SUPPLEMENTAL MATERIALS

Title: Matching-Adjusted Indirect Comparison of Crisaborole Ointment 2% vs. Topical Calcineurin Inhibitors in the Treatment of Patients with Mild-to-Moderate Atopic Dermatitis

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SUPPLEMENTAL FILE 1

Summary of regression analyses assessing evidence of effect modifiers and prognostic variables

Statistical methods

A univariate binomial-logistic regression was conducted to evaluate primary efficacy endpoint of Investigator's Static Global Assessment (ISGA) 0-1, two secondary endpoints of ISGA success, and improvement in pruritus at 29 days, which used pooled data from the two crisaborole registration studies (AD301/AD302). Further, at 29 days a univariate Poisson-log regression was conducted to evaluate safety endpoints of treatment-emergent adverse events and application site pain, which also used pooled AD301 and AD302 data. Evidence of covariate effects to evaluate prognostic variables and treatment-by-covariate interactions was assessed using evidence of effect modification. At 52 weeks, a Poisson-log regression was conducted to evaluate safety endpoints of treatment-emergent adverse events and application site pain using AD303 data. Evidence of covariate effects were used to assess potential prognostic variables.

Guide to interpretation

The trials were not powered to detect either prognostic factors or treatment effect modifiers, and therefore, p-values between 0.05 and 0.10 provided evidence of prognostic variable or effect modifier status. Additionally, the mean and 95% confidence intervals were used for the odds ratios to qualitatively judge the magnitude and certainty of effect modifier or prognostic variable status. Variables were categorized as 'maybe' if the p-value was between either 0.1 and 0.2 or greater than 1.1 or less than 0.9. These variables were counted as prognostic factors or effect modifiers.

Findings on prognostic variables at 29 days

For ISGA 0/1, there was evidence that age, body surface area (BSA), prior atopic dermatitis treatment, current use of antihistamines, baseline ISGA 2 versus 3, baseline temperature, systolic and diastolic blood pressure were prognostic factors, although history of asthma or allergic rhinitis was likely a prognostic factor (**Supplementary Table 1**). Prior atopic dermatitis treatment and the history of asthma or allergic rhinitis were prognostic variables and related to ISGA success.

Pruritus success was associated with prior atopic dermatitis treatment, gender, and systolic and diastolic blood pressure as prognostic variables. Regarding treatment emergent adverse events, there was evidence that BSA, gender, and prior atopic dermatitis treatment were prognostic and that ethnicity, being Caucasian, and disease duration were likely prognostic. There was evidence that temperature, systolic and diastolic blood pressure were prognostic variables.

The evidence for prognostic variables for application site pain was broadly consistent with those for treatment emergent adverse events except that disease duration was more clearly prognostic.

Findings on effect modifiers at 29 days

On the outcome of ISGA 0/1, there was evidence that ethnicity and history of asthma or allergic rhinitis were effect modifiers, and that age was likely an effect modifier. There was evidence that baseline temperature, systolic and diastolic blood pressure were effect modifiers (**Supplementary Table 2**). Regarding ISGA success, there was evidence that ISGA 2 versus 3 and systolic and diastolic blood pressure were effect modifiers, and that ethnicity was likely an effect modifier. On pruritus success, there was evidence that ethnicity, baseline ISGA 2 versus 3, and systolic blood pressure were effect modifiers.

For treatment emergent adverse events and application site pain, there was evidence that medical history of asthma or allergic rhinitis, systolic blood pressure, and ISGA 2 vs 3 were effect modifiers.

Findings on prognostic variables at 52 weeks

For treatment emergent adverse events, there was evidence that age, gender, disease duration, white skin, medical history of asthma or allergic rhinitis, use of antihistamines, and ISGA 2 versus 3, diastolic blood pressure, pulse rate, and respiratory rate were prognostic variables (**Supplementary Table 3**). This list of potential prognostic variables at 52 weeks was slightly different to the list at 4 weeks, which was BSA, gender, prior atopic dermatitis treatment, disease duration, and Caucasian.

