Original Article

Efficacy and Safety of Crisaborole Ointment 2% in Mild to Moderate Atopic dermatitis

Remi SA[1], Bhuiyan I[2], Hossain S[3], Alahi MN[4] , Hossain M[5], Islam S[6]

Conflict of Interest: None
Received: 01.11.2024
Accepted: 05.11.2024
www.banglajol.info/index.php/JSSMC

ABSTRACT:

Background: *Atopic dermatitis is a common chronic inflammatory skin condition. It affects upto 20% of children and 3% of atopic dermatitisults; most of them are mild to moderate in severity. There are onle a few effective topical therapeutic options available for long term use. This study was aimed to evaluate the efficacy and safety of Crisaborole ointment (2%), a new non-steroidal topical anti-inflammatory phosphodiesterase-4 (PDE4) inhibitor for the treatment of mild to moderate Atopic dermatitis.*

Methods: *This prospective clinical trial was conducted at the Department of Dermatology & Venereology in Shaheed Suhrawardy Medical College Hospital, Dhaka, for a period of 12-months following approval of this protocol. A total of 226 patients with Mild to moderate Atopic dermatitis were included after getting informed written consent and divided into two equal groups: Crisaborole 2% ointment and placebo. Patients were followed up at 4 th, 8th and 12th weeks of intervention. However, 20 patients were lost in this trial period, and finally 103 patients in each group were analyzed as per-protocol analysis. Data were analyzed by the SPSS 26.*

Results: *Demographic characteristics were similar across the two groups in terms of age and gender ($p>0.05$ in all cases). No significant difference was noted in age of onset, family history, personal history, precipitating factors and pre-operative ISGA score ($p>0.05$). Mean ISGA score of Crisaborole 2% ointment atopic dermatitis significantly decreased from baseline to 12th week follow up (2.32 vs 0.89, $p<0.001$). After 12 weeks of follow-up, respondents with Crisaborole 2% ointment atopic dermatitis significant improvement from atopic dermatitis compared to placebo group (63.1% vs. 44.7%, $p=0.008$). Though, in both Crisaborole 2% ointment and placebo group showed very few adverse effect after 12 weeks of follow up (10.7% vs. 5.8%).*

Conclusion: *Crisaborole ointment (2%) is effective in the treatment of mild to moderate Atopic dermatitis, with very few adverse effect.*

Key Words:
Atopic dermatitis, Crisaborole 2% ointment, Phosphodiesterase-4 (PDE4) inhibitor, Investigator's Static Global Assessment (ISGA)

[J Shaheed Suhrawardy Med Coll 2024; 16(2): 7-15]
DOI:https://doi.org/10.3329/jssmc.v16i2.88262

Authors:

1. Saima Ahmed Remi, Indoor medical officer (Skin & VD), Shaheed Suhrawardy Medical College
2. Ishrat Bhuiyan, Professor (C.C.) (Skin & VD), Shaheed Suhrawardy Medical College
3. Md. Shahadat Hossain, Professor (Skin & VD), Ex. Shaheed Suhrawardy Medical College
4. Mohammad Niamat Alahi, Assistant professor (Skin & VD), Shaheed Suhrawardy Medical College
5. Md. Motiul Hossain, Assistant professor (Skin & VD), Shaheed Suhrawardy Medical College
6. Shiropa Islam, Assistant professor (Skin & VD), Shaheed Suhrawardy Medical College

Correspondence:
Dr. Md. Motiul Hossain, Assistant Professor (Skin & VD), Skin & VD Dept., Shaheed Suhrawardy Medical College Hospital, Dhaka.
Mobile: 01857222258; Email: mmotiulh@yahoo.com

Introduction

Atopic dermatitis is a complex chronic or chronically relapsing inflammatory skin disease that often starts in early childhood (usually before 2 years of age) characterized by pruritus, erythema, papules, papulo vesicles and lichenification which typically has a flexural distribution.1 It is globally prevalent affecting 15- 20% of children and 1-3% of atopic dermatitisults.2,3

Many immune cytokine pathways upregulated in i.e. T helper-2, T helper-22, T helper-17 and T helper-1. Phosphodiesterase 4(PDE4) regulates cyclic AMP in cells and has contribution in the pathophysiology of atopic dermatitis.4 Phosphodiesterase 4 (PDE4) is a key regulator of inflammatory cytokine production in atopic dermatitis through the degradation of cyclic adenosine monophosphate.5,6 PDE4 activity is upregulated in circulating inflammatory cells of patients with atopic dermatitis. 7

A topical PDE4 inhibitor formulation could address the need for targeted inhibition of inflammation in skin diseases while avoiding unwanted side effects. Crisaborole ointment, 2% (formerly known as AN2728) is a benzoxaborole, nonsteroidal, topical, anti-inflammatory phosphodiesterase 4 (PDE4) inhibitor. Crisaborole enhances cellular control of inflammation by inhibiting PDE4 and its ability to degrade intracellular cyclic adenosine monophosphate, thereby suppressing the release of cytokines by affecting down stream regulation of the nuclear factor-κB and nuclear factor of activated T-cell signaling pathways. 5,8–10

The mechanism through which PDE4 regulates pruritus is an indirect result of reducing inflammation, similar to the anti pruritic effects observed with topical cortico steroid treatment. PDE4 directly regulates pruritus through reduction of cutaneous neuron11 and dorsal root ganglion neuron activity.12,13

Although systemic exposure to Crisaborole may vary with the percentage of body surface area involved, it is rapidly and substantially metabolized to inactive metabolites that have no effect on PDE4 activity or cytokine release, thus limiting systemic exposure and reducing the risk of adverse effects.14

