Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Crisaborole

Proprietary Product Name: Staquis

Sponsor: Pfizer Australia Pty Ltd

August 2019

TGA Health Safety Regulation

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- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Contents

Common abbreviations

Abbreviation	Meaning
AD	Atopic dermatitis
ADSI	Atopic Dermatitis Severity Index
AE	Adverse event
ALT	Alanine aminotransferase
ASA	Australian Specific Annex
AST	Aspartate aminotransferase
AUC	Area under the (plasma concentration time) curve
AUC_{0-12}	Area under the plasma concentration time curve from time 0 to 12 hours post dosing
AUC_{0-24}	Area under the plasma concentration time curve from time 0 to 24 hours post dosing
BSA	Body surface area
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Maximum observed plasma concentration
CMI	Consumer Medicines Information
CNS	Central Nervous System
DAE	Discontinuation due to adverse event
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonisation
ISGA	Investigator's Static Global Assessment

Abbreviation	Meaning
ITT	Intention to Treat
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PDE	Phosphodiesterase
PDE4	Phosphodiesterase-4
PI	Product information
PK	Pharmacokinetic
PO	per oral
QTc	corrected QT interval
QTcF	Fridericia's Correction Formula
RCT	Randomised controlled trial
RMP	Risk Management Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SIB	suicidal ideation and behaviour
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TEAE	Treatment emergent adverse event
T_{max}	Time to maximum plasma concentration
Treatable %BSA	Percentage of a patient's total body surface area that was AD involved excluding the scalp
US	United States
vehicle	crisaborole topical ointment, vehicle

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	15 February 2019
Date of entry onto ARTG:	20 February 2019
ARTG number:	295283
, *Black Triangle Scheme*	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Active ingredient:	Crisaborole
Product name:	Staquis
Sponsor's name and address:	Pfizer Australia Pty Ltd Level 15-18 151 Clarence Street Sydney NSW 2000
Dose form:	ointment
Strength:	2% w/w
Container:	Ointment tube
Pack sizes:	30 g, 60 g, 100 g, and 2.5 g x 6
Approved therapeutic use:	*Staquis is indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.*
Route of administration:	Topical
Dosage:	Staquis is to be applied as a thin layer twice daily to affected areas. Staquis can be used on all skin areas, including the head and face, neck and intertriginous areas.

Product background

This AusPAR describes the application by Pfizer Australia Pty Ltd (the sponsor) to register Staquis (crisaborole) as 2% weight/weight (w/w) ointment, a new chemical entity for the proposed indication of:

> *Staquis is indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older*.

Crisaborole is a phosphodiesterase 4 (PDE4)[1] inhibitor that suppresses inflammation and secretion of certain cytokines, such as tissue necrosis factor alpha (TNFα), from the peripheral blood mononuclear cells. However, the specific mechanism(s) by which crisaborole exerts its therapeutic action is not well defined.

Atopic dermatitis (AD), often referred to as 'eczema', is a chronic inflammatory condition of the skin. It is characterised by dryness of the skin (xerosis), itching (pruritus) and in more severe conditions inflamed, red and weeping lesions.

Atopic dermatitis can occur at any age but is more common in children and may improve with age. The prevalence of AD in Australia is estimated to be approximately 7%;[2] with approximately 83% being classified as mild and a further 15% as moderate and 2.6% as severe.

Atopic dermatitis has a high disease burden due to itch and discomfort and may be associated with sleep and mood disturbances. Broken skin is susceptible to infections, particularly with *Staphylococcus aureus* which may further exacerbate AD due to staphylococcal antigens.

Common comorbidities in patients with AD include allergic rhinitis, asthma, allergic rhinitis and food allergies. Hence, common co-medications include inhaled beta-agonists, inhaled steroids, inhaled anticholinergics, oral steroids and oral leukotriene antagonists.

Current treatment options

The current treatment options for atopic dermatitis are:

- topical treatments such as, emollients, topical corticosteroids and topical calcineurin inhibitors (for example, tacrolimus and pimecrolimus);
- systemic treatments such as, oral corticosteroids, ciclosporin, methotrexate and azathioprine; and
- adjunctive treatments such as, antibiotics (anti-staphylococcal; used for infected lesions), antivirals (acyclovir; used for herpetic lesions and antihistamines (used to treat itch).

Initial management of AD in includes identifying and avoiding trigger factors, such as irritants, skin infections, contact allergens, food allergens and inhalant allergens.[3] Further management includes a stepwise approach;[3] with mild AD usually controlled with measures such as avoiding precipitants, use of emulsifying ointment instead of soap and liberal use of emollients. Occasional use of low potency topical steroids may be required. Treatment of moderate AD includes emollients, moderate potency topical corticosteroids, topical calcineurin inhibitors (TCI), and bandages. Severe AD requires the above measures plus high potency topical steroids, phototherapy and systemic treatments. All of the systemic treatments have a high risk of adverse events.

Severe itching or urticaria should be treated with a non-sedating antihistamine; however, if the patient has significant sleep disturbance a sedating antihistamine could be used instead. Bacterial infections should be treated with an antibiotic with effective staphylococcal and streptococcal coverage.

[1] Phosphodiesterase 4 (PDE4) is an enzyme that regulates inflammatory cytokine production in atopic dermatitis through the degradation of cyclic adenosine monophosphate (cAMP). PDE4 activity is increased in circulating inflammatory cells of patients with atopic dermatitis.
[2] Plunckett A, et al. (1999) The frequency of common nonmalignant skin conditions in adults in central Victoria, Australia. *Int J Dermatol*; 1999; 38: 901-908.
[3] National Institute for Health and Care Excellence (NICE). (2007) Atopic eczema in under 12s: diagnosis and management (Clinical Guideline [CG57]). Accessed: 22 March 2019.

Topical corticosteroids and TCIs both carry significant risk of inducing undesirable and serious side effects that may be of particular concern in young children. Medications from both classes must be used carefully and are restricted to short term, intermittent use as each carry the risk of considerable long term side effects.

Dupixent (dupilumab), an IL-4Rα receptor antagonist, has been developed for the treatment of severe AD in adults and has recently been registered in Australia. However, it is not indicated for the treatment of AD in children.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 20 February 2019.

Crisaborole was approved in the United States of America (USA) on 14 December 2016 and in Canada on 7 June 2018. In both the USA and Canada, crisaborole is known by the trade name Eucrisa.

At the time of submission, the proposed tradename was [information redacted] this was subsequently updated to Staquis.

At the time TGA considered this application, a similar application was submitted in the European Union (EU).

Product Information

The PI approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table (Table 1) captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for submission PM-2017-03748-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	30 November 2018
First round evaluation completed	3 August 2018
Sponsor provides responses on questions raised in first round evaluation	3 October 2018
Second round evaluation completed	12 November 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	24 October 2018
Sponsor's pre-Advisory Committee response	20 November 2018
Advisory Committee meeting	7 December 2018

Description	Date
Registration decision (Outcome)	15 February 2019
Completion of administrative activities and registration on ARTG	20 February 2019
Number of working days from submission dossier acceptance to registration decision*	249

*Statutory timeframe for standard applications is 255 working days

Evaluations included under Quality findings and Nonclinical findings incorporate both the first and second round evaluations.

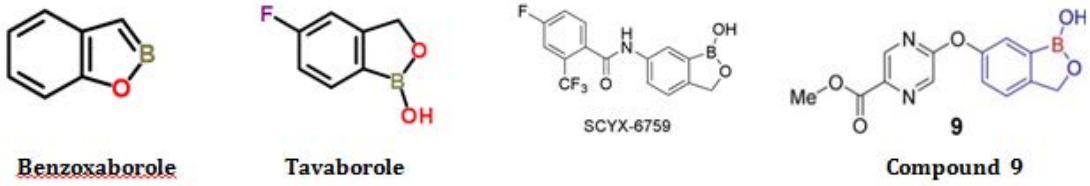
III. Quality findings

Introduction

The proposed new chemical entity, crisaborole, is an anti-inflammatory PDE4 inhibitor and is believed to act by decreasing the production of several inflammatory cytokines implicated in the pathophysiology of AD (for example, TNFα, interleukin (IL)-2, IL-4, IL-5, and interferon (IFN)γ) as has been shown for other PDE4 inhibitors.

Crisaborole is a low molecular weight benzoxaborole (see Figure 1), and although benzoxaborole was first synthesised in 1957,[4] this class of compounds did not find use in medicinal chemistry until 2006 when tavaborole (5-fluorobenzoxaborole, or AN2690; structure also shown in Figure 1, below) was found to have antifungal activity against *Trichophyton spp*.[5] Subsequently, tavaborole has been approved in the USA as a 5% topical solution for the treatment of onychomycosis of the toenail in adults. Other compounds in this class having physiological activity include benzoxaborole-6-carboxamides such as SCYX-6759 (found to be orally active in murine models of human African trypanosomiasis;[6] structure shown in Figure 1, below), and a series of 6-hetaryloxy benzoxaborole compounds (for example, Compound 9 below) shown to be efficacious against cultured *Plasmodium falciparum* W2 and 3D7 strains.[7]

Figure 1: Structure of benzoxaborole, tavaborole, SCYX-6759 and compound 9



[4] Torssell K, et al. (1957) Bromination of tolylboronic acids according to Wohl-Ziegler. *Ark. Kemi.* 1957; 10: 507-511.
[5] Baker SJ, et al. (2006) Discovery of a new boron-containing antifungal agent, 5-fluoro-1,3-dihydro-1-hydroxy-2,1- benzoxaborole (AN2690), for the potential treatment of onychomycosis. J Med Chem; 49: 4447-4450
[6] Jacobs RT et al. (2011) Benzoxaboroles: a new class of potential drugs for human African trypanosomiasis. *Future Med Chem*. 2011; 3: 1259-1278.
[7] Zhang YK et al. (2015) Benzoxaborole antimalarial agents. Part 4. Discovery of potent 6-(2-(alkoxycarbonyl)pyrazinyl-5-oxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaboroles. *J Med Chem.* 2015; 58: 5344-5354.

Drug substance (active ingredient)

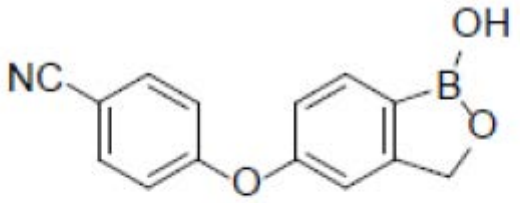
Nomenclature

Staquis (crisaborole) has the International Union of Pure and Applied Chemistry (IUPAC) name of 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-[2,1]-benzoxaborole.

Structure

Figure 2 shows the chemical structure of crisaborole.

Figure 2: Structural formula of crisaborole



Molecular Formula: $C_{14}H_{10}BNO_3$

Molecular Mass: 251.1 Daltons

The drug substance is a white to pale yellow crystalline powder, which is insoluble in water, but is sparingly soluble in methanol, soluble in ethanol, acetonitrile, acetic acid: water (90:10 volume/volume (v/v)) and freely soluble in isopropyl alcohol, propylene glycol, tetrahydrofuran and N,N-dimethylformamide.

Crisaborole has a reported melting range of 128.8 to 134.6°C, a partition coefficient (log P) of 3.24 and a dissociation constant (pKa) value of 6.98.

Particle size was not considered to be a critical attribute as the drug substance is fully dissolved in propylene glycol in the drug product. The absence of a test for this parameter in the drug substance specification was considered acceptable.

The quality of the drug substance is controlled. All tests and limits proposed for the drug specification are considered acceptable.

The analytical methods used for the routine quality control assessment of the drug substance were all adequately validated and appropriate for use.

Drug product

The drug product has been formulated as a white soft paraffin based ointment containing 20 mg per gram (2% w/w) of crisaborole. The ointment is white to off white in appearance and is to be packaged in multi-laminate aluminium tubes with a polypropylene cap, high density polyethylene tube head, and multi-laminate orifice seal. The drug product is filled into four packaging presentations with nominal contents of 2.5 g, 30 g, 60 g, and 100 g. The 2.5 g tube will only be available as a 6 x 2.5 g presentation.

The crisaborole drug substance is fully dissolved in the propylene glycol solvent before homogenisation into the ointment base of white soft paraffin, glyceryl monostearate, synthetic paraffin, butylated hydroxytoluene and sodium calcium edetate.

The manufacturing process is well documented, optimised and validated to ensure a drug product of reproducible quality at a commercial scale.

Good Manufacturing Practice (GMP) clearances for the drug substance and drug product manufacturing sites are all currently valid past the expected decision date.

The quality of the drug product is controlled by an acceptable specification.

The analytical methods used to analyse the product were adequately described and validated.

The drug product is stable upon storage and stability data supplied supported a shelf life of 36 months for the unopened product when stored at or below 25°C. No other storage conditions are required.

Quality summary and conclusions

Approval was recommended from a pharmaceutical chemistry and quality control perspective.

IV. Nonclinical findings

Introduction

The submitted nonclinical dossier was in accordance with the relevant International Conference on Harmonisation (ICH) guideline for the nonclinical assessment of pharmaceuticals.[8] The overall quality of the nonclinical dossier was high.

The nonclinical dossier included adequate primary and secondary pharmacology studies (*in vitro* and *in vivo*); 14 repeat dose toxicity studies in three species, up to 3 months duration in mice, 6 months in rats and 9 months in mini-pigs; genotoxicity studies; carcinogenicity studies in mice and rats; reproductive toxicity studies; studies in juvenile animals; and local tolerance studies. All pivotal safety related studies were Good Laboratory Practice (GLP) compliant.

Pharmacology

Primary pharmacology

Crisaborole is a benzoxaborole PDE4 inhibitor which suppresses inflammation and secretion of cytokines including TNFα, IL-2 and INFγ from peripheral blood mononuclear cells. The lesions of patients with atopic dermatitis contain infiltrates of T helper cell type 2 (Th2) T cells and dendritic cells;[9,10] with the production of cytokines associated with the Th2 phenotype (IL-4, IL-5, IL-13 and IL-31) elevated in early and chronic lesions, and IFNγ also elevated in chronic lesions.[10]

[8] International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use (2009). Guidance on Nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2).
[9] Guttman-Yassky E, et al. (2011) Contrasting pathogenesis of atopic dermatitis and psoriasis-part I: clinical and pathologic concepts. *J Allergy Clin Immunol.* 2011; 127:1110-1118.
[10] Gittler JK, et al. (2012) Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol.* 2012; 130:1344-1354.

There are 11 known gene families of PDE, each containing a highly homologous catalytic domain located at the carboxyl end of the protein and divergent regions at the amino acid end of the protein. The PDE4 gene family contains 4 genes (4A, 4B, 4C and 4D) and each gene may be transcribed into several different splice variants, all of which contain the full catalytic domain and various amino-localised regulatory domains. The cyclic adenosine monophosphate (cAMP) substrate selectivity varies between PDE gene families, with PDE4 being highly selective for cAMP.

In vitro

Crisaborole is a potent inhibitor of PDE4 (half maximal inhibitory concentration (IC_{50}) 0.11 to 0.49 μM) in various cell systems, with inhibition of PDE7A1 also observed (IC_{50} 0.73 μM). Less potent inhibition was observed for other PDE isotypes including PDE1A3 and PDE3 (IC_{50} 6.12 to 6.41 μM). The PDE4 catalytic domains of several PDE4 enzymes interact with crisaborole, with IC_{50} values ranging from 75 to 124 nM. Other known PDE4 inhibitors (including roflumilast and apremilast) showed greater potency than crisaborole with IC_{50} values ranging from 0.0002 to 0.05 μM.

The comparative isoform selectivity of crisaborole was determined in human recombinant enzyme preparations. Crisaborole inhibited all PDE4 subtypes examined (> 92% inhibition) as well as PDE enzymes PDE1A1, PDE1C, PDE1B, PDE2A1, PDE3A, PDE6C and PDE7B with between 50 to 80% inhibition. PDE1B, PDE2A1, PDE3A, PDE6C and PDE7B have shown to have affinity for crisaborole with IC_{50} values ranging from 3.7-9.4 μM. Crisaborole inhibits PDE4B in a competitive manner (inhibitory constant (K_i) 182 nM), with the binding site of crisaborole partially overlapping the binding site for adenosine monophosphate (AMP) as shown in x-ray diffraction studies.

Crisaborole inhibited secretion of pro-inflammatory cytokines in cultured human cells, in particular TNFα (IC_{50} 0.172 μM), the Type 1 T helper (Th1) cytokines IL-2 (IC_{50} 0.205 μM) and IFNγ (IC_{50} 0.696), and Th2-type cytokines IL-5 (IC_{50} 2.03) and IL-4 (IC_{50} 0.48). Crisaborole exhibited lower potency against IL-1β, IL-6, IL-8, IL-12 and IL-23 secretion.

Crisaborole metabolites, AN7602 and AN8323, had no inhibitory activity on PDE4 (IC_{50} > 100 μM) and had no effect on cytokine secretion (IC_{50} values > 50 μM).

In vivo

Crisaborole was examined topically in mouse models of skin inflammation. In the mouse phorbol ester ear oedema model, crisaborole (in acetone: ethanol, 1:1) inhibited phorbol myristate acetate (PMA) induced ear swelling in a concentration dependent manner (48 to 98% inhibition at doses of 1 to 6 mg/ear). When formulated as a cream or ointment reductions in inflammation were found to be due to the vehicle used (56 to 85% inhibition of ear swelling compared with the acetone: ethanol vehicle). However it is noted that the cream B vehicle formulation used in this study was different to the formulated product used in clinical studies. The effect of crisaborole on delayed type hypersensitivity in the mouse oxazolone induced sensitisation model was also examined. Crisaborole inhibited oxazolone induced ear swelling by 29% in pre-sensitised mice.