For application site pain, only gender and history of asthma or allergic rhinitis were prognostic; however, fewer events were observed for application site pain than general adverse events and the statistical power was therefore lower due to sample size.

SUPPLEMENTAL FILE 2

Targeted literature review for effect modifiers and prognostic variables

Searches to identify prognostic variables

In the literature search, 785 records were identified using two electronic databases (Ovid Medline and Embase) and 57 records through screening of reference lists of relevant reviews (Ovid Embase). In total, 17 studies were selected for data extraction. **Supplementary Table 4** provides a summary of the prognostic variables identified by these studies. Potential prognostic variables that are likely reported across randomized controlled trials in atopic dermatitis include gender, onset age, eczema distribution (i.e. location of lesions), presence of asthma or allergic respiratory disease.

Most studies focused on risk factors, prevalence, diagnostic factors, exacerbating factors (triggering factors), causing/developing adverse events versus affecting severity of atopic dermatitis. Results should be treated with caution as most studies used scoring atopic dermatitis (SCORAD) as a measure of severity of atopic dermatitis rather than ISGA/IGA/EASI; thus, these studies provide plausible guidance only.

Searches to identify treatment (any topical phosphodiesterase-4 [PDE-4] inhibitor effect modifiers

A search was conducted for articles that reported subgroup or regression analyses on PDE-4 inhibitors; only two PDE-4 randomized controlled trials (RCTs) were included (Hanifin 2016, OPA-15406 and AD301/AD302, crisaborole trials). Additionally, a search was conducted on ClinicalTrial.gov for relevant studies of PDE-4 inhibitors using keywords, “atopic dermatitis”, “atopic eczema”, “phosphodiesterase-4”, “crisaborole”, “OPA-15406”, “E6005”, “RVT-501”, “roflumilast”, “LEO29102”, “GW842470X “, and “DRM02” to retrieve all relevant studies of

topical PDE-4 inhibitors. Only the Hanifin 2016 study on OPA-15406 was found to provide evidence on PDE-4 treatment effect modifiers. Due to the small sample size (N=121 patients), the results of the subgroup analyses are inconclusive. For example, Fitzpatrick skin type appears to be different for score I-III vs IV-VI, but only for OPA-15406 0.3% and not 1% and in any case with 95% confidence intervals that overlap entirely. There does not appear to be evidence of effect modification (95% confidence intervals overlap, point estimates for relative risks similar) for the likely reported variables of age, body surface area at baseline, gender, or white versus non-white skin.

Targeted literature review for supporting evidence on prognostic variables and PDE-4 treatment effect modifiers

The searches identified 19 studies reporting potential prognostic variables. Potential prognostic variables that are likely reported across randomized controlled trials for atopic dermatitis include gender, onset age, eczema distribution (i.e. location of lesions), and presence of asthma or allergic respiratory disease. No effect modifiers were identified due to low number of agents, trials, and small sample size of the only available RCT (Hanifin 2016). This targeted literature search was only conducted by one reviewer, and this limitation may have introduced publication bias. There is also a lack of prognostic research in the atopic dermatitis field to inform potential factors.

SUPPLEMENTAL FILE 3

Clinical expert opinion on effect modifiers and prognostic variables in atopic dermatitis

Summary of clinical expert opinion

A clinical expert gave their opinion on whether a variable was prognostic or an effect modifier, the magnitude of effect, the direction, and the basis for their belief (**Supplementary Table 5**). The feedback was primarily based on clinical observation (personal experience) and extrapolation from experience with non-crisaborole topical therapies. Although the expert did not clearly distinguish between effect modifiers and prognostic variables, the comments generally distinguish between a prognostic variable or an effect modifier.

For example, the expert identified lesion location as prognostic because of differential responses to topical corticosteroids/topical calcineurin inhibitors (TCS/TCI), but this explanation indicated that the expert believed it to be an effect modifier.