Investigator's Static Global Assessment (ISGA):

The US Food and Drug Administration recommends the Investigator's (Static) Global Assessment (ISGA), which assesses global disease severity using a single-item, multiple construct scale. In general, the ISGA consists of a four- or five- point scale, with each score describing an overall body assessment of atopic dermatitis signs/symptoms such as erythema, induration/papulation, lichenification, oozing/crusting, and sometimes excoriation and scaling. 29

Score	Grade	Definition
0	Clear	Minor residual hypo/hyperpigmentation; no erythema or induration/papulation; no oozing/crusting
1	Almost clear	Trace faint-pink erythema, with barely perceptible induration/papulation and no oozing/crusting
2	Mild	Faint-pink erythema with mild induration/-papulation and no oozing/crusting
3	Moderate	Pink-red erythema with moderate induration/papulation with or without oozing/crusting
4	Severe	Deep- or bright-red erythema with severe induration/papulation & with oozing/crusting.

Table-1: Investigator's Static Global Assessment (ISGA)

Materials and Methods:

Study Design: Prospective clinical trial.

Place of Study: Department of Dermatology & Venereology in Shaheed Suhrawardy Medical College Hospital, Dhaka.

Study Period: One year.

Study population:

Patients with mild to moderate Atopic dermatitis attending Dermatology outpatient department of Shaheed Suhrawardy Medical College Hospital, Dhaka.

Sampling Method:

Consecutive type of non-probability sampling technique.

Sample size: Sample size was calculated by using this formula (Haque, 2019) The formula is, $n = p1(100-p1)+p2(100-p2)\ (p1-p2)^2 \times (Z\alpha + Z\beta)^2$ Where, n = sample size P1 = 33.3% [Success rate of Crisaborole] (Eichenfield et al. 2020) P2 = 16.7% [Success rate of Vehicle] (Eichenfield et al. 2020) Zα = Z value at a define level of significance (1.96 at 5% level of significance) Z β =Z value at a define power of test (0.84 at 80% power of test) $n = 33.3(100 - 33.3) + 16.7(100 - 16.7)\ (33.3 - 16.7)^2 \times (1.96 + 0.84)^2$ $n = 2221.1 + 1391.11\ 275.56 \times (2.8)^2$ $n = 3612.2\ 275.56 \times 7.84\ 24$ $n = 102.77 \approx 103$ So,

estimated sample size was 103 in each group (intervention and placebo group). Considering 10% dropout rate, my final sample size was calculated as 206+10% ≈ 226.

Selection criteria:

Inclusion criteria:

- Age: more than 2 years old
- Sex: Male & Female.
- Patients with current diagnosis of mild to moderate atopic dermatitis (Score 2 & 3 based on ISGA Scale) and ≤40% body surface area involved.
- Willing to participate.

Exclusion criteria:

- Pregnant and lactating women or women who are planning for pregnancy.
- Severe atopic dermatitis (ISGA Score 4) and ≥ 40% body surface area involved. • Known case of any systemic illness.
- Active skin infection
- Any topical medication within previous 2 weeks.
- Any systemic medication for atopic dermatitis within previous 28 days

Study procedure:

Patients were selected by careful history taking, general examination and complete dermatological examination for atopic dermatitis where type, distribution and lesion count was done. A total of 226 patients with Mild to moderate atopic dermatitis were included after getting informed written consent and divided into two equal groups: Crisaborole 2% ointment and placebo.

Intervention group was treated by application of pea sized amount of Crisaborole ointment (2%) in a thin layer to the affected area of the body twice daily for 4 weeks.

The patients were reevaluated at 8 and 12 weeks of treatment (the end of therapy). Stable regimens of antihistamines, inhaled corticosteroids and topical retinoids for non-atopic dermatitis lesion treatment were permitted, as were acceptable bland emollients to manage dry skin areas around but not overlapping the treatable atopic dermatitis involved areas.47

There were 2 efficacy end points, 1) Achieving an ISGA scoring of clear [0] or almost clear [1] and at least a 2-grade or more change from baseline at week 12; 2) Reduction in pruritus

The safety assessments include

1. Treatment emergent adverse events;
2. Standard laboratory safety test results at screening; and results at the last study visit, including the following: CBC, SGPT, Creatinine and Urine RE.
3. Physical examination findings and monitoring of vital signs. Patients were followed up at 4 th, 8th and 12th weeks of intervention.

Ethical issues:

The protocol was submitted to the ethical review committee & research review committee of ShSMCH.

Flow chart:

Selection of patients on the basis of inclusion and exclusion criteria.

↓

Explanation of the purpose of the study and taking informed written consent

↓

226 subjects enrolled

↓

Base line data collection by semi-structured questionnaire form & standard laboratory test results

↓

Treated with Crisaborole ointment 2% in Group A and Placebo in Group B

↓

Follow up at 4th, 8th and 12th week

↓

Data collection

↓

Statistical analysis of data

Result:

This Prospective clinical trial was conducted in the Department of Dermatology &Venereology in Shaheed Suhrawardy Medical College Hospital, Dhaka. After careful history taking, examination and appropriate investigations fulfilling inclusion and exclusion criteria, total 226 patients with mild to moderate atopic dermatitis

attending dermatology out-patient department, were included in this study, which was divided into two equal groups. One group was given with Crisaborole 2% ointment and other group placebo. After collecting socio-demographic data and ISGA score of all patients, interventions were given. Then again data was collected over 4th, 8th and 12th week follow-up. However, 20 patients were lost in this trial period. Finally, after 12th week 103 patients in each group were analyzed as lost to follow-up analysis. The main aim of the study was to evaluate the efficacy and safety of Crisaborole ointment 2% in the treatment of mild to moderate atopic dermatitis.