Secondary pharmacodynamics and safety pharmacology

Crisaborole was tested for secondary activity at a number of other receptors, ion channels and transporters as well as its ability to modulate enzyme activity including cyclooxygenase and protease enzyme activity and cell adhesion. Crisaborole did not significantly inhibit any of the panel of 50 transmembrane and soluble receptors, ion channels and monoamine transporters tested. It had no effect on the activity of cyclooxygenase (COX)-1 and COX-2 enzymes, kinase activity protease activity or cell adhesion; however, a 77% inhibition of prostaglandin E2 (PGE2) secretion was observed

in vitro and crisaborole was found to moderately suppress the secretion of monocyte chemoattractant protein (MCP)-1 from primary human monocytes (IC_{50} 8.2 µM).

The effect of crisaborole on collagen induced arthritis in mice and the emetic activity of crisaborole in ferrets and shrews were also examined, and the antifungal and antibacterial activity of crisaborole was investigated. Crisaborole had no effect on collagen induced arthritis in mice, with disease severity and burden similar between control and treated animals. Crisaborole was shown to have limited antimicrobial or antifungal activity, with antifungal activity shown against *T. metagrophytes* F311 at 4 µg/mL and inhibitory activity against other fungal and bacterial strains at ≥ 8 µg/mL.

PDE4 inhibitors are known to have emetic effects when administered orally.[11] Oral administration of crisaborole at doses of 10 to 100 mg/kg caused vomiting in shrews, but not in ferrets. Plasma levels of crisaborole were 0.0677 and 4.46 µg/mL in ferrets and shrews, respectively, indicating a higher level of absorption of crisaborole in shrews compared to ferrets, with systemic exposure in the shrew following oral dosing also shown to be high ($AUC_{0\text{-tlast}}$ of 452 µg.h/mL). However, given that crisaborole is intended to be applied topically, systemic exposure will be limited. Any parent compound that gets absorbed systemically is rapidly metabolised into inactive metabolites. Therefore an emetic response is not expected in the clinical setting. Results of clinical studies did not indicate a high incidence of vomiting reported by subjects dermally administered crisaborole ointment (2%), despite crisaborole plasma levels as high as 1.34 µg/mL.

Dedicated safety pharmacology studies covered the cardiovascular system and central nervous system effects. *In vitro*, there was no clinically relevant inhibition of the hERG[12] potassium (K^+) tail current (15.3% inhibition). No abnormalities in electrocardiogram (ECG) parameters were evident in dogs treated with 300 mg/kg oral (PO) crisaborole. Decreased blood pressure and increased heart rate were noted in dogs at oral doses of 100 and 300 mg/kg; however, these changes were of small magnitude and short duration (< 45 min post dose) and therefore not considered to be biologically relevant. No adverse effects on cardiovascular function are predicted in patients. There was limited evidence of effects on central nervous system function in rats dosed with between 300 and 1000 mg/kg PO. At these doses, mild effects on gait were noted in most animals, 1 hour post dose, however symptoms resolved in all animals within 24 hours. No adverse effects on cardiovascular or central nervous system function are predicted in patients.

Pharmacokinetics

The absorption of crisaborole was moderate following dermal application (time of maximum measured plasma concentration (T_{max}) of 2 h) in mini-pigs and humans (T_{max} ~3 h), with minimal systemic exposure at doses of crisaborole of up to 7%. Dermal application at concentrations up to 7% in mice and mini-pigs resulted in low levels of systemic exposure to crisaborole. Pharmacokinetic parameters were similar in juvenile animals following dermal application of crisaborole in mini-pigs.

Following intravenous, intramuscular, or subcutaneous administration of crisaborole, absorption was rapid (T_{max} 0.25 h), clearance was high (1765 mL/h/kg in dogs, 5354 mL/h/kg in mice), exposure was dose proportional, and bioavailability was low (< 1% in dogs and 9% in rats at 300 mg/kg PO). Following PO administration in rats, rabbits, shrews and dogs, absorption was relatively rapid (T_{max} ~1 to 5 h) and exposure was dose proportional.

[11] Spina D. (2008). PDE4 inhibitors: current status. *Br. J. Pharmacol*. 2008; 155: 308-315.
[12] hERG (human ether-a-go-go-related gene) encodes the alpha subunit of a potassium ion channel that is important for cardiac repolarisation.

Plasma protein binding by crisaborole *in vitro* was high in humans and laboratory animal species (93 to 97% in animals and 97.9% in humans at 10 µg/mL). Plasma protein binding by the metabolite AN8232 was > 98% in all species.

Tissue distribution of radioactivity in rats after intravenous administration of radiolabelled crisaborole was rapid and wide. Tissues with concentrations (maximum concentration (C_{max}) or area under the curve (AUC)) higher than those in blood included the kidney and liver with lower levels observed in all other tissues including the brain and reproductive organs. There was no specific affinity or retention of radioactivity in melanin containing tissues.

Metabolism of crisaborole *in vivo* involved initial oxidative deboronation/hydrolysis to AN7602, followed by subsequent downstream oxidation to form AN8323. AN7602 undergoes further metabolism to sulfate and glucuronide conjugates. The most prominent metabolite in rat plasma was AN7602-sulfate (M9), followed by AN7602 and AN8323. In humans, the most abundant metabolite in plasma is AN8323, followed by AN7602-sulfate, while the concentration of crisaborole and AN7602 are generally low in plasma. AN7602-sulfate is the major metabolite excreted in human urine. There were no unique human metabolites. AN7602 was the only primary metabolite of ^{14}C crisaborole in human hepatic microsomes, with isoenzymes cytochrome P450 (CYP)-3A4 and CYP1A1/2 found to play major roles in metabolism of crisaborole, while CYP2B6 and CYP2E1 were found to contribute to a minor extent.

Excretion of crisaborole following intravenous administration was predominantly via the urine in rats and humans, with a small amount also excreted in the faeces suggesting that biliary excretion is a minor route of elimination.

The pharmacokinetic profile of crisaborole was qualitatively similar in humans and the species used in toxicity studies (rodents and mini-pigs) and they are considered adequate to serve as appropriate models for toxicity.

Pharmacokinetic drug interactions

Crisaborole does not inhibit (either by competitive/reversible or metabolism dependent mechanisms) CYP1A2, 2B6, 2C8, 2C9, 2D6, and 3A4/5, and has weak activity against CYP2C8 (IC_{50} > 15 µM). Crisaborole was found to competitively inhibit CYP2C19 with a K_i of 8.96 µM and IC_{50} of 25.4 µM. Based on static modelling and pharmacokinetic data on systemic and portal vein concentrations of crisaborole obtained from a Phase I clinical study (Clinical Study AN2728-AD-102), clinically relevant drug-drug interactions due to 2C19 inhibition are unlikely to occur in patients who received a clinical dose of crisaborole ointment (2%).

Metabolite AN7602 did not inhibit any CYP enzymes in human liver microsomes, while AN8323 was a weak inhibitor of CYP1A2, and 2B6 and a moderate inhibitor of CYP2C8 and 2C9. Furthermore, AN8323 inhibited CYP2C8 in a competitive manner with a K_i of 6.7 µM, and 2C9 in a competitive and non-competitive manner with a K_i of 5.2 µM. Metabolism dependent inhibition of CYP enzymes was not evident. However, a clinical drug-drug interaction study (Clinical Study AN2728-PK-101) showed no interaction between crisaborole and warfarin, a known CYP2C9 substrate.

Treatment with crisaborole induced CYP2B6 enzyme activity (58.1% induction in one donor only, with < 40% for the other 3 donors) and messenger RNA (mRNA) expression (0.8 to 4.1 fold versus control). Crisaborole had no significant effect on CYP1A2, 2C9, 2C19 or 3A4/5 activity or mRNA expression.

The metabolite AN7602 was not an inducer of CYP enzymes in primary human hepatocytes, while AN8323 was a weak inducer of CYP1A but not CYP2B6 or 3A4/5. AN8323 was found to be a weak substrate for the uptake transporters organic anion

transporter (OAT)-1, OAT3, OATP1B1, and a strong substrate for efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). AN8323 was also found to be an inhibitor of OAT1, OAT3, OATP1B3, P-gp, and BCRP.

In conclusion, pharmacokinetic drug interactions involving transporters are not predicted. Crisaborole is not expected to alter exposures to CYP450 substrates.

Toxicology

Acute toxicity

A GLP compliant single dose toxicity study was conducted with crisaborole following intravenous dosing to dogs. Dosing of up to 5 mg/kg was well tolerated in dogs with no target organs for toxicity identified. The maximal non-lethal dose in dogs was 5 mg/kg (intravenous), the highest dose tested, indicating a low order of acute toxicity (23 times the clinical exposure based on C_{max}).

Repeat dose toxicity

Repeat dose toxicity studies were conducted in mice for up to 13 weeks duration, in rats for up to 6 months duration and mini-pigs for up to 9 months duration. The dosing regimen in pivotal GLP compliant studies in mice and mini-pig were via topical administration (applied once or twice daily), the proposed clinical route. Rats were dosed orally, in four GLP compliant studies and via subcutaneous injection in two non-GLP compliant studies. The choice of species (rats and mice, and mini-pig as the non-rodent species) is considered acceptable.

Relative exposure

Exposure ratios have been calculated based on daily exposures (that is, animal: human plasma AUC from dosing to 24 hours (AUC_{0-24h})). Human reference values are from Clinical Study AN2728-AD-102. The AUC data used for animals is the mean of male and females values on the last sampling occasion. Exposures were generally subclinical in mice, mini-pigs and juvenile rats, while exposure up to 26 times the clinical exposure was achieved in long term rat studies. Given the low margins, the toxicities below should all be considered as potentially clinically relevant.

Relative exposure for the metabolites AN7602 and AN8323 was high in long term studies in rats (> 8 at the no observed adverse effect level (NOAEL) of 450 mg/kg/day) and low in juvenile studies (relative exposure 0.4 and 0.04 for AN7602 and AN8323, respectively at the NOAEL of 50 mg/kg/day).

The following table (Table 2) describes the relative exposures in animals versus humans.

Table 2: Relative exposure in repeat dose toxicity, juvenile and carcinogenicity studies across species

Species	Study duration [Study no.]	Dose (mg/kg/day or %)	AUC0–24 h^ (ng·h/mL)	Exposure ratio#
Mouse (CD-1)	13 weeks [Pivotal] Study 003-NCL TX-035-01	0.3%	194	0.1
		2%	1565	0.8
		5%	3490	1.8

Species	Study duration [Study no.]	Dose (mg/kg/day or %)	AUC0–24 h^ (ng·h/mL)	Exposure ratio#
	13 weeks* [Pivotal] Study 003-NCL TX-045-01	2%	1601	0.8
		5%	3505	1.8
		7%	2800	1.5
	2 years [Carcinogenicity] Study 003-NCL TX-050-01	2%	320	0.2
		5%	1423	0.7
		7%	1975	1.0
Rat (Sprague-Dawley)	4 weeks Study 003-NCL TX-021-01	50; PO	692	0.4
		150; PO	1585	0.8
		400; PO	16740	8.8
		1000; PO	49300	26
	13 weeks Study 003-NCL TX-034-01	50; PO	1148	0.6
		150; PO	4330	2.3
		300; PO	15300	8.1
		600; PO	42750	22.5
	6 months [Pivotal] Study 003-NCL TX-052-01	50; PO	793	0.4
		150; PO	2645	1.4
		450; PO	14650	7.7
	2 years [carcinogenicity] Study 003-NCL TX-049-01	30; PO	149	0.1
		100; PO	872	0.5
		300; PO	4385	2.3
	4 weeks [Juvenile] Study 003- NCL TX-055-01	15; PO	3990	2
		50; PO	17300	9
		150; PO	47650	25
	4 weeks [Juvenile]	15; PO	532	0.3
		50; PO	6420	3.4

Species	Study duration [Study no.]	Dose (mg/kg/day or %)	AUC0–24 h^ (ng·h/mL)	Exposure ratio#
	Study 20093673 (16GR400)	100; PO	16550	8.7
Mini-pig (Göttingen)	4 weeks Study 003-NCL TX-025-01	0.3%	245	0.1
		2%	1490	0.8
		5%	3250	1.7
	3 months* Study 003-NCL TX-043-01	0.5%	705	0.4
		2%	966	0.5
		5%	1390	0.7
	9 months* [Pivotal] Study 003-NCL TX-051-01	2%	685	0.4
		5%	1018	05
		7%	984	0.5
	4 weeks* [Juvenile] Study 003-NCL TX-054-01	2%	275	0.1
		5%	303	0.2
		7%	302	0.2
Human (patients; age 2 to 17 y)	steady state [Study AN2728-AD-102]	[2%]	1898a	–

= animal:human plasma $AUC_{0-24\ h}$; ^ = data are for the sexes combined at the last sampling occasion; = twice daily application. [a] calculated at AUC_{0-12h} x2 to account for twice daily application (949 x 2 = 1898).

Major toxicities

Crisaborole was well tolerated in repeat dose toxicity studies following dermal dosing up to 7% w/w to mice and mini-pigs. No crisaborole related mortality, morbidity or clinical signs were observed in mice, while two mini-pigs treated with 5% crisaborole and one control (Cream B vehicle) animal were euthanised *in extremis* due to severe skin irritation. Prior to death, these animals showed reduced activity, red discoloured skin and scabbing at test site, skin warm to touch, low carriage, hypersensitive to touch and vocalisation. Clinical signs in surviving animals included transient incidences of decreased activity and an increased incidence of red discoloured skin.

In mice, no remarkable adverse effects on body weight, food consumption, body temperature or clinical pathology parameters were observed following topical crisaborole administration. There were also no crisaborole related findings in ophthalmoscopic and physical examinations. Post mortem examinations revealed no crisaborole related macroscopic observations or adverse effects on organ weights. Increased weight of the liver and spleen were noted in the 2 week study in mice at a dose of 5%, however, these

changes were not observed in 13 week studies at a dose of 7% and no corresponding histopathology was observed. In mini-pigs treated topically for 3 months with crisaborole ointment B, haematology and clinical chemistry analysis showed a few changes in clinical pathology parameters including increased urea, decreased aspartate aminotransferase and triglycerides and decreased lymphocytes, monocytes and basophils compared to controls. No histological correlations were observed for these changes and therefore they were not considered to be toxicologically relevant. Observed increases in kidney and thyroid weight and a decrease in adrenal weight were resolved following the recovery period and were not associated with any histological correlates. No changes in gross pathology or histopathology were observed.

In 2 and 4 week studies with crisaborole Ointment C and Cream B formulations at doses up to 5%, there was an increase in heart rate and a shortening of QTc in all groups compared to pre-test values; however, there were no differences in ECG parameters in treated groups compared to the vehicle control. Increased alanine aminotransferase and total bilirubin levels and decreased cholesterol levels observed in animals dosed at 5% could not be correlated with changes in organ weight or histopathology. Increased lymphocytes were observed in males dosed at 5%; however, this was not observed in female animals and is not considered to be toxicologically relevant.

Histopathological changes following topical dosing in mice and mini-pigs included mild to moderate epidermal hyperplasia, hyperkeratosis, perivascular infiltration and acute inflammation of the skin. The incidence and severity of these microscopic findings were similar among all groups, and therefore the changes were considered to be vehicle related. Epidermal necrosis of treated skin was also observed in two euthanised mini-pigs dosed at 5%.

Dermal irritation

In 2 and 4 week studies in mini-pigs with crisaborole Ointment C and Cream B formulations at doses up to 5% crisaborole, two animals dosed at 5% (Cream B) and 1 control (Cream B vehicle) animal were euthanised in extremis on Days 8 and 13, respectively, due to severe skin irritation. In surviving animals, dermal irritation was noted in all animals, including controls, with the incidence of moderate to severe erythema and /or oedema increased at doses of 2% and 5%. At these dose levels, animals also displayed decreased activity and red discoloured skin. Due to the severity of the dermal irritation in animals dosed at 2 and 5%, treatment was suspended in animals with moderate to severe dermal irritation until the application site had improved (very slight to well defined erythema and/or oedema). Similarly, in 3 and 9 month studies in mini-pigs, dermal irritation was observed in all groups including control and consisted of mild to severe erythema, with or without oedema, throughout the treatment and recovery periods. Dermal lesions improved over time and were not considered to be adverse by the study author. However, the dermal irritation was not completely resolved by the end of the study period and was at times severe in nature. Therefore, dermal irritation is considered to be related to treatment with crisaborole and/or the formulation vehicle.

While dermal irritation was not observed in mice treated with up to 5% Cream B formulation for 13 weeks, however mild to moderate erythema was observed in all treated animals in a 2 week study, with an increased incidence at the high dose of 5%.

Systemic exposure

In oral studies in rats for up to 6 months, no systemic toxicity and no target organ toxicity was identified at doses up to 450 mg/kg/day.

