

Magnitude of benefit for topical crisaborole in the treatment of atopic dermatitis in children and adults does not look promising: a critical appraisal

DOI: 10.1111/bjd.16046

ORIGINAL ARTICLE: Paller AS, Tom WL, Lebwohl MG et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol* 2016; 75:494–503.

Summary

Aim To assess the efficacy and safety of crisaborole ointment, a phosphodiesterase 4 inhibitor, for the treatment of mild or moderate atopic dermatitis (AD) in two phase III studies (AD-301 and AD-302).

Design and setting Two identically designed multicentre, double-blind randomized controlled trials were conducted in the U.S.A. Participants were randomized 2 : 1 to receive crisaborole or vehicle treatment. In total 47 and 42 investigational centres were identified for AD-301 and AD-302, respectively.

Study participants Inclusion criteria were identified as age ≥ 2 years, clinical diagnosis of AD (as per the Hanifin and Rajka criteria), $\geq 5\%$ body surface area involvement, and baseline Investigator's Static Global Assessment (ISGA) mild or moderate. Exclusion criteria included previous use of biologics or systemic corticosteroids (within the last 28 days) or a topical calcineurin inhibitor/corticosteroid (within the last 14 days), and active skin infection.

Exposures Participants were instructed to apply the study drug twice daily to all lesions identified at baseline, and all new lesions identified after day 1 (with weekly review of application instructions). Bland emollients were permitted to be used on skin not treated with the study drug.

Primary outcome The primary outcome was defined as ISGA clear or almost clear at day 29, with a 2-grade or more improvement from baseline.

Outcomes Secondary outcomes included the proportion of patients with an ISGA score of clear or almost clear at day 29, and time to success in ISGA score. Additional outcomes included pruritus severity and signs of AD (erythema, exudation, excoriation, induration/papulation and lichenification), and were measured on a 4-point scale (none, mild, moderate, severe). Adverse events were also recorded.

Results More participants in the crisaborole-treated group achieved ISGA scores of clear or almost clear with ≥ 2 -grade improvement than in the vehicle-treated group (AD-301, 32.8% vs. 25.4%, $P = 0.38$; AD-302, 31.4% vs. 18.0%, $P < 0.001$). Greater percentages of clear and almost clear scores were observed in the treatment groups (51.7% vs. 40.6%, $P = 0.005$; 48.5% vs. 29.7%; $P < 0.001$), as well as earlier success in ISGA score and improvement in pruritus ($P \leq 0.001$). No serious treatment-related adverse events were identified.

Conclusions Based on the study results, the authors suggest that crisaborole is a safe treatment that improves disease severity, pruritus and clinical signs associated with AD.

Comment

What is already known about this topic?

Atopic dermatitis (AD), also known as atopic eczema, or just eczema, is a chronic inflammatory skin condition affecting approximately 20% of children in developed countries.¹ Around 90% of patients present with mild-to-moderate disease,^{2,3} making mild disease a potentially lucrative market for new and more effective and/or safer treatments than those already in use. Topical corticosteroids (TCS) have been recommended as the first-line anti-inflammatory treatment for AD for over 60 years and they have a well-established adverse-effect profile. A degree of anxiety when using any strength of TCS still exists because of widely publicized skin atrophy risk, which is associated with long-term use of potent and very potent TCS. Mild-to-moderate TCS have an extremely low risk of clinically significant skin thinning when used appropriately.⁴ Topical calcineurin inhibitors (TCIs), pimecrolimus and tacrolimus, have been licensed in the U.K. since 2001. TCIs are second-line treatment for patients in whom AD is not adequately controlled with TCS. Adverse effects include transient burning and erythema. In 2006 the U.S. Food and Drug Administration (FDA) placed a boxed warning for risk of lymphoma; however, a subsequent meta-analysis did not find a statistically significant association between the use of TCIs and increased risk of lymphoma.⁵

Crisaborole is a new, boron-based, topical phosphodiesterase (PDE)4 inhibitor that was approved for the treatment of mild-to-moderate AD in December 2016 by the FDA.

Inhibition of PDE4 reduces the production of proinflammatory cytokines thought to cause the signs and symptoms of AD. To our knowledge, the study by Paller *et al.* is the first phase III study into the effect of a topical PDE4 inhibitor on the management of AD.⁶

Strengths of the research

The study was conducted as per the Consolidated Standards of Reporting Clinical Trials (CONSORT guidelines).⁷ Particular strengths were the prospective registration of the trial at clinicaltrials.gov, use of clear inclusion and exclusion criteria, and reporting of patient enrolment, allocation and follow-up using a flow diagram. Primary safety assessments were also incorporated into the study design.