Table-4.1: Age group and gender of respondents (n = 206)

Variables	Crisaborole ointment 2% n = 103 n (%)	Placebo n = 103 n (%)	Total n = 206 n (%)	P value
Age group				0.653*
2-10 year	77(74.8)	81(78.6)	158(76.7)	
11-18 year	22(21.4)	17(16.5)	39(18.9)	
>18 year	4 (3.9)	5(4.9)	9(4.4)	
Mean age	10.08±7.47	9.78± 5.39	9.93 ± 6.5	0.749**
Gender				0.674*
Male	58(56.3)	55(53.4)	113(54.9)	
Female	45(43.7)	48(46.6)	93(45.1)	

*Chi-square test and **Independent t-test was done. Values were expressed as frequency with percentage in parenthesis over column

Table-4.2: Socio-demographic status of respondents (n=206)

Variables	Crisaborole ointment 2% n = 103 n (%)	Placebo n = 103 n (%)	Total n = 206 n (%)	P value
Area of residence				0.457
Rural	36 (35)	31 (30.1)	67(32.5)	
Urban	67 (65)	72 (69.9)	139(67.5)	
Economic condition				0.349
Lower	26 (25.2)	29 (28.2)	55(26.7)	
Middle	60 (58.3)	64 (62.1)	124(60.2)	
Rich	17(16.5)	10 (9.7)	27(13.1)	

*Chi-square test was done. Values were expressed as frequency with percentage in parenthesis over column

Table-4.3: Age of onset, family history and personal history of respondents

Variables	Crisaborole ointment 2% n = 103 n (%)	Placebo n = 103 n (%)	Total n = 206 n (%)	P value
Mean age of onset	7.08 ± 6.8	6.23 ± 4.8	6.66 ± 5.89	0.30
Positive family history	63 (61.2)	58(56.3)	121(58.7)	0.479
History of asthma	26 (25.2)	23(22.3)	49(23.8)	0.623
History of allergy	13(12.6)	23(22.3)	36(17.5)	0.067

*Chi-square test and **Independent t test were done. Values were expressed as frequency with percentage in parenthesis over column.

Table-4.4: Precipitating factors of atopic dermatitis of respondents (n = 206)

Precipitating factors	Crisaborole ointment 2% n = 103 n (%)	Placebo n = 103 n (%)	Total n = 206 n (%)	P value
Stress	13 (12.6)	12 (11.7)	25 (12.1)	0.869
Winter season	51(49.5)	57(55.3)	108(52.4)	
Woolen cloth allergy	24 (23.3)	21 (20.4)	45 (21.8)	
None	15(14.6)	13(12.6)	28(13.6)	

*Chi-square test was done. Values were expressed as frequency with percentage in parenthesis over column

Table-4.5: Investigation parameters of atopic dermatitis of respondents (n=206)

Investigation	Crisaborole ointment 2% n = 103 mean±SD	Placebo n = 103 mean±SD	P value
WBC (/µl)			
Baseline	9588.07±2424.9	9413.71±2976.9	0.645
After 4th week	9412.15±2828.07	9905.9±3445.3	0.262
After 8th week	9312.24+2896.9	9438.88±2816.4	0.751
After 12th week	9461.4±2753.5	9450.6±2899.4	0.978
SGPT (U/L)			
Baseline	30.07±13.8	31.9±4.9	0.203
After 4th week	29.22±10.9	29.14±14.5	0.964
After 8th week	26.45±14.1	28.77±10.1	0.176
After 12th week	28.06±14.11	26.18±11.76	0.301
S. Creatinine (mg/dl)			
Baseline	1.11±0.16	1.12±0.17	0.768
After 4th week	1.09±0.19	1.11±0.16	0.351
After 8th week	1.10±0.19	1.09±0.19	0.741
After 12th week	1.07±0.2	1.08±0.2	0.797

*p value was determined by Independent t test. WBC= White blood count, SGPT= Serum glutamic pyruvic transaminase

Table-4.6: Baseline ISGA scale for severity of atopic dermitis of respondents (n=206)

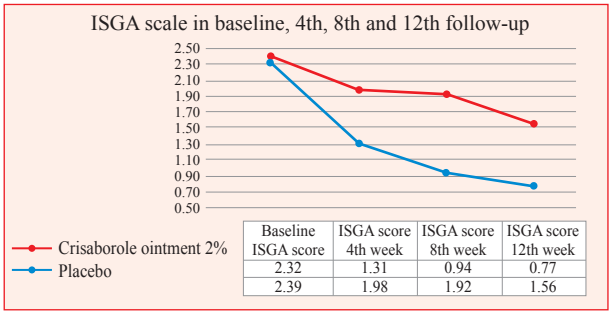
Variables	Crisaborole ointment 2% n = 103 n (%)	Placebo n = 103 n (%)	Total n = 206 n (%)	P value
ISGA score baseline				**0.245***
Mild (2)	70 (68)	62 (60.2)	132 (64.1)	
Moderate (3)	33 (32)	41 (39.8)	74 (35.9)	
Median (IQR)	2 (2-3)	2 (2-3)	2 (2-3)	**0.246****

*Chi-square test and **Mann Whitney U test were done. Values were expressed as frequency with percentage in parenthesis over column and in median with interquartile range.

