

LETTER TO THE EDITOR

Incidence of nonmelanoma skin cancer in patients with vitiligo who applied ruxolitinib cream

Dear Editor,

Patients with vitiligo may have a decreased risk of skin cancers, including nonmelanoma skin cancer (NMSC).¹ However, it is unknown if NMSC risk is elevated with topical Janus kinase (JAK) inhibitors. Ruxolitinib cream, a topical formulation of the JAK1/JAK2 inhibitor ruxolitinib, is currently the only approved repigmentation therapy for nonsegmental vitiligo.² Here, we evaluated NMSC risk using safety and pharmacokinetic data from studies of ruxolitinib cream in patients with vitiligo.

In a Phase 2, randomized, dose-ranging study and two randomized, vehicle-controlled Phase 3 studies with a

rollover treatment extension, the efficacy and safety of ruxolitinib cream were evaluated in patients with vitiligo.^{3,4} In the Phase 2 study (NCT03099304), several ruxolitinib cream strengths were assessed with a vehicle control and open-label period of 1.5% ruxolitinib cream twice daily (BID) with optional concurrent narrow-band UVB phototherapy; adults (18–75 years) applied ruxolitinib cream for up to 3 years.^{3,5} In the Phase 3 studies (TRuE-V1 [NCT04052425], TRuE-V2 [NCT04057573] and TRuE-V long-term extension [NCT04530344]), 1.5% ruxolitinib cream BID was evaluated for up to 2 years in adults and adolescents (≥ 12 years).⁴

TABLE 1 Patient-level details regarding NMSC events.

Patient ^a	Age [years]/sex, race (Fitzpatrick skin type)	PT (location)	Study day	AE grade/serious/resolved [Y/N]	Related to treatment/at application site [Y/N]	Action with study drug	Relevant medical history/prior therapy for vitiligo
0.15% RUX cream QD							
1	42/F, White (II)	BCC (chest)	198	2/N/Y	N/Y	Study drug interrupted	Prior therapies: TCS (≤ 1 year)
0.5% RUX cream QD to Week 52, then 1.5% RUX cream BID							
2	68/M, White (II)	BCC (left lower leg)	680	2/N/Y	Y/Y	Study drug discontinued	Prior therapies: topical tacrolimus, PUVA (6–8 years for each)
1.5% RUX cream BID							
3	50/M, White (II)	BCC (right shoulder)	203	2/N/Y	N/N	Study drug interrupted	Prior skin lesion on adjacent region. Prior therapies: topical tacrolimus (≤ 1 year), phototherapy (1–3 years)
		BCC (right neck)	378	2/N/Y	N/Y	Study drug interrupted ^b	
		BCC (left upper arm)	378	2/N/Y	N/N	Study drug interrupted ^b	
		BCC (left shoulder)	378	2/N/Y	N/N	Study drug interrupted ^b	
4	52/M, White (II)	Bowen's disease (unspecified)	1090	2/N/Y	N/Y	None	Prior therapies: TCS (1 year), PUVA (< 1 year)
5	71/M, White (III)	BCC (left pretibial)	302	1/N/Y	N/N	None	Prior BCC and seborrheic keratosis. Prior therapies: TCS (1 year), OCS (< 1 year), topical tacrolimus (1 year)
Vehicle cream BID to Week 24, then 1.5% RUX cream BID							
6	66/M, White (I)	SCC of skin (unspecified)	42	2/N/Y	N/Y	None	Prior skin lesion. Prior therapies: TCS (≤ 1 year)

Abbreviations: AE, adverse event; BCC, basal cell carcinoma; BID, twice daily; NMSC, nonmelanoma skin cancer; OCS, oral corticosteroids; PT, preferred term; PUVA, psoralen UVA; QD, once daily; RUX, ruxolitinib; SCC, squamous cell carcinoma; TCS, topical corticosteroids.

^aAll patients included in this table had nonsegmental vitiligo.

^bStudy drug was not restarted following interruption at Day 378.

