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Integrated Safety Analysis of Ruxolitinib Cream: Data From 20 Clinical Studies in Inflammatory Dermatologic Conditions

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Objective

- To investigate the incidence of JAK inhibitor warning adverse events among 20 clinical studies of ruxolitinib cream in patients with AA, AD, HS, LP, LS, or vitiligo

Conclusions

- **With >2000 PY of follow-up and up to 3 years of exposure, EAIRs of adverse events in the JAK inhibitor safety warning (serious infections, MACE, thromboembolic events, malignancies, and mortality) among patients who applied 1.5% ruxolitinib cream twice daily were generally low or absent and consistent with available published literature**
- **These findings may be attributable to low systemic exposure owing to topical administration of ruxolitinib cream**
- **No new safety signals were identified across the studies**

Abbreviations

AA, alopecia areata; AE, adverse event; AD, atopic dermatitis; BID, twice daily; EAIR, exposure-adjusted incidence rate; HS, hidradenitis suppurativa; IC_{50}, half-maximal inhibitory concentration; JAK, Janus kinase; LP, lichen planus; LS, lichen sclerosus; MACE, major adverse cardiac event; NMSC, nonmelanoma skin cancer; PY, person-year; STAT, signal transducer and activator of transcription.

Disclosures

CGB has served as an investigator for AbbVie, Almirall, Apogee, Daiichi Sankyo, LEO Pharma, Ortho Dermatologics, Palvella, Sun Pharma, and Timber; a consultant for AbbVie, Almirall, Apogee, Arcutis, Connect BioPharma, Eli Lilly, EPI Health/Novan, Incyte Corporation, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Sanofi-Regeneron, Takeda, Teladoc, and UCB; and a speaker for and received honoraria from Allergan, Almirall, LEO Pharma, and UCB. KE has served as a consultant for AbbVie, Almirall, Bristol Myers Squibb, Incyte Corporation, La Roche-Posay, Lilly, Pfizer, Pierre Fabre Pharmaceuticals, and Sanofi. LFE has served as a consultant, speaker, advisory board member, or investigator for AbbVie, Almirall, Amgen, Apogee, Arcutis, Attovia, Bristol Myers Squibb, Castle Biosciences, CorEvitas, Dermavant, Eli Lilly, Forte, Galderma, Incyte Corporation, Janssen, Johnson & Johnson, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi Genzyme, Target RWE, T-Rex, and UCB. RB has served as an advisory board member, consultant, speaker and/or investigator for and has received honoraria and/or grants from AbbVie, Aclaris, Amgen, Apogee, Arcutis, Areteia, Asana BioSciences, Bellus, BioMimetix, Bluefin, Biomedicine, Boehringer Ingelheim, Boston Pharma, CARA, Dermavant, Eli Lilly, Escient, Evidera, Fresh Tracks (Brickell), Galderma, GlaxoSmithKline, Incyte Corporation, Inmagene Bio, Janssen, LEO Pharma, Merck, Novartis, Opsidio, Pfizer, RAPT, Sanofi, Sitryx, Target RWE, Vyne Therapeutics, and Zencor and is an employee and shareholder of Innovaderm Research. TP has received grants and/or honoraria from AbbVie, ACM Pharma, Almirall, Amgen, Astellas, Bristol Myers Squibb, Calypso, Celgene, Eli Lilly, Galderma, Genzyme/Sanofi, GlaxoSmithKline, Incyte Corporation, Janssen, LEO Pharma, Novartis, Pfizer, Sun Pharmaceuticals, Takeda, UCB, and Vyne Therapeutics; is the cofounder of NIKAIA Pharmaceuticals; and has patents on WNT agonists and GSK3b antagonists for repigmentation of vitiligo and on the use of CXCR3B blockers in vitiligo. DS, HR, and YS are employees and shareholders of Incyte Corporation. DR has served as a consultant, speaker, or investigator for AbbVie, Abcuro, Almirall, AltruBio, Amgen, Arena, Astria, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Concert, CSL Behring, Dermavant Sciences, Dermira, Dualitas, EMD Serono, Galderma, Incyte Corporation, Janssen, Kymera, Kyowa Kirin, Lilly, Merck, Nektar, Novartis, Pfizer, RAPT Therapeutics, Recludix, Regeneron Pharmaceuticals, Revolo Biotherapeutics, Sanofi, Sun Pharmaceuticals, UCB, Viela Bio, and Zura Bio.

