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Serum Protein Biomarkers May Reveal Clues to Early Immune Activity Upon Ruxolitinib Cream Withdrawal in the TRuE-V Long-Term Extension Study

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Introduction

- Ruxolitinib cream is a topical formulation of the selective Janus kinase (JAK) 1/JAK2 inhibitor ruxolitinib[1] and is the first and only repigmentation treatment[2] approved in the United States,[3] European Union,[4] and the United Kingdom[5] for the topical treatment of nonsegmental vitiligo in patients aged ≥12 years
- The TRuE-V long-term extension (LTE; NCT04530344) was a phase 3 double-blind, vehicle-controlled, randomized-withdrawal and treatment extension study of ruxolitinib cream in vitiligo
  - Patients who completed TRuE-V1/TRuE-V2 (NCT04052425/NCT04057573) could continue in the TRuE-V LTE

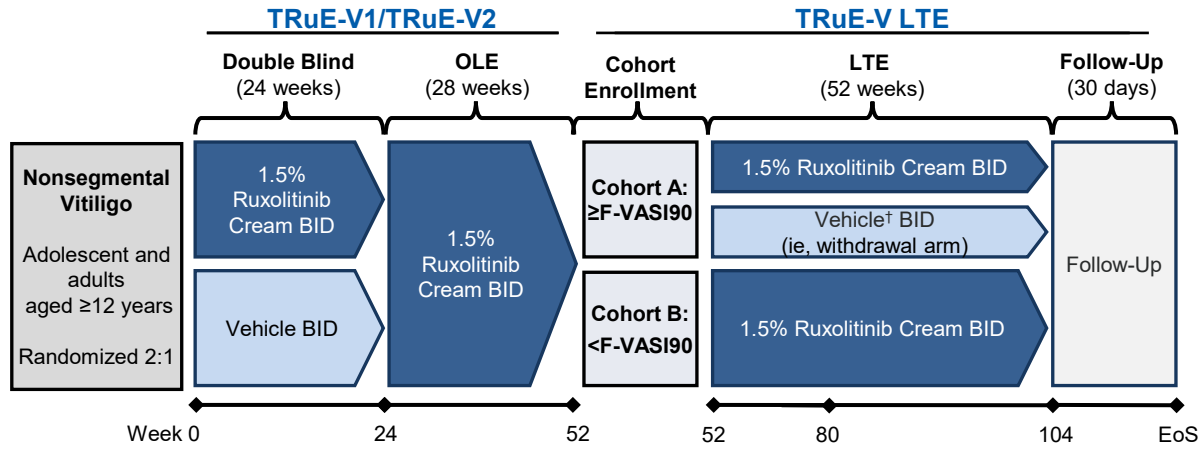
Objective

- To evaluate changes in serum biomarkers at Weeks 52, 80, and 104 in patients with nonsegmental vitiligo who applied either vehicle cream or 1.5% ruxolitinib cream in the TRuE-V LTE study after previously applying ruxolitinib cream in the TRuE-V parent studies

Methods

- In the TRuE-V1/TRuE-V2 parent studies, adults and adolescents (aged ≥12 y) with nonsegmental vitiligo were randomized to apply twice-daily (BID) 1.5% ruxolitinib cream or vehicle[6]
- In the TRuE-V LTE, patients who applied ruxolitinib cream in the parent studies were divided into 2 cohorts based on their facial Vitiligo Area Scoring Index (VASI) response at Week 52 (**Figure 1**)
  - Patients who achieved ≥90% facial repigmentation (F-VASI90) were assigned to Cohort A and randomized 1:1 to either vehicle (withdrawal arm) or 1.5% ruxolitinib cream BID (treatment-continuous arm) until Week 104
  - Patients who achieved <F-VASI90 were assigned to Cohort B and continued to apply 1.5% ruxolitinib cream BID until Week 104
- Serum samples were collected at Week 52 of TRuE-V1/TRuE-V2 (TRuE-V LTE baseline), Week 80, and Week 104 (end of treatment; **Figure 1**)
  - For patients randomized to vehicle in Cohort A, post-baseline assessments at Weeks 80 and 104 reflect 28 and 52 weeks off treatment, respectively