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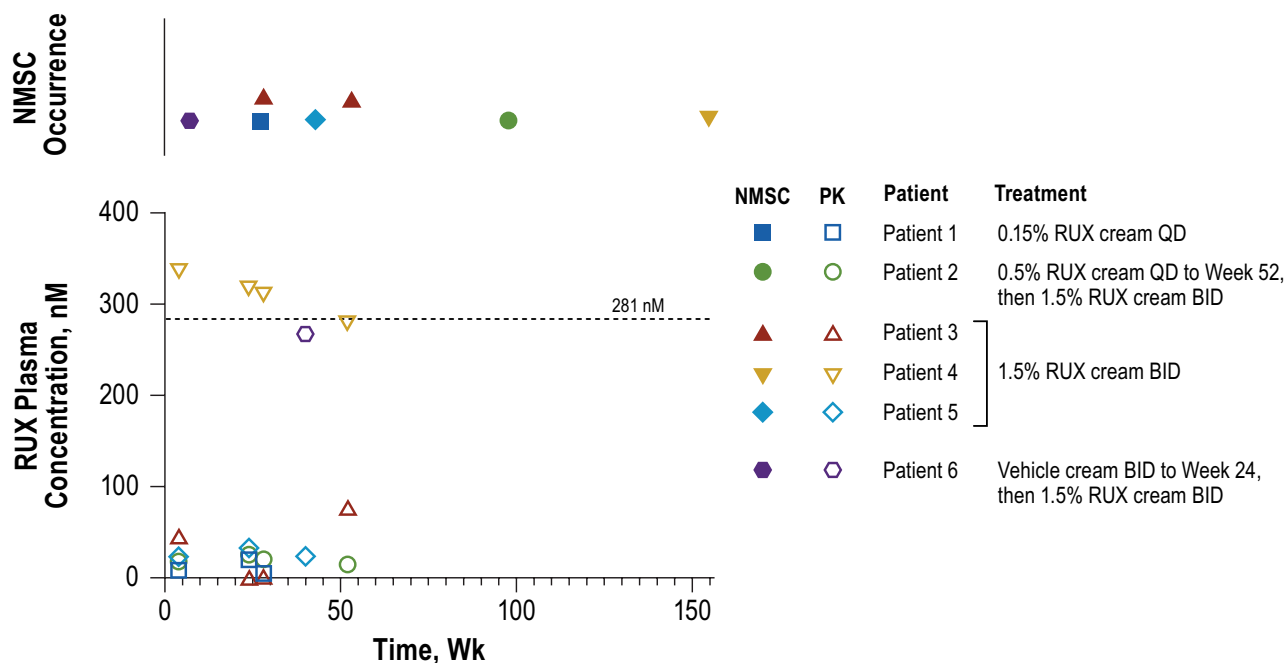


FIGURE 1 Ruxolitinib plasma concentrations throughout the studies in patients with NMSC events. Samples were drawn at Weeks 4, 24, 28 and 52 in the Phase 2 study and at Weeks 4, 24 and 40 in the Phase 3 studies; pre-application plasma concentrations of ruxolitinib at all available time points are shown. The half-maximal concentration for thrombopoietin-stimulated phosphorylated signal transducer and activator of transcription protein 3 (281 nM; proxy for evaluating JAK-related myelosuppression)⁷ is shown with a dashed line. BID, twice daily; JAK, Janus kinase; NMSC, nonmelanoma skin cancer; PK, pharmacokinetics; QD, once daily; RUX, ruxolitinib.

Across studies, a total of 789 and 256 patients applied ruxolitinib cream and vehicle cream, respectively. The duration of study drug exposure was substantially longer with ruxolitinib cream versus vehicle (mean [SD] treatment duration, 528.5 [270.0] vs. 156.4 [39.3] days; 1141.7 vs. 109.6 person-years).

