# A Systematic Literature Review and Network Meta-Analysis of 1.5% Ruxolitinib Cream vs Other Pharmacologic Agents in the Treatment of Atopic Dermatitis

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## Introduction

- Atopic dermatitis (AD) is a chronic, heterogeneous, highly pruritic, relapsing inflammatory disease with underlying skin barrier defects and is associated with high quality-of-life burden for patients and their caregivers[1]
- 1.5% ruxolitinib cream is a topically administered selective Janus kinase (JAK)1/JAK2 inhibitor applied directly to AD lesions to regulate inflammatory, pruritic, and skin barrier pathways in AD
- The efficacy and safety of 1.5% ruxolitinib cream were studied in 2 randomized controlled trials (RCTs), TRuE-AD1 (NCT03745638) and TRuE-AD2 (NCT03745651), which demonstrated that 1.5% ruxolitinib cream is effective, safe, and well tolerated in achieving disease control and improves areas that matter to patients, such as itch and lesion clearance
  - Patients recruited into the TRuE-AD1 and TRuE-AD2 studies were adults and adolescents ≥12 years of age with a clinician-confirmed diagnosis of AD for a duration of ≥2 years, an Investigator's Global Assessment (IGA) score of 2 to 3 at screening and baseline, and affected body surface area (BSA) of 3% to 20% (excluding the scalp) at screening and baseline

## Objectives

- Currently, there are no head-to-head phase 3 trials that compare the efficacy of 1.5% ruxolitinib cream with relevant active treatments for patients ≥12 years old with AD
- The primary objective of this analysis was to assess the comparative efficacy of 1.5% ruxolitinib cream against other therapies in the treatment of AD among patients ≥12 years old through an indirect treatment comparison (ITC)

## Methods

### *Systematic Literature Review*

- A formal systematic literature review (SLR) was conducted to identify phase 3 or 4 RCTs in patients with AD evaluating 1.5% ruxolitinib cream and other therapies used in AD, including oral JAK inhibitors, monoclonal antibodies, phosphodiesterase-4 (PDE4) inhibitors, and systemic immunosuppressants

### *Feasibility Assessment*

- A feasibility assessment was conducted (for the trial full population and relevant subgroups) to assess whether an ITC was appropriate for deriving estimates of relative efficacy and safety for 1.5% ruxolitinib cream vs other therapies used in AD and to determine appropriate ITC methods
- To conduct the feasibility assessment, publications and clinical study reports from TRuE-AD1 and TRuE-AD2 were used; for comparator trials, the review was limited to published manuscripts, abstracts, and posters

### *Network Meta-Analyses*

- Network meta-analyses (NMAs) were conducted in a frequentist framework using a penalized likelihood NMA (PL-NMA) as described in Evrenoglou et al[2]
- A PL-NMA was used to attempt to reduce the bias of the maximum likelihood estimate that is known to occur in the presence of rare events such as IGA (0/1) in certain treatment arms[2]
- Evaluated outcomes included in the NMA:
  - IGA score of 0 (clear) or 1 (almost clear) with a ≥2-point improvement from baseline (referred to as IGA 0/1)
  - Eczema Area and Severity Index (EASI)-75, defined as a ≥75% improvement in EASI score from baseline
  - Itch numerical rating scale (NRS) 4, defined as a ≥4-point improvement from baseline
- The outcomes included in the NMA included IGA (0/1), EASI-75, and Itch NRS4 (as defined above); treatment-emergent adverse events were also assessed in the feasibility assessment

## Results

### *Systematic Literature Review*

- The SLR identified 23 unique studies that assessed the efficacy and safety of relevant comparators
  - Of the 23 studies, 12 also reported outcomes for patients with IGA=3, EASI≥16, and BSA≥10%; herein, referred to as the "more severe subset of moderate AD"
  - The 12 studies included 4 unique interventions: 1.5% ruxolitinib cream, dupilumab, upadacitinib, and abrocitinib. These interventions were compared against placebo or placebo + topical corticosteroids (TCS)

### *Feasibility Assessment for the Full Trial Population*

- An ITC for 1.5% ruxolitinib cream with oral JAK inhibitors, monoclonal antibodies, PDE4 inhibitors, and systemic immunosuppressants for the treatment of AD was deemed not feasible due to significantly different trial eligibility criteria (variability in age, disease severity, and prior treatment), as well as higher baseline AD duration and severity in the comparator trials

