolescents. Nevertheless, considering that in vitiligo Phase 3 studies, only 43 adolescents applied ruxolitinib 1.5% cream BID during at least 52 weeks and that these studies were not designed to identify a specific risk in the adolescent population (i.e., clinical data on growth are not available for ruxolitinib cream in vitiligo), the CHMP considered it appropriate to address this safety issue as missing information. As a result, in addition to routine pharmacovigilance activities (follow-up in future PSURs), clinical studies INCB 18424-309 and INCB 18424-308 were added as category 3 additional pharmacovigilance activities to further characterise this safety concern (see RMP section).

3.6. Effects Table

Table 53: Effects table for ruxolitinib cream 1.5% BID for the treatment of vitiligo (updated data without study site 710)

Effect	Short Description	Unit	Vehicle	Ruxolitinib 1.5% BID	Uncertainties (Unc)/ Strength of evidence (SoE)	References
	n=		218	443		
Favourable Effects						
F-VASI75 (primary endpoint)	F-VASI75 at 24 weeks	% (SE)	9.6 (2.17)	30.7 (2.29)	SoE: p < 0.0001 in both pivotal studies, sensitivity analyses showed similar results. Unc: New measure, some support for clinical relevance.	Studies 306 and 307
T-VASI50 (key secondary endpoint)	T-VASI50 at 24 weeks	% (SE)	5.8 (1.64)	21.9 (2.04)	SoE: p < 0.0001 in both pivotal studies, sensitivity analyses showed similar results. Clinically relevant outcome. Unc: new measure, some support for clinical relevance.	
VNS (key secondary endpoint)	Vitiligo Noticeable Scale score 4 or 5 (almost- or not noticeable) at 24 weeks	% (SE)	4.2 (1.45)	22.5 (2.09)	SoE: p < 0.0001 in both pivotal studies, sensitivity analyses showed similar results. Clinically relevant outcome. Unc: No specific uncertainties.	
Unfavourable Effects						
Infections		%	17	22	Unc: no single type of infection that fully explains the difference	Studies 306 and 307
- Serious infections		n=	1	3	Unc: In the Pool 3 ruxolitinib cream total group, there were 14 serious infections including 9 serious infections on ruxolitinib 1.5% cream BID.	
Application site reactions		%	5.8	15	SoE: consistent over a broad spectrum of ASRs	

Effect	Short Description	Unit	Vehicle	Ruxolitinib 1.5% BID	Uncertainties (Unc)/ Strength of evidence (SoE)	References
	n=		218	443		
- Acne		%	0.9	5.8	Unc: not more prevalent in ruxolitinib versus vehicle in atopic dermatitis studies Unc: Not more prevalent in over dose groups	Studies 102, 103, 206. Study 211
- Pruritus		%	2.7	5.1		

Notes: Primary outcome (F-VASI75) and key secondary outcomes (including T-VASI50 and VNS)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Favourable effects

In both pivotal studies the primary endpoint, F-VASI75 at 24 weeks, was met. This was supported by the results of all key secondary outcomes over 24 weeks, including F-VASI90 and T-VASI50 and the patient reported Vitiligo Noticeability Scale (VNS) which were corrected for multiplicity. The treatment effect of about 20% as reached in facial vitiligo over 24 weeks is considered to be clinically relevant for the patients and equates to a number needed to treat (NNT) =5. The relevance of at least 75% improvement in facial vitiligo was confirmed by validity studies inside and outside the clinical development programme. The treatment effect in the VNS (not noticeable/nearly not noticeable) was similar in size to the effect in F-VASI75 and is thus considered of clinical relevance as well.

At week 24 in the pivotal studies, for 31% of patients on ruxolitinib cream F-VASI75 was reached and 16% reached F-VASI90, and treatment response further increased up to week 52 (49% and 30% respectively). Preliminary data from cohort B of study 308 suggested further improvement up to at least week 68. Generally, the response to treatment in vitiligo takes more time than in other inflammatory diseases, due to the lag-time in the regeneration following the inflammatory process. The data showed that more than half of the patients who did not have a response by 24 weeks (F-VASI or T-VASI) may get a response >25% before 52 weeks, however patients who did not have a response by 52 weeks may have a reduced chance to get a satisfactory response later. In line with the above, a 52-week cut-off for non-response for the treatment of vitiligo with ruxolitinib cream was considered appropriate, as reflected in the SmPC section 4.2.