A total of six patients developed NMSC events (Table 1), including five who applied ruxolitinib cream (Phase 2, $n=4$ [Bowen's disease, one event; basal cell carcinoma (BCC), six events]; TRuE-V1, $n=1$ [BCC, one event]) and one who applied vehicle (TRuE-V1; squamous cell carcinoma [SCC], one event). All events were nonserious and mild or moderate in severity. No NMSC events were reported with concomitant phototherapy during the Phase 2 open-label period.⁶ All patients with NMSC events were White adults (42–71 years) with Fitzpatrick skin types I, II or III; most had risk factors potentially predisposing them to NMSC (e.g. history of skin lesions, previous phototherapy or calcineurin inhibitor use). Approximately half of NMSC events occurred at the site of study drug application, including the SCC event that occurred in a patient while applying vehicle. Interestingly, four BCC events (only one at application site) occurred in a 50-year-old man (history of skin lesions; prior phototherapy and topical tacrolimus); this patient's ruxolitinib plasma concentrations ranged from 0.5 to 77.0 nM in the first year of treatment (<30% of the half-maximal concentration for JAK-mediated myelosuppression [281 nM]).⁷ Most NMSC events were not considered by the investigator to be related to ruxolitinib cream, except for a BCC event occurring in a 68-year-old man (~7 year history of psoralen UVA and topical tacrolimus) after 680 days of ruxolitinib cream application that resulted in

treatment discontinuation. This patient's ruxolitinib plasma concentrations ranged from 14.8 to 25.3 nM in the first year of treatment (<10% of the 281 nM threshold). Most patients who applied ruxolitinib cream and developed NMSC events had ruxolitinib plasma concentrations well below the 281 nM threshold prior to NMSC development and throughout the studies, although pharmacokinetic data were only available up to 1 year (Figure 1). One patient, a 52-year-old man, had ruxolitinib plasma concentrations that exceeded 281 nM (range, 278–336 nM in the first year) and developed Bowen's disease after nearly 3 years of ruxolitinib cream application; however, this event was not considered by the investigator to be related to treatment and did not result in study drug interruption.

In conclusion, evidence to date has not identified an association between NMSC and ruxolitinib plasma concentrations following ruxolitinib cream application in patients with vitiligo. Additional follow-up is needed to confirm these findings.

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CONFLICT OF INTEREST STATEMENT

KE has served as a consultant for AbbVie, Incyte Corporation, Pfizer, Pierre Fabre Pharmaceuticals, Sanofi and Viela Bio.

AW has served as principal investigator for AbbVie, Avita Medical, Incyte Corporation, MSD and Novartis; has served as an advisory board member for Incyte Corporation; has received research grants from Avita Medical and Lumenis; and has received devices from Humeca and PerfAction. SW and DK are employees and shareholders of Incyte Corporation. AAK is an employee of Incyte Biosciences International and a shareholder of Incyte Corporation. DR has received honoraria as a consultant and/or speaker for and/or received research support from AbbVie, Abcuro, AltruBio, Amgen, Arena, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Concert, CSL Behring, Dermavant Sciences, Dermira, Galderma, Incyte Corporation, Janssen, Kyowa Kirin, Lilly, Merck, Nektar, Novartis, Pfizer, RAPT Therapeutics, Regeneron Pharmaceuticals, Recludix, Revolo Biotherapeutics, Sanofi, Sun Pharmaceuticals, UCB, Viela Bio and Zura Bio.

DATA AVAILABILITY STATEMENT







Incyte Corporation (Wilmington, DE, USA) is committed to data sharing that advances science and medicine while protecting patient privacy. Qualified external scientific researchers may request anonymized datasets owned by Incyte for the purpose of conducting legitimate scientific research. Researchers may request anonymized datasets from any interventional study (except Phase 1 studies) for which the product and indication have been approved on or after 1 January 2020 in at least one major market (e.g. US, EU and JPN). Data will be available for request after the primary publication or 2 years after the study has ended. Information on Incyte's clinical trial data sharing policy and instructions for submitting clinical trial data requests are available at <https://www.incyte.com/Portals/0/Assets/Compliance%20and%20Transparency/clinical-trial-data-sharing.pdf?ver=2020-05-21-132,838-960>.

ETHICAL APPROVAL

The trial protocols were reviewed and approved by an institutional review board or ethics committee at participating centres. The trials were conducted in accordance with the Declaration of Helsinki and adhered to Good Clinical Practice guidelines and applicable country-specific laws and regulations.

ETHICS STATEMENT

Written informed consent was provided by all patients. The patients in this article have given written informed consent for publication of their case details.

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