Assessment of validity

Internal validity

Randomization

The authors describe a centralized allocation process for randomization. Participants were randomized 2 : 1 to receive crisaborole or vehicle treatment. The likely underlying reason for this unequal allocation ratio is to improve recruitment to the study, as participants had a higher chance of receiving the study product than vehicle. Patient demographics and disease severity were similar across treatment groups in both studies. Concealment of the allocation sequence from those entering participants into the study is a key element of the Cochrane risk of bias tool;⁸ while likely, this was not described. Baseline secondary measures are not reported (pruritus, signs of AD). It would be helpful to know how symptomatic the two groups were at baseline.

Blinding

Although the study was described as 'double' blind,⁹ the authors make it clear that at least four groups (including principal investigators, study staff, participants and parents/guardians) were blinded until database lock. It would be helpful to know how the blinding was achieved and maintained – for example were there any differences between the vehicle and study product in terms of smell, colour or consistency, and were efforts made to prevent interactions between study participants (e.g. in the waiting room prior to assessment). The methods section of the study report does not contain any information on whether the authors attempted to measure contamination between the active and vehicle groups or whether cointerventions were permitted and to what extent they occurred.

Intention to treat

The results of the study report a modified intention-to-treat analysis that included all patients randomized and dispensed the study drug or vehicle.

Power

The sample size was selected to yield at least 90% power to achieve a statistically significant difference, assuming rather unambitious 'success' rates of 20% (crisaborole-treated group) and 10% (vehicle-treated group). Each study included very large numbers of participants for a simple vehicle-controlled comparison ($n = 763$ and 764), which was presumably needed in order to demonstrate a statistically significant result for the relatively small treatment signal that the investigators were pursuing.

External validity

External validity in relation to patients with mild-to-moderate AD seen in dermatology departments is likely to be good in terms of age, sex, ethnicity and severity. The study was conducted over a 28-day period. Participants received a weekly review of the treatment application instructions – a trial feature that could have enhanced medication adherence and is therefore unlikely to mimic the real-world conditions of routine AD care.

Small magnitude of benefit

Study AD-301 shows a percentage response rate of 32.8% for the active treatment vs. 25.4% for vehicle – thus only around one-third receiving crisaborole achieved a successful result overall. The absolute percentage difference in success between active treatment and vehicle is 7.4%, which translates to a number needed to treat of 14.¹⁰ This means that on average 14 patients with mild-to-moderate AD need to be treated with crisaborole in order to see one extra benefit when compared with treatment with vehicle. For study AD-302, less than one-third achieved a successful result on crisaborole (31.4%), and 18.0% achieved success with vehicle, a difference of 13.4% and a number needed to treat of eight. The authors stated that crisaborole-treated patients achieved improvement in pruritus earlier than vehicle-treated patients: 1.37 days (32.9 h) vs. 1.7 days (40.8 h), $P = 0.01$. The difference in pruritus improvement is 7.9 h, which although statistically significant is probably not clinically important.

Figure 2(a) in the original article (Fig. 1a here) used an inflated scale that exaggerates the small difference between active treatment and vehicle. The figure should ideally show percentages 0–100 on the y-axis, as shown in Figure 1(b).

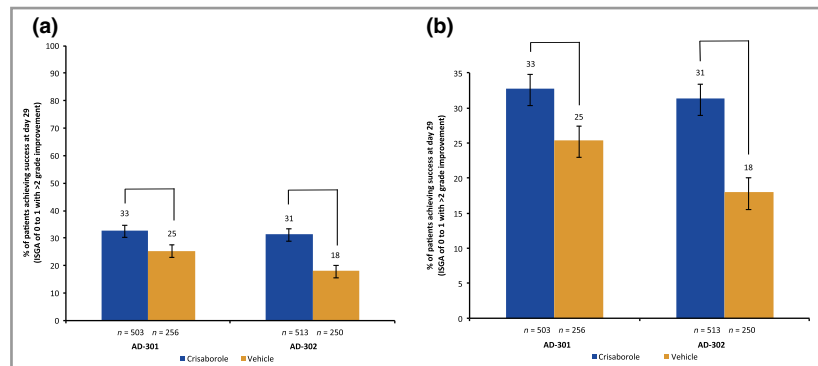
Overall, the magnitude of benefit of this new active drug compared with the vehicle is disappointing, although both we and the authors acknowledge that vehicles used for topical treatments may have mild anti-inflammatory properties of their own.