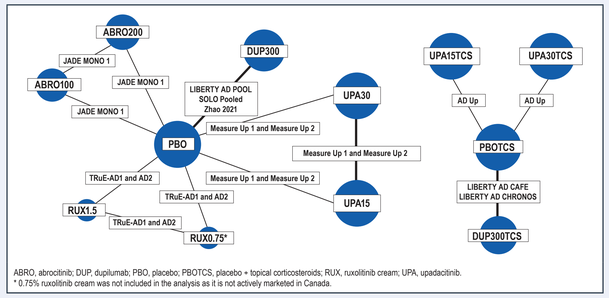
### *Feasibility Assessment for the More Severe Subset of Moderate AD*

- Disease severity characteristics at baseline (ie, IGA and EASI scores) were more comparable across trials for the more severe subset of moderate AD, and an ITC was deemed feasible for this subgroup

### *Network Meta-Analyses for the More Severe Subset of Moderate AD*

- A network of 7 RCTs (sample sizes summarized in **Table 1**) connected 1.5% ruxolitinib cream to the following comparators:
  - Dupilumab (300 mg), upadacitinib (15 mg, 30 mg), and placebo for IGA (0/1), EASI-75, and NRS4
  - Abrocitinib (100 mg, 200 mg) for EASI-75
- Outcomes were assessed at Wk 8 for 1.5% ruxolitinib cream trials, and Wk 12 or 16 in comparator trials
- There were insufficient data available to conduct analyses of safety outcomes, as the active comparator trials did not report adverse event rates specific to the subgroup of interest
- Five trials were connected to 1.5% ruxolitinib cream through a common placebo comparator. Two trials compared against placebo + TCS (**Figure 1**)

**Figure 1. Network Connectivity for the More Severe Subset of Moderate AD[3-9]**




ABRO, abrocitinib; DUP, dupilumab; PBO, placebo; PBOTCS, placebo + topical corticosteroids; RUX, ruxolitinib cream; UPA, upadacitinib.
* 0.75% ruxolitinib cream was not included in the analysis as it is not actively marketed in Canada.

**Table 1. Sample Sizes by Treatment Arm, More Severe Subset of Moderate AD[3-9]**

| TRuE-AD1 & TRuE-AD2 | LIBERTY AD ADOL | LIBERTY AD CAFÉ | LIBERTY AD CHRONOS | SOLO Pooled | Zhao (2021) | JADE MONO 1 | Measure UP 1 & 2 | AD Up |
|---|---|---|---|---|---|---|---|---|
| RUX1.5 (n=32) | DUP (n=39) | DUP300TCS (n=57) | DUP300TCS (n=53) | DUP300 (n=234) | DUP300 (n=35) | ABRO100 (n=65) | UPA15 (n=280) | UPA15TCS (n=143) |
| RUX0.75* (n=33) | PBO (n=39) | PBOTCS (n=56) | PBOTCS (n=168) | PBO (n=234) | PBO (n=37) | ABRO200 (n=72) | UPA30 (n=280) | UPA30TCS (n=140) |
| PBO (n=13) | | | | | | PBO (n=40) | PBO (n=281) | PBOTCS (n=141) |

ABRO, abrocitinib; DUP, dupilumab; PBO, placebo; PBOTCS, placebo + topical corticosteroids; RUX, ruxolitinib cream; UPA, upadacitinib.
* 0.75% ruxolitinib cream was not included in the analysis as it is not actively marketed in Canada.

### *IGA (0/1)*

- Seven studies were identified that included 1.5% ruxolitinib cream, dupilumab 300 mg, and upadacitinib (15 mg and 30 mg)
- 1.5% ruxolitinib cream was not statistically different compared with all active treatments and statistically superior to placebo (**Table 2**)

**Table 2. Frequentist NMA Results for IGA (0/1), More Severe Subset of Moderate AD**

| RUX1.5 | | | | |
|---|---|---|---|---|
| 2.10 (0.10, 44.41) | UPA30 | | | |
| 3.60 (0.17, 76.04) | 1.71 (1.22, 2.40) | UPA15 | | |
| 6.69 (0.32, 140.26) | 3.19 (1.67, 6.09) | 1.86 (0.98, 3.54) | DUP300 | |
| 39.00 (1.92, 793.43) | 18.58 (11.41, 30.25) | 10.84 (6.69, 17.59) | 5.83 (3.81, 8.92) | PBO |

Results are presented as OR and associated 95% CI. Statistically significant results are depicted by green shading (where 95% CI does not include 1.0).
CI, confidence interval; DUP, dupilumab; IGA, Investigator's Global Assessment; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; RUX, ruxolitinib cream; UPA, upadacitinib.