The expert suggested that age, severity (incl. BSA, ISGA), African-American ethnicity, and lesion location were effect modifiers. Prior atopic dermatitis treatment was indicated to be an effect modifier only in special circumstances:

> "Possible if for example patient was in a rebound after stopping TCS, but this would not be a common scenario"

The expert suggested that age, severity (incl. BSA, ISGA), lesion characteristics, and lesion location were prognostic variables. Past medical history of asthma or allergic rhinitis were indicated to be prognostic variables or effect modifiers but only as surrogates for severity. The opinion was generally in line with the regression and TLR results but indicated age is an effect modifier with lower age have greater response.

Tables

Supplementary Table 1. Pooled data to indicate whether characteristics are prognostic variable at 4 weeks

Characteristic	ISGA 0/1	ISGA Success	Pruritus success	Treatment emergent AE	Application site pain
Age (years)	Yes	No	No	No	No
Baseline BSA (%)	Yes	No	No	Yes	Yes
Gender (male or female)	No	No	Maybe	Yes	Yes
Prior atopic dermatitis treatment (yes or no)	Yes	Yes	Yes	Yes	Yes
Disease duration (years)	No	No	No	Maybe	Yes
Ethnicity (“Hispanic or Latino” vs “not Hispanic or Latino”)	No	No	No	No	No
White skin (vs not white skin)	No	No	No	Maybe	Maybe
Past medical history of asthma or allergic rhinitis (yes or no)	Maybe	Maybe	Yes	No	No
Current use of antihistamines (yes or no)	Yes	No	No	No	No
Baseline ISGA 2 vs 3 (mild vs. moderate AD)	Yes	No	No	No	No
Baseline temperature (F)	Yes	No	No	Yes	Yes
Baseline systolic blood pressure (mmHg)	Yes	Yes	Yes	Yes	Yes
Baseline diastolic blood pressure (mmHg)	Yes	No	Yes	Yes	Yes
Pulse Baseline pulse rate (BEATS/min)	No	No	No	No	No
Baseline respiratory rate (BREATHS/min)	No	No	No	No	No

Abbreviations: AD, atopic dermatitis; AE, adverse event; BSA, body surface area; F, Fahrenheit; ISGA, Investigator's Static Global Assessment.

Supplementary Table 2. Pooled data to indicate whether characteristics are effect modifiers at 4 weeks

Characteristic	ISGA 0/1	ISGA Success	Pruritus success	Treatment emergent AE	Application site pain
Age (years)	Maybe	No	No	No	No
Baseline BSA (%)	No	No	No	No	No
Gender (male or female)	No	No	No	No	No
Prior atopic dermatitis treatment (yes or no)	No	No	No	No	No
Disease duration (years)	No	No	No	No	No
Ethnicity ("Hispanic or Latino" vs "not Hispanic or Latino")	Yes	Maybe	Yes	No	No
White skin (vs not white skin)	No	No	No	No	No
Past medical history of asthma or allergic rhinitis (yes or no)	Yes	No	No	Yes	Yes
Current use of antihistamines (yes or no)	No	No	No	No	No
Baseline ISGA 2 vs 3 (mild vs. moderate AD)	No	Yes	Yes	Yes	Yes
Baseline temperature (F)	Yes	No	No	No	No
Baseline systolic blood pressure (mmHg)	Yes	Yes	Yes	Yes	Yes
Baseline diastolic blood pressure (mmHg)	Yes	Yes	No	No	No
Pulse Baseline pulse rate (BEATS/min)	No	No	No	No	No
Baseline respiratory rate (BREATHS/min)	No	No	No	No	No

Abbreviations: AD, atopic dermatitis; AE, adverse event; BSA, body surface area; F, Fahrenheit; ISGA, Investigator's Static Global Assessment.