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Introduction

- JAK inhibitors are an effective therapy in a variety of inflammatory conditions[1-6]
- A safety warning for serious infections, MACE, thromboembolic events, malignancies, and mortality accompanies most of the US and Canadian labels of JAK inhibitors for inflammatory conditions[7,8]
  - This warning is based on safety findings from the use of a systemic pan-JAK inhibitor (tofacitinib) when compared with a tumor necrosis factor inhibitor in patients with rheumatoid arthritis aged ≥50 years and ≥1 additional cardiovascular disease risk factor while on concomitant methotrexate[9,10]
- Ruxolitinib cream, a selective JAK1/JAK2 inhibitor, is currently approved in patients aged ≥2 years with AD in the US,[7] patients aged ≥12 years with AD in Canada,[8] and patients aged ≥12 years with nonsegmental vitiligo (US, Canada, UK, and various European and Asian countries)[7,8,11-13]
  - In clinical studies with ruxolitinib cream, plasma concentrations of ruxolitinib were low,[2,3] suggesting minimal systemic exposure and limited systemic JAK inhibition

Methods

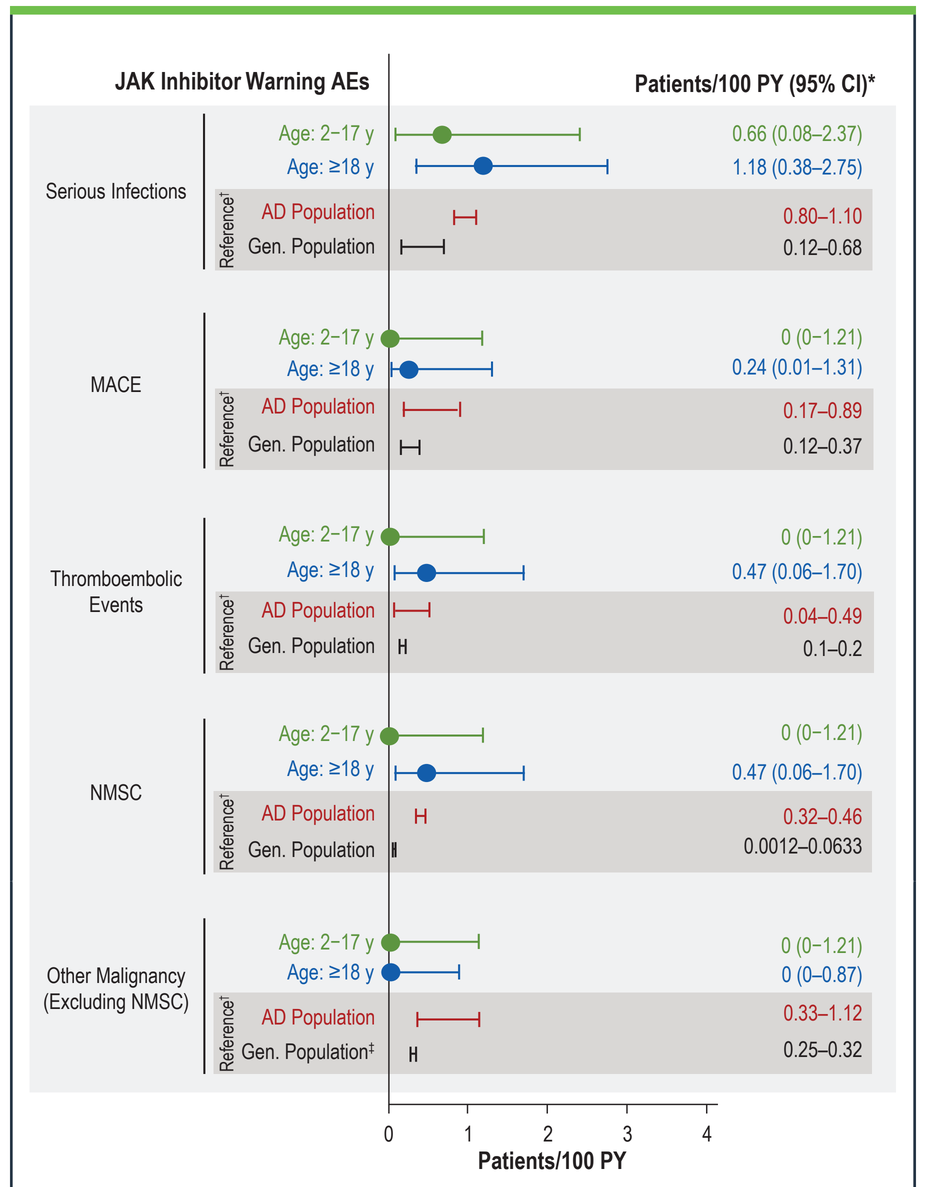