### *EASI-75*

- Seven studies were identified that included 1.5% ruxolitinib cream, dupilumab 300 mg, upadacitinib (15 mg and 30 mg), and abrocitinib (100 mg and 200 mg)
- 1.5% ruxolitinib cream was not statistically different compared with all active treatments and statistically superior to placebo (**Table 3**)

**Table 3. Frequentist NMA Results for EASI-75, More Severe Subset of Moderate AD**

| RUX1.5 | | | | | | |
|---|---|---|---|---|---|---|
| 1.52 (0.17, 13.39) | ABRO200 | | | | | |
| 1.56 (0.22, 11.03) | 1.03 (0.34, 3.12) | UPA30 | | | | |
| 2.56 (0.36, 18.12) | 1.69 (0.56, 5.11) | 1.65 (1.14, 2.38) | UPA15 | | | |
| 3.10 (0.35, 27.32) | 2.04 (1.02, 4.09) | 1.99 (0.66, 6.03) | 1.21 (0.40, 3.63) | ABRO100 | | |
| 3.36 (0.47, 23.87) | 2.21 (0.72, 6.76) | 2.16 (1.21, 3.86) | 1.31 (0.74, 2.31) | 1.08 (0.36, 3.29) | DUP300 | |
| 20.61 (3.03, 140.17) | 13.6 (4.83, 38.27) | 13.25 (8.84, 19.85) | 8.04 (5.46, 11.83) | 6.65 (2.37, 18.66) | 6.14 (4.04, 9.33) | PBO |

Results are presented as OR and associated 95% CI. Statistically significant results are depicted by green shading (where 95% CI does not include 1.0).
ABRO, abrocitinib; CI, confidence interval; DUP, dupilumab; EASI, Eczema Area and Severity Index; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; RUX, ruxolitinib cream; UPA, upadacitinib.

### *Itch NRS4*

- Six studies were identified that included 1.5% ruxolitinib cream, dupilumab 300 mg, and upadacitinib (15 mg and 30 mg)
- There was no statistical difference between 1.5% ruxolitinib cream and all other comparators (**Table 4**). Differences between 1.5% ruxolitinib cream and placebo with regards to Itch NRS4 were not statistically significant, which may be due to the small sample size

**Table 4. Frequentist NMA Results for Itch NRS4, More Severe Subset of Moderate AD**

| UPA30 | | | | |
|---|---|---|---|---|
| 1.46 (1.04, 2.05) | UPA15 | | | |
| 2.04 (1.08, 3.83) | 1.39 (0.74, 2.62) | DUP300 | | |
| 2.42 (0.46, 12.79) | 1.65 (0.31, 8.74) | 1.19 (0.22, 6.32) | RUX1.5 | |
| 9.00 (5.82, 13.94) | 6.15 (3.97, 9.54) | 4.42 (2.80, 6.99) | 3.72 (0.75, 18.58) | PBO |

Results are presented as OR and associated 95% CI. Statistically significant results are depicted by green shading (where 95% CI does not include 1.0).
CI, confidence interval; DUP, dupilumab; NMA, network meta-analysis; NRS, numerical rating scale; OR, odds ratio; PBO, placebo; RUX, ruxolitinib cream; UPA, upadacitinib.

### *Sensitivity Analyses and Bayesian NMAs*

- Two sensitivity analyses were conducted:
  1. An analysis to assess the impact of excluding a trial (LIBERTY-AD ADOL, which only included adolescent patients)[4] in the main analysis due to a significant difference in age
  2. An analysis assessed using pooled doses for upadacitinib (pooled 15 mg and 30 mg) and abrocitinib (pooled 100 mg and 200 mg)[6,7]
- Results were consistent with the main analysis, ie,1.5% ruxolitinib cream was not statistically different compared to other active treatments and statistically superior to placebo (with regards to IGA [0/1] and EASI-75) in the more severe subset of moderate AD
- Fixed-effect Bayesian NMAs were also conducted where feasible (EASI-75 and Itch NRS4), and the results and conclusions aligned with the frequentist NMAs