Supplementary Table 3. Pooled data to indicate whether characteristics are prognostic variable on safety outcomes at 52 weeks

Characteristic	Treatment emergent AE	Application site pain
Age (years)	Yes	No
Baseline BSA (%)	No	No
Gender (male or female)	Yes	Yes
Prior atopic dermatitis treatment (yes or no)	No	No
Disease duration (years)	Yes	No
Ethnicity (“Hispanic or Latino” vs “not Hispanic or Latino”)	No	No
White skin (vs not white skin)	Yes	No
Past medical history of asthma or allergic rhinitis (yes or no)	Yes	Yes
Current use of antihistamines (yes or no)	Yes	No
Baseline ISGA 2 vs 3 (mild vs. moderate AD)	Yes	No
Baseline temperature (F)	No	No
Baseline systolic blood pressure (mmHg)	No	No
Baseline diastolic blood pressure (mmHg)	Yes	No
Pulse Baseline pulse rate (BEATS/min)	Yes	No
Baseline respiratory rate (BREATHS/min)	Yes	No

Abbreviations: AD, atopic dermatitis; AE, adverse event; BSA, body surface area; F, Fahrenheit; ISGA, Investigator's Static Global Assessment.

Supplementary Table 4. Summary of studies providing evidence on prognostic variables

Category	Sub-category	Direction	Number of studies	Outcome	Reference
Gender		Males had worse outcomes	1	SCORAD	Holm et al. 2019
Onset age		-	1	SCORAD	Ben-Gashir et al. 2004
Urban area		-	1	SCORAD	Ben-Gashir et al. 2004
Eczema distribution	Position of body (eg. Hands)	+	1	SCORAD, BAMSE Eczema Severity Score	Gronhagen 2015
	Total area	+	1	SCORAD	Holm et al. 2019
History of AD infection		+	1	SCORAD	Wananukul et al. 2015
Asthma		+	2	SCORAD	Holm et al. 2019, Kim et al. 2018
IgE		+	7	SCORAD, Area of involvements	Holm et al. 2019, Coclici et al. 2016, Wananukul et al 2015, Orfali et al. 2013, Katoh et al. 2008, Dhar, et al. 2005
Eosinophil counts		+	5	SCORAD	Holm et al. 2019, Wu et al. 2017, Wananukul et al. 2015, Orfali et al. 2013, Dhar et al. 2005
Extrinsic AE (IgE & sensitization)		+	1	SCORAD	Holm et al. 2019
Food allergy		+	2	SCORAD	Gray et al. 2014, Kim et al. 2018
Allergic respiratory disease		+	1	Rajka and Langeland	Patrizi et a. 2000
Sensitization		+	2	SCORAD	Schafer et al. 1999, Mailhol et al. 2009
Genes	GM-CSF gene	+	1	Surface area affected	Rafatpanah et al. 2003
	SNPs	+	1	SCORAD	Kim et al. 2018

TEWL	+	2	SCORAD	Gupta et al. 2008, Nemoto-Hasebe et al. 2009

Abbreviations: AD, atopic dermatitis; AE, adverse events; BAMSE. (Swedish abbreviation for Children, Allergy, Milieu, Stockholm, Epidemiology); IgE, Immunoglobulin E; SNP, Single nucleotide polymorphisms; SCORAD, SCORing Atopic Dermatitis; TEWL, Transepidermal water loss

Supplementary Table 5. Feedback from clinical expert on potential prognostic variables and effect modifiers

Patient characteristic (concomitant treatments and treatment history)	**Prognostic variable (Likely, speculative, implausible)**	**Magnitude (1=lowest, 5=highest)**	**Direction (i.e. increases or decreases ISGA response)**	**Basis for belief (e.g. empirical observation, biological mechanism, anecdotal, personal clinical experience)**	**Effect modifier (Likely, speculative, implausible)**	**Magnitude (1=lowest, 5=highest)**	**Direction (i.e. increases or decreases ISGA response)**	**Basis for belief (e.g. empirical observation, biological mechanism, anecdotal, personal clinical experience)**
Age	Possible	3	Lower age increases responsiveness to all topical therapies such as TCS and TCI Also consider the effect of age on decreasing concordance with topical treatments in certain age groups such as teenagers	AD tends to be more responsive to topical therapy in younger children clinical observation	Lower age increases responsiveness to all topical therapies such as TCS and TCI extrapolation to Crisaborole Also consider the effect of age on decreasing concordance with topical treatments in certain age groups such as teenagers	3	Increase ISGA response the lower the age is	Clinical observation by extrapolation from other topical therapy
Severity of disease	Likely	5	The more severe AD is less responsive to TCS and TCI	Clinical observation and this is a definition of severe AD	This is likely to be a modifier for Crisaborole	5	Increasing disease severity decreasing response to Crisaborole	Clinical observation by extrapolation from other topical therapy
Gender	Unlikely	1	No effect	Clinical observation	unlikely	1	No effect	
Prior atopic dermatitis treatment	Possible if for example patient was in a rebound after stopping TCS but this would not be a common scenario	If this particular scenario is occurring it can have a big effect on subsequent	Just for this scenario would decrease ISGA response	Clinical observation	Only as described under prognostic variable if patient was in a post TCS rebound flare when Crisaborole was started	If this particular scenario is applying then the effect on Crisaborole response could be high, 5 education how to	Decrease ISGA response in this particular scenario	Clinical extrapolation from what we see in this scenario for TCI used when a patient is in a