Other key observations

Phase II rather than phase III?

Although the publication is marketed as a phase III study, the study product is not being compared with the most

Fig 1. (a) Graph from the original article, showing a truncated scale with 0–35% on the y-axis. (b) The same data are shown with 0–100% on the y-axis. ISGA, Investigator's Static Global Assessment.



commonly used active treatment for mild-to-moderate AD, which in this case should be topical 1% hydrocortisone or clobetasone butyrate ointment.¹¹ Perhaps a more accurate description for such a short, vehicle-controlled and intensely monitored study would be a phase II study. Now that marginal superiority has been demonstrated for crisaborole over vehicle, it is essential not to conduct further vehicle-controlled studies,¹² but to proceed to test crisaborole against active comparators (such as 1% hydrocortisone or tacrolimus ointment) in pragmatic long-term studies.¹³

Conflicts of interest

This study was sponsored by Anacor Pharmaceuticals. Out of 16 authors, 12 declared a conflict of interest with Anacor Pharmaceuticals and three authors are Anacor Pharmaceuticals employees or stockholders. These conflicts might have affected the way the study was framed and reported.

Combining study results without appropriate adjustments

The trial consists of two identically designed studies testing the same hypotheses, which is an FDA requirement for drug approval.¹⁴ Apart from the main outcomes, many of the study results are not reported separately. Pooled data have been used to present results on pruritus, clinical signs of AD and severity, all of which show improvement in the crisaborole-treated group vs. the vehicle-treated group. Combining the data for these outcomes can result in a lower P-value, and hence a more significant result, whereas separate analyses may not yield the same P-values (i.e. a higher P-value that is not significant), as we have pointed out previously in relation to the reporting of pairs of pivotal studies required by the FDA.¹⁵ The authors would benefit from reporting all trial data as two independent studies [as they have done for the Investigators' Static Global Assessment (ISGA) scores] and then using appropriate meta-analysis techniques to account for variability between them.¹⁶

Choice of primary outcome

The authors used the ISGA as their primary outcome measure. ISGA is not validated in studies of AD and does not take into

account affected surface areas. The Eczema Area and Severity Index is a validated scoring system that grades the physical signs of AD and is recommended as a core outcome measure by the international Harmonising Outcome Measures for Eczema initiative (of which some of the authors are members).¹⁷

Overall assessment and application of the research to clinical practice

The follow-up time for the primary outcome is very short (28 days) for a chronic inflammatory disease characterized by flares and remission periods. It is not clear what is meant to happen after the 28-day period, for example whether the drug has to be used twice daily lifelong to maintain treatment effect or only used reactively for subsequent disease flares. Longer treatment regimens and follow-up periods may have provided useful additional information (e.g. maintenance of improvement and long-term adverse effects).

Eucrisa™ (trade name for crisaborole) will carry a wholesale price of \$580¹⁸ (approximately £434 when converted to British pounds, 27 November 2017) for a 60-g tube. In comparison, two 30-g tubes of hydrocortisone 1% ointment cost £3.96, and two 30-g tubes of clobetasone butyrate ointment cost £3.72. This reflects a more than 100-fold increase in price in comparison with the standard recommended treatment for mild-to-moderate AD.¹⁹

Conclusions and future directions

The authors appreciate the valiant efforts that the industry and its paid clinical collaborators undertake in developing and promoting new drugs in dermatology, and they are to be commended for clear and timely reporting of these two pivotal studies of crisaborole for mild-to-moderate AD. Sometimes, new drugs, although disappointing in clinical practice, draw attention to clues to the mechanisms of itch and inflammation,²⁰ and we look forward to better PDE4 inhibitors appearing in the future. One could argue that the efficacy of existing topical treatments for mild-to-moderate AD is not a primary hurdle. More salient therapeutic challenges for AD might include ease of use and/or treatment of severe disease with topical treatments that overcome the local adverse effects of

very potent TCS. Although the authors are correct in suggesting that crisaborole is a safe treatment that improves disease severity, pruritus and clinical signs associated with AD, the treatment benefit in absolute terms, and the benefit over and above vehicle in these two very short-term studies, was small and disappointing. In the absence of any clear additional advantages such as safety, cost or convenience over other existing topical treatments for mild-to-moderate AD, it is difficult to see how another topical product would be commissioned by countries such as the U.K. that depend largely on state funding. We might be wrong in assuming that the marginal benefit over vehicle in the study report translates to no clear benefit over other existing treatments, so it is essential that crisaborole testing now rapidly progresses from vehicle-controlled studies to studies using active comparators and long-term studies of drug safety.

