Direct and Indirect Effects of Crisaborole Ointment on Quality of Life in Patients With Atopic Dermatitis: A Mediation Analysis

Eric Simpson,[1] Gil Yosipovitch,[2] Andrew G. Bushmakin,[3] Joseph C. Cappelleri,[3] Thomas Luger,[4] Sonja Ständer,[5] Wynnis Tom,[6] William C. Ports,[3] Anna M. Tallman,[7] Huaming Tan,[3] Robert A. Gerber[3]

[1]Oregon Health and Science University, Portland, OR, USA; [2]University of Miami, Miller School of Medicine, Miami, FL, USA; [3]Pfizer Inc., Groton, CT, USA; [4]Department of Dermatology, University Hospital Münster, Münster, Germany; [5]Center for Chronic Pruritus, Department of Dermatology, University Hospital Münster, Münster, Germany; [6]Rady Children's Hospital-San Diego, San Diego, CA, USA; [7]Pfizer Inc., New York, NY, USA

BACKGROUND

- Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by intensely pruritic eczematous lesions[1,2]
- Itch has a significant impact on quality of life (QoL) in children and adults, and it is one of the most important aspects of the disease that patients use to judge treatment response[3,4]
- Corticosteroids and calcineurin inhibitors are recommended for topical treatment of AD[5-7]; however, there is a need for new, effective, nonsteroidal treatments that address inflammation and itch without the potential limitations associated with current topical agents
- Crisaborole ointment is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild to moderate AD[8]
  - In 2 identically designed Phase 3 clinical studies (AD-301: NCT02118766; AD-302: NCT02118792), crisaborole ointment, 2%, significantly improved global disease severity and all measured signs and symptoms of AD, and did not result in any treatment-related serious treatment-emergent adverse events[8]
    - The most common treatment-related adverse event was application site pain (pooled AD-301 and AD-302 population; crisaborole: 4.4%, vehicle: 1.2%)
- A qualitative and psychometric analysis of the Severity of Pruritus Scale (SPS), a 4-point rating scale ranging from 0 ("no itching") to 3 ("bothersome itching/scratching which is disturbing sleep"), used in the Phase 3 studies, was recently completed, supporting the use of SPS as a valid measure of pruritus in AD (see posters on display by Yosipovitch G et al)[9,10]
- Mediation modeling has been used to establish the contributions of direct and indirect effects of a treatment on an outcome[11,12]

OBJECTIVES

- Through mediation modeling, determine the interrelationship among patient-reported pruritus (as measured by SPS), QoL (as measured by the Dermatology Life Quality Index [DLQI] or the Children's Dermatology Life Quality Index [CDLQI]), and treatment using pooled data from AD-301 and AD-302

METHODS

Study Treatment

- In the Phase 3 studies, patients aged ≥2 years were randomly assigned in a 2:1 ratio to receive crisaborole or vehicle ointment
- Treatment was applied twice daily for 28 days
- QoL was measured using the DLQI in patients aged ≥16 years and the CDLQI in patients aged 2-15 years (**Table 1**)[13,14]

Table 1. QoL Assessment Scales and Subscales: CDLQI and DLQI

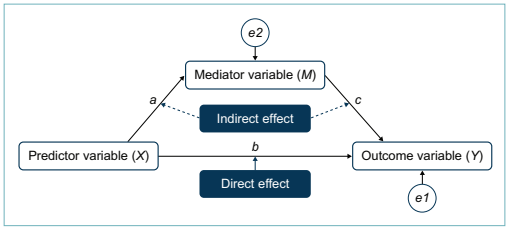
Category	Assessment	CDLQI Patients Aged 2-15 Years	DLQI Patients Aged ≥16 Years
Symptoms & Feelings	Severity of symptoms (itch, soreness, pain, stinging)	0-3 pts	0-3 pts
	Embarrassment or self-consciousness	0-3 pts	0-3 pts
Personal Relationships	Effect on friendships and social interactions (eg, teasing, bullying avoidance)	0-6 pts	NA
	Effect on friendships, relatives, and/or partner, and sex life	NA	0-6 pts
School/Work & Holidays	Effect of skin on work/school or vacation time	0-3 pts	0-3 pts
Leisure	Effect on playing sports and leisure activities	0-6 pts	0-6 pts
	Wearing different clothes/shoes	0-3 pts	NA
Burden of Treatment	Treatment burden on daily life	0-3 pts	0-3 pts
Sleep	Effect of skin on sleep	0-3 pts	NA
Daily Activities	Influence on clothes worn and daily tasks	NA	0-6 pts
Total	Comprehensive assessment of patient QoL	0-30 pts	0-30 pts

CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; NA, not applicable; pts, points; QoL, quality of life.

Pruritus Scale and Mediation Modeling

- Mediation in its simplest form is represented by a third variable (*M*, the mediator), so that the predictor *X* influences the mediator *M*, which, in turn, influences the outcome *Y* (*X* affects *M* and then *M* affects *Y*) (**Figure 1**)[15]

Figure 1. Basic mediation model.



a represents the effect of the predictor (independent) variable *X* on the mediator variable *M*; *b* represents the direct effect of the predictor variable *X* on the outcome variable *Y*; *c* represents the effect of the mediator variable *M* on the outcome variable *Y*; *e1* and *e2* are the error terms.