In 4 and 13 week oral studies in rats, 13 males dosed at 1000 mg/kg/day died or were euthanised *in extremis* between Days 4 and 10. These animals showed decreased activity, breathing abnormalities, material around the nose, eyes and mouth, cold to touch,

unkempt appearance, hunched posture, impaired righting reflex, salivation and piloerection. Microscopic findings were observed in the heart and in organs such as the adrenal gland, bone marrow depletion, stomach ulcers, and lymphoid depletion indicating stress. At this dose, animals had decreased mean erythrocyte numbers, haemoglobin, haematocrit, and increased reticulocyte numbers relative to control animals. These haematological changes were within normal clinical ranges and suggest mild blood loss with a regenerative response and inflammation. Decreased sodium and chloride levels were also observed in females, which are suggestive of a loss of body fluids and may be associated with mild blood loss. All haematology and clinical chemistry changes resolved in females during the recovery period. At lower doses, changes in haematology (decreased erythrocytes, haemoglobin, and haematocrit at 300 and 600 mg/kg/day) and clinical chemistry (increase in alkaline phosphatase, creatinine and total bilirubin at 600 mg/kg/day) parameters were observed, with most resolving during the recovery period.

A dose dependent increase in liver weights was observed in both sexes at doses of ≥ 300 mg/kg/day, with corresponding panlobular hepatocellular hypertrophy observed in these animals. This finding is considered to be a pharmacologically adaptive response resulting from the induction of metabolising enzymes within hepatocytes and is not considered adverse. The observed decrease in thymus weights in females at doses of 1000 mg/kg/day showed no histopathological correlation. An increase in kidney weight was noted in males at 300 and 600 mg/kg/day and in females at 600 mg/kg/day, which was not observed at higher doses. In addition, there was no histopathological correlation for the increase in kidney weight and this effect resolved during the recovery period. A decrease in ovary weight and a decrease in the number of *corpus lutea* were noted in females at 600 mg/kg/day during the treatment period and at the end of the recovery phase. These effects were not observed at higher doses or in reproductive toxicity studies at this dose, and therefore the toxicological relevance of this are unknown. Subacute inflammation of the heart, with or without myofiber degeneration/necrosis was observed in males that died or were euthanised *in extremis* during the study and was considered to be treatment related. Other histopathological changes in males dosed at 1000 mg/kg/day included hypertrophy/hyperplasia of the adrenal gland, bone marrow depletion, erosion/ulceration in the glandular stomach. These changes are considered to be secondary to stress. Adenocarcinoma of the mammary gland was observed in one female at 1000 mg/kg/day; however, as this was present in only one animal and similar findings were not observed in any other repeat dose study in rats, this was considered to be spontaneous and not treatment related (relative exposure 26).

Overall, the repeat dose toxicity studies did not identify any target organs of toxicity that would have clinical relevance at the systemic exposures anticipated for the proposed indication.

Genotoxicity

The genotoxic potential of crisaborole was assessed in a bacterial mutagenesis assay, in an *in vitro* clastogenicity study in human peripheral blood lymphocytes, and an *in vivo* rat micronucleus study. All assays were appropriately validated and conducted under GLP conditions. Negative results were obtained in all assays. Crisaborole was not mutagenic to bacterial cells, did not cause chromosomal aberrations in human peripheral blood lymphocytes or in the rat micronucleus test.

Carcinogenicity

Two carcinogenicity studies were submitted: a 2 year oral study in rats and a 2 year dermal study in mice. The high dose in the mouse dermal study was 7% (w/w) which is the maximum strength that can be achieved for the ointment formulation. The high dose in

the rat oral study was 300 mg/kg/day. The high doses selected for these studies were well tolerated, with no treatment related effects on mortality or bodyweight. Overall, the high dose was considered adequate, and the study design and conduct was consistent with the relevant ICH guidelines (S1A, S1B and S1C (R2)).[13]

Crisaborole was not carcinogenic in mice that received daily dermal doses of up to 7% (w/w) per day crisaborole ointment for 104 weeks (relative exposure 1.0).

There was a treatment related increase in the incidence of benign granular cell tumours in the uterus with cervix or vagina combined, in female rats dosed at 300 mg/kg/day (relative exposure 2.3) (tumour incidence rate: 9.38%, 9.23%, 6.15% and 29.23% for vehicle control, low, mid and high doses, respectively). The incidence of this tumour type in high dose females was outside the historical control range for this laboratory (23.33%). These data indicate that crisaborole may be carcinogenic in rats. However, these findings are unlikely to be of clinical relevance for the proposed indication due to relatively low systemic exposures.

Reproductive toxicity

The effects of oral crisaborole on male and female fertility, embryofetal development (non-GLP) and pre-/postnatal development were investigated in Sprague-Dawley rats, with embryofetal development studies also conducted in New Zealand white rabbits. In the fertility study, crisaborole was administered to male rats for 4 weeks prior to mating which is appropriate. Female rats received crisaborole from 2 weeks prior to mating through to gestation day (GD) 7. In the embryofetal development studies, rats and rabbits were dosed during the period of organogenesis, GD7 to 17 in rats and GD7 to 19 in rabbits. In the pre-/postnatal development study, rats were dosed from implantation through to the end of lactation. Overall, the range, design and conduct of studies were consistent with the relevant ICH guideline (S5(R2)).[14]

Relative exposure

The following table describes the relative exposures in animals versus humans (Table 3).

Table3: Relative exposure in reproductive toxicity studies

Species	Study [Study no.]	Dose (mg/kg/day)	AUC0–24 h (ng·h/mL)	Exposure ratio#
Rat (Sprague-Dawley)	Embryofetal development [Study 003-NCL TX-046-01]	150	1740	0.9
		300	6270	3.3
		600	24000	12.6
Rabbit (NZW)	Embryofetal development [Study 003-NCL TX-047-01]	25	1080	0.6
		50	1630	0.9

[13] International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. Guideline on the need for carcinogenicity studies of pharmaceuticals S1A, November 1995; Guideline on testing for carcinogenicity of pharmaceuticals S1B, July 1997; Guideline on dose selection for carcinogenicity studies of pharmaceuticals S1C (R2), March 2008.
[14] International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. (2000) Detection of toxicity to reproduction for medicinal products and toxicity to male fertility S5(R2), November 2000.

Species	Study [Study no.]	Dose (mg/kg/day)	AUC0–24 h (ng·h/mL)	Exposure ratio#
		100	4070	2.1
	Embryofetal development [Study 003-NCL TX-053-01]	50	3120	1.6
		150	7380	3.9
		450	2510	1.3
Human (patients; age 2 to 17 y)	steady state [Study AN2728-AD-102]	[2%]	1898	–

= animal:human plasma $AUC_{0-24\,h}$

Maximum relative exposures were low in embryofetal development studies in rats and rabbits. Studies of placental transfer and excretion into milk of crisaborole were not submitted.

There was no effect on male or female fertility in rats at doses up to 600 mg/kg/day (relative exposure 12.6).

In an embryofetal development study in rats at oral doses up to 600 mg/kg/day, there was a dose dependent reduction in foetal bodyweight (12%). The reduction in foetal bodyweight was associated with an increase in the incidence of skeletal variations at 600 mg/kg/day. These included incomplete ossification of the arches of the cervical and lumbar vertebrae, incomplete ossification of the pelvic bones and reduced numbers of ossified caudals, sternal centres, metacarpals, metatarsals and forepaw and hindpaw phalanges. These effects occurred at a dose that resulted in maternal toxicity (decreased maternal bodyweight, food consumption and faecal changes). Exposures at the NOAEL for embryofetal toxicity (300 mg/kg/day) were low compared to the clinical exposure (relative exposure 3.3).

Crisaborole was not teratogenic in rabbits that were dosed daily during the period of organogenesis with doses up to 100 mg/kg/day (relative exposure 2.1). In a dose range finding study in rabbits at doses of up to 450 mg/kg/day, increased pre- and post-implantation loss, late resorptions, and increased male to female sex ratio were observed at a dose that caused maternal toxicity (150 mg/kg/day; relative exposure 3.9).

In a pre-/postnatal development study in rats, maternal toxicity was observed at an oral dose of 600 mg/kg/day (the highest dose tested; relative exposure 12.6). This included litter loss (1 dam), decreased bodyweight (~91% of control) and food consumption during gestation and lactation. At this dose, pup survival was significantly reduced, with an increase in the number of still born pups and an increase in the number of pups found dead or missing (presumed cannibalised) during the period (included 1 entire litter of pups found dead on lactation day 1). There was a significant reduction in pup weight during the first week of lactation (14 to 16% lower than controls) and a reduction in food consumption (11 to 16%). Based on these results, the NOAEL for maternal toxicity was 300 mg/kg/day (relative exposure 3.3). Postweaning, there were no treatment related deaths in the first filial generation. Treatment related effects included decreased bodyweight during the postweaning period, reduced bodyweight gain during gestation (GD 8 to 21 and 0 to 21, 93% of control on GD 21) and reduced food consumption during the postweaning and gestation at 600 mg/kg/day (maternal dose). No treatment related changes in sexual maturation, neurological parameters, reproductive parameters or at

caesarean section were noted. Thus, the offspring NOAEL was 300 mg/kg/day (relative exposure 3.3).

Pregnancy classification

The sponsor has proposed Pregnancy Category B1. This category is for drugs which studies in animals have not shown evidence of an increased occurrence of fetal damage. This is considered acceptable.[15]

Local tolerance

The local tolerance of crisaborole was assessed in repeat dose toxicity studies as well as in three GLP compliant studies. In dermal irritation studies, 2% crisaborole cream B formulation was classified as a slight irritant with very slight erythema observed in all animals up to Day 8 of the study. No differences were observed between intact and abraded skin or between vehicle and crisaborole treated animals. In repeat dose studies, topical application of crisaborole formulations resulted in dermal irritation (mild to severe, with or without oedema) throughout the treatment and recovery periods. This was considered to be related to treatment with crisaborole and/or the vehicle. In clinical studies, minimal skin irritation was observed when 2% crisaborole was applied to healthy human skin. No skin sensitisation was observed. Overall the available data indicated that crisaborole may cause local dermal irritation.

Slight conjunctival redness was observed in two rabbits 1 hour after application of 2% crisaborole cream formulation to the eye. Redness had resolved by 24 hours. While the formulation used in the irritation studies (cream formulation) differed from the proposed ointment formulation, the available evidence indicates a potential for the proposed clinical formulation of crisaborole to cause mild ocular irritation.

Antigenicity

The skin sensitisation potential of crisaborole (1, 5 and 10% w/v) was examined in mice using the local lymph node assay. Stimulation indices (SI) indicated that crisaborole at concentrations up to 10% w/v did not cause skin sensitisation (SI < 3). However, the clinical formulation was not tested.

Immunotoxicity

No immunotoxicity studies were submitted.

Phototoxicity

Phototoxicity studies were not conducted using crisaborole. This is acceptable as no components of the drug product absorbed light between 290 to 700 nm, which indicate crisaborole is unlikely to be photoreactive.

Metabolites

No dedicated toxicity studies were performed with the two main oxidative metabolites of crisaborole, AN7602 and AN8323 however these metabolites were quantified in the plasma of rats and mini-pigs repeat dose toxicity studies following dermal and oral dosing. AN7602 was found in very low amounts in the systemic circulation, likely due to its rapid

[15]Australian Pregnancy Category B1: Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

conversion to AN8323, which is found in much higher concentrations. As described above, pharmacology studies demonstrated that AN7602 and AN8323 were inactive against PDE4 (IC_{50} > 100 μM).

Impurities

All potential specified and unspecified impurities in the drug substance and the drug product at the maximum potential human dose have been adequately qualified.

Paediatric use

Crisaborole is proposed for patients aged 2 years and older. The toxicity of crisaborole in juvenile animals was assessed in three GLP compliant studies in juvenile rats (oral administration) and mini-pigs (topical administration).

In juvenile rats (postnatal day (PND) 7 to 35 or PND 21 to 48) treated orally with crisaborole at doses up to 300 mg/kg/day for 1 day and 150 mg/kg/day for 4 weeks, a number of effects were observed at this high dose, including death of one animal of each sex on Day 3 to 4 of dosing, clinical signs including ptosis, mild dehydration and decreased motor activity, and decreased bodyweight (up to 17.6% on PND 21 to 28).

Some haematology and clinical chemistry changes observed at doses of 50 and 100 mg/kg/day (decreased glucose, increased triglycerides and lymphocytes) were not observed at higher doses (300/150 mg/kg/day) and are therefore unlikely to be clinically relevant. There was a decrease in pituitary weight and an increase in the weight of the uterus at 300/150 mg/kg/day, however there were no pathological correlates and thus these changes are not considered to be treatment related. There were no treatment related effects on gross pathology, histopathology or neurological function at doses up to 300/150 mg/kg/day. The NOAEL in juvenile rats was considered to be 100/50 mg/kg/day (relative exposure 9).

In juvenile mini-pigs (7 weeks old) treated topically with crisaborole ointment (up to 7% w/w) twice daily, there were no treatment related effects on mortality, clinical signs, bodyweight, clinical chemistry organ weights or histopathology. Dermal irritation was not observed at the treatment site. An increase in neutrophils and a decrease in eosinophils were observed in males at 7%; however, there was no toxicological relevance to these findings. The NOAEL in juvenile mini-pigs was 7% (relative exposure 0.2).

Nonclinical summary and conclusions

Summary

- The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of pharmaceuticals (ICH M3(R2)).[8] The overall quality of the nonclinical dossier was high. All pivotal safety related studies were GLP compliant.
- *In vitro*, crisaborole bound the PDE4 receptor with nanomolar affinity in a cAMP competitive manner and inhibited the PDE4 receptor with IC_{50} values of 0.11 to 0.49 μM. Less potent inhibition was observed for other PDE isotypes. Crisaborole inhibits the secretion of pro-inflammatory cytokines, in particular TNFα, IL-2, IFNγ, IL-4 and IL-5. Crisaborole metabolites, AN7602 and AN8323, had no inhibitory activity on PDE4 and had no effect on cytokine secretion. *In vivo*, crisaborole inhibited PMA induced ear swelling in the mouse model of skin inflammation and oxazolone induced sensitisation in the mouse model of delayed type hypersensitivity supporting the proposed clinical indication.

- Crisaborole also had inhibitory activity against prostaglandin E2 (PGE2) *in vitro* and suppress the secretion of MCP-1. Crisaborole had no effect on collagen induced arthritis in mice and had limited antimicrobial or antifungal activity. The known emetic effect of PDE4 inhibitors is not expected due to the low systemic exposures achieved following topical dosing of crisaborole.
- Safety pharmacology studies assessed effects on the cardiovascular and central nervous systems. No adverse effects were seen on CNS function in rats or cardiovascular function in rats and dogs. No significant inhibition of hERG K+ channel tail current was observed at clinically relevant concentrations.
- Overall, the pharmacokinetic profile in animals was qualitatively similar to that of humans. Crisaborole was readily and rapidly absorbed with a similar T_{max} in all species. Dermal application at concentrations up to 7% in mice and mini-pigs resulted in low levels of systemic exposure to crisaborole. Plasma protein binding of crisaborole and its metabolites was high all animal species and humans. Tissue distribution of crisaborole was rapid and wide but penetration into brain, spinal cord and reproductive organs was limited. The main human metabolite (AN8323) was also a significant metabolite in animals. Drug related material was excreted predominately via urine in rats and humans, with a small amount also excreted via the faeces. Secondary pharmacodynamics studies show that crisaborole has low potential for off target binding.
- Based on *in vitro* studies, crisaborole has weak inhibitory activity against CYP2C8 and competitively inhibits CYP2C19 however modelling data shows that clinically relevant drug-drug interactions would be unlikely. Metabolite AN7602 did not inhibit any CYP enzymes in human liver microsomes, while AN8323 was a weak inhibitor of CYP1A2, and 2B6 and a moderate inhibitor of CYP2C8 and 2C9. Clinical drug-drug interaction studies showed no interaction between crisaborole and the known CYP2C9 substrate, warfarin. AN8323 was found to be a weak substrate for uptake transporters OAT1, OAT3, OATP1B1, and a strong substrate for efflux transporters P-gp and BCRP. AN8323 was also found to be an inhibitor of OAT1, OAT3, OATP1B3, P-gp, and BCRP.
- Crisaborole had a low order of acute oral toxicity in rats and dogs.
- Repeat dose toxicity studies by the topical route were conducted in mice (up to 2 years) and mini-pigs (up to 9 months) and by the oral route in rats (up to 2 years). Maximum exposures (AUC) were subclinical to low in mice, mini-pigs and juvenile rats, while slightly higher exposures were achieved in rat studies. No target organs for toxicity were identified and treatment related effects confined to local irritation following topical dosing.
- Crisaborole was not mutagenic in a bacterial reverse mutation assay, was not clastogenic in *in vitro* chromosome aberration test or in an *in vivo* rat micronucleus test. Two carcinogenicity studies were submitted: a 2 year oral study in rats and a 2 year dermal study in mice. Crisaborole was not carcinogenic in mice at topical doses up to 7%. In female rats dosed orally at 300 mg/kg/day, there was a treatment related increase in the incidence of benign granular cell tumours in the uterus with cervix or vagina combined (tumour incidence rate: 29.23%). These data indicate that crisaborole is carcinogenic in rats. However, these findings are unlikely to be of clinical relevance for the proposed indication due to relatively low systemic exposures.
- Fertility was unaffected in male and female rats treated with crisaborole at exposure levels 12.6 times the clinical AUC (600 mg/kg/day). Reduced foetal bodyweight and increased incidence of skeletal variations were observed in rats at the maternotoxic dose of 600 mg/kg/day (12.6 times the clinical AUC). Lower birth weight, reduced pup survival and still births, were evident in pups of rats treated with crisaborole during pregnancy and lactation, again at maternotoxic doses.