Figure 1. Study Design



BID, twice daily; EoS, end of study; F-VASI75, ≥75% improvement in facial Vitiligo Area Scoring Index; F-VASI90, ≥90% improvement in facial Vitiligo Area Scoring Index; LTE, long-term extension; OLE, open-label extension.
† Patients randomized to vehicle who relapsed (ie, <F-VASI75) could apply 1.5% ruxolitinib cream BID rescue treatment for the remainder of the LTE period.

Methods *(cont.)*

- Proteomic profiling of serum samples was performed with the Olink® Proximity Extension Assay technology platform (Olink Proteomics, Watertown, MA, USA) using 2 Target 96 panels (inflammation and immune-oncology)
- Differential expression analysis was performed and visualized in R (v.4.1.1) to identify differentially expressed proteins (DEPs)
  - A cutoff of log fold change ≥1.25 and adjusted *P* value ≤0.05 was used for all differential expression analyses

Results

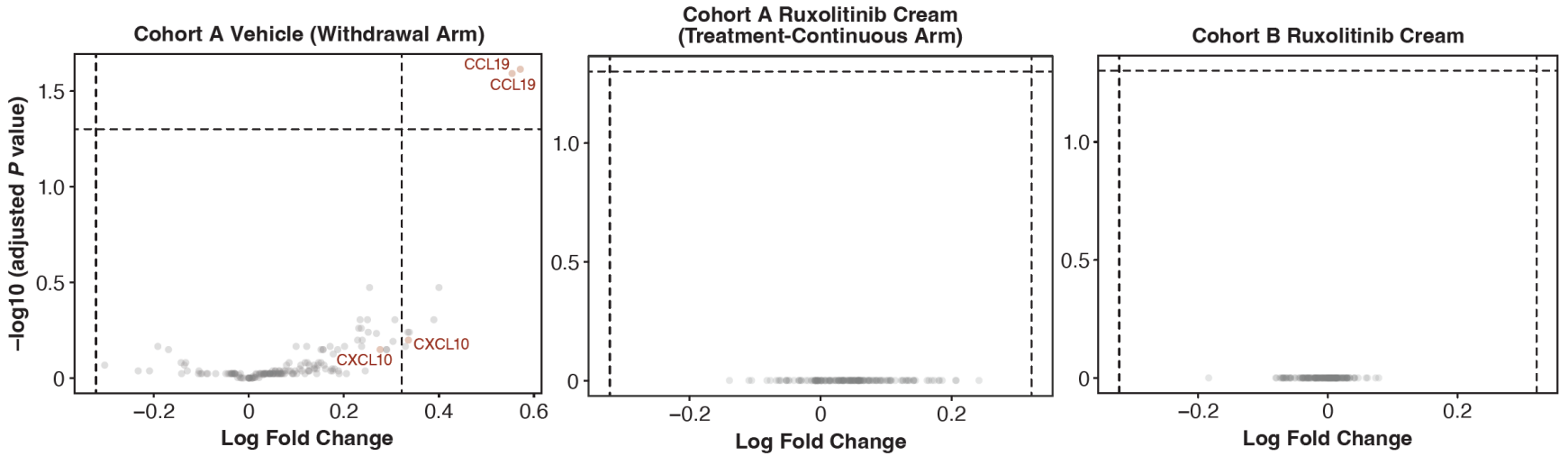
- The number of patients included in the biomarker analysis is shown in **Table 1**
- In patients randomized to vehicle in Cohort A, only C-C motif chemokine ligand 19 (CCL19) was differentially expressed between TRuE-V LTE baseline (Week 52 of parent study) and Weeks 80 (**Figure 2**; adjusted *P*<0.05, fold change ≥1.5) or 104 (data not shown)
- No DEPs were identified in patients who continued using 1.5% ruxolitinib cream from Week 52 through Week 104 (Cohort A treatment-continuous arm or Cohort B)