- Severity of pruritus was assessed using the SPS (**Table 2**)
  - SPS was administered via electronic diary twice a day (morning and evening, with a recall period of 24 hours)

Table 2. Severity of Pruritus Scale (SPS)

Score	Grade	Definition
0	None	No itching
1	Mild	Occasional, slight itching/scratching
2	Moderate	Constant or intermittent itching/scratching which is not disturbing sleep
3	Severe	Bothersome itching/scratching which is disturbing sleep

- Mediation model consisted of the following variables:
  - Independent variable—treatment (crisaborole vs vehicle)
  - Mediator variable—SPS score (averaged SPS scores over week 4 [days 23-29] for every patient to be consistent with 1-week recall period of the DLQI and CDLQI)
  - Outcome variable—DLQI or CDLQI (at day 29; 1-week recall)
- All available data were used, and no imputations of missing data were performed

RESULTS

Patients Demographics and Disposition

- Between both studies, 1016 patients were randomly assigned to receive crisaborole and 506 patients were randomly assigned to receive vehicle (intent-to-treat population)
- Baseline demographics and disease characteristics were balanced between the treatment arms
  - The mean age between both groups was approximately 12.2 years; most patients (>86%) were 2-17 years of age
  - Approximately 55.6% were female; most (80%) were non-Hispanic
  - Between both groups, distribution by race was approximately 61% white, 28% black, 5% Asian, and 6% other
  - Baseline disease characteristics are summarized in **Table 3**

Table 3: Baseline Disease Characteristics

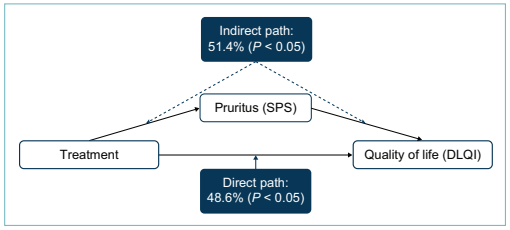
	Crisaborole n = 1016	Vehicle n = 506
ISGA, n (%)		
Mild – 2	393 (38.7)	193 (38.1)
Moderate – 3	623 (61.3)	313 (61.9)
Severity of pruritus,[a] %		
None – 0	35 (3.9)	19 (4.3)
Mild – 1	229 (25.4)	119 (27.0)
Moderate – 2	331 (36.7)	167 (37.9)
Severe – 3	308 (34.1)	136 (30.8)
Treatable % BSA		
Mean (SD)	18.3 (18.02)	18.1 (17.33)
Range	5-95	5-90
CDLQI		
N	797	403
Mean (SD)	9.3 (5.99)	9.0 (6.02)
DLQI		
N	192	92
Mean (SD)	9.7 (6.29)	9.3 (6.55)

BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; ISGA, Investigator's Static Global Assessment; SD, standard deviation; SPS, Severity of Pruritus Scale.
[a]Severity of pruritus was patient- or parent/caregiver-reported and measured using the SPS.

Mediation Models

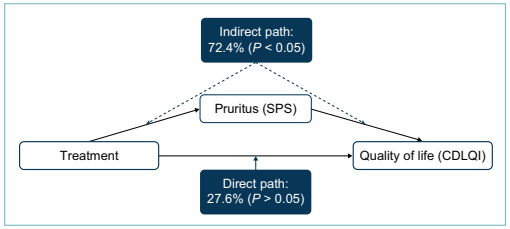
- 226 patients were included in the DLQI analysis, and 1112 patients were included in the CDLQI analysis
- The indirect effect of crisaborole on QoL via pruritus constituted 51% of the overall effect of active treatment ($P = 0.0272$) in the DLQI-based model and 72% in the CDLQI-based model ($P < 0.0001$) (**Figures 2, 3**)
- This suggested that the effects of crisaborole on QoL were mostly mediated by improvement in severity of pruritus
  - The direct effect (*representing all other effects*) of crisaborole on QoL was less than half (49% [DLQI-based model; $P = 0.0365$] and 28% [CDLQI-based model; $P = 0.0701$]) the total, or overall, effect of the active treatment on QoL (**Figures 2, 3**)

Figure 2. DLQI-based mediation model.



SPS, Severity of Pruritus Scale; DLQI, Dermatology Life Quality Index.

Figure 3. CDLQI-based mediation model.



SPS, Severity of Pruritus Scale; DLQI, Dermatology Life Quality Index.

CONCLUSIONS

- **Mediation modeling can be used to help explain the effect of a treatment on an outcome**
- **The presented mediation models indicate that crisaborole affects QoL mostly indirectly through improvement in the severity of pruritus**
- **Indirect effects in the CDLQI-based model were more pronounced, possibly because of differences in item composition of the questionnaires; for example, CDLQI includes sleep, which is highly affected by pruritus**

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