Table-4.7: After 4th (th) 8th (th) and 12th (th) week follow-up of ISGA scale for severity of atopic dermatitis of respondents (n = 206)

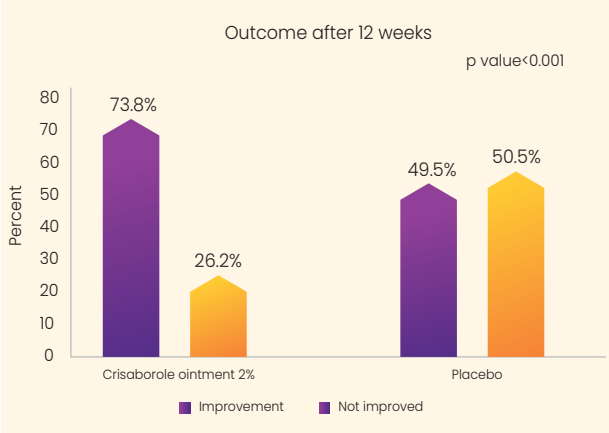
	Crisaborole ointment 2% n = 103 n (%)	Placebo n = 103 n (%)	Total n = 206 n (%)	P value
After 4th week				<0.001*
Clear (0)	11(10.7)	2(1.9)	13(6.3)	0.009
Almost (1)	51(49.5)	19(18.4)	70(34)	<0.001*
Mild (2)	39(37.9)	61(59.2)	100(48.5)	0.002
Moderate (3)	2(1.9)	21(20.4)	23(11.2)	<0.001
Median (IQR)	2(1-2)	2(1-2)	2(1-2)	0.081**
After 8th week				<0.001*
Clear (0)	39(37.9)	2(1.9)	41(19.9)	<0.001*
Almost (1)	33(32)	31(30.1)	64(31.1)	0.763
Mild (2)	29(28.2)	62(60.2)	91(44.2)	<0.001*
Moderate (3)	2(1.9)	8(7.8)	10(4.9)	0.051
Median (IQR)	1(1-2)	2(1-2)	1(1-2)	0.002**
After 12th week				<0.001*
Clear (0)	53(51.5)	8(7.8)	33(16)	<0.001*
Almost (1)	23(22.3)	38(36.9)	82(39.8)	0.022
Mild (2)	25(24.3)	49(47.6)	80(38.8)	0.001*
Moderate (3)	2(1.9)	8(7.8)	10(4.9)	0.051
Median (IQR)	1(1-2)	2(1-2)	1(1-2)	0.001**

*Chi-square test and **Mann Whitney U test were done. Values were expressed as frequency with percentage in parenthesis over column and in median with interquartile range.



P value was determined by repeated measure ANOVA with Bonferroni test

Figure-4.1: Association of baseline ISGA scale with 4th, 8th and 12th week follow-up of respondents (n = 206)



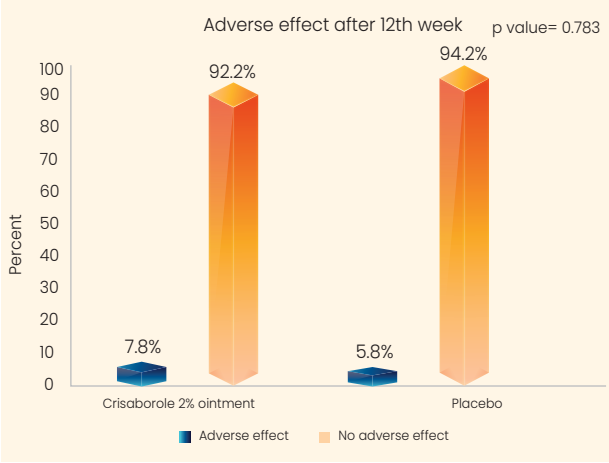
* Chi-square test was done.

Figure-4.2: Outcome of atopic dermatitis respondents after 12 week (n = 206)

Table-4.8: Adverse effect of intervention among atopic dermatitis respondents (n=206)

Variables	Crisaborole ointment 2% n = 103 n (%)	Placebo n = 103 n (%)	Total n = 206 n (%)	P value
Application site burn	3(2.9)	0	3(1.5)	0.246
Pain	2(1.9)	2(1.9)	4(1.9)	>0.999
Tingling	1(1.0)	2(1.9)	3(1.5)	>0.999
Itching	1(1.0)	0	1(0.5)	0.498
Contact urticaria	1(1.0)	2(1.9)	3(1.5)	>0.999
No adverse effect	95(92.2)	97(94.2)	192(93.2)	0.347

*Fishers exact test done. Values were expressed as frequency with percentage in parenthesis over column.



*Chi-square test was done. Values were expressed as frequency with percentage in parenthesis over column.