Study Design and Patients

- EAIRs (number of patients experiencing the event per 100 PY of exposure) of adverse events in the JAK inhibitor safety warning were calculated for patients who applied 1.5% ruxolitinib cream twice daily
- Data were derived from clinical studies in patients with AD (10 studies; ages 2−17 y, n=461, 304.98 PY; ages ≥18 y, n=882, 423.98 PY); vitiligo (6 studies; n=877; 1157.08 PY); and AA (n=89; 73.51 PY), HS (n=66; 24.22 PY), LP (n=60; 25.17 PY), and LS (N=58; 19.20 PY; all 1 study each), with exposure durations ranging from approximately 4 weeks to 3 years
  - For study design details, please scan the QR code

Results

- Patients with AD aged 2−17 years who applied 1.5% ruxolitinib cream had an EAIR (95% CI) of 0.66 (0.08−2.37) for serious infections, with no MACE, thromboembolic events, or malignancies (**Figure 1**)
- Patients with AD aged ≥18 years who applied 1.5% ruxolitinib cream had EAIRs (95% CI) of 1.18 (0.38−2.75) for serious infections, 0.24 (0.01−1.31) for MACE, 0.47 (0.06−1.70) for thromboembolic events, 0.47 (0.06−1.70) for NMSC, and 0 (0–0.87) for malignancies excluding NMSC