Acknowledgments

A.A. and L.S. wish to thank the U.K. Dermatology Clinical Trials Network for providing them with a Specialist Registrar Training Fellowship, from which this work has emerged.

Funding sources

None.

Conflicts of interest

None declared.

¹Department of Dermatology, Watford General Hospital, Watford, U.K.

²Department of Paediatric Dermatology, Great Ormond Street Hospital for Children, London WC1N 3JH, U.K.

³Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, U.K.

Correspondence: Lea Solman.

E-mail: lea.solmankosutic@gosh.nhs.uk

A.A. and L.S. contributed equally.

References

- Williams H, Stewart A, von Mutius E et al. Is eczema really on the increase worldwide? *J Allergy Clin Immunol* 2008; **121**:947–54.
- Arkwright PD, Motala C, Subramanian H et al. Management of difficult-to-treat atopic dermatitis. *J Allergy Clin Immunol Pract* 2013; **1**:142–51.
- Charman C, Williams H. The use of corticosteroids and corticosteroid phobia in atopic dermatitis. *Clin Dermatol* 2003; **21**:193–200.
- Grindlay DJ. Pediatrics. 'Petite' bit of vital information still missing. Available at: <http://pediatrics.aappublications.org/content/135/4/597.comments#re-petite-bit-of-vital-information-still-missing> (last accessed 27 November 2017).
- Legendre L, Barnette T, Mazereeuw-Hautier J et al. Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: a systematic review and meta-analysis. *J Am Acad Dermatol* 2015; **72**:992–1002.
- Paller AS, Tom WL, Lebwohl MG et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol* 2016; **75**:494–503.
- Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Obstet Gynecol* 2010; **115**:1063–70.
- Higgins JP, Altman DG, Gotzsche PC et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**:d5928.
- Devereaux PJ, Manns BJ, Ghali WA et al. Physician interpretations and textbook definitions of blinding terminology in randomized controlled trials. *JAMA* 2001; **285**:2000–3.
- Manriquez JJ, Villouta MF, Williams HC. Evidence-based dermatology: number needed to treat and its relation to other risk measures. *J Am Acad Dermatol* 2007; **56**:664–71.
- Sigurgeirsson B, Boznanski A, Todd G et al. Safety and efficacy of pimecrolimus in atopic dermatitis: a 5-year randomized trial. *Pediatrics* 2015; **135**:597–606.
- Wilkes SR, Nankervis H, Tavernier E et al. How clinically relevant are treatment comparisons of topical calcineurin inhibitor trials for atopic eczema? *J Invest Dermatol* 2016; **136**:1944–9.
- Wilkes SR, Nankervis H, Tavernier E et al. More atopic dermatitis trials using standard treatments as active comparators please. *J Invest Dermatol* 2017; **137**:1365–6.
- U.S. Department of Health and Human Services Food and Drug Administration. Guidance for industry. Providing clinical evidence of effectiveness for human drug and biological products. Available at: www.fda.gov/ohrtms/dockets/ac/06/briefing/2006-4227B1-02-02-FDA-Appendix1.pdf (last accessed 27 November 2017).
- Katz KA, Kim CY, Williams HC. Reporting clinical trials: why one plus one does not equal two. *J Am Acad Dermatol* 2009; **61**:1082–3.
- Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *BMJ* 1997; **315**:1533–7.
- Schmitt J, Spuls PI, Thomas KS et al. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *J Allergy Clin Immunol* 2014; **134**:800–7.
- Pharmaphorum. Pfizer's eczema drug Eucrisa approved. Available at: <https://pharmaphorum.com/news/pfizers-eczema-drug-eucrisa-approved> (last accessed 27 November 2017).
- Eichenfield LF, Tom WL, Berger TG et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol* 2014; **71**:116–32.
- Hanifin JM. Commentary: new drugs for atopic dermatitis may provide clues to basic mechanisms of itch and inflammation. *J Am Acad Dermatol* 2016; **75**:504–5.