- Toxicity in juvenile animals was examined in repeat dose studies in juvenile mini-pigs (topical dosing) and rats (oral dosing). There are no specific concerns (that is, beyond those raised in the core repeat dose toxicity studies) for the paediatric use of crisaborole compared to use in adults.
- In local tolerance studies, mild to severe erythema, with or without oedema were observed in most groups throughout the treatment period. This was considered to be related to treatment with crisaborole and/or the vehicle. No skin sensitisation was observed. A 2% crisaborole formulation caused mild ocular irritation in rabbits (resolved within 24 hours).
- The proposed limits for a number of impurities in the drug substance and drug product have been adequately qualified by the submitted toxicity data.

Conclusions and recommendation

There were no deficiencies in nonclinical data.

Primary pharmacology studies provided sufficient evidence of crisaborole's affinity and selectivity for human PDE4, as well the inhibition of pro-inflammatory cytokine secretion. This supports the sponsors proposed indication.

Treatment related effects associated with topical dosing of crisaborole were minimal and limited local irritation following topical dosing. Minimal skin irritation was also observed in clinical studies following topical application of 2% crisaborole.

The available data indicate that crisaborole does not pose a genotoxic or carcinogenic risk.

Pregnancy Category B1 is considered appropriate.[15]

There are no nonclinical objections to the registration of 2% crisaborole for the proposed indication.

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

Information on the condition being treated

Atopic dermatitis (AD), often referred to as 'eczema', is a chronic inflammatory condition of the skin. It is characterised by dryness of the skin (xerosis), itching (pruritus) and in more severe conditions inflamed, red and weeping lesions.

Current treatment options

The current treatment options for AD are:

- Topical treatments:
  - emollients
  - topical corticosteroids (TCSs)
  - topical calcineurin inhibitors (TCIs): tacrolimus, pimecrolimus.
- Systemic treatments:
  - oral corticosteroids

  - ciclosporin
  - methotrexate
  - azathioprine.
- Adjunctive treatments
  - antibiotics (anti-staphylococcal) are used for infected lesions
  - antivirals (acyclovir) are used for herpetic lesions
  - antihistamines for itch

Clinical rationale

The sponsor states, with particular reference to TCSs and TCIs:

> '…these approved products carry significant risks, particularly in the setting of prolonged or long term use which is often necessary for AD disease management. Consequently, there is unmet medical need for a safe and efficacious topical treatment for AD, a serious condition for which no new drugs have been approved in more than a decade'.

However, in the opinion of the clinical evaluator (at the first round of evaluation): crisaborole has not been developed as an alternative to TCS or TCIs, and the clinical rationale for crisaborole is actually for the development of a safe and efficacious adjunctive treatment for AD, in order to improve the management of a chronic condition with significant burden.

Formulation

The formulation used in the clinical trials appears to be the same as that proposed for marketing. The dosage and instructions in the application are consistent with those used in the clinical trials. The patient population included in the indication is consistent with the patient population in the clinical trials.

It is not clear from the background information whether, in addition to being a new chemical entity, crisaborole is also first in class. Apremilast is a PDE4 inhibitor approved by the TGA and the FDA that has been developed for the systemic treatment of psoriatic arthritis and plaque psoriasis. Roflumilast has been approved by the EMA and FDA for the treatment of chronic obstructive pulmonary disease, but an application for approval by the TGA was withdrawn. Ibudilast has been approved in Japan for the treatment of asthma. However, use of PDE4 inhibitors for AD does not appear to have been previously approved by the TGA.

The place in treatment of crisaborole is not clear. It is not clear whether crisaborole would be used as monotherapy or as part of a multimodal regimen. No studies have been performed where crisaborole is part of a multimodal regimen. Although the sponsor proposes crisaborole to be an alternative to TCS and/or TCI, no comparator studies have been performed. Hence, crisaborole has not been tested in the context of a treatment regimen that a patient in Australia with AD would be expected to use.

Guidance

The regulatory guidance that applies to the present application includes:

- Note for guidance on the clinical evaluation of QT/QTc interval prolongation and pro-arrhythmic potential for non-antiarrhythmic drugs (CHMP/ICH/2/04)

- Note for guidance on population exposure: the extent of population exposure to assess clinical safety (CPMP/ICH/375/95)
- Note for guidance on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99).

Contents of the clinical dossier

The dossier contained efficacy and safety data for crisaborole for the indication of AD and in addition safety data in patients with psoriasis.

The dossier contained the following studies and reports:

- Pharmacokinetics:
  - Study AN2728-PSR-105
  - Study AN2898-PSR-102
  - Study AN2728-PSR-104
  - Study AN2728-PK-101
  - Study AN2728-AD-102
  - Study AN2728-TQT-108
  - Study AN2728-AD-203
  - Study AN2728-PSR-106.
- Dermal tolerability:
  - Study AN2898-PSR-102
  - Study AN2728-PSR-107
  - Study AN2728-RIPT-101.
- Two additional Phase II studies:
  - Study AN2898-AD-202
  - Study AN2728-AD-204
- Two Phase III efficacy studies:
  - Study AN2728-AD-301
  - Study AN2728-AD-302.
- One long term follow-on study:
  - Study AN2728-AD-303.
- Eight studies evaluable for safety only, conducted in patients with psoriasis:
  - Study AN2728-PSR-101
  - Study AN2728-PSR-102
  - Study AN2728-PSR-103
  - Study AN2898-PSR-103
  - Study AN2728-PSR-201
  - Study AN2728-PSR-202
  - Study AN2728-PSR-203

  - Study AN2728-PSR-204.
- In addition, the dossier included an Integrated Summary of Efficacy, Integrated Summary of Safety, a Combined Cardiovascular Report, and a Combined Pruritus Report.

Paediatric data

The dossier contains data for children aged 2 to 17 years.

The sponsor has an agreed Pediatric Plan under the Pediatric Research Equity Act (PREA) in the USA. The sponsor has a waiver from having to conduct a paediatric assessment in children < 3 months of age. A trial in children aged 3 months to < 2 years is planned.

Good clinical practice

The studies submitted in the dossier were all stated to have been, and appeared to have been, conducted according to Good Clinical Practice (GCP).

Evaluator's commentary on the clinical dossier

The data presented in the submission represent a development program for crisaborole as monotherapy in patients aged ≥ 2 years with mild to moderate AD. The dossier does not contain studies using TCS and/or TCI as comparator. The dossier does not contain photosensitisation studies. The sponsor states that 'based on the absorption spectra of the drug substance and excipients, phototoxicity and photoallergenicity trials were not required by FDA'.

Pharmacokinetics

Studies providing pharmacokinetic data

A list of the studies that provided pharmacokinetic information is given in Table 4 below.

Table 4: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID
PK in healthy adults	General PK (single dose)	Study AN2728-PSR-105
	General PK (multi-dose)	Study AN2728-PSR-104
		Study AN2898-PSR-102
		Study AN2728-TQT-108
		Study AN2728-AD-203
PK in special populations	Children/adolescents	Study AN2728-AD-102
	Other special population: psoriasis	Study AN2728-PSR-106
PK interactions	Warfarin	Study AN2728-PK-101

Evaluator's conclusions on pharmacokinetics

Applied topically, a significant proportion of the dose (25%) is absorbed systemically. Systemically absorbed crisaborole is rapidly metabolised to AN7602 and AN8323. There was no significant accumulation of AN7602 but the accumulation ratio for AN8323 was approximately 4. Hence the main exposure following topical application of crisaborole is to AN8323.

In children and adolescents, metabolism of crisaborole and clearance of AN7602 and AN8323 appear to be increased.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 5, shown below, lists the studies relating to each pharmacodynamics (PD) topic.

Table 5: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on PD parameter A	Not applicable
Secondary Pharmacology	Effect on tolerability	Study AN2728-PSR-107
		Study AN2728-RIPT-101
		Study AN2728-AD-203
	Effect on QTcF	Study AN2728-TQT-108
PD Interactions	Warfarin	Study AN2728-PK-101

‡ = and adolescents, if applicable.

Evaluator's conclusions on pharmacodynamics

The dossier contained limited PD data and there were no PK/PD data. However, crisaborole is intended for topical administration and there would be technical difficulties in performing PK/PD studies.

The dermal tolerability studies were supportive for crisaborole and there was no indication of sensitisation.

The thorough QT study did not indicate any QT prolongation with supratherapeutic topical crisaborole treatment.

There was no clinically significant PD interaction with warfarin.

Dosage selection for the pivotal studies

Pharmacokinetics and pharmacodynamics: dose finding studies

The PK and PD studies indicated good dermal tolerability for the crisaborole 2% ointment formulation.

Phase II dose finding studies

Study AN2728-AD-204 examined crisaborole 2% ointment and crisaborole 0.5% ointment, either once or twice daily. The change from Baseline in Atopic Dermatitis Severity Index (ADSI) was greatest with crisaborole 2% twice daily: mean (SD) change 4.47 (3.185) for 0.5% once daily, 5.07 (2.214) for 2% once daily, 5.06 (2.361) for 0.5% twice daily and 5.81 (1.714) for 2% twice daily (Table 6). Benefit was apparent from Day 8 (Figure 3). The least squares (LS) mean (95% CI) difference, crisaborole 2% twice daily to crisaborole 2% once daily was 0.74 (–0.10 to 1.58). The LS mean (95% CI) difference, crisaborole 2% twice daily to crisaborole 0.5% twice daily was 0.75 (0.05 to 1.45). The proportion of patients with a greater decrease in ASDI score favoured crisaborole 2%, either once or twice daily (Table 7). In all the component subscores, the greatest improvement was with the 2% twice daily treatment.

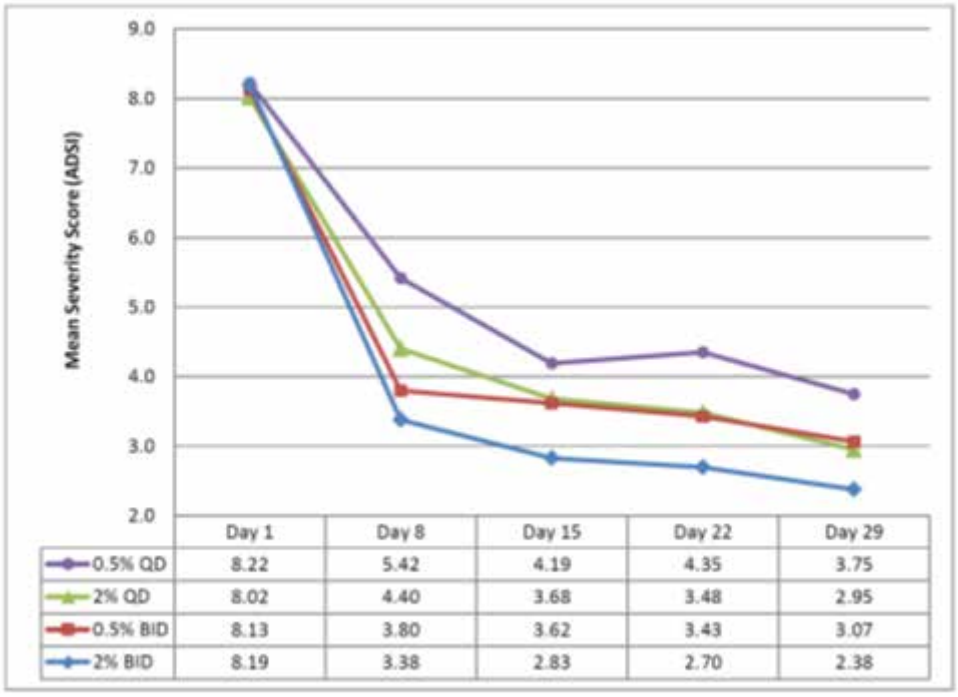
Table 6: Summary and improvement from Baseline in ADSI score for target lesions (ITT population)

	QD (N=44)				BID (N=42)			
	AN2728, 0.5%		AN2728, 2%		AN2728, 0.5%		AN2728, 2%	
Study Day Parameter	Score	Improvement From Baseline*	Score	Improvement From Baseline*	Score	Improvement From Baseline*	Score	Improvement From Baseline*
Baseline								
Mean	8.22		8.02		8.13		8.19	
SD	1.891		1.852		1.811		1.811	
Median	8.00		8.00		7.50		8.00	
Min, Max	5.5, 13.5		5.5, 14.0		6.0, 13.0		6.0, 12.0	
Day 8								
Mean	5.42	2.80	4.40	3.63	3.80	4.33	3.38	4.81
SD	2.538	2.431	1.993	1.695	2.156	2.208	1.860	1.972
Median	5.25	2.50	4.50	3.50	3.75	4.25	3.50	5.00
Min, Max	0.0, 10.0	-2.0, 9.0	0.0, 9.5	0.0, 7.0	0.0, 9.0	0.0, 9.0	0.0, 8.5	0.5, 9.0
Day 15								
Mean	4.19	4.02	3.68	4.34	3.62	4.51	2.83	5.36
SD	2.752	2.781	2.382	2.394	2.804	2.400	2.431	2.028
Median	4.00	4.00	3.25	4.25	3.25	4.50	2.00	5.50
Min, Max	0.0, 10.0	-1.0, 12.0	0.0, 9.0	-1.0, 8.5	0.0, 12.5	-1.0, 9.0	0.0, 10.0	1.5, 9.0
Day 22								
Mean	4.35	3.86	3.48	4.55	3.43	4.70	2.70	5.49
SD	3.108	3.157	2.841	2.551	2.617	2.271	2.417	1.803
Median	4.00	3.75	3.00	5.00	3.00	5.25	2.25	5.50
Min, Max	0.0, 13.0	-4.5, 13.0	0.0, 12.5	-4.0, 8.0	0.5, 11.0	0.5, 9.5	0.0, 11.0	1.0, 9.0
Day 29								
Mean	3.75	4.47	2.95	5.07	3.07	5.06	2.38	5.81
SD	3.081	3.185	2.107	2.214	2.834	2.361	2.358	1.714
Median	3.00	4.50	3.00	5.25	2.25	5.75	1.75	6.00
Min, Max	0.0, 12.5	-5.0, 13.0	0.0, 8.0	-0.5, 9.0	0.0, 10.5	-1.0, 9.0	0.0, 7.5	2.0, 9.0

BID, twice daily; max, maximum; min, minimum; QD, once daily; SD, standard deviation.

* Calculated as Baseline score minus follow-up score

Figure 3: Decrease in mean ADSI scores for target lesions over time (ITT population)



	Day 1	Day 8	Day 15	Day 22	Day 29
0.5% QD	8.22	5.42	4.19	4.35	3.75
2% QD	8.02	4.40	3.68	3.48	2.95
0.5% BID	8.13	3.80	3.62	3.43	3.07
2% BID	8.19	3.38	2.83	2.70	2.38

Table 7: Summary and improvement from Baseline in ADSI score; Summary of drug concentrations within each dosing frequency (ITT population)

	QD (N=44) n (%)			BID (N=42) n (%)		
Visit	Greater Decrease in ADSI Score AN2728, 0.5%	Greater Decrease in ADSI Score AN2728, 2%	Equal Decrease in ADSI Score Both Treated Lesions	Greater Decrease in ADSI Score AN2728, 0.5%	Greater Decrease in ADSI Score AN2728, 2%	Equal Decrease in ADSI Score Both Treated Lesions
Day 8	10 (22.7%)	25 (56.8%)	9 (20.5%)	10 (23.8%)	19 (45.2%)	13 (31.0%)
Day 15	14 (31.8%)	20 (45.5%)	10 (22.7%)	12 (28.6%)	21 (50.0%)	9 (21.4%)
Day 22	11 (25.0%)	24 (54.5%)	9 (20.5%)	12 (28.6%)	21 (50.0%)	9 (21.4%)
Day 29	13 (29.5%)	25 (56.8%)	6 (13.6%)	13 (31.0%)	22 (52.4%)	7 (16.7%)

ADSI, Atopic Dermatitis Severity Index; BID, twice daily; QD, once

Phase III pivotal studies investigating more than one dose regimen

The Phase III pivotal studies examined only one dosing regimen.

Evaluator's conclusions on dose finding for the pivotal studies

There were limited dose finding studies performed in patients with AD. These studies compared the 0.5% and 2% formulations and indicated greater efficacy for the 2% formulation; and greater efficacy for twice daily application compared to once daily. Studies were performed in patients with psoriasis with a 5% formulation that indicated better tolerability with the 2% formulation. This may have influenced the sponsor's choice of the 2% formulation.

Efficacy

Studies providing efficacy data

There were two pivotal Phase III efficacy studies:

- Study AN2728-AD-301
- Study AN2728-AD-302.

There were four other efficacy studies:

- Study AN2728-AD-102
- Study AN2898-AD-202
- Study AN2728-AD-203
- Study AN2728-AD-204.

There was an Integrated Summary of Efficacy that pooled data from the two pivotal efficacy studies.

Evaluator's conclusions on efficacy

In the Integrated Summary of Efficacy the difference in success rate between crisaborole 2% ointment and vehicle was 10.3% of patients. Overall, the difference between crisaborole and vehicle in success in improvement in pruritus at Day 29 was 10% of patients. This indicates a number needed to treat of 10. Improvement in pruritus score was demonstrated from Day 8 and increased through to Day 29. The median time to improvement in pruritus was 5.0 days earlier with crisaborole. The difference in improvement in treatable %BSA for crisaborole compared to vehicle was –3%.[16] Improvements in AD were measurable from Day 8 of treatment and increased to Day 29.

In Study AN2728-AD-301, overall, the difference in success rate between crisaborole 2% ointment and vehicle was 7.4% of patients. The difference in proportion of patients with an Investigator's Static Global Assessment (ISGA) score of Clear or Almost Clear at Day 29 was 11.1%. Crisaborole improved all the symptoms of AD, compared with vehicle. The improvements occurred in a shorter time period than for vehicle.