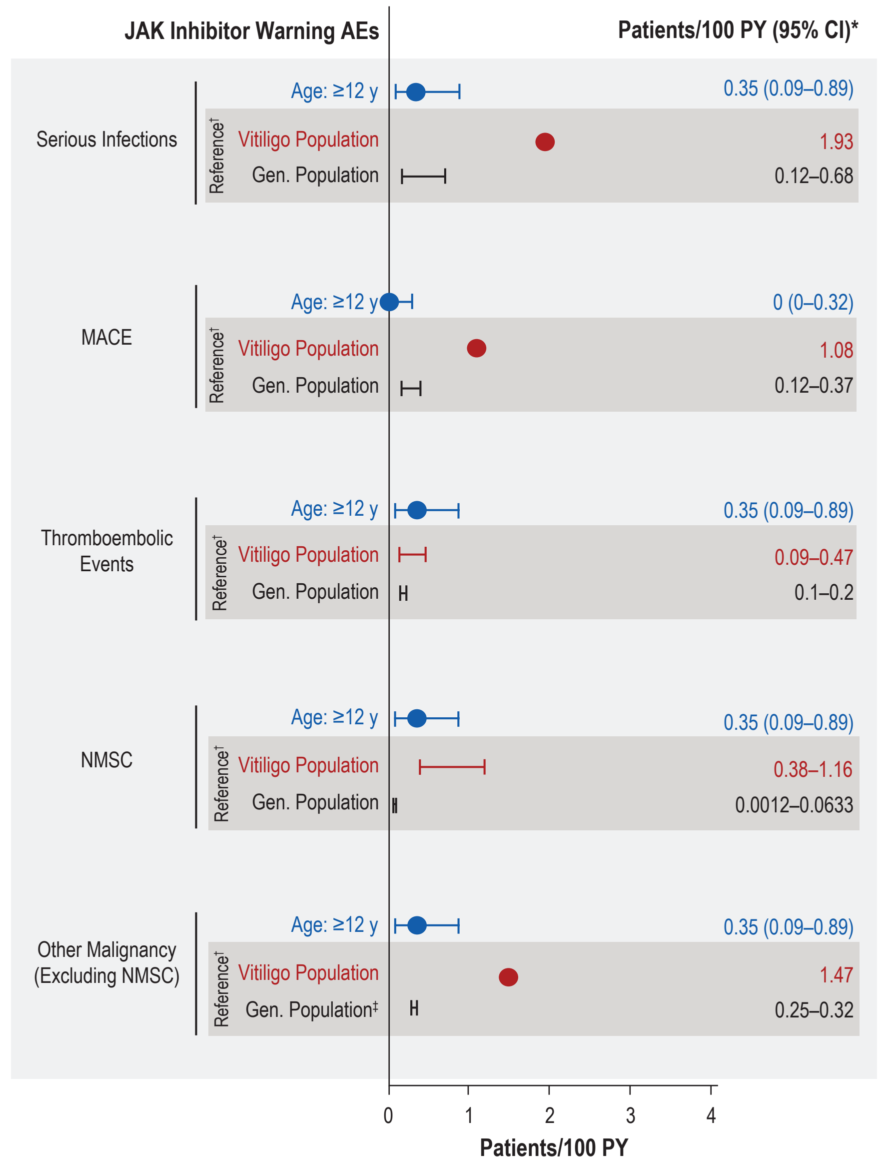
Figure 1. Atopic Dermatitis EAIRs With 1.5% Ruxolitinib Cream Application



* For patients aged 2−17 years, serious infections were eczema herpeticum and pneumonia mycoplasmal (each n=1). For patients aged ≥18 years, serious infections were abscess limb, bronchitis, cholecystitis infective, chronic tonsillitis, and pneumonia (all n=1); MACE was a cerebrovascular accident (n=1); thromboembolic events were cardiovascular accident, deep vein thrombosis, and pulmonary embolism (all n=1); and NMSC events were squamous cell carcinoma of the skin (n=2).
† AD (serious infections,[14] MACE,[15-18] thromboembolic events,[15,18-20] NMSC,[21-23] and other malignancy[24,25]) and general population (serious infections,[26,27] MACE,[28-30] thromboembolic events,[31] NMSC,[32] and other malignancy[32]) references are a range of point estimates from studies in the literature. The AD reference includes patients with AD ≥12 years of age (≥18 years when available) with mild to moderate disease severity (when data are available). MACE ranges are comprised of individual components (eg, stroke, myocardial infarction) in addition to composite estimates, as not all studies reported a composite.
‡ Rate also excludes lymphoma.

- AD EAIRs were generally consistent with rates observed in adolescents and adults with AD reported in the literature
- Patients with vitiligo who applied 1.5% ruxolitinib cream had EAIRs (95% CI) of 0.35 (0.09−0.89) for serious infections, 0 (0−0.32) for MACE, 0.35 (0.09−0.89) for thromboembolic events, 0.35 (0.09−0.89) for NMSC, and 0.35 (0.09−0.89) for malignancies excluding NMSC, which are consistent with disease-specific rates reported in the literature (**Figure 2**)