### *Strengths, Limitations, and Other Considerations*

- A major strength of this analysis was that the NMAs were based on a recent comprehensive SLR that identified relevant evidence for 1.5% ruxolitinib cream and comparator agents for the treatment of AD
- Heterogeneity between trials was thoroughly assessed in the feasibility assessment
- Statistical analyses and NMAs were performed according to well-established methods outlined by the National Institute for Health and Care Excellence Decision Support Unit Technical Support Document[10]
- This analysis did not show a statistical difference between 1.5% ruxolitinib cream and placebo with regard to Itch NRS4. However, a significantly greater number of patients achieved clinically relevant improvements in itch as measured by NRS4 vs vehicle in the full population of the TRuE-AD trials
- The NMA results should be interpreted with the following limitations:
  - 1.5% ruxolitinib cream was assessed at Wk 8 in comparison to the other interventions (Wk 12 or 16); therefore, results may be biased against 1.5% ruxolitinib cream
  - There was reduced data availability due to the use of subgroup data, and some heterogeneity remained between trials. In particular, the TRuE-AD population had lower mean EASI, which may bias results against 1.5% ruxolitinib cream
- A separate feasibility assessment for 1.5% ruxolitinib cream with topical calcineurin inhibitors and TCSs was conducted, and an ITC was deemed not feasible due to substantial differences in primary endpoints, outcome definitions, trial eligibility criteria, and baseline AD disease severity in the comparator trials

## Conclusions

- **1.5% ruxolitinib cream was not statistically different vs all active comparators and statistically superior to placebo in terms of IGA (0/1) and EASI-75, across all analyses of the more severe subset of moderate AD (IGA=3, EASI≥16, BSA≥10%). 1.5% ruxolitinib cream was not statistically different vs any of the comparators with regards to NRS4**
  - **Comparator treatments included: dupilumab 300 mg, upadacitinib (15 mg, 30 mg), abrocitinib (100 mg, 200 mg [EASI-75 outcome only]) and placebo**
- **There were no significant differences between active comparators for all outcomes, although point estimates numerically favored 1.5% ruxolitinib cream for IGA (0/1) and EASI-75**
- **For patients with moderate AD who may be eligible for systemic therapies, 1.5% ruxolitinib cream might offer similar disease control as the available systemic treatments with regard to IGA (0/1), EASI-75, and Itch NRS4**
- **Results may be conservative, given the shorter time to response assessment for 1.5% ruxolitinib cream**

## Disclosures

MG has served as a principal investigator for AbbVie, Akros Pharma Inc., Amgen, Arcutis Pharmaceuticals, AnaptysBio, Aslan, Bausch Health, Boehringer Ingelheim International GmbH, Bristol Myers Squibb, Celgene, Coherus Biosciences, Dermira, Eli Lilly and Company, Galderma SA, GlaxoSmithKline, Incyte, Janssen, Kyowa Kirin, LEO Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron, Roche Laboratories, Sanofi Genzyme, Sun Pharmaceuticals, Takeda Pharmaceutical Company, UCB, and Ventyx; a consultant for AbbVie, Akros Pharma, Amgen, Aslan, Bausch Health, Boehringer Ingelheim International GmbH, Celgene, Eli Lilly and Company, Janssen, Kyowa Kirin, Nektar, Novartis Pharmaceuticals, Sanofi Genzyme, Sun Pharmaceuticals, and UCB; an advisory board member for AbbVie, Actelion Pharmaceuticals, Amgen, Arena Pharmaceuticals, Asana BioSciences, Aslan, Bausch Health, Boehringer Ingelheim International GmbH, Celgene, Eli Lilly, Galderma SA, Incyte, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron, Sanofi Genzyme, Sun Pharmaceuticals, and UCB; and a paid speaker for AbbVie, Amgen, Bausch Health, Boehringer Ingelheim International GmbH, Celgene, Eli Lilly and Company, Galderma SA, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron, Sanofi Genzyme, Sun Pharmaceuticals, and UCB. HCH has been an investigator and/or consultant and/or speaker for AbbVie, Amgen, Arcutis, Bausch Health, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Cutanea, Dermira, Dermavant, DS Biopharma, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Janssen, LEO Pharma, MedImmune, Merck, Mirimar, Novartis, Pfizer, Regeneron, Sanofi Genzyme, Roche, and UCB. DW, BH, AH-M, and HC are employees of EVERSANA and were commissioned by Incyte Biosciences Canada Corporation to conduct the analysis. GW, RM, M-LD, and ML are employees and shareholders of Incyte Corporation.

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