In Study AN2728-AD-302, overall, the difference in success rate between crisaborole 2% ointment and vehicle was 13.4% of patients. The difference in proportion of patients with ISGA of Clear or Almost Clear at Day 29 was 18.8%. Crisaborole improved the symptoms of AD, compared with vehicle. There was no statistically significant difference in time to improvement in pruritus.

The pivotal studies were well designed and conducted. The study population is representative of the proposed target patient population in Australia. The outcome measures were previously tested and were clinically relevant. The statistical analysis was appropriate. The analysis included all patients in the ITT population. All outcome measures were reported.

In the pivotal studies, the formulation used was that proposed for marketing in Australia, and the dosing regimen and administration instructions were the same as that in the proposed PI and CMI.

The efficacy data are restricted to crisaborole 2% as monotherapy and the only direct comparisons have been with vehicle. Specific issues are:

- No studies with proprietary emollients as comparator.
- No studies with TCS as comparator.
- No studies with TCI as comparator.
- No studies in combination therapy.

[16] Treatable %BSA = Percentage of a patient's total body surface area that has AD involved excluding the scalp

The efficacy data only cover a duration of therapy of 4 weeks. There are no long term efficacy data, and it is not clear whether response to crisaborole is maintained over time. There were also no data assessing for rebound phenomena.

Safety

Studies providing safety data

Pivotal studies that assessed safety as the sole primary outcome

There was one pivotal study that assessed safety as the sole primary outcome: Study AN2728-AD-303.

Pivotal and/or main efficacy studies

The Phase III efficacy studies were: Study AN2728-AD-301 and Study AN2728-AD-302. These studies provided data on dermal tolerability, adverse events (AE), clinical laboratory tests, ECGs and vital signs.

Other studies

Other efficacy studies

The additional efficacy studies were: Study AN2898-AD-202 and Study AN2728-AD-204.

Studies with evaluable safety data: dose finding and pharmacology

The clinical pharmacology studies with safety data were:

- Study AN2728-PSR-105
- Study AN2898-PSR-102
- Study AN2728-PSR-104
- Study AN2728-PK-101
- Study AN2728-AD-102
- Study AN2728-TQT-108
- Study AN2728-AD-203
- Study AN2728-PSR-106
- Study AN2898-PSR-102
- Study AN2728-RIPT-101.

Studies evaluable for safety only

Study AN2728-PSR-101 was a single centre, randomised, vehicle and comparator controlled study in patients with psoriasis. The study included 12 males aged 32 to 64 years. The study treatments included crisaborole 5% ointment.

Study AN2728-PSR-102 was a single centre, randomised, investigator blind, psoriasis plaque test, vehicle and comparator controlled dose finding study. The study included 12 males aged 37 to 64 years. The study treatments included crisaborole 0.5% ointment, crisaborole 2% ointment and crisaborole 5% ointment.

Study AN2728-PSR-103 was a single centre, randomised, investigator blind, psoriasis plaque test, vehicle and comparator controlled dose finding study. The study included 12 males aged 31 to 76 years. The study treatments included crisaborole 0.3% ointment, crisaborole 1% ointment and crisaborole 2% ointment.

Study AN2898-PSR-103 was a single centre, randomised, investigator blind, psoriasis plaque test, vehicle and comparator controlled dose finding study. The study included 12 males aged 38 to 60 years. The study treatments included crisaborole 5% ointment.

Study AN2728-PSR-201 was a single centre, randomised, double-blind, within subject bilateral lesion comparison of crisaborole 5% ointment with vehicle in patients with psoriasis. Crisaborole 5% ointment was applied twice daily for 4 weeks. The study included 35 males aged 25 to 61 years.

Study AN2728-PSR-202 was a single centre, randomised, double blind, bilateral lesion comparison of crisaborole 5% ointment with vehicle in patients with psoriasis. Crisaborole 5% ointment was applied twice daily for 12 weeks. The study included 30 males aged 29 to 63 years.

Study AN2728-PSR-203 was a multicentre, randomised, double blind, dose ranging, within subject, bilateral lesion comparison of crisaborole 0.5% ointment or crisaborole 2% ointment, once or twice daily, with vehicle in patients with psoriasis. Treatment duration was for 12 weeks. The study included 145 patients: 127 males and 18 females, aged 18 to 83 years.

Study AN2728-PSR-204 was a multicentre, randomised, double blind, parallel group comparison of crisaborole 2% ointment and vehicle in patients with psoriasis. The treatments were applied twice daily for 12 weeks. The study included 68 patients: 47 males and 21 females aged 20 to 74 years.

Patient exposure

A total of 2157 patients or volunteers have been exposed to crisaborole during the development program. There were 1340 patients with AD, of whom 1293 were exposed to crisaborole 2% twice daily. There were 272 patients aged 2 to 4 years, 465 aged 5 to 11 years, 412 aged 12 to 17 years, and 188 aged ≥ 18 years. Four patients aged ≥ 65 years have been exposed to crisaborole. There were 575 males and 762 females. In addition, there have been 335 patients with psoriasis and 482 healthy volunteers exposed to crisaborole.

The Integrated Analysis of Safety pooled data from Study AN2728-AD-301 and Study AN2728-AD-302. There were 1012 patients with AD treated with crisaborole 2% ointment topically, twice daily for 4 weeks, and 499 treated with vehicle.

Studies in volunteers and patients with atopic dermatitis

- In Study AN2728-PSR-105 six volunteers were exposed to a single application to 10% of body surface area (BSA).
- In Study AN2728-PSR-104 six volunteers were exposed to twice daily crisaborole 2% to 10% BSA and six to 35% BSA for 7 days.
- In Study AN2728-PK-101 21 volunteers were exposed to crisaborole 2% ointment applied to 60% of BSA for two 1 week periods.
- In Study AN2728-AD-102 34 children and adolescents with AD aged 2 to 17 years were exposed to crisaborole 2% for 29 days.
- In Study AN2728-RIPT-101 in Cohort 1, there were 238 volunteers randomised to treatment; and in Cohort 2 there were 40.
- In Study AN2728-PSR-107 24 volunteers had crisaborole 2% ointment applied twice daily to extensor area, intertriginous areas, genitals and face/hairline for 21 days.

- In Study AN2728-TQT-108 there were 60 volunteers exposed to 15 g crisaborole 2% ointment applied to 30% BSA twice daily for 7 days and 59 exposed to 45 g applied to 45% BSA twice daily for 7 days.
- In Study AN2898-AD-202 25 adult patients with AD were exposed to crisaborole 2% twice daily on a test region for 6 weeks.
- In Study AN2728-AD-203 there were 23 adolescents exposed to crisaborole 2% ointment twice daily for 28 days.
- In Study AN2728-AD-204 there were 44 adolescents exposed to crisaborole 0.5% / 2% once daily and 42 to crisaborole 0.5% / 2% twice daily.
- In Study AN2728-AD-301 there were 503 patients exposed to crisaborole for a median (range) duration of 29 (1 to 52) days, and 256 exposed to vehicle for 28 (1 to 46) days.
- In Study AN2728-AD-302 there were 513 patients exposed to crisaborole for a median (range) duration of 28 (1 to 38) days, and 250 exposed to vehicle for 28 (1 to 38) days.
- In Study AN2728-AD-303 there were 517 patients enrolled: 308 aged 2 to 11 years, 146 aged 12 to 17 and 63 aged ≥ 18 years. There were 510 patients with drug application data and there were a mean (range) crisaborole applications of 347.5 (8 to 748). The mean (range) amount of drug used was 435.10 (0 to 9979.7) g. The mean (range) amount of drug used per application was 1.504 (0 to 21.71) g. The median (range) of on-treatment periods was 6 (1 to 13) and the median (range) of duration of on-treatment periods was 29 (1 to 73) days.

Studies in patients with psoriasis

- In Study AN2728-PSR-106 33 adult patients with plaque psoriasis were treated with crisaborole 2% twice daily for 8 days.
- In Study AN2728-PSR-101 there were 12 male patients with psoriasis exposed to crisaborole 5% ointment twice daily for 5 days.
- In Study AN2728-PSR-102 12 males aged 37 to 64 years were treated with crisaborole 0.5% ointment, crisaborole 2% ointment and crisaborole 5% ointment twice daily for 10 days.
- In Study AN2728-PSR-103 12 males aged 31 to 76 years were treated with crisaborole 0.3% ointment, crisaborole 1% ointment and crisaborole 2% ointment twice daily for 5 days.
- In Study AN2898-PSR-103 12 males aged 38 to 60 years were treated with crisaborole 5% ointment twice daily for 5 days.
- In Study AN2728-PSR-201 35 males aged 25 to 61 years were treated with crisaborole 5% ointment for 4 weeks.
- In Study AN2728-PSR-202 30 males aged 29 to 63 years were treated with crisaborole 5% ointment twice daily for 12 weeks.
- In Study AN2728-PSR-203 145 patients (127 males and 18 females, aged 18 to 83 years) were treated with either crisaborole 0.5% ointment or crisaborole 2% ointment for 12 weeks.
- In Study AN2728-PSR-204 64 patients were exposed to crisaborole 2% ointment for 12 weeks.

Safety issues with the potential for major regulatory impact

Liver function and liver toxicity

Main/pivotal studies that assessed safety as the sole primary outcome

- In Study AN2728-AD-303 two patients had increased alanine transaminase (ALT) (one considered related to study medication) and three had increased aspartate transaminase (AST) (all considered related to study medication).

Pivotal and/or main efficacy studies

- In Study AN2728-AD-301 two patients in the crisaborole group had mild elevations in transaminases, in one associated with a mild intercurrent infectious illness.
- In Study AN2728-AD-302 two patients in the crisaborole group and two in the vehicle had mild transient elevations in ALT and/or AST.

Other studies

Other efficacy studies

- In Study AN2898-AD-202 there were no abnormalities in laboratory tests with crisaborole 2% ointment.
- In Study AN2728-AD-204 there were no clinically significant abnormalities in laboratory tests.

Studies with evaluable safety data: dose finding and pharmacology

- In Study AN2728-PSR-107 there were no clinically significant laboratory test abnormalities.
- In Study AN2728-PK-101 there were no clinically significant laboratory test abnormalities during treatment with crisaborole.
- In Study AN2728-AD-102 there were no treatment emergent clinically significant abnormalities in clinical chemistry.
- In Study AN2728-TQT-108 there were no abnormalities in laboratory tests with crisaborole.

Studies evaluable for safety only

- In Study AN2728-PSR-203 one patient, in the crisaborole 2% group, had treatment emergent elevated AST and total bilirubin concentrations, and one, also in the crisaborole 2% group, had elevated ALT and AST.
- In Study AN2728-PSR-204 one patient in the crisaborole group had elevate ALT.

Renal function and renal toxicity

- There were no reports of treatment emergent renal dysfunction.

Other clinical chemistry

Main/pivotal studies that assessed safety as the sole primary outcome

- In Study AN2728-AD-303 one patient had elevated blood glucose, subsequently diagnosed as diabetes mellitus.

Pivotal and/or main efficacy studies

- In Study AN2728-AD-302 one patient in the crisaborole group had transient elevation of non-fasting blood glucose.

Other studies

- In the other studies there were no clinically significant abnormalities in other clinical chemistry.

Haematology and haematological toxicity

Main/pivotal studies that assessed safety as the sole primary outcome

- In Study AN2728-AD-303 three patients had elevated eosinophil count, two had neutrophil/WCC increased, two had leukocyte/lymphocyte count decreased and one had anaemia.

Pivotal and/or main efficacy studies

- In Study AN2728-AD-301 seven patients in the crisaborole group had mild abnormalities in blood count associated with mild intercurrent infectious illnesses.
- In Study AN2728-AD-302 one patient in the crisaborole group and one in the vehicle had eosinophilia. One patient in the vehicle group had transient lymphocytosis and thrombocytopaenia.

Other studies

Studies with evaluable safety data: dose finding and pharmacology

- In Study AN2728-PSR-104 one volunteer in the 10% BSA group had a reduced platelet count on Day 9 that recovered spontaneously.
- In Study AN2728-AD-102 one patient had elevated WCC associated with cervical lymphadenopathy and staphylococcal skin infection.
- In Study AN2728-AD-203 one patient had an elevated WCC and eosinophil count associated with contact dermatitis.

Electrocardiograph findings and cardiovascular safety

- The Cardiovascular Safety Report pooled ECG data from Study AN2728-AD-301 and Study AN2728-AD-302. ECG data were available for 695 patients: 365 females and 330 males. Two patients in the crisaborole group had QTcF > 450 at Day 8: 462 ms, Baseline 435 ms, and 458 ms, Baseline 455 ms. Mean (SD) change in heart rate was -0.4 (11.43) ms in the crisaborole group and 1.4 (10.95) ms in the vehicle. Mean (SD) change in PR interval was –0.1 (11.51) ms in the crisaborole group and 0.0 (9.27) ms in the vehicle. Mean (SD) change in QRS interval was 0.0 (5.60) ms in the crisaborole group and –0.2 (5.55) ms in the vehicle. Mean (SD) change in QTcF was 1.1 (13.44) ms in the crisaborole group and –0.1 (13.28) ms in the vehicle. There were ten (2.4%) patients in the crisaborole group and two (1.0%) in the vehicle group with a change in QTcF from Baseline > 30 to ≥ 60 ms. There were no patients with a change from Baseline in QTcF > 60 ms.

Main/pivotal studies that assessed safety as the sole primary outcome

Other studies

Studies with evaluable safety data: dose finding and pharmacology

- In Study AN2728-PSR-104 and Study AN2728-PK-101 there were no clinically significant ECG abnormalities.
- In Study AN2728-TQT-108 there was no increase in QTcF with crisaborole, and the 90% CI for difference in QTcF did not include 10 ms. There was an increase of QTcF > 10 ms with moxifloxacin positive control and no increase with negative control.

Vital signs and clinical examination findings

Pivotal studies that assessed safety as the sole primary outcome

- In Study AN2728-AD-303 there were no clinically significant changes in vital signs or physical examination.

Pivotal and/or main efficacy studies

- In Study AN2728-AD-301 and Study AN2728-AD-302 there were no treatment related changes in vital signs.

Other studies

Other efficacy studies

- In Study AN2898-AD-202 and Study AN2728-AD-204 there were no clinically significant abnormalities in vital signs.

Studies with evaluable safety data: dose finding and pharmacology

- In Study AN2728-PSR-104 one volunteer in the 35% group had an episode of hypotension.
- In Study AN2728-PSR-107 and Study AN2728-AD-203 there were no clinically significant abnormalities in vital signs.
- In Study AN2728-PK-101 there were no clinically significant abnormalities in vital signs during treatment with crisaborole.
- In Study AN2728-AD-102 there were no clinically significant abnormalities in vital signs attributable to treatment.

Serious skin reactions

Pivotal studies that assessed safety as the sole primary outcome

- In Study AN2728-AD-303 there was one serious adverse event (SAE) of application site infection. Local tolerability improved over time from 346 (66.9%) patients with no stinging/burning at Baseline to 212 (77.7%) at Week 48.

Pivotal and/or main efficacy studies

- In Study AN2728-AD-301 there was one episode of cellulitis in the vehicle group. Tolerability scores were similar between crisaborole and vehicle. At Day 29, there were 345 (72.3%) patients in the crisaborole group with no burning/stinging and 171 (75.0%) in the vehicle.
- In Study AN2728-AD-302 there was one application site infection in the crisaborole group. Tolerability scores were slightly better in the vehicle group, and in both treatment groups improved over time. At Day 29, there were 342 (70.4%) patients in the crisaborole group with no burning/stinging and 164 (73.9%) in the vehicle.

Other studies

Other efficacy studies

- In Study AN2898-AD-202 and Study AN2728-AD-204 there were no serious cutaneous adverse events (AE).

Studies with evaluable safety data: dose finding and pharmacology

- In Study AN2898-PSR-102 erythema scores were similar for AN2728 5% ointment compared to vehicle and negative control. Positive control elicited a reaction in all of the volunteers.

- In Study AN2728-PSR-104 application site erythema/pain was reported in one volunteer in the 10% BSA group and two in the 35%. One volunteer was withdrawn due to an AE (urticaria).
- In Study AN2728-PSR-107 there were no serious skin reactions and crisaborole 2% ointment had similar tolerability to vehicle.
- In Study AN2728-PK-101 there were no serious skin reactions. There were 38 application site treatment emergent adverse events (TEAE) in 13 (54%) volunteers with crisaborole: pruritus and application site pain were both reported in eight (33%) volunteers, and application site erythema in seven (29%).
- In Study AN2728-AD-102 there were no serious skin reactions. The most common treatment related TEAEs were application site pain in 12 (35.3%) patients, AD in four (11.8%) and application site paraesthesia in two (5.9%).
- In Study AN2728-TQT-108 there were no serious skin reactions. Application site AEs were dose related. Pruritus was reported in four (7%) volunteers with 15 g crisaborole 2% ointment applied to 30% BSA, 15 (17%) with to 45 g crisaborole 2% ointment applied to 45% BSA and two (1%) with vehicle. Application site rash was reported in two (3%) volunteers with 15 g crisaborole 2% ointment applied to 30% BSA, eight (13%) with to 45 g crisaborole 2% ointment applied to 45% BSA and none with vehicle.
- In Study AN2728-AD-203 local tolerability improved from Baseline to Day 28. There was one DAE due to application site dermatitis, with an elevated WCC and eosinophil.