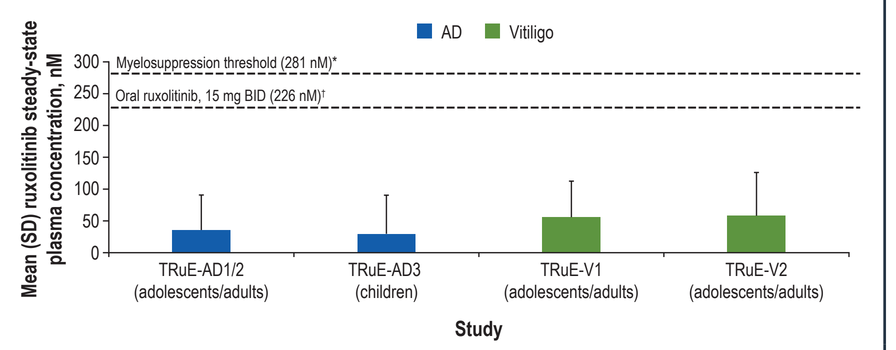
Figure 2. Vitiligo EAIRs With 1.5% Ruxolitinib Cream Application



* Serious infections were appendiceal abscess, appendicitis, COVID-19, pneumonia, hepatitis infectious mononucleosus (all n=1); thromboembolic events were acute coronary syndrome, cardiac ventricular thrombosis, thrombosis, transient ischemic attack (all n=1); NMSC were basal cell carcinoma (n=3) and Bowen's disease (n=1); and other malignancies were breast cancer, ovarian cancer, papillary thyroid cancer, and prostate cancer (all n=1).
† Vitiligo population (serious infections,[33] MACE,[33] thromboembolic events,[33,34] NMSC,[33,35] and other malignancy[33]) reference is an estimate from a single study/dataset; more studies are needed to validate the background rates in the vitiligo population. General population (serious infections,[26,27] MACE,[28-30] thromboembolic events,[31] NMSC,[32] and other malignancy[32]) reference is a range of point estimates from studies in the literature; MACE ranges are comprised of individual components (eg, stroke, myocardial infarction) in addition to composite estimates, as not all studies reported a composite.
‡ Rate also excludes lymphoma.

- In studies of patients applying 1.5% ruxolitinib cream having other diseases in which patient years were limited, patients with AA experienced serious infections (diverticulitis [n=1] and sepsis [n=1]) and a malignancy excluding NMSC (lentigo maligna, n=1); patients with LP experienced NMSC (squamous cell carcinoma of skin, n=1), and patients with LS experienced NMSC (basal cell carcinoma, n=1)
- No patients with HS had serious infections, MACE, thromboembolic events, NMSC, or other malignancies
- No fatalities occurred in any study
- Ruxolitinib plasma concentrations, as measured in the pivotal studies of patients with AD or vitiligo, generally remained low (eg, well below the threshold of 281 nM associated with JAK-mediated myelosuppression using in vitro assays in whole blood in adults[36]; **Figure 3**)

Figure 3. Ruxolitinib Plasma Concentrations With 1.5% Ruxolitinib Cream Application in Pivotal Studies for AD and Vitiligo