Table 1. Patients in Each Treatment Arm

TRuE-V Parent Arm	TRuE-V LTE Randomization	N	Patients Receiving Rescue Treatment (N)
1.5% Ruxolitinib cream	Cohort A: vehicle cream (withdrawal arm)	42	17
	Cohort A: 1.5% ruxolitinib cream	43	–
	Cohort B: 1.5 % ruxolitinib cream	205	–
Vehicle cream	Cohort A: vehicle cream (withdrawal arm)	10	5
	Cohort A: 1.5% ruxolitinib cream	11	–
	Cohort B: 1.5% ruxolitinib cream	112	–

LTE, long-term extension.

Figure 2. Differentially Expressed Proteins Compared With Baseline for Each Cohort at Week 80

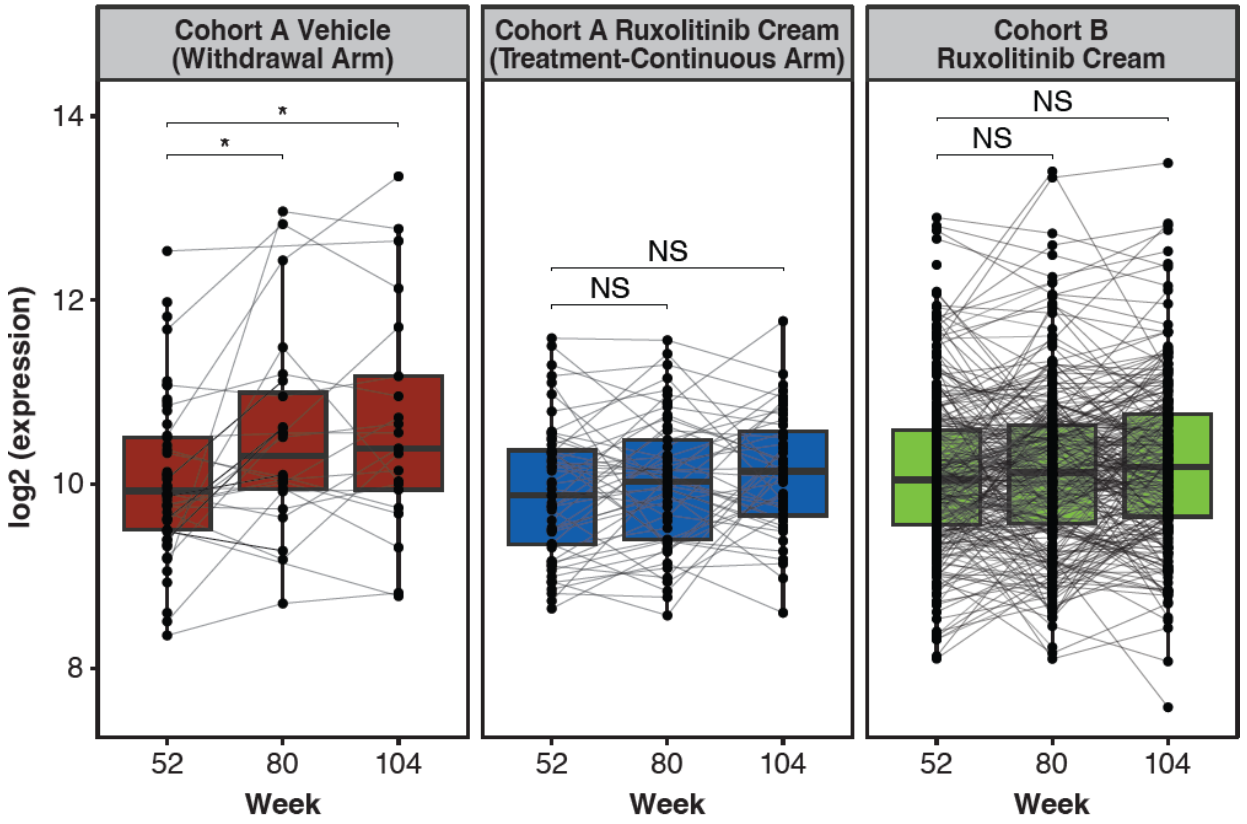


CCL19, C-C motif chemokine ligand 19.