Figure-4.3: Adverse effects of respondents after 12-week follow-up (n = 206)

Discussion:

Atopic dermatitis is the most common chronic inflammatory skin diseases in infancy and childhood.48 Atopic dermatitis displays varied clinical features, course, and response to treatment during early infancy and after childhood.49 The study included a predominantly young population (aged 2-10 years), with a relatively even distribution between the Crisaborole ointment (74.8%) and placebo (78.6%) group of respondents. Also, the mean age of respondents quite similar in both groups, which were 10.08±7.47 years and 9.78±5.39 years, respectively. Both groups have higher proportion of male participants (56.3% and 53.4%, respectively) according to this study. Following this study, majority of participants in both groups came from urban residence (65% and 69.9%, respectively) and atopic dermatitis a middle-income economic status (58.3% and 62.1%). In a study in China done by Xu et al. showed that atopic dermatitis was higher in urban residence than rural, which is in concordance with this study.50 These demographic similarities suggest that the groups were well matched at baseline. In this study, it was found that, mean age of onset in Crisaborole 2% ointment group was 7.08±6.8 years and placebo group was 6.23±4.8 years. This findings highly indicated that school going aged children are more prone to have atopic dermatitis. Also, positive family history of atopic dermatitis was found in 61.2% respondents in Crisaborole 2% ointment group and 56.3% respondents in placebo group in this study. As personal history of respondents, history of asthma and history of allergy were found 25.2% and 12.6% respectively in Crisaborole 2% ointment group, while, 45.6% and 22.3% accordingly in placebo group in this study. According to Doğruel et al. 48 positive family history of atopic diatheses, prenatal infections and presence of food allergy are the risk factors for early presentation of atopic dermatits.51 According to Munivrana et al, positive family atopy might be the factors found to be associated to the symptoms of atopic dermatitis.52 However, this study revealed no significant differences between the two groups regarding the age of onset, family history of atopic dermatitis, history of asthma, or history of allergies. This demonstrates that the baseline characteristics of the participants were similar in both groups, reinforcing the validity of the study. Stress, woolen cloth allergy, and winter season were common precipitating factors for atopic dermatitis in both groups. According to this study, winter season was most commonly found in both Crisaborole 2% ointment (49.5%) and placebo group (55.3%). Also, 23.3% respondents atopic dermatitis woolen cloth allergy and 12.6% atopic dermatitis stress as risk factor for atopic dermatitis in Crisaborole 2% ointment group in this study. On the other hand, 11.7% respondents atopic dermatitis stress and 20.4% atopic dermatitis woolen cloth allergy as precipitating factor for atopic dermatitis in placebo group following this study. As these precipitating factors were commonly found among atopic dermatitis patients, these factors showed no significant difference in Crisaborole 2% ointment and placebo group. Another study done by Kwon et al. suggested that stress was associated with atopic dermatitis.53 However, positive and significant association was observed between being born in fall and winter and developing atopic dermatitis on the Northern hemisphere.54 Also, another study done by Munivrana et al. showed sleeping on feather pillow might precipitate atopic dermatitis, which suggested clothing is also an important factor for atopic dermatitis.52 Also another study by Li et al. suggested morning time, winter season, and cold air were the most common trigger factors for allergy mediated condition.55

According baseline ISGA score, majority of the respondents atopic dermatitis mild severity in both Crisaborole 2% ointment (68%) and placebo group (60.2%). And median ISGA score of both groups were also quite alike with no statistical difference was found on ISGA scale of severity in both groups. Stress, woolen cloth allergy, and winter season were common precipitating factors for atopic dermatitis in both groups. The study demonstrated that after 12 weeks of follow-up, Crisaborole 2% ointment resulted in a significantly greater improvement in atopic dermatitis compared to the placebo group. Crisaborole- treated patients showed a significantly greater reduction versus vehicle in percentage change from baseline in Eczema Area and Severity Index total score at day 29 (P = 0.0002).21 Though, at 4th week follow-up in this study, majority of the respondents atopic dermatitis almost clear in Crisaborole 2% ointment (49.5%), while in placebo group (59.2%) most had mild atopic dermatitis and 8 th week of follow-up, respondents in Crisaborole 2% ointment group atopic dermatitis clear atopic dermatitis (37.9%) and in placebo group most had still mild atopic dermatitis(60.2%). Therefore, after 12th week of follow-up, 51.5% respondents in Crisaborole 2% ointment group were clear, while in placebo group, 47.6% had mild atopic dermatitis, which was significant-

ly associated. Also, after 12 week, ISGA score in Crisaborole 2% ointment group was significantly lower than placebo group following this study.

Again, mean ISGA score of Crisaborole 2% ointment atopic dermatitis significantly decreased from baseline to 12th week follow-up (2.32 vs 0.77, p <0.001). However, ISGA score in placebo respondents also, significantly decreased from baseline to 8th week (2.39 vs, 1.92, p<0.001) though, no significant difference was found between 8th week and 12th week ISGA score among placebo respondents (1.92 vs, 1.56, p=0.499) according to this study. Findings showed a statistical difference where after 12 weeks follow-up Crisaborole 2% ointment atopic dermatitis less severity than placebo. Another similar study by Spergel et al. also showed ISGA clear or almost clear at day 29 occurred in 55.9% (48.0%-63.8%) vs 29.2% (18.8%-39.6%) among atopic dermatitis with AR (difference, P< 0.0001) and 45.9% (39.5%-52.3%) vs 31.8% (23.5%-40.1%) among atopic dermatitis with asthma patients (difference, P=0.008).56

After 12 weeks of follow-up, respondents with Crisaborole 2% ointment atopic dermatitis significant improvement from atopic dermatitis compared to placebo group (73.8% vs. 49.5%, p< 0.001). Additionally, the significant reduction in ISGA scores in the Crisaborole group over the 12-week period further supports the efficacy of this treatment. And no systemic involvement was found after 12 week follow-up according to investigation findings of this study. This findings were agreed with other study findings by Callender et al. as Crisaborole demonstrated efficacy for the treatment of mild-to-moderate atopic dermatitis, with a low frequency of treatment related adverse events.57 Compared to those treated with vehicle, patients on Crisaborole experienced a greater improvement in ISGA (RR 1.45; 95% CI 1.28 to 1.63).58

