This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

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Crisaborole for adults, adolescents and children with atopic dermatitis

LAY SUMMARY

Atopic dermatitis, also known as eczema, is a long term condition that affects the skin. People with atopic dermatitis have sore, dry skin that causes intense itching, which can ooze and weep. This can lead to skin infections and trouble sleeping. It usually starts in infancy and can sometimes last into adulthood.

Crisaborole is a new anti-inflammatory cream for atopic dermatitis. Some studies have suggested that crisaborole can improve the symptoms of atopic dermatitis. If crisaborole is licensed for use in the UK, it could be a new treatment option for patients with atopic dermatitis.

NIHR HSRIC ID: 8307
TARGET GROUP

• Atopic dermatitis: adults, adolescents and children.

TECHNOLOGY

DESCRIPTION

Crisaborole (AN-2728) is a novel non-steroidal boron-containing small molecule that inhibits phosphodiesterase 4 (PDE4) and reduces the production of tumour necrosis factor (TNF)-alpha and other cytokines, including IL-12 and IL-23, which are proteins believed to be involved in the inflammation process and immune responses. In a phase III clinical trial, patients with atopic dermatitis were administered crisaborole 2% topical ointment twice daily for up to 28 days.

Crisaborole does not currently have Marketing Authorisation in the EU for any indication.

Crisaborole is also in phase II trials for psoriasis.

INNOVATION and/or ADVANTAGES

If licensed, crisaborole will offer an additional topical treatment option for this patient group.

DEVELOPER

Anacor Pharmaceuticals, Inc.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Atopic dermatitis (AD), also known as atopic eczema, is a skin condition causing inflammation and intense irritation, which is usually the result of dry skin. It often appears in children in their first year of life as scaly and dry patches on the scalp, forehead and face. Symptoms in infants can appear suddenly as a rash that is itchy that may cause them to rub against bedding, carpeting and other material to relieve the itching. The rash may ooze and weep. Other symptoms can include trouble sleeping and skin infections. In children between the ages of two years and puberty, the rash may appear in the creases of elbows and knees, neck, wrists, ankles, and/or creases in between buttocks and legs. Eventually, the affected skin may become bumpy, lighten or darken, thicken, develop knots and itch all the time in the thickened areas. AD in adults also leads to dry skin and non-stop itching, and can also cover much of the body, particularly around the eyes, neck and face, and appear in the creases of elbows, knees and nape of the neck. The thickened parts appear scalier than in infants and children. Those who had AD as children may be prone to extremely dry skin that is easily irritated, hand eczema and eye problems (such as eczema on eyelids or cataracts).
Atopy (the state of being atopic) describes a genetic tendency for the immune system to increase production and maintain high levels of IgE antibodies to certain allergens. An atopic individual is likely to have more than one allergic condition during their lifetime, such as eczema, asthma, hay fever or food allergy. Some people with IgE associated AD may have a worsening skin condition when they come into contact with airborne allergens, such as house dust mite allergens, pollens, or animal hairs, and improve after appropriate allergen avoidance strategies are introduced.

This topic is relevant to:

About one in five children in the UK has AD, with 8 out of 10 cases developing before a child reaches the age of five. Many children develop it before their first birthday. In some children AD can improve significantly, or even clear completely, as they get older. About 50% of all cases improve considerably by the time a child reaches 11 years, and around two-thirds improve by the age of 16. However, about half of people who get AD during childhood continue to have milder signs and symptoms of AD as an adult, and AD can sometimes develop for the first time in adults.

In 2014-15, there were 895 admissions for atopic dermatitis (ICD-10 L20) in England, resulting in 1,259 bed days and 967 finished consultant episodes.

In 2007, it was estimated that the prevalence of AD in children up to 12 years of age was about 16.5% (around 1,289,000 based on a population of approximately 7,810,000). Of those, 80% (1,031,000) were mild, 18% (232,000) were moderate and 2% (25,800) were severe.

The population likely to be eligible to receive crisaborole could not be estimated from available published sources.

NICE Guidance
- NICE technology appraisal. Tacrolimus and pimecrolimus for atopic eczema (TA82). August 2004
• NICE quality standard. Atopic eczema in under 12s (QS44). September 2013.

Other Guidance


CURRENT TREATMENT OPTIONS

There is currently no cure for AD4. Treatment strategies aim to reduce symptoms and improve the appearance of the condition4.