Studies evaluable for safety only

- In Study AN2728-PSR-202 there was one drug eruption, reported as a SAE, 3 days after intramuscular penicillin.

Other safety issues

Safety in special populations

Data were included for children and adolescents and there were no safety issues identified in these populations. There were few data for older persons, pregnancy and lactation.

Safety related to drug-drug interactions and other interactions

The studies were conducted in monotherapy. There was no significant interaction with warfarin.

Post marketing data

No post marketing data were included in the dossier.

Evaluator's conclusions on safety

Crisaborole has a favourable safety profile. There was a similar rate of TEAEs with crisaborole and vehicle. There was a slightly higher rate of treatment related TEAEs due to application site TEAEs. Application site pain was reported in 2.3% to 6.2% of patients.

There were no deaths during the development program. There were few SAEs, only one of which could have been related to treatment: application site infection. Discontinuation due to adverse events was uncommon and discontinuation of treatment due to an application site reaction was in < 3% of patients.

There were occasional reports of elevated hepatic transaminases, one with associated hyperbilirubinaemia. There were no other clinically significant abnormalities in clinical

chemistry. There were occasional reports of haematological abnormalities that were attributable to intercurrent illness or to atopic conditions.

One patient reported to have an anaphylactic reaction attributed to crisaborole 2% topical (this may have been due to a nut allergy). A significant proportion of the crisaborole dose is absorbed transdermally and results in systemic exposure to the two primary metabolites of crisaborole: AN7602 and AN8323. Hence, there is potential for immunologically mediated adverse drug reactions.

There were few serious cutaneous reactions. One volunteer discontinued because of urticaria. There were several skin and/or soft tissue infections that would be consistent with AD. There was one drug eruption, reported as a SAE, and attributed to penicillin.

The long term safety data appear to be for < 1 year duration and this will need to be clarified with the sponsor.

First round benefit-risk assessment

First round assessment of benefits

Table 8 gives the benefits along with the strengths and uncertainties as was assessed at the first round evaluation.

Table 8: First round assessment of benefits

Benefits	Strengths and Uncertainties
Crisaborole 2% ointment is superior to vehicle for the treatment of mild to moderate AD. In the Integrated Summary of Efficacy the difference in success rate between crisaborole 2% ointment and vehicle was 10.3% of patients. This indicates a number needed to treat of 10. Overall, the difference between crisaborole and vehicle in success in improvement in pruritus at Day 29 was 10% of patients. This indicates a number needed to treat of 10. Improvement in pruritus score was demonstrated from Day 8 and increased through to Day 29. The median time to improvement in pruritus of 5.0 days earlier with crisaborole. The difference in improvement in treatable %BSA for crisaborole compared to vehicle was –3%. In Study AN2728-AD-301, the difference in proportion of patients with ISGA of Clear or Almost Clear at Day 29 was 11.1%. In Study AN2728-AD-302, the difference in proportion of patients with ISGA of Clear or Almost Clear at Day 29 was 18.8%. Crisaborole improved all the symptoms of AD, compared with vehicle. Improvements in AD were measurable from Day 8 of treatment and increased to Day 29.	The pivotal studies were well designed and conducted. The study population is representative of the proposed target patient population in Australia. The outcome measures were previously tested and were clinically relevant. The statistical analysis was appropriate. The analysis included all patients in the ITT population. All outcome measures were reported. The efficacy data are restricted to crisaborole 2% in monotherapy and the only direct comparisons have been with vehicle. Specific issues are: • No studies with proprietary emollients as comparator • No studies with TCS as comparator • No studies with TCI as comparator • No studies as combination therapy The efficacy data only cover a duration of therapy of 4 weeks. There are no long term efficacy data, and it is not clear whether response to crisaborole is maintained over time. There were also no data assessing for rebound phenomenon.

First round assessment of risks

Table 9, below, gives the risks along with their strengths and uncertainties as assessed at the first round evaluation.

Table 9: First round assessment of risks

Risks	Strengths and Uncertainties
Crisaborole has a favourable safety profile. There was a similar rate of TEAEs with crisaborole and vehicle. There was a slightly higher rate of treatment related TEAEs due to application site TEAEs. Application site pain was reported in 2.3% to 6.2% of patients. There were no deaths during the development program. There were few SAEs, only one of which could have been related to treatment: application site infection. DAE was uncommon and discontinuation of treatment due to an application site reaction was in < 3% of patients. There were few serious cutaneous reactions.	There were occasional reports of elevated hepatic transaminases, one with associated hyperbilirubinaemia. It is not clear how many patients fulfilled the criteria of Hy's Law.[17] One patient reported to have an anaphylactic reaction attributed to crisaborole 2% topical. A significant proportion of the crisaborole dose is absorbed transdermally and results in systemic exposure to the two primary metabolites of crisaborole: AN7602 and AN8323. Hence, there is potential for immunologically mediated adverse drug reactions. The long term safety data appear to be for < 1 year duration and this will need to be clarified with the sponsor.

First round assessment of benefit-risk balance

In short term use crisaborole has a favourable benefit-risk balance, primarily because of the low risk of adverse reactions, and a particularly low risk for serious adverse reactions. This use would have to be as monotherapy because of the absence of data in combination treatment regimens. Crisaborole has only moderate efficacy and is unlikely to be used as a substitute for TCS and/or TCI, particularly since there are no comparative data with these other treatments. Hence, the place in the management of AD is most likely as a substitute for, or as a step up from, emollients. However, superiority to proprietary emollients has not been demonstrated. The proposed usage of crisaborole requires clarification, and the proposed indication needs to reflect the proposed usage.

First round recommendation regarding authorisation

The clinical evaluator recommends rejection of the application to authorise Staquis (crisaborole) 2% ointment for the therapeutic indication of:

> *Staquis is indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.*

The reason for this recommendation is that the proposed usage requires clarification and the indication should be modified to reflect the proposed usage. The clinical data support short term use as monotherapy in patients who would not otherwise be considered for TCS or TCI.

[17] Hy's Law is a predictor of drug induced hepatotoxicity.

Clinical questions and second round evaluation

Pharmacodynamics

1. What are the known pharmacological effects of AN7602?

Sponsor response

AN7602 is a main oxidative metabolite of Staquis identified in human, rodent, and mini-pig plasma. The ability of this metabolite to inhibit PDE4 activity was investigated in various recombinant and cell extract derived PDE4 preparations. AN7602 failed to inhibit PDE4 enzymatic activity. [Information redacted]

Evaluation of response

The sponsor's response has been noted.

2. What are the known pharmacological effects of AN8323?

Sponsor response

AN8323 is a main oxidative metabolite of AN7602 (the primary metabolite of Staquis) and has been identified in human, rodent and mini-pig plasma. The ability of this metabolite to inhibit PDE4 activity was investigated in various recombinant and cell extract derived PDE4 preparations. AN8323 failed to inhibit PDE4 enzymatic activity. [Information redacted]

Evaluation of response

The sponsor's response has been noted.

Efficacy

3. Does the sponsor have data comparing the efficacy of crisaborole with proprietary emollients? Is there any evidence that crisaborole is superior to proprietary emollients?

Sponsor response

The sponsor does not have data comparing the efficacy of crisaborole with a proprietary emollient. The sponsor notes there is no EU guidance that requires a head-to-head comparison with, or demonstration of superiority to, a proprietary emollient(s). However, the vehicle developed by the sponsor, which is the base of crisaborole ointment, is an emollient that contains white soft paraffin, propylene glycol, glyceryl monostearate, synthetic paraffin, butylated hydroxytoluene, and sodium calcium edetate. Crisaborole was compared to this vehicle.

It is known that some vehicle excipients have a more pronounced beneficial effect on the skin and can improve clinical appearance and skin barrier function. In particular, white soft paraffin, also known as petrolatum, is the main excipient and base of crisaborole ointment, which was selected for its emollient properties and favourable tolerability profile. White soft paraffin has been demonstrated to significantly up regulate antimicrobial peptides, induce expression of key barrier differentiation markers (filaggrin and loricrin), increase stratum corneum thickness, and significantly reduce T-cell infiltrates in the setting of ''normal appearing'' or nonlesional AD skin, which is known to exhibit epidermal barrier and immune defects even in the absence of phenotypic expression.

White soft paraffin is a common ingredient in proprietary emollients. For example, in Australia, 5 of the top 10 selling pharmacy brands of proprietary emollients contain white

soft paraffin. The white soft paraffin content of these formulations is as much as 100%, reflecting the broad recognition of this ingredient as an effective emollient.

As described in the response to Question 6 (below), the vehicle in the crisaborole clinical trials had therapeutic benefit and this benefit was significantly improved upon by the addition of the active drug substance, crisaborole. Crisaborole ointment consistently provided additional benefit on top of the vehicle's therapeutic effect across all efficacy and quality of life endpoints.

In conclusion, considering the benefit of some vehicle excipients and based upon the success demonstrated in the primary, secondary, and other efficacy endpoints in the Phase III registration studies of crisaborole versus vehicle, crisaborole would also be expected to demonstrate superior efficacy over proprietary emollients in patients with mild to moderate AD.

Evaluation of response

The sponsor response has been noted. The sponsor states that no EU guideline requires a comparison with proprietary emollient(s). There is no TGA adopted EMA guideline specific to AD. Any query with regard to comparison data with proprietary emollients would have been derived from the evaluation and the best practice approach of comparing new treatments with existing treatments for the same indication in the absence of specific guidance.

4. Does the sponsor have data comparing crisaborole with TCS?

Sponsor response

The sponsor does not currently have data directly or indirectly comparing the safety and efficacy of crisaborole with a TCS, in part due to the restrictions associated with the use of TCSs. The sponsor notes there is no EU guidance that requires a head-to-head comparison with existing active therapies.

[Information redacted]

The main side effects of TCSs, which have been well documented and reported, are striae rubrae, skin atrophy, telangiectasia, skin burning, erythema and acneiform or rosacea-like eruptions. There are also concerns over higher systemic glucocorticoid effects of TCS in some situations in younger children. Of greatest concern is skin atrophy, which can be induced by any TCS, although higher potency agents, occlusion, use on thinner skin, and older patient age increase this risk. Many of these side effects will resolve after discontinuing TCS use, but this resolution may take months; other side effects may be permanent.

In comparison, the safety findings in the crisaborole AD program showed no evidence of sustained cutaneous reactions at the application site (for example, atrophy, telangiectasia, or hypopigmentation as have been described with the use of TCSs). Furthermore, there was no signal for immunosuppression, including no evidence for increased risk of serious infections or malignancies, consistent with results of nonclinical safety studies. Application site pain (mostly localised burning and stinging) was the only treatment related AE that showed a clinically relevant difference in rates between the crisaborole and vehicle treatment groups in the Phase III registration studies (AN2728-AD-301 and AN2728-AD-302). Generally, application site pain was noted early in the treatment period and was transient in nature, resolving spontaneously.

T The sponsor is conducting Study C3291037, a Phase IIIb/IV, multicentre, randomised, assessor blinded, vehicle and active (TCS, TCI) controlled study of the efficacy, safety and local tolerability of Staquis ointment applied twice daily in paediatric and adult subjects (ages 2 years and older) with mild to moderate AD involving at least 5% treatable %BSA. The study is ongoing and targeted to be completed by July 2020.

Given that there are no relevant EU clinical guidelines mandating the need for active comparator studies for the purpose of registering a medicine such as Staquis ointment, the sponsor considers that the completed Phase III registration Studies AN2728-AD-301 and AN2728-AD-302, and the long term safety extension Study AN2728-AD-303 provide sufficient clinical efficacy and safety information to establish the benefit-risk profile of crisaborole ointment.

Evaluation of response

The sponsor response has been noted. Similar to the response to first round Question 3, the sponsor states that no EU guideline requires a comparison with TCS. There is no TGA adopted EMA guideline specific to AD. In the response, the sponsor has placed much emphasis on safety and, in particular, the known adverse events of TCS products. It is noted, however, that no efficacy data has been presented from the literature.

5. Does the sponsor have data comparing crisaborole with TCI?

Sponsor response

The sponsor does not currently have data directly comparing the safety and efficacy of crisaborole with a TCI. The sponsor notes there is no EU guidance that requires a head-to-head comparison with existing active therapies.

[Information redacted]

Evaluation of response

The sponsor response has been noted. Similar to the response to first round Question 3, the sponsor states that no EU guideline requires a comparison with TCI. There is no TGA adopted EMA guideline specific to AD. The point estimate values were all expressed as odds ratios rather than risk ratios, and no confidence intervals were shown, but the Bayesian credible interval. With regard to crisaborole 2% compared with active comparator, all of the OR credible intervals contain 1, pointing towards statistical indifference.

6. How does the sponsor envisage that crisaborole will be used in clinical practice?

Sponsor response

The sponsor envisions that Staquis (crisaborole ointment, 2%) will be used in clinical practice as a short term continuous and long term intermittent therapeutic option for the treatment of mild to moderate AD in patients aged 2 years and older on all skin areas typically involved in AD, including sensitive skin areas; thus fulfilling a medical need in the therapeutic armamentarium for clinicians. This position is supported by the clinical development program of crisaborole as follows:

- The Phase III clinical studies evaluated crisaborole ointment in short term continuous (AN2728-AD-301 and AN2728-AD-302) and long term intermittent (AN2728-AD-303) use for the treatment of mild to moderate AD as defined by the Baseline ISGA score. The study populations, which were broadly representative of the proposed target patient population in Australia, included subjects aged 2 years and older (range, 2 to 79 years) with an extent of disease ranging from 5 to 95% at the Baseline of the 2 registration studies, as well as an AD treatment history that included subjects that were treatment naïve and treatment experienced.
- While the vehicle in the crisaborole clinical trials had therapeutic benefit (see response to Question 3 above), it was significantly improved upon by the addition of the active drug substance, crisaborole. Table 10 summarises Staquis' treatment benefit compared to vehicle across efficacy and quality of life endpoints. Staquis consistently provided additional benefit on top of the vehicle therapeutic effect.

Table 10: Summary of efficacy endpoints at Day 29 (Studies AN2728-AD-301 and AN2728-AD-302 pooled)(ITT population)

Endpoint	Crisaborole ,Ointment, 2% BID	Vehicle	Treatment Difference	P-Value
Success in ISGA (%)	32.1	21.8	10.3	<0.001
ISGA Clear or Almost Clear (%)	50.1	35.2	14.9	<0.001
Change from Baseline in ISGA (Mean)	-1.1	-0.7	-0.4	<0.001
Improvement in AD Signs and Symptoms (Rate, %)				
Erythema	58.8	40.0	18.8	<0.001
Induration/Papulation	54.8	47.6	7.2	0.008
Exudation	39.5	30.3	9.2	<0.001
Excoration	60.1	48.0	12.1	<0.001
Lichenification	51.6	40.9	10.7	<0.001
Pruritus	62.7	52.7	10.0	0.002
Time to Improvement in Pruritus (Median days)	1.37	1.70	-0.33	0.001
Change from Baseline in Treatable %BSA (LS mean)	-7.4	-4.4	-3.0	<0.001
Change from Baseline in DLQI Score (Mean)	-5.2	-3.5	-1.7	0.015
Change from Baseline in CDLQI Score (Mean)	-4.6	-3.0	-1.6	<0.001
Change from Baseline in DFI Score (Mean)	-3.7	-2.7	-1.0	0.003

Source: Pfizer data on file; available upon request.
AD=atopic dermatitis; BID=twice daily; BSA=Body Surface Area; CDLQI=Children's Dermatology Life Quality Index; DLQI=Dermatology Life Quality Index.; DFI=Dermatitis Family Impact Questionnaire; ISGA=Investigator's Static Global Assessment; LS=least squares.

In the pooled Phase III registration studies, higher rates of success in ISGA at Day 29 were observed in the crisaborole group than in the vehicle group for the subgroups of sex, age, race, ethnicity, and prior AD treatment.

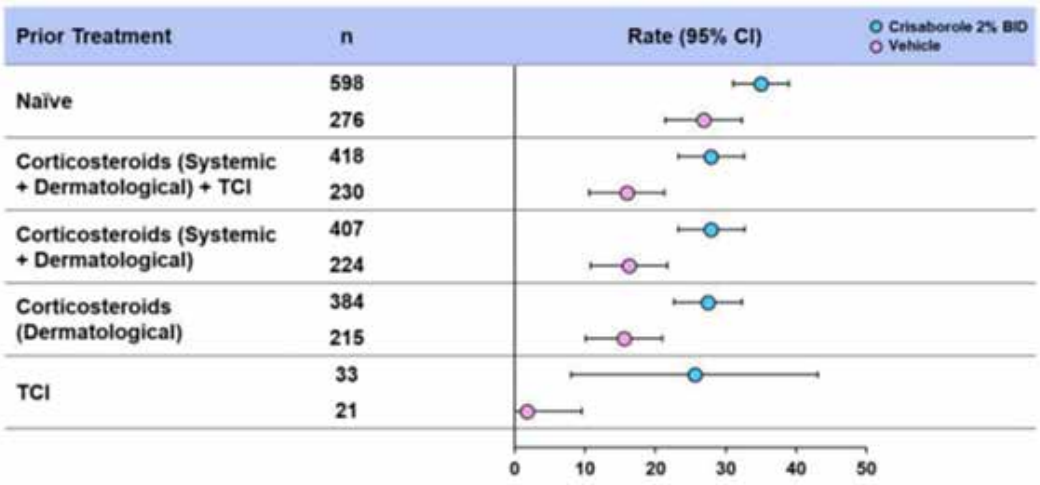
- Since the Marketing Authorisation Application, an *ad hoc* analysis was conducted to determine the effect of prior AD treatment (treatment naïve or treatment experienced) on the primary efficacy endpoint (success in ISGA). Treatment naïve was defined as subjects with no prior medication record (within 90 days of the pivotal registration studies' screening visit, as per protocol) for a corticosteroid (systemic and dermatologic preparations) or a TCI such as, Elidel (pimecrolimus) or Protopic (tacrolimus). In the pooled pivotal study population, 58.9% and 54.3% of subjects in the crisaborole and vehicle groups, respectively, were defined as 'treatment naïve' (Table 11) and similar percentages were observed in the individual studies. The proportion of subjects who had prior corticosteroid use (systemic and dermatologic preparations), 40.0% and 44.5% of subjects in the crisaborole and vehicle groups, respectively, was also similar in the individual studies. Analysis of the success of ISGA by prior medication (Figure 4) shows that treatment naïve subjects had a modestly greater response compared to those subjects exposed to a prior corticosteroid and/or a TCI (treatment experienced). No difference in response was observed for crisaborole in relationship to the type of prior AD medication. These data support the use of crisaborole in both patients who are treatment naïve or treatment experienced.