After 12 weeks of follow-up in this study, the majority of respondents in the Crisaborole 2% ointment group and placebo group had no adverse impact of intervention; nevertheless, 3(2.9%) respondents experienced application site burn, 2(1.9%) discomfort, 1 respondent tingling, and 1 respondent itching sensation in Crisaborole 2% ointment group. Furthermore, just 2 responders in the placebo group reported discomfort and 2 reported tingling. Frequency of Crisaborol related adverse events was 7.1–8.5% in the pivotal trials.57 Also another study done by Ma et al. agreed to the treatment with Crisaborole was effective and well tolerated in Chinese and Japanese patients with mild- to- moderate atopic dermatitis, with no new safety signals were identified.21 This suggests that the treatment was not only more effective but also better tolerated by the patients. This is a crucial consideration when assessing the overall benefit-risk profile of a medication. In conclusion, the study provides evidence that Crisaborole 2% ointment is an effective and safe treatment option for atopic dermatitis, particularly in pediatric patients.

Conclusion:

This study assessed the efficacy and safety of Crisaborole ointment (2%) for the treatment of mild to moderate atopic dermatitis. Mean ISGA score of Crisaborole 2% ointment atopic dermatitis significantly decreased from baseline to 12th week follow-up. Besides, Crisaborole 2% ointment atopic dermatitis significantly higher frequency of improvement than placebo group. Though, very less adverse effect was seen in both intervention and placebo group. Hence, it can be concluded that Crisaborole ointment (2%) is an effective and safe treatment option for mild to moderate atopic dermatitis. However, further study with larger sample size is recommended to corroborate my research findings.

Limitations of the study:

• Study was conducted in a selected hospital. So, the study population might not represent the whole community

• Sample size was small

Recommendations:

√ Further multicenter study with larger sample size is recommended.

√ Crisaborole ointment (2%) is an effective and safe treatment option for mild to moderate Atopic dermatitis.

References:

1. Griffiths CEM, Barker J, Bleiker TO, Chalmers R, Creamer D. Rook's textbook of dermatology. 9th ed. Vol. 1. John Wiley & Sons; 2016. Available at: http://surl.li/mwlac, (Last accessed on 22, November 2023).

2. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI, Group IPTS. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. J Allergy Clin Immunol. 2009;124(6):1251–8.

3. Arkwright PD, Motala C, Subramanian H, Spergel J, Schneider LC, Wollenberg A. Management of difficult-to-treat atopic dermatitis. J allergy Clin Immunol Pract. 2013;1(2):142–51.

4. Eichenfield LF, Friedlander SF, McR SELM, Irvine ATOPIC DERMATITIS. Assessing the New and Emerging Treatments for Atopic dermatitis. In: Seminars in cutaneous medicine and surgery. 2016; 35(5):92-6.

5. Jimenez JL, Punzón C, Navarro J, Muñoz-Fernández MA, Fresno M. Phosphodiesterase 4 inhibitors prevent cytokine secretion by T lymphocytes by inhibiting nuclear factor-κB and nuclear factor of activated T cells activation. J Pharmacol Exp Ther. 2001;299(2):753–9.

6. Baumer W, Hoppmann J, Rundfeldt C, Kietzmann M. Highly selective phosphodiesterase 4 inhibitors for the treatment of allergic skin diseases and psoriasis. Inflamm Allergy-Drug Targets (Formerly Curr Drug TargetsInflammation Allergy)(Discontinued). 2007;6(1):17–26. 58

7. Hanifin JM. Phosphodiesterase and immune dysfunction in atopic dermatitis. J Dermatol Sci. 1990;1(1):1–6.

8. Jarnagin K, Chanda S, Coronatopic dermatitiso D, Ciaravino V, Zane LT, Guttman-Yassky E, et al. Crisaborole Topical Ointment, 2%: A Nonsteroidal, Topical, AntiInflammatory Phosphodiesterase 4 Inhibitor in Clinical Development for the Treatment of Atopic dermatitis. J Drugs Dermatol. 2016;15(4):390–6.

9. Jimenez JL, Íñiguez MA, Muñoz-Fernández MA, Fresno M. Effect of phosphodiesterase 4 inhibitors on NFAT-dependent cyclooxygenase-2 expression in human T lymphocytes. Cell Signal. 2004;16(12):1363–73.

10. Zane L, Chanda S, Jarnagin K, Nelson D, Spelman L, Gold LS. Crisaborole and its potential role in treating atopic dermatitis: overview of early clinical studies. Immunotherapy. 2016;8(8):853–66.

11. Andoh T, Yoshida T, Kuraishi Y. Topical E6005, a novel phosphodiesterase 4 inhibitor, attenuates spontaneous itch-related responses in mice with chronic atopy-like dermatitis. Exp Dermatol. 2014;23(5):359–61.

12. Mollanazar NK, Smith PK, Yosipovitch G. Mediators of Chronic Pruritus in Atopic dermatitis: Getting the Itch Out? Clin Rev Allergy Immunol. 2016;51(3):263–92.

13. Wakita H, Ohkuro M, Ishii N, Hishinuma I, Shirato M. A putative antipruritic mechanism of the phosphodiesterase-4 inhibitor E6005 by attenuating capsaicin-induced depolarization of C-fibre nerves. Exp Dermatol. 2015;24(3):215–6. 59

14. Zane LT, Kircik L, Call R, Tschen E, Draelos ZD, Chanda S, et al. Crisaborole Topical Ointment, 2% in Patients Ages 2 to 17 Years with Atopic dermatitis: A Phase 1b, Open-Label, Maximal-Use Systemic Exposure Study. Pediatr Dermatol. 2016;33(4):380–7.

15. Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, et al. Guidelines of care for the management of atopic dermatitis. J Am Acatopic dermatitis Dermatol. 2014;71(1):116–32.

16. Schneider L, Tilles S, Lio P, Boguniewicz M, Beck L, LeBovidge J, et al. Atopic dermatitis: A practice parameter update 2012. J Allergy Clin Immunol. 2013;131(2):295-299.

17. Siegfried EC, Jaworski JC, Hebert AA. Topical Calcineurin Inhibitors and Lymphoma Risk: Evidence Update with Implications for Daily Practice. Am J Clin Dermatol. 2013;14(3):163–78.

18. Walling H. Update on the management of chronic eczema: new approaches and emerging treatment options. Clin Cosmet Investig Dermatol. 2010;99-117.

19. ATOPIC DERMATITISA. Global Report on Atopic dermatitis. 2022; 1-68. Available at: http://surl.li/mwkzw, (Last accessed on 22, November 2023).

20. Spergel JM, Blaiss MS, Lio P, Kessel A, Cantrell WC, Takiya L, et al. Efficacy and safety of crisaborole in patients with mild-tomoderate atopic dermatitis and other atopic comorbidities. Allergy Asthma Proc. 2021;42(5):425–31.

21. Ma L, Zhang L, Kobayashi M, Tao X, Qian Q, Cheng H, et al. Efficacy and safety of crisaborole ointment in Chinese and Japanese patients aged ≥2 years 60 with mild-to-moderate atopic dermatitis. J Dermatol. 2023;50(7):847–55.

22. De A, Karekar S, Atopic dermatitishav C. Current Burden of Atopic dermatitis in India: A Systematic Literature Review. Indian J Dermatol. 2023;68:487.

23. Pedersen CJ, Uddin MJ, Saha SK, Darmstatopic dermatitist GL. Prevalence and psychosocial impact of atopic dermatitis in Banglatopic dermatitiseshi children and families. PLoS One. 2021;16(4):1–14.

24. Kamruzzaman M, Das B, Kaiser MR. Study of Pattern of Skin Disease in Patients Attending OPD of Dermatology and Venereology Department in Shere-Bangla Medical College Hospital, Barisal, Banglatopic dermatitisesh. IOSR J Dent Med Sci e-ISSN. 2020;19(3):60–5.

25. Godse K, De A, Sharma N, Rajagopalan M, Shah B, Girdhar M, et al. Crisaborole for the treatment of atopic dermatitis in Indian patients: An evidence-based consensus statement. Indian J Drugs Dermatology. 2021;7(1):7.

26. Atakan N, Yalçın B, Özkaya E, Küçük ÖS, Öztürkcan S, Salman A, et al. Atopic dermatitis diagnosis and treatment consensus report. TURKDER-MTurkish Archives of Dermatology and Venereology. 2022; 56(2):86-121

27. Katayama I, Aihara M, Ohya Y, Saeki H, Shimojo N, Shoji S, et al. Japanese guidelines for atopic dermatitis 2017. Allergol Int. 2017;66(2):230–47.

28. Caffarelli C, Giannetti A, Giannì G, Ricci G. Anti-inflammatory and biologic drugs for atopic dermatitis: a therapeutic approach in children and atopic dermatitisolescents. Front Med. 2023;10(9):1–11. 61

29. Thyssen JP, Zang C, Neary MP, Bushmakin AG, Cappelleri JC, Cha A, et al. Translating the Investigator's Static Global Assessment to the Eczema Area and Severity Index in Studies of Crisaborole for Atopic dermatitis. Dermatol Ther (Heidelb). 2021;11(3):845–53.

30. Ramachandran V, Cline A, Feldman SR, Strowd LC. Evaluating crisaborole as a treatment option for atopic dermatitis. Expert Opin Pharmacother. 2019;20(9):1057–63.

31. Diaz A, Guttman-Yassky E. Topical agents for the treatment of atopic dermatitis. Expert Rev Clin Immunol. 2019;15(4):369–82.

32. Guttman-Yassky E, Hanifin JM, Boguniewicz M, Wollenberg A, Bissonnette R, Purohit V, et al. The role of phosphodiesterase 4 in the pathophysiology of atopic dermatitis and the perspective for its inhibition. Exp Dermatol. 2019;28(1):3–10.

33. McDowell L, Olin B. Crisaborole: A Novel Nonsteroidal Topical Treatment for Atopic dermatitis. J Pharm Technol. 2019;35(4):172–8.

34. Poulos J. Eucrisa® (crisaborole): A New Topical Agent for the Treatment of Atopic dermatitis. 2017;32(10):1–4.

35. Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Boguniewicz M, Call RS, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (ATOPIC DERMATITIS) in children and atopic dermatitisults. J Am Acatopic dermatitis Dermatol. 2016;75(3):494- 503. 62

36. Alonso EM, Writer M, Gonzales V, Pharmacist C, Heath L, Crook J, et al. UTAH Medicaid DUR Report February 2019 Crisaborole For The Treatment Of Mild To Moderate Atopic dermatitis. 2019;1-19.

37. Buck ML. Pediatric pharmacotherapy. Koda-Kimble Young's Appl Ther Clin Use Drugs. 2013;23(4):2265–76.

38. Bissonnette R, Pavel AB, Diaz A, Werth JL, Zang C, Vranic I, et al. Crisaborole and atopic dermatitis skin biomarkers: An intrapatient randomized trial. J Allergy Clin Immunol. 2019;144(5):1274–89.