AD is typically managed by a stepped approach8:

• In mild cases:
  o Emollients
  o Mild potency topical corticosteroids

• In moderate cases:
  o Emollients
  o Mild potency topical corticosteroids
  o Topical calcineurin inhibitors
  o Bandages

• In severe AD:
  o Emollients
  o Potent topical corticosteroids
  o Topical calcineurin inhibitors
  o Bandages
  o Phototherapy
  o Systemic therapy: including systemic antibiotics against Staphylococcus aureus and streptococcus to treat widespread bacterial infection. Acyclovir should be used for suspected cases of widespread herpes simplex viral infections.

Treatment for flare ups should be started as soon as symptoms appear and continued for 48 hours after symptoms recede8.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02118792, AN2728-AD-302; crisaborole vs placebo; phase III.</th>
<th>NCT02118766, AN2728-AD-301; crisaborole vs placebo; phase III.</th>
<th>NCT01301508, AN2898-AD-202; crisaborole or AN28988 vs placebo; phase II.</th>
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<tbody>
<tr>
<td>Status</td>
<td>Complete but unpublished.</td>
<td>Complete but unpublished.</td>
<td>Published.</td>
</tr>
<tr>
<td>Location</td>
<td>USA.</td>
<td>USA.</td>
<td>Australia.</td>
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8 AN2898 is a type 4 cyclic nucleotide phosphodiesterase inhibitor, the development of which appears to have been discontinued.
| Participants | n= 763; aged ≥2 yrs; AD affecting ≥5% treatable body surface area (BSA), excluding the scalp; ISGA score of mild (2) or moderate (3) at baseline; no unstable AD or any consistent requirement for high potency topical corticosteroids; no history of biologic therapy (including intravenous); no recent or anticipated concomitant use of systemic or topical therapies that might alter the course of AD. | n= 759; aged ≥2 yrs; AD ≥5% treatable BSA (excluding the scalp); ISGA score of 2 or 3 at baseline; no unstable AD or any consistent requirement for high potency topical corticosteroids; no history of biologic therapy (including intravenous); no recent or anticipated concomitant use of systemic or topical therapies that might alter the course of AD. | n=25; aged 18-75 yrs; AD involvement ≤35%, BSA excluding involvement of the face, scalp, and groin; presence of 2 comparable target lesions; no active or potentially recurrent dermatologic condition other than AD in the target lesion; no concurrent or recent use of certain topical or systemic medications or phototherapy without a sufficient washout period; no history or evidence of allergies requiring acute or chronic treatment (except seasonal allergic rhinitis). |
| Schedule | Randomised to crisaborole topical ointment 2%, or placebo ointment, both applied twice daily. | Randomised to crisaborole topical ointment 2%, or placebo ointment, both applied twice daily. | Randomised to crisaborole topical ointment 2%, or AN2898 topical ointment 1%, or placebo ointment, all applied twice daily. |
| Follow-up | Active treatment for up to 28 days, follow-up for up to 36 days. | Active treatment for up to 28 days, follow-up for up to 36 days. | Active treatment for up to 6 wks, follow-up for up to 42 days. |
| Primary outcome/s | Proportion of subjects achieving success in ISGA at day 29. | Proportion of subjects achieving success in ISGA at day 29. | Atopic Dermatitis Severity Index (ADSI) score on day 28. |
| Secondary outcome/s | Frequency of treatment emergent adverse events (TEAEs), serious adverse events (SAEs) and clinically significant changes in vital signs and clinical laboratory parameters; proportion of subjects with an ISGA score of clear (0) or almost clear (1) at day 29; time to success in ISGA; signs of AD; time to improvement in pruritus; dermatology related quality of life (QoL) scores. | Frequency of TEAEs, SAEs and clinically significant changes in vital signs and clinical laboratory parameters; proportion of subjects with an ISGA score of 0 or 1 at day 29; time to success in ISGA; signs of AD; time to improvement in pruritus; dermatology related QoL scores. | ADSI component sub-scores; clearance of target lesions; number of participants with AEs. |
| Key results | At day 29, more crisaborole-treated patients achieved ISGA success than those treated with placebo (31.4% vs 18.0%, p<0.001) with a greater percentage of 1 or 0 ISGA scores (48.5% vs 29.7%, p<0.001). Success in ISGA and improvement | At day 29, more crisaborole-treated patients achieved ISGA success than those treated with placebo (32.8% vs 25.4%, p=0.038) with a greater percentage of 1 or 0 ISGA scores (51.7% vs 40.6%, p=0.005). Success in ISGA and improvement | At day 28, 17 patients (68%) experienced a greater decrease in ADSI score in the active-treated lesion (both arms) than in the placebo-treated lesion; 5 patients (20%) had a greater decrease in ADSI score in the placebo-treated lesion than in the placebo. |