Table 11: Number (%) of subjects with prior corticosteroids, TCI or treatment naïve, Phase III studies AN2728-AD-301 and AN2728-AD-302 pooled (safety population)

Category	Crisaborole 2% BID (N = 1012) n (%)	Vehicle (N = 499) n (%)	Total (N = 1511) n (%)
Naïve	596 (58.9%)	271 (54.3%)	867 (57.4%)
Corticosteroids for Systemic Use or Dermatological Preparations or TCI	416 (41.1%)	228 (45.7%)	644 (42.6%)
Corticosteroids for Systemic Use or Dermatological Preparations	405 (40.0%)	222 (44.5%)	627 (41.5%)
Corticosteroids for Systemic Use	309 (30.5%)	172 (34.5%)	481 (31.8%)
Corticosteroids Dermatological Preparations	382 (37.7%)	213 (42.7%)	595 (39.4%)
TCI	33 (3.3%)	21 (4.2%)	54 (3.6%)

Source: Pfizer data on file; available upon request.
BID=twice daily; TCI=topical calcineurin inhibitors.
TCI includes Elidel (pimecrolimus); and Protopic (tacrolimus).

Figure 4: Summary of subjects achieving ISGA clear or almost clear with 2-point reduction at Day 29 by prior treatment, Phase III studies AN2728-AD-301 and AN2728-AD-302 pooled (ITT population, multiple imputation)



Source: Pfizer data on file; available upon request.
BID=twice daily; CI=confidence interval; ISGA=Investigator's Static Global Assessment; ITT=intent-to-treat; TCI=topical calcineurin inhibitors.

In summary, when evaluated both individually and collectively, the success achieved in the primary, secondary, and other endpoints provide robust, clinically meaningful evidence of the overall efficacy of Staquis for the treatment of AD in patients ≥ 2 years old. The secondary and other endpoints reinforce the primary endpoint and provide clinically relevant information to better inform clinicians, patients, and caregivers about the beneficial effects of crisaborole treatment on all the important aspects of AD.

- As described in greater detail in the response to Efficacy Question 8, an indirect assessment of efficacy in the open label, single arm, long term extension Study AN2728-AD-303 provided evidence that clinical benefit, as assessed by ISGA, was sustained with long term intermittent treatment with Staquis.
- The safety findings in the crisaborole AD program did not include evidence of sustained cutaneous reactions at the application site (for example, atrophy, telangiectasia, or hypopigmentation as have been described with the use of TCSs). Furthermore, there was no signal for immunosuppression, including no evidence for

increased risk of serious infections or malignancies, consistent with results of nonclinical safety studies.

Currently, there is no cure for AD, and treatment is focused on alleviating the debilitating signs and symptoms and gaining control over recurrent flares throughout the extended natural history of the disease. For patients with mild to moderate AD, general measures to protect the skin barrier and avoid infection, and the judicious use of TCSs of low or moderate potency may provide symptomatic relief. Because of the chronic, relapsing nature of the disease, such treatment may be needed for many years. However, these available treatment options for AD pose potential safety concerns that limit their use. For TCS, the limitations are especially applicable to sensitive skin areas (for example, face, intertriginous areas, genital area), and in the paediatric population, as the dosage and duration of treatment often varies for infants and children compared with adults due to the increased risk of side effects in younger patients. Furthermore, fluorinated or halogenated TCSs are restricted from use on facial, intertriginous, or genital skin, limiting their potential benefit to treat all affected body regions. TCIs had significant warnings in their product labelling relating to a potential risk of malignancy as described in the response to Question 5. As a consequence, the treatment of AD can be complicated by the use of multiple topical therapies together, such as different potencies of TCS for specific body locations or at different stages of disease, leading to confusion and frustration for patients and their caregivers. This often results in poor treatment adherence and consequentially, poor treatment outcomes. Based on these considerations, there is a clear medical need for a safe and efficacious topical treatment that can be used as short term continuous and long term intermittent therapy on all skin areas typically involved in AD, including sensitive skin areas.

In conclusion, the sponsor envisions that Staquis (crisaborole ointment, 2%) will be used in clinical practice as a short term continuous and long term intermittent therapeutic option for the treatment of mild to moderate AD in patients aged 2 years and older on all skin areas typically involved in AD, including sensitive skin areas; thus fulfilling a medical need in the therapeutic armamentarium for clinicians. The results from the development program provide substantial evidence that the benefit-risk of Staquis is favourable for the topical treatment of mild to moderate AD in this patient population:

- Satisfactory local tolerability and limited systemic exposure of Staquis combine to offer a safety profile that differentiates it from the currently available treatment options for mild to moderate AD
- No difference in response was observed for crisaborole in relationship to the type of prior AD medication.

The points above combine to offer a safety profile that differentiates it from the currently available treatment options for mild to moderate AD, namely TCSs and TCIs, which each carry known risks.

Evaluation of response

The sponsor's response with regard to proposed clinical usage has been noted. The perceived clinical need has also been noted. Several important issues were not addressed by the sponsor, including the potential for off-label use (for example, in psoriasis or other conditions potentially responsive to crisaborole ointment, or use as 'proactive therapy', as suggested by the sponsor's expert), the use in the Asian population, and the lack of rebound or relapse data (and usage associated with that). This should be reflected in an updated RMP/ASA.

The sponsor envisions 'short term continuous and long term intermittent' treatment using crisaborole. It is unclear exactly what the sponsor means by 'long term intermittent': either a time period of 52 weeks in which crisaborole is given in one or more cycles, or an

indefinite period in which crisaborole is given in one or more cycles, or something else. There is no objection to short term continuous treatment, but comprehensive data beyond 52 weeks is severely limited or lacking altogether. Study AN2728-AD-303 (the 48 week open label extension study of Studies AN2728-AD-301 or AN2728-AD-302) was not designed to assess efficacy, even though some efficacy measurements were made. The only RCT efficacy data available ends at 28 days.

The sponsor's Australian dermatology expert additionally states that crisaborole could be used as 'proactive therapy' 2 to 3 times a week, and mentions studies using TCSs and TCIs as evidence for this approach. However, no supporting clinical trial data with regard to crisaborole appears to have been provided by the sponsor.

7. Does the sponsor have data for the efficacy of crisaborole in combination with other treatments for AD?

Sponsor response

While rescue treatment was allowed in the long term extension study based solely on Investigator's judgment, it was not permitted in combination with crisaborole. Thus, the sponsor does not have efficacy data of crisaborole in combination with other treatments for AD.

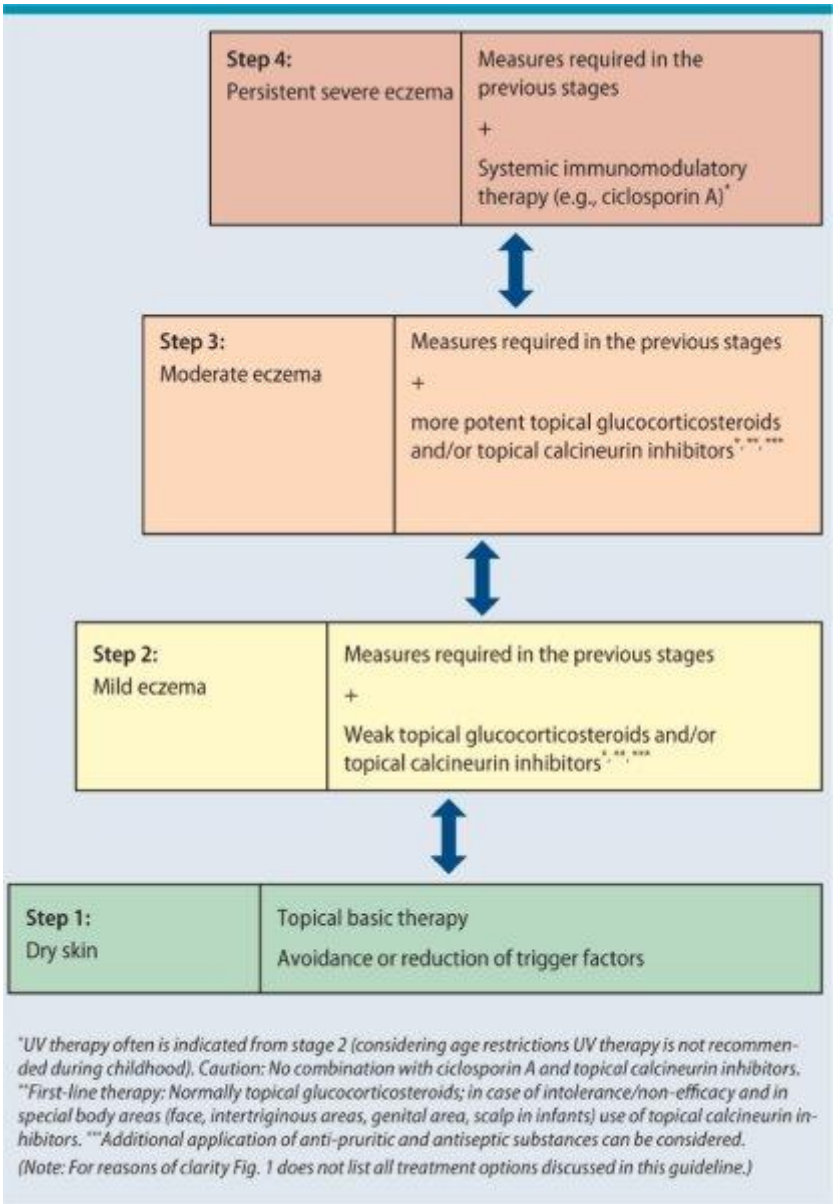
In the Phase III clinical studies (AN2728-AD-301, AN2728-AD-302 and AN2728-AD-303) crisaborole was evaluated as a monotherapy treatment only.

In Studies AN2728-AD-301 and AN2728-AD-302, subjects were required to washout of a number of prohibited concomitant therapies including systemic and/or topical therapies that might alter the course of AD during the Screening period (see AN2728-AD-301 and AN2728-AD-302 Protocol). These limitations were stipulated so that the safety and efficacy evaluations of crisaborole were not confounded. Such therapies included systemic immunosuppressives and antihistamines, TCSs and TCIs. Use of emollients on treatable AD lesions, within 1 day prior to Baseline/Day 1 (in other words, during the 24 hour period before the Baseline/Day 1 Visit) was allowed but after the Baseline/Day 1 Visit; use of acceptable bland emollient(s) was permitted during the study to manage dry skin in areas surrounding but not on or overlapping the treatable AD involved areas.

In Study AN2728-AD-303, an open label, long term safety study, the use of low-to-mid potency TCS or TCI was permitted, if prescribed by the Investigator or designee, to treat AD involved areas. Parameters for use of rescue medication were not based on predefined ISGA scores at scheduled or unscheduled visits or on safety or tolerability findings; the need for rescue medication was based solely on the Investigator's judgment. The European consensus-based (S2k) guidelines on the diagnosis and treatment of AD[18] recommend implementing a stepwise approach based on the clinical severity (Figure 5 below) similar to other published guidelines. Emollients should form the basis of AD management and should always be used, even when the AD is clear. Management can then be stepped up or down, according to the severity of symptoms, with the addition of the other treatments. Systemic immunomodulatory therapies are reserved for persistent severe AD. These treatment principals and recommendations are also incorporated within the Consensus guidelines for the management of AD from an Asia Pacific perspective).

[18] Werfel T et al 2016 S2k guideline on diagnosis and treatment of atopic dermatitis – short version. *Allergo J Int* 2016; 25: 82-95

Figure 5: Multi-stage treatment concept for atopic dermatitis (reproduced from Werfel et al. 2016 Error! Bookmark not defined.**)**



Co-applying topical treatments is not in line with current treatment practices, or product labelling for TCSs and TCIs. Co-applying emollient with crisaborole or with other topical treatments could have a dilution effect resulting in a reduction of the active agent concentration. Additionally, if the active agent has appreciable solubility in the emollient, for example, decreased skin permeation and penetration of the active agent may occur due to reduced diffusion of the active from the emollient into the skin. These factors have the potential to reduce the skin permeation of crisaborole and other topical treatments and impact the effectiveness of the treatments.

In conclusion, for the treatment of mild to moderate AD, Staquis has only been evaluated as a monotherapy treatment. In Studies AN2728-AD-301 and AN2728-AD-302, subjects with moderate disease had a statistically significant treatment response to crisaborole; and in Study AN2728-AD-303, most subjects did not require rescue medication (TCS or TCI). As per guidelines and product labelling, co-applying topical treatments is not supported by current treatment practices, or product labelling for TCSs and TCIs. Co-applying emollient with crisaborole or with other topical treatments could have a dilution effect resulting in a reduction of the active agent concentration.

Evaluation of response

The sponsor response has been noted. The sponsor's Australian dermatology expert states that use with moisturisers (most of which would contain emollients) is acceptable, if applied after a 15 to 20 minute gap. From a clinical evaluation point of view, there is no definite objection to use of emollients/moisturisers in patients using topical crisaborole ointment, as long as there are no interactions. In general terms, one way to achieve this is to observe an appropriate time period in between applications of crisaborole and the moisturiser/emollient. The length of this period would depend on the absorption time of the particular moisturiser/emollient.

8. Does the sponsor have efficacy data for durations of treatment longer than 4 weeks?

Sponsor response

Study AN2728-AD-303 was an open label, single arm, long term safety study in subjects who completed Study AN2728-AD-301 or Study AN2728-AD-302 without safety issues that precluded further treatment with crisaborole in the opinion of the Investigator and who met the study inclusion/exclusion criteria. The objective of the study was to evaluate the long term safety of open label treatment with crisaborole ointment in children, adolescents, and adults (ages 2 years and older) with mild to moderate AD.

Subjects participated in the study for up to 48 weeks (twelve 28 day treatment cycles).

No predefined efficacy analysis was conducted for the study. The ISGA was the only efficacy endpoint recorded during the study which was utilised by Investigators to determine whether the subject would receive crisaborole (on-treatment) or no study drug (off-treatment) at the beginning of each cycle. Ad hoc efficacy analyses have been conducted to indirectly assess the treatment effect over time by analysing the ISGA response over time.

[Information redacted]

Evaluation of response

The sponsor response has been noted. The only RCT efficacy data available (Studies AN2728-AD-301 and AN2728-AD-302) did not assess efficacy beyond 28 days of treatment. Study AN2728-AD-303 (the 48 week open label extension study of Studies AN2728-AD-301 or AN2728-AD-302) was not designed to assess efficacy, even though some efficacy measurements were made, and those appear to support efficacy, but were conducted using an open label approach with post hoc analyses. Furthermore, the selection criteria for Study AN2728-AD-303 may have skewed the population towards a larger proportion of responders. Given that there was only one treatment group, confounding may not have been adequately controlled.

9. Does the sponsor have data that evaluate whether there are rebound phenomena after ceasing crisaborole?

Sponsor response

[Information redacted]

Evaluation of response

The sponsor response has been noted. The sponsor essentially states that there is no evidence for a rebound phenomenon based on their ad hoc analysis using existing clinical study data.

The subset of patients assessed for this in the ad hoc analysis described above may have been too small to draw definite conclusions, and no statistical analysis appears to have been conducted. Furthermore, there appears to be no distinction between:

- patients with Mild AD who had initially responded to crisaborole in Studies AN2728-AD-301 and AN2728-AD-302 (that is, cleared it), but then had Moderate AD at the start of Study AN2728-AD-303; and,
- patients that had not responded to crisaborole (that is, remained with Mild AD) in Studies AN2728-AD-301 and AN2728-AD-302 and had Moderate AD at the start of Study AN2728-AD-303. Moreover, only patients from Studies AN2728-AD-301 and AN2728-AD-302 who fulfilled certain requirements (for example, no treatment related AEs) could have progressed to Study AN2728-AD-303. This may have reduced the number of patients with rebound in Study AN2728-AD-303 at Baseline. This is partially offset by AE data on worsening in Studies AN2728-AD-301 and AN2728-AD-302, but there is no definite evidence for the absence of rebound at a population level.