39. Cheape AC, Murrell DF. 2% Crisaborole topical ointment for the treatment of mild-to-moderate atopic dermatitis. Expert Rev Clin Immunol. 2017;13(5):415–23.

40. Eichenfield LF, Call RS, Forsha DW, Fowler J, Hebert AA, Spellman M, et al. Long-term safety of crisaborole ointment 2 % in children and atopic dermatitisults with mild to moderate atopic dermatitis. J Am Dermatology. 2017;77(4):641-649.

41. Simpson EL, Paller AS, Boguniewicz M, Eichenfield LF, Feldman SR, Silverberg JI, et al. Crisaborole Ointment Improves Quality of Life of Patients with Mild to Moderate Atopic dermatitis and Their Families. Dermatol Ther (Heidelb). 2018;8(4):605–19.

42. Zane LT, Chanda S, Jarnagin K, Nelson DB, Spelman L, Gold LFS. Crisaborole and its potential role in treating atopic dermatitis: Overview of early clinical studies. Immunotherapy. 2016;8(8):853–66.

43. Eichenfield LF, Gower RG, Xu JH, Alam MS, Su JC, Myers DE, et al. Once- 63 Daily Crisaborole Ointment, 2%, as a Long-Term Maintenance Treatment in Patients Aged ≥ 3 Months with Mild-to-Moderate Atopic dermatitis: A 52- Week Clinical Study. Am J Clin Dermatol. 2023;24(4):623–35.

44. Geng B, Hebert AA, Takiya L, Miller L, Werth JL, Zang C, et al. Efficacy and Safety Trends with Continuous, Long-Term Crisaborole Use in Patients Aged ≥ 2 Years with Mild-to-Moderate Atopic dermatitis. Dermatol Ther (Heidelb). 2021;11(5):1667–78.

45. Silverberg JI, Tallman AM, Ports WC, Gerber RA, Tan H, Zielinski MA. Evaluating the efficacy of crisaborole using the atopic dermatitis severity index and percentage of affected body surface area. Acta Derm Venereol. 2020;100(13):1–6.

46. William J, DE JT, Misha R, Robert E. Atopic dermatitis, and Noninfectious Immunodeficiency Disorders. 13th ed. Andrews Diseases of the Skin. 2020. Available at: http://surl.li/mwkzg, (Last accessed on 22, November 2023).

47. Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Boguniewicz M, Call RS, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (ATOPIC DERMATITIS) in children and atopic dermatitisults. J Am Acatopic dermatitis Dermatol. 2016;75(3):494– 503.

48. Pyun BY. Natural history and risk factors of atopic dermatitis in children. Allergy, Asthma Immunol Res. 2014;7(2):101–5.

49. Murota H, Katayama I. Exacerbating factors of itch in atopic dermatitis. 64 Allergol Int. 2017;66(1):8–13.

50. Xu F, Yan S, Li F, Cai M, Chai W, Wu M, et al. Prevalence of childhood atopic dermatitis: An urban and rural community-based study in Shanghai, Chaina. PLoS One. 2012;7(5):5-8.

51. Doğruel D, Bingöl G, Altintaş DU, Yilmaz M, Kendirli SG. Prevalence of and risk factors for atopic dermatitis: A birth cohort study of infants in southeast Turkey. Allergol Immunopathol (Matopic dermatitisr). 2016;44(3):214–20.

52. Munivrana Skvorc H, Plavec D, Munivrana S, Skvorc M, Nogalo B, Turkalj M. Prevalence of and risk factors for the development of atopic dermatitis in schoolchildren aged 12-14 in northwest Croatia. Allergol Immunopathol (Matopic dermatitisr). 2014;42(2):142–8.

53. Kwon JA, Park EC, Lee M, Yoo KB, Park S. Does Stress Increase the Risk of Atopic dermatitis in Atopic dermatitisolescents? Results of the Korea Youth Risk Behavior Web-Based Survey (KYRBWS-VI). PLoS One. 2013;8(8):1–9.

54. Calov M, Alinaghi F, Hamann CR, Silverberg J, Egeberg A, Thyssen JP. The Association Between Season of Birth and Atopic dermatitis in the Northern Hemisphere: A Systematic Review and Meta-Analysis. J Allergy Clin Immunol Pract. 2020;8(2):674-680.

55. Li CW, De Chen H, Zhong JT, Lin Z Bin, Peng H, Lu HG, et al. Epidemiological characterization and risk factors of allergic rhinitis in the general population in Guangzhou City in China. PLoS One. 2014;9(12):1–16.

56. Spergel J, Blaiss M, Lio P, Kessel A, Takiya L, Werth J, et al. Efficacy and 65 Safety of Crisaborole in Patients With Mild-to-Moderate Atopic dermatitis With Comorbid Allergic Rhinitis or Asthma. J Allergy Clin Immunol. 2021;147(2):2-8.

57. Callender VD, Alexis AF, Stein Gold LF, Lebwohl MG, Paller AS, Desai SR, et al. Efficacy and Safety of Crisaborole Ointment, 2%, for the Treatment of Mild-to-Moderate Atopic dermatitis Across Racial and Ethnic Groups. Am J Clin Dermatol. 2019;20(5):711–23.

58. Yang H, Wang J, Zhang X, Zhang Y, Qin ZL, Wang H, et al. Application of Topical Phosphodiesterase 4 Inhibitors in Mild to Moderate Atopic dermatitis: A Systematic Review and Meta-analysis. JAMA Dermatology. 2019;155(5):585–93.