b Investigator Static Global Assessment (ISGA) score is a 5-point scale from 0 ("clear") to 4 ("severe").
in pruritus were achieved earlier with crisaborole than placebo (p<0.001). A greater proportion of crisaborole-treated patients achieved success for all clinical signs of AD by day 29.

<table>
<thead>
<tr>
<th>Adverse effects (AEs)</th>
<th>TEAEs were infrequent, transient, and mild/moderate in severity.</th>
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<td></td>
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<td></td>
<td>No serious or severe AEs were reported, and no patient discontinued due to an AE. Local application-site reactions were reported in 3 patients (12%). A total of 29 AEs were reported in 11 patients; most (90%) were mild in intensity and unrelated to study medication.</td>
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<thead>
<tr>
<th>Trial</th>
<th>NCT01602341, AN2728-AD-204; crisaborole; phase II.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Anacor.</td>
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<tr>
<td>Status</td>
<td>Published.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Publication 13, trial registry 14.</td>
</tr>
<tr>
<td>Location</td>
<td>USA and Australia.</td>
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<tr>
<td>Design</td>
<td>Randomised, controlled.</td>
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<tr>
<th>Participants</th>
<th>n=86; aged 12-17 yrs; AD involvement ≤35% BSA; presence of two comparable target lesions; no unstable or actively infected AD; no active or potentially recurrent dermatologic condition other than AD in the target lesion area; no history or evidence of allergies requiring acute or chronic treatment (except seasonal allergic rhinitis); no concurrent or recent use of certain topical or systemic medications or phototherapy without a sufficient washout period; no treatment for any type of cancer (except squamous cell carcinoma, basal cell carcinoma, or carcinoma in situ of the skin, curatively treated with cryosurgery or surgical excision only) within the last 5 yrs.</th>
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<tbody>
<tr>
<td>Schedule</td>
<td>Randomised to topical crisaborole 0.5% or 2%, once a day or twice daily on two target lesions on each patient.</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment for up to 29 days, follow-up for up to 29 days.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>ADSI score.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Number of participants with AEs; ADSI component sub-scores.</td>
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### Key results

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<th>All regimens produced dose-related improvements in ADSI as well as symptoms of AD, including erythema, excoriation, exudation, lichenification, and pruritus. The greatest improvements were consistently observed with 2% crisaborole applied twice daily. With this regimen, ADSI improved from baseline by 71%, and total or partial clearance of target lesions was achieved by 62% of patients after 29 days of treatment. Mean ISGA score decreased by 1.08 points from baseline; 73.9% of subjects achieved an ISGA score of 0 or 1 and treatment success, defined as an ISGA score of 1 with a minimum 2-grade improvement from baseline, was achieved in 34.8% of subjects. Mean values for the individual signs and symptoms of AD improved during treatment, most notably a 70% reduction in mean pruritus severity score.</th>
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</thead>
<tbody>
<tr>
<td>Adverse effects (AEs)</td>
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### ESTIMATED COST and IMPACT

#### COST

The cost of crisaborole is not yet known.

#### IMPACT - SPECULATIVE

#### Impact on Patients and Carers

- Reduced mortality/increased length of survival
- Other:
  - Reduced symptoms or disability
  - No impact identified

#### Impact on Health and Social Care Services

- Increased use of existing services
- Re-organisation of existing services
- Other:
  - Decreased use of existing services
  - Need for new services
  - None identified

#### Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Other increase in costs:
  - Reduced drug treatment costs
  - Other reduction in costs:
  - None identified

#### Other Issues

- Clinical uncertainty or other research question identified:
  - None identified
12 Stein Gold LF, Spelman L, Spellman MC et al. A phase 2, randomised, controlled, dose-ranging study evaluating crisaborole topical ointment, 0.5% and 2% in adolescents with mild to moderate atopic dermatitis. Journal of Drugs in Dermatology 2015;14(12):1394-99.