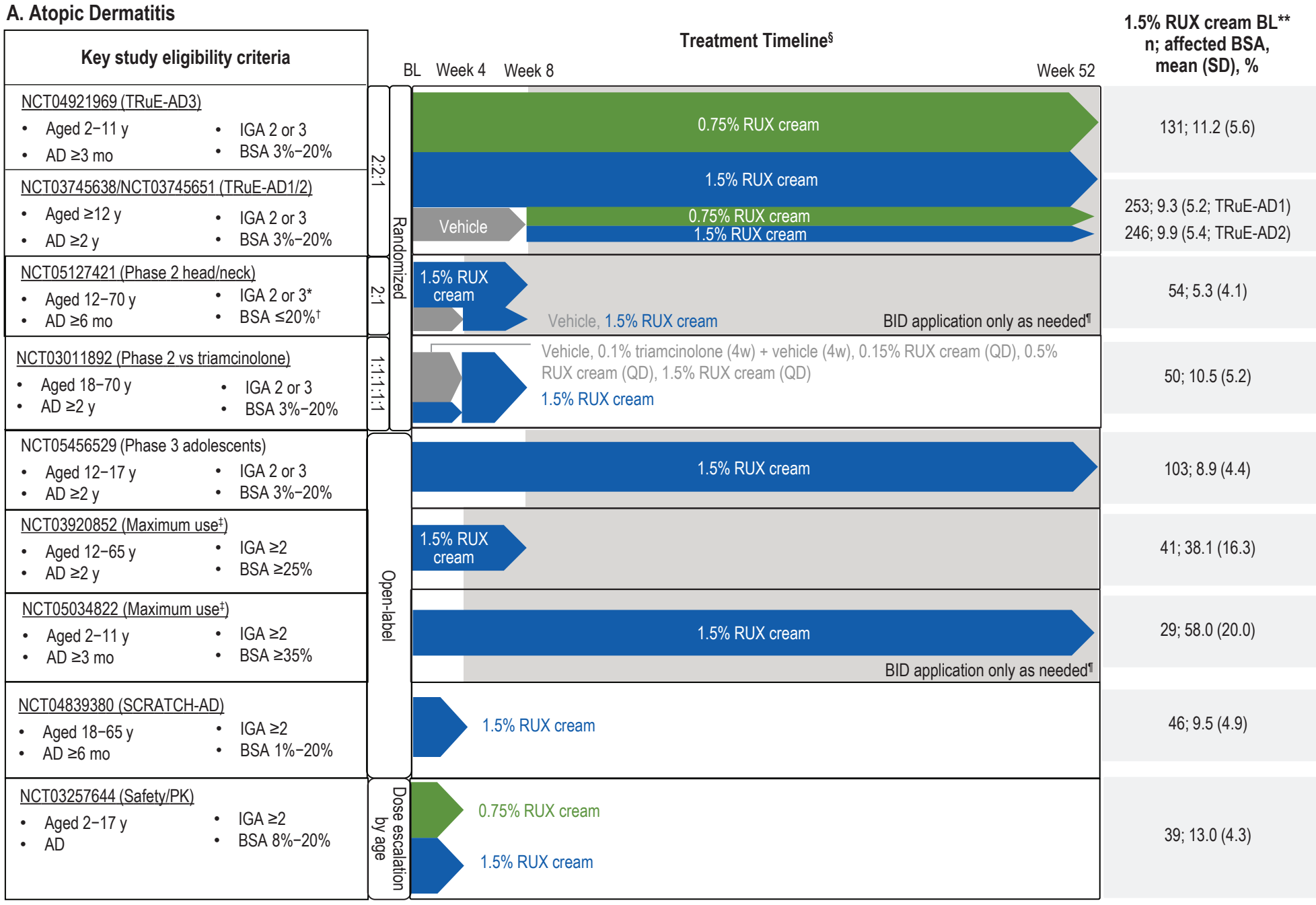


Patient ruxolitinib concentrations reflect continuous BID administration of ruxolitinib cream.
* Dashed line at 281 nM indicates the IC_{50} for thrombopoietin-stimulated phosphorylated STAT3 (a proxy parameter to assess JAK-related myelosuppression in bone marrow). This threshold was established using in vitro assays with adult whole blood.[36]
† Dashed line at 226 nM indicates the steady-state ruxolitinib concentration following oral administration of 15 mg BID ruxolitinib as previously reported.[37]