		therapy used such as TCI, 5				move from TCS to Crisaborole is very important		post TCS rebound flare
Extent of disease (e.g. %BSA affected)	All of comments in this line would reflect severity and so when increasing BSA is going with increasing BSA then the response to TCS TCI would decrease				All of comments in this line would reflect severity and so when increasing BSA is going with increasing BSA then the response to TCS TCI would decrease			
Past medical history of asthma or allergic rhinitis	Unlikely unless as a surrogate marker for AD severity				Unlikely unless as a surrogate marker for AD severity			
Current use of antihistamines	Unlikely				Unlikely			
ISGA score at baseline	Same comments as for higher disease severity				Same comments as for higher disease severity			
Serum IgE levels	Yes if acting as a marker for disease severity, high IgE correlates with AD severity				Yes if IgE is acting as a marker for disease severity high IgE correlates with diseases			
Afro-American ethnicity	Can be more resistant to AD treatments especially if lichenification is pronounced	3			Can be more resistant to AD treatments especially if lichenification is pronounced	3		
Disease duration								
Use of emollients as background treatment	This should be standard background therapy as it is part of all AD guidelines				This should be standard background therapy as it is part of all AD guidelines			
Smoking status	Unlikely				unlikely			
BMI	Unlikely				Unlikely			
Location of lesion	Lesions on the eyelid, rest face, flexures and then rest of body, have the thinnest epidermal	4, this is established in clinical trials if the EASI scores are separated for	Thinnest skin (eyelid, rest of face and so on) respond to a greater extent than a thicker skin site	This is based on EASI data for the different skin sites from clinical trials	Lesions on the eyelid, rest face, flexures and then rest of body, have the thinnest epidermal barrier and would be most likely to be	4	Thinnest skin (eyelid, rest of face and so on) respond to a greater extent than a thicker skin site	This is a prediction by extrapolation from TCI and TCS data

	barrier and are most responsive to TCS and TCI in that order	the different body regions			most responsive to Crisaborole in that order		
Lesion characteristics - exudation	This is a sign of more severe AD and so the comments about AD severity apply here	4	Presence of exudation decreasing ISGA response	This is based on clinical observation			
Lesion characteristics - erythema	This is one of the earliest signs of AD and would tend to least effect a response to current topical therapy	1		This is based on clinical observation using EASI	This is one of the earliest signs of AD and would tend to least effect a response to current topical therapy	1	Extrapolation from clinical use of TCS and TCI
Lesion characteristics - edema							
Lesion characteristics - excoriation							
Lesion characteristics – in duration/population							
Lesion characteristics - lichenification)	Lichenification is a marker of more severe, chronic disease and this is the slowest to respond of all of the signs of AD. It can take many months to respond				Lichenification is a marker of more severe, chronic disease and this is the slowest to respond of all of the signs of AD. It can take many months to respond		

Abbreviations: AD, atopic dermatitis; BMI, body mass index; BSA, body surface area; EASI, Eczema Area and Severity Index; IgE, Immunoglobulin E; ISGA, Improvement in Investigator's Static Global Assessment; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.