Results *(cont.)*

- Among patients randomized to vehicle in Cohort A, serum levels of CCL19 showed a significant increase between Week 52 (TRuE-V LTE baseline) and Weeks 80 and 104 (**Figure 3**)
  - Patients in Cohort A who were randomized to vehicle and used rescue treatment with 1.5% ruxolitinib cream were excluded from this analysis
  - CCL19 plays an important role in directing lymphocyte homing and activation during adaptive immune responses[7]
  - Its role in vitiligo pathogenesis or relapse has not been fully elucidated, although it has been reported to be elevated in the serum of patients with melanoma after being treated with immune checkpoint inhibitors[8]
- In contrast, serum levels of CCL19 did not change significantly in patients who continued to apply ruxolitinib cream in Cohort A or Cohort B (**Figure 3**)
- Other chemokines are known to be elevated in vitiligo, including C-X-C motif chemokine ligand 10 (CXCL10), which is induced by interferon gamma receptor signaling and has been identified as a key biomarker in vitiligo, correlating with disease severity[9]
  - In previous studies, ruxolitinib cream application resulted in reduced serum levels of CXCL10 compared with baseline,[10,11] suggesting that it may serve as an early biomarker of effective treatment following ruxolitinib cream application
- Mean percentage change in CCL19 and CXCL10 levels are shown in **Figure 4A** and **Figure 4B**, respectively
  - After randomization to vehicle in the TRuE-V LTE, CXCL10 levels increased and were higher compared with patients who remained on ruxolitinib cream (**Figure 4B**)
- Notably, CCL19 did not correlate with a change in VASI (facial or total VASI) under any condition measured (data not shown)

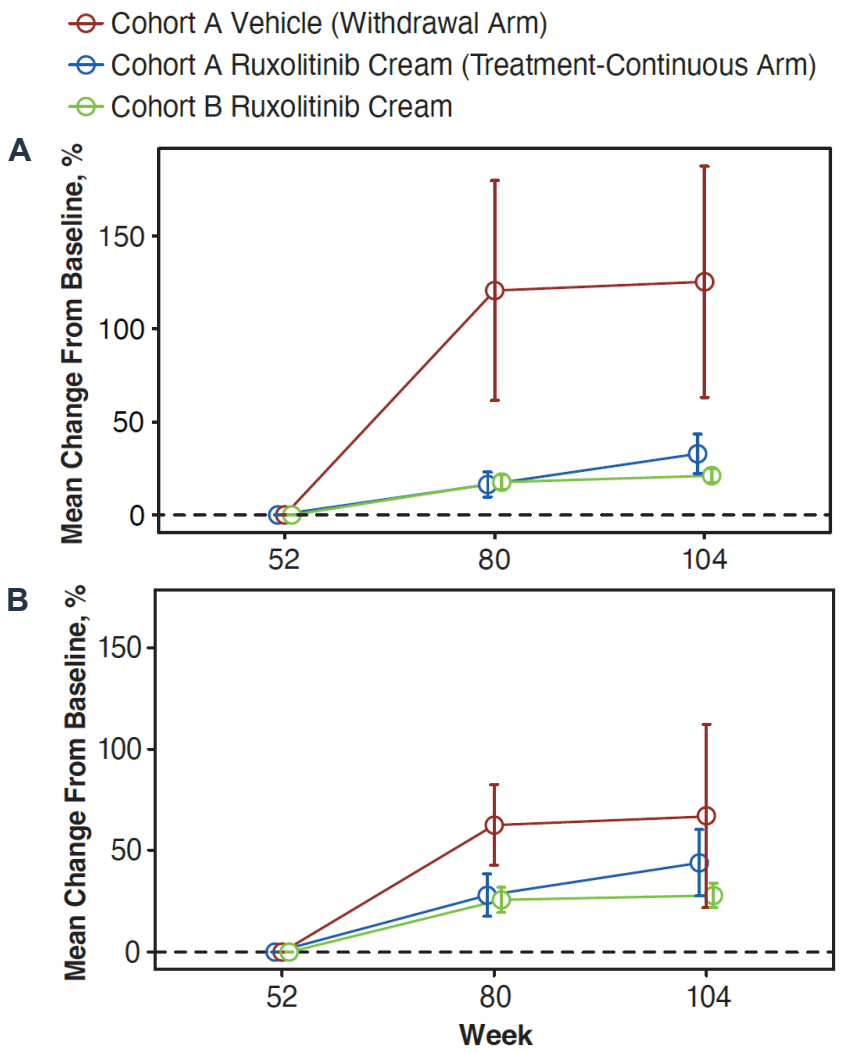
Figure 3. CCL19 (OID00794) Expression by Visit in the Serum of Patients Who Applied Ruxolitinib Cream or Vehicle