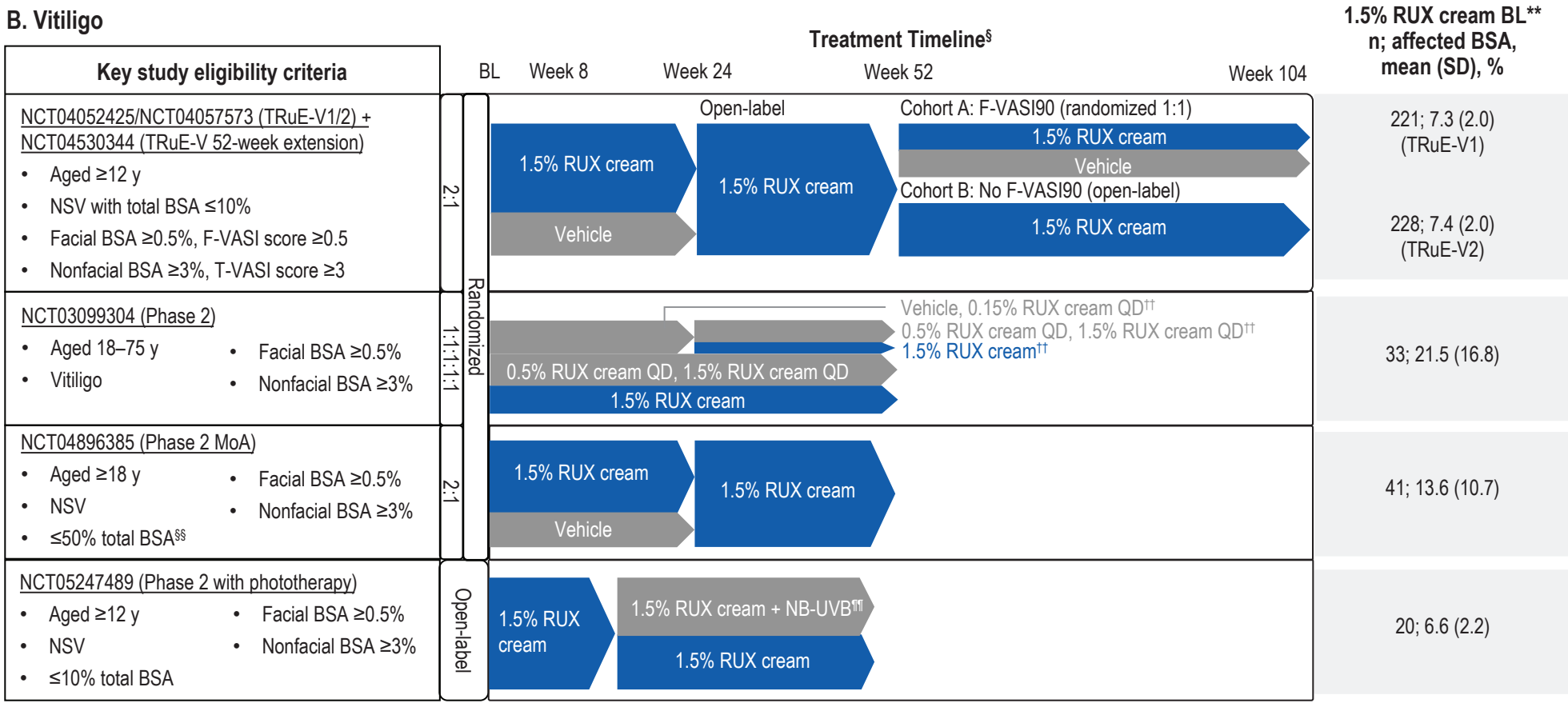
Limitations

- Between-study variability (eg, different durations, controls, ascertainment) when pooling 20 heterogeneous studies may bias findings
- Reference vitiligo population EAIRs for JAK inhibitor warning AEs were determined from the King et al. (2025) conference poster, which calculated incidence rates of first event, not overall incidence rates