Adolescents (12 - 18 years) are included in the indication and comprised about 10% (n=72) of the total study population, which is rather limited. Stratified analyses for the primary and key secondary endpoints suggested a consistently similar response rate pattern in adolescents compared to adults. Thus, although numbers were small, based on the above data and the assumed similar pathophysiology as well as an identical negligible systemic exposure level, the inclusion of adolescents in the indication is acceptable.

The proposed indication does not incorporate a treatment-line, in line with the CHMP Scientific Advice received. This is accepted as the results indicate there was no relevant heterogeneity in results across lines of treatment. Further, there are no available authorised treatments and for none of the alternative treatments efficacy has been established in randomised trials in vitiligo.

Unfavourable effects

Overall, the findings when adding the 52-week data including the maintenance period (pool 4), are in line with the safety findings from the vehicle-controlled phase. The overall safety profile of ruxolitinib cream is acceptable.

Based on the available data, treating more than 10% of BSA is unlikely leading to safety concerns. However, long term safety data are limited, and therefore a warning not to exceed the posology instructions was included in the SmPC section 4.2.

When ruxolitinib is applied on maximally 10% of the body surface area, plasma concentration of ruxolitinib will be far below the levels of orally administered ruxolitinib 5 mg BID PO for most of the time. In line with the above, there were no systemic TEAEs that appeared as ADRs for ruxolitinib cream; the only ADR is application site acne. Accordingly, the class effects identified for oral JAK

inhibitors as part of the recently concluded Article 20 referral on JAKi used in chronic inflammatory disorders, and thus potentially applicable to ruxolitinib as a substance, are not considered relevant for the current application as the systemic exposure of ruxolitinib cream is considered to be sufficiently low, not to lead to systemic effects including VTE, MACE, malignancy other than NMSC, and serious infections. In addition, the occurrence of severe AEs and SAEs was infrequent and did not appear to be treatment related; and the occurrence of temporary or permanent treatment discontinuations due to AEs was infrequent, in both adults and adolescents.

The acceptability of the safety profile of ruxolitinib cream to treat NSV in adolescents was further supported by the long-term data in adults and by the data from adolescents treated in studies on atopic dermatitis. Although detrimental bone effects were seen in a single short-term study in juvenile rats (equivalence to 2 years of age in humans), these effects were not reproduced in the pivotal repeat-dose toxicity in rats and other species of adolescent age. Due to the safety margins, the occurrence of detrimental bone effects in the paediatric population is unlikely. Nevertheless, the completion of the studies in adolescents (308) and children (309) are awaited and will be submitted once available, the applicant will also follow this issue further in future PSURs.

Based on the lack of long-term follow-up and because data showed that 4 out of the 5 NMCS's occurred at areas at which ruxolitinib was applied locally, a warning was included in SmPC section 4.4; this safety concern will also be followed up post-approval as part of PASS. Because there is limited evidence from developmental rat and rabbit studies, but there is a proven developmental risk in the class of JAK inhibitors and considering that the treatment of vitiligo can be postponed until the end of pregnancy, ruxolitinib cream is contraindicated during pregnancy and lactation.

3.7.2. Balance of benefits and risks

There is an unmet medical need for the treatment of non-segmental vitiligo as there are currently no authorised treatments available with established efficacy and safety for this condition.

The short-term 24 weeks treatment data, the long-term data up to week 52 and beyond, supported by preliminary data from study 308 and safety data of studies performed in atopic dermatitis, showed a clinically relevant and statistically significant response for ruxolitinib 1.5% cream and an acceptable safety profile for adults and adolescents.

Contraindications for pregnancy and breast-feeding has been implemented in the product information.

3.8. Conclusions

The overall benefit/risk balance of Opzelura is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Opzelura is favourable in the following indication:

Opzelura is indicated for the treatment of non-segmental vitiligo with facial involvement in adults and adolescents from 12 years of age.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following

conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0145/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.