* *P*<0.05.
CCL19, C-C motif chemokine ligand 19.

Results *(cont.)*

Figure 4. Mean Percentage Change in (A) CCL19 and (B) CXCL10 by Cohort



CCL19, C-C motif chemokine ligand 19; CXCL10, C-X-C motif chemokine ligand 10. Patients in Cohort A who were randomized to vehicle and used rescue treatment with 1.5% ruxolitinib cream were excluded from this analysis.

Conclusions

- **Biomarkers remained stable in patients who continued ruxolitinib cream treatment in the TRuE-V LTE**
- **Serum levels of CCL19, a cognate ligand for C-C motif chemokine receptor-7 (CCR7), were increased among patients who withdrew from active treatment (ie, randomized to vehicle after achieving F-VASI90 in parent studies)**
  - **We hypothesize that increased serum levels of CCL19 in patients who withdrew from treatment could be a marker of memory response activation, preceding vitiligo recurrence, via central memory T cells[7,12]**
- **Patients who withdrew from active treatment also showed a trend toward increased serum levels of CXCL10, which has previously been identified as a key biomarker in vitiligo, both correlating with disease severity and serving as an early pharmacodynamic marker of ruxolitinib cream treatment**

Disclosures

AV, SW, DK, SHS are employees and shareholders 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. TP has received grants and/or honoraria from AbbVie, ACM Pharma, Almirall, Amgen, Astellas, Bristol Myers Squibb, Celgene, Galderma, Genzyme/Sanofi, GlaxoSmithKline, Incyte Corporation, Janssen, LEO Pharma, Eli Lilly, Novartis, Pfizer, Sun Pharmaceuticals, UCB, and Vyne Therapeutics; is the cofounder of YUKIN Therapeutics; and has patents on WNT agonists and GSK3b antagonists for repigmentation of vitiligo and on the use of CXCR3B blockers in vitiligo. JS has received grants and/or honoraria from AbbVie, Bristol Myers Squibb, Calypso Biotech, Eli Lilly, Incyte Corporation, LEO Pharma, Novartis, Pfizer, Pierre Fabre, Sanofi, Sun Pharmaceuticals, and Viela Bio; and has patents on MMP9 inhibitors and uses thereof in the prevention or treatment of a depigmenting disorder and 3-dimensional model of depigmenting disorder. AW is a dermatologist at the Netherlands Institute for Pigment Disorders and the Department of Dermatology at the Amsterdam University Medical Center; has served as principal investigator for Avita Medical, Incyte Corporation, 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.

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