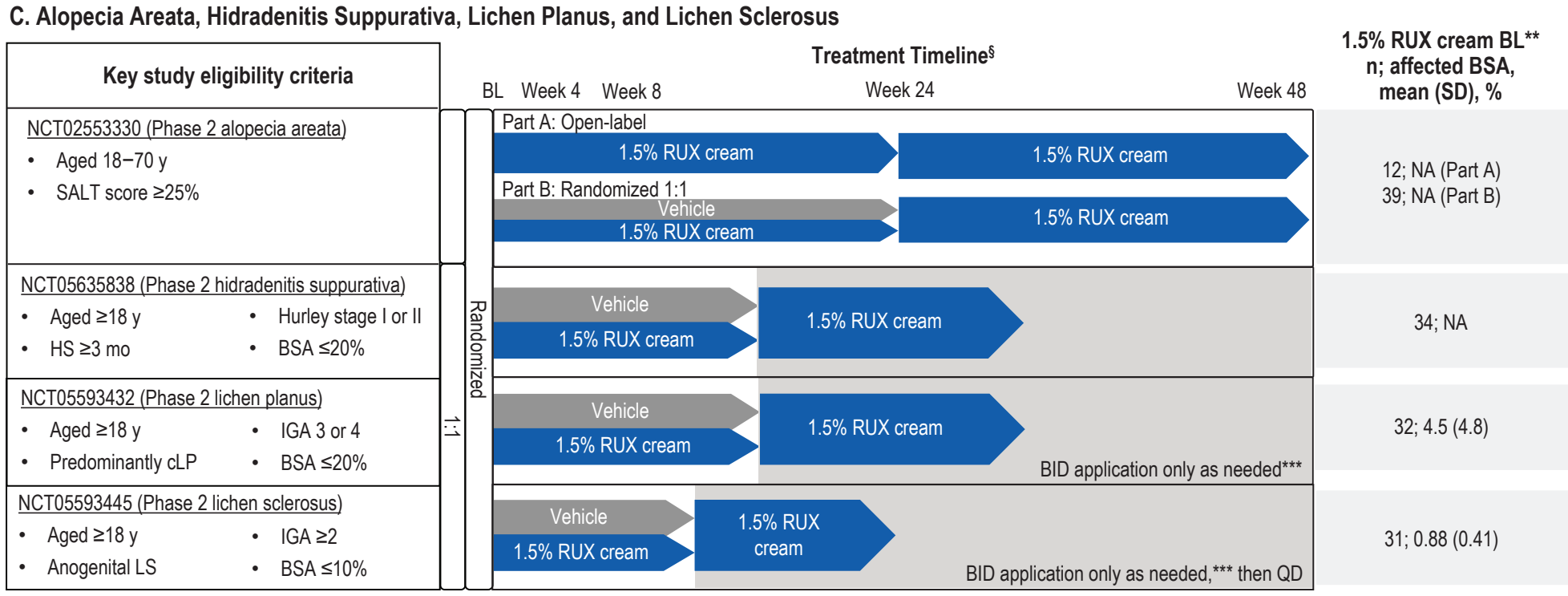
A. Atopic Dermatitis



B. Vitiligo



C. Alopecia Areata, Hidradenitis Suppurativa, Lichen Planus, and Lichen Sclerosus



AD, atopic dermatitis; BID, twice daily; BL, baseline; BSA, body surface area; cLP, cutaneous lichen planus; F-VASI, Facial Vitiligo Area Scoring Index; F-VASI90, ≥90% improvement in F-VASI from baseline; HS, hidradenitis suppurativa; IGA, Investigator's Global Assessment; LS, lichen sclerosus; MoA, mechanism of action; NB-UVB, narrowband ultraviolet B; NSV, nonsegmental vitiligo; PK, pharmacokinetic; QD, once daily; RUX, ruxolitinib; SALT, Severity of Alopecia Tool; T-VASI, Total Body Vitiligo Area Scoring Index.

* Overall and on the face/neck.

† With ≥0.5% of total BSA on the face and/or neck.

‡ Maximum-use studies are those enrolling patients with elevated levels of affected BSA.

§ Patients applied treatment continuously BID unless otherwise indicated.

¶ Patients self-evaluated recurrence of lesions between study visits and treated lesions with active AD (≤20% BSA). If lesions cleared between study visits, patients stopped treatment 3 days after lesion disappearance. If new lesions were extensive or appeared in new areas, patients contacted the investigator to determine if an unscheduled additional visit was needed.

** Data provided for patients at baseline initially randomized to RUX cream, where applicable.

†† Patients not achieving 25% improvement in F-VASI from baseline at Week 24 were re-randomized 1:1:1 to 0.5% RUX cream QD, 1.5% RUX cream QD, or 1.5% RUX cream BID.

§§ Treatment limited to ≤20% total affected BSA.

¶¶ Patients not achieving 25% improvement in T-VASI from baseline at Week 12 had NB-UVB added to 1.5% RUX cream.

*** Treatment limited to active lesions.