Safety

10. How many patients have received continuous treatment with crisaborole for more than one year?

11. How many patients have received intermittent treatment with crisaborole for more than one year?

Sponsor response

The Phase III program did not collect data beyond 1 year of treatment. However, the pattern of AEs was similar across study time intervals (12 week periods), including > 250 days. Based upon the safety profile observed during the 4 week pivotal Phase III registration studies (AN2728-AD-301 and AN2728-AD-302) and the 48 week open label safety study (AN2728- AD-303) described below, the overall safety profile following more than 1 year of intermittent treatment with crisaborole ointment twice daily is likely to be comparable to the current safety profile. The sponsor will continue to monitor the safety of Staquis post marketing through its pharmacovigilance activities and will make appropriate amendments to the PI as required.

The objective of Study AN2728-AD-303 was to evaluate the long term safety of open label treatment with crisaborole ointment in children, adolescents, and adults (ages 2 years and older) with mild to moderate AD. The study included twelve 28 day treatment cycles. Thus, the study design allowed the assessment of long term safety over 52 weeks (with the inclusion of the 4 weeks from the pivotal Phase III registration Studies AN2728-AD-301 and AN2728-AD-302) with long term intermittent therapy. Subjects were evaluated by the Investigator for AD severity approximately every 28 days to determine if they entered or continued an 'on-treatment' (subject had an Investigator's ISGA score ≥ 2) or 'off-treatment' (subject had an ISGA score ≤ 1) cycle. Thus, consistent with ICH E1 guidance[19], the study design allowed for up to 1 year of treatment whether intermittent or continuous.

While treatment cycles were intended to be approximately 28 days (nominally 4 weeks), treatment cycles ranged from 1 to 73 days in duration with a median duration of 29 days. Most subjects did not receive treatment at every cycle. The mean number of on-treatment cycles was 6.2While treatment cycles were intended to be approximately 28 days (nominally 4 weeks), treatment cycles ranged from 1 to 73 days in duration with a median duration of 29 days. Most subjects did not receive treatment at every cycle. The mean number of on-treatment cycles was 6.2. [Information redacted]*Evaluation of response*

The sponsor response has been noted. The sponsor essentially states that there were nearly no patients treated with crisaborole for longer than 1 year (continuously or intermittently). The range of continuous treatment was given as 0 to 377 days. The

[19] ICH harmonised tripartite guideline. The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions E1.

median cycle length was 29 days. Eight patients (out of 517; 1.55%) had 13 cycles, that is, they were treated for longer than 1 year (assuming 29 days per cycle).

The clinical evaluator does not agree with the sponsor's proposed PI change.

12. Does the sponsor have data with regard to the potential for photosensitivity with crisaborole?

Sponsor response

Data from structure elucidation study shows that crisaborole does not absorb in the ultraviolet (UV) range; therefore, no phototoxicity testing was considered necessary per ICH S10 Guidance on Photosafety Evaluation of Pharmaceuticals;[20] and crisaborole is not expected to pose a risk for photosensitivity.

Clinical data

Study AN2728-PSR-107, was a randomised, double blind, vehicle controlled study to assess the local tolerability of crisaborole in sensitive areas in healthy adult subjects. Subjects applied investigational product to the extensor areas, intertriginous areas, genitals, and face/hairline twice daily for 21 days. Sunburn was reported in 4 subjects (17%) in active and 1 subject (13%) in vehicle.

[Information redacted]

Evaluation of response

The sponsor response has been noted.

13. How many patients fulfilled the criteria of Hy's Law?[17]

Sponsor response

Among the overall safety population, which included 1679 subjects with AD (of which 1150 were ≤ 17 years of age) none fulfilled the criteria of Hy's Law.

[Information redacted]

Evaluation of response

The sponsor response has been noted.

Second round benefit-risk assessment

Second round assessment of benefits

Table 12 gives the benefits along with the strengths and uncertainties as was assessed at the second round of evaluation.

Table 12: Second round assessment of benefits

Benefits	Strengths and Uncertainties
Crisaborole 2% ointment was shown to be superior to vehicle for the treatment of mild to moderate AD in Studies AN2728-AD-301 and AN2728-AD-302. The pooled efficacy endpoints (difference between crisaborole 2% ointment and vehicle at Day 29) of those	The two pivotal studies were adequately designed and conducted. The study population was largely representative of the target patient population in Australia. The AD endpoints chosen were validated and clinically relevant. However, the endpoints heavily relied on ISGA;

20 International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use; Photosafety evaluation of Pharmaceuticals S10

Benefits	Strengths and Uncertainties
studies were as follows: • ISGA responder proportion (%): 10.3 (p < 0.001) (number needed to treat (NNT) = 9.7) • ISGA Clear or Almost Clear proportion (%): 14.9 (p < 0.001) • Mean ISGA change from Baseline: −0.4 (p < 0.001) • Proportion of improvement in AD signs and symptoms (%): – Erythema: 18.8 (p < 0.001) – Excoration: 12.1 (p < 0.001) – Lichenification: 10.7 (p < 0.001) – Pruritus: 10.0 (p = 0.002) • Median time to Improvement of pruritus (days): −0.33 (p = 0.001) • Change from Baseline in treatable %BSA (LS mean): −3.0 (p < 0.001) Overall, crisaborole improved all assessed AD symptoms in a greater proportion of patients when compared to vehicle. Patients' mean Dermatitis Life Quality Index (DLQI) Score, Children's Dermatology Life Quality Index (CDLQI) Score, and Dermatitis Family Impact Questionnaire (DFI) Score all improved. The results also appear to be clinically significant.	Scoring Atopic Dermatitis index (SCORAD) and Eczema Area and Severity Index (EASI) appear to not have been considered. Only crisaborole 2% ointment in monotherapy (no combination with other products) was investigated with no active comparator. Comparisons have only been made to vehicle. Specifically, no studies were provided that included the following active comparators: proprietary emollients, TCSs or TCIs. In the response, the sponsor provided some literature data with active comparators. However, there was no evidence for superiority. The only randomised control trial (RCT) efficacy data available (Studies AN2728-AD-301 and AN2728-AD-302) did not assess efficacy beyond 28 days of treatment. Study AN2728-AD-303 (the 48 week open label extension study of Studies AN2728-AD-301 and AN2728-AD-302) was not designed to assess efficacy; the selection criteria may have skewed the population towards a larger proportion of responders; confounding may not have been adequately controlled. Relapse and rebound were not formally assessed. The pivotal trials included Asian patients, but the overall responder proportion was smaller. Due to the small numbers that may not have been representative or significant, but a large Asian Australian paediatric population is affected by AD. There is no human data on use in pregnancy. There is potential for off-label use in psoriasis or other conditions potentially responsive to crisaborole ointment. The precise mechanism of action of crisaborole in AD remains unknown.

Second round assessment of risks

Table 13 gives the risks along with their strengths and uncertainties as assessed at the second round of evaluation.

Table 13: Second round assessment of risks

Risks	Strengths and Uncertainties
Crisaborole has a relatively favourable safety profile. In the Phase III clinical development program: • Overall, the proportion of all TEAEs was slightly larger in the crisaborole	2157 patients or HVs were exposed to crisaborole ointment. Some of the alternative treatments for AD may have more frequent and potential more significant AEs when compared to crisaborole ointment. However, no direct safety comparison to vehicle or active comparator was conducted.

Risks	Strengths and Uncertainties
group (compared to vehicle) (Study AN2728-AD-301: 29.3% versus 19.8%; Study AN2728-AD-302: 29.4% versus 32.0%; Study AN2728-AD-303: 65.0%). • Overall, the proportion of treatment related TEAEs was slightly larger in the crisaborole group (compared to vehicle) (Study AN2728-AD-301: 9.6% versus 6.2%; Study AN2728-AD-302: 5.1% versus 5.3%; Study AN2728-AD-303: 10.8%). This may have been mainly due to application site TEAEs. • There were no deaths. • Only a few SAEs were observed, only one (application site infection) was related to treatment. • DAE was uncommon and discontinuation of treatment due to an application site reaction was in < 3% of patients. • None of the patients fulfilled the criteria for Hy's law.	Uncertainties include: • The two pivotal trials included a control group that enabled comparison until Day 29. Study AN2728-AD-303 had no control group which allowed for comparison. Consequently, the data until Week 48 had no comparator. • Eligibility in Study AN2728-AD-303 included the absence of drug related safety issues from Studies AN2728-AD-301 and AN2728-AD-302 and may have biased the study population. • The Phase III clinical development program used crisaborole 2% ointment, whereas some studies in Phase I and II had a lower or higher concentration (up to 5%). • One patient reported to have an anaphylactic reaction, but this may have been due to a nut allergy. • A significant proportion (25% was recovered) of the crisaborole dose is absorbed through the skin and results in systemic exposure to the two primary metabolites: AN7602 and AN8323. There is a potential for immunologically mediated adverse drug reactions. • No PSUR/PBRER has not been submitted with the dossier (it may not be available yet). • There is no human data on use in pregnancy. • Long term safety has only been assessed in the confines of a single group open label trial up to a total of 48 weeks (additional to the 4 weeks in the RCT); nearly no patients were treated with crisaborole for longer than 1 year.

Second round assessment of benefit-risk balance

As per the first round assessment, crisaborole has a favourable benefit-risk balance in short term use for the treatment of AD.

Regarding efficacy: in sponsor conducted clinical trials, superiority was only established compared to placebo and not against active comparators, and only up to 28 days. Some literature data (not evaluated for validity) suggests similar efficacy to TCSs (see sponsor response to first round question 5). Relapse and rebound were not formally assessed.

It is unclear to the second round evaluator why the sponsor has not conducted a RCT that incorporates active comparators. It is that noted that the sponsor is currently conducting such a Phase IIIb/IV trial (NCT03539601).

Regarding safety: crisaborole is likely to have a more beneficial safety profile compared to TCSs and TCIs, but not necessarily compared to proprietary emollients.

Regarding duration of use: the data for use beyond 28 days (in Study AN2728-AD-303) is rather limited (when compared to the RCT data in the pivotal Studies AN2728-AD-301 and AN2728-AD-302) and not sufficiently robust to recommend approval for use longer than 28 days.

From the data available at this stage:

- Rather than providing a superior treatment, crisaborole would add to the management options available to treat AD based on individual patient circumstances.
- Given the potential significant adverse effects of some of the other treatments, the use of crisaborole does have merit in many instances, and may be beneficial in improving quality of life. However, given the limitations of the data beyond 28 days, the indication should be restricted to short term use, until more longer term data becomes available.

In the PI, the restriction to short term use could be either achieved by either:

- stating this in the indication directly; or,
- retaining the currently proposed indication, but stating elsewhere in the PI, that the data for use beyond 28 days is rather limited and not based on RCT data, but on open label single group data.

At this stage the second round clinical evaluator would favour the latter approach.

The benefit-risk balance of crisaborole 2% ointment is unfavourable for the proposed usage, but would become favourable if the changes recommended in this section (restriction to short term use) are adopted.

Second round recommendation regarding authorisation

The clinical evaluator recommends approval of the application to authorise Staquis (crisaborole 2% ointment) for the therapeutic indication of:

> *Staquis is indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.*

Additional to the restrictions already in place in the proposed PI, this recommendation is in the context of restricting the drug for short term use up to 28 days. Furthermore, the positive recommendation would be conditional on the sponsor committing to making the PI changes and the changes to the proposed risk management plan (RMP)/Australian specific annex (ASA) as recommended by the clinical evaluator.

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation[21]

The sponsor has submitted a Core RMP version 1.0 (dated 26 May 2017; data lock point 30 November 2016) and ASA version 1.0 (dated 30 September 2017) in support of this application. The sponsor has provided an updated ASA version 2.0 dated 1 June 2018; data lock point 30 November 2016 with its response to incorporate recommendations made in the first round RMP evaluation.

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 14.

Table 14: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None identified	n/a	n/a	n/a	n/a
Important potential risks	None identified	n/a	n/a	n/a	n/a
Missing information	Effects on pregnancy and the foetus	ü	–	ü	–
	Use during breastfeeding	ü	–	ü	–
	Use in paediatric patients 3 months to < 2 years of age	ü[1, 2]	ü	ü	–
	Effects on elderly patient population	ü	–	–	–
	Use in renal impaired patients	ü	–	ü	–
	Use in hepatic impaired patients	ü	–	ü	–

[1] = post authorisation paediatric study; [2] = toxicology study in rats

The sponsor has proposed routine pharmacovigilance for all safety concerns.

[21] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

The sponsor has proposed additional pharmacovigilance activities which include one post marketing study and one animal study to further characterise the use of crisaborole in patients less than 2 years of age. The EMA has recommended a Paediatric Investigation Plan which should also be included as additional pharmacovigilance in the RMP/ASA.

The sponsor has proposed routine risk minimisation for all safety concerns.

No additional risk minimisation activities are proposed which is acceptable as the Consumer Medicine Information (CMI) has been updated to provide instructions regarding application of the ointment.

New and outstanding recommendations from second round evaluation

The sponsor has adequately addressed the recommendations made in the second round RMP evaluation report. There is no outstanding RMP issue with this submission.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> The Staquis EU-Risk Management Plan (RMP) (version 1.0, dated 26 May 2017, data lock point 30 November 2016), with Australian Specific Annex (version 2.0, dated 1 June 2018, data lock point 30 November 2016), included with submission PM-2017-03748-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The following wording is recommended for the PSUR requirement:

> An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).

As Staquis is a new chemical entity, it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> Staquis (crisaborole) is to be included in the Black Triangle Scheme. The PI and CMI for Staquis must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Introduction

Background on condition being treated

The sponsor has applied to register a new chemical entity, crisaborole (Staquis). Staquis is proposed to be used as indicated for topical treatment of mild to moderate AD in patients 2 years of age and older.

Atopic dermatitis (AD) is a chronic pruritic inflammatory condition of the skin more common occurrence in children and may improve with age. It is characterised by dryness of the skin (xerosis), itching (pruritus) and in more severe conditions inflamed, red and weeping lesions. It is characterised by remitting and recurring course.

The current treatment options for AD include topical treatments such as emollients, TCSs/TCIs; systemic treatments such as oral corticosteroids, ciclosporin, methotrexate and azathioprine; adjunctive treatments such as antibiotics, antivirals and antihistamines.

Initial management of AD includes identifying and avoiding trigger factors, such as irritants, skin infections, contact allergens, food allergens and inhalant allergens.[3] There should be a stepwise approach to further management with:

1. Mild AD being treated with: emollients and mild potency topical corticosteroids
2. Moderate AD being treated with: emollients, moderate potency topical corticosteroids, TCIs, and bandages
3. Severe AD being treated with: emollients, potent topical corticosteroids, TCIs, bandages, phototherapy and systemic therapy.

Severe itching or urticaria should be treated with a non-sedating antihistamine, and if there is also significant sleep disturbance a sedating antihistamine could be used instead. Bacterial infections should be treated with an antibiotic with effective staphylococcal and streptococcal coverage. Herpes simplex infections should be treated with aciclovir.

Dupilumab, an IL-4Rα receptor antagonist, has been developed for the treatment of severe AD in adults and has recently been registered. However, it is not indicated for the treatment of AD in children.

Crisaborole is a PDE-4 inhibitor and is developed for topical treatment of mild to moderate AD. The specific mechanism(s) by which crisaborole exerts its therapeutic action is not well defined.

Quality

Approval is recommended from a pharmaceutical chemistry and quality control perspective pending minor deficiencies which need to be addressed by the sponsor.[22]

The drug product has been formulated as a white soft paraffin based ointment containing 20 mg per gram (2% w/w) of crisaborole packaged in multi-laminate aluminium tubes with a polypropylene cap, high density polyethylene tube head and multi-laminate orifice seal. The drug product is filled into four packaging presentations with nominal content of 2.5 g, 30 g, 60 g, and 100 g.

GMP clearances for the drug substance and drug product manufacturing sites are all currently valid past the expected decision date.

[22] These issues were resolved prior to registration

Nonclinical

There were no deficiencies in nonclinical data.

Primary pharmacology studies provided sufficient evidence of crisaborole's affinity and selectivity for human PDE4, as well the inhibition of pro-inflammatory cytokine secretion. This supports the sponsors proposed indication.

Treatment related effects associated with topical dosing of crisaborole were minimal and limited local irritation following topical dosing. Minimal skin irritation was also observed in clinical studies following topical application of 2% crisaborole.

The available data indicate that crisaborole does not pose a genotoxic or carcinogenic risk.

Pregnancy Category B1 is considered appropriate.[15]

There are no nonclinical objections to the registration of 2% crisaborole for the proposed indication.

The nonclinical evaluator also made recommendations on changes to the PI; however, description of these is beyond the scope of the AusPAR.

Clinical

The clinical evaluator has recommended rejection initially but on second review, recommended approval of crisaborole for indication for the topical treatment of patients with AD (provided it is restricting for short-term use up to 28 days only).

> *Staquis is indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.*

In the response and subsequent reviews, the sponsor has accepted most of the changes to the proposed product information.

Pharmacology

Pharmacokinetics

Crisaborole ointment (2% concentration) will be administrated topically and the dose regimen is twice daily application.

The sponsor conducted a PK study under maximal use conditions in 33 subjects with AD ages 2 to 17 years. Crisaborole and its metabolites were quantified in serum from all subjects. Steady state was reached by Day 8. For crisaborole on Day 8, the C_{max} was 127 ± 196 ng/mL, and the AUC_{0-12} was 949 ± 1240 ng-h/mL.

The sponsor conducted *in vitro* and clinical drug interaction assessments. Crisaborole and its major metabolite AN7602 are not expected to impact CYP enzymes under the condition of clinical use. Downstream metabolite AN8323 was identified as a weak to moderate inhibitor of CYP enzymes *in vitro*, a clinical study found no drug interaction effect on the most sensitive enzyme, CYP2C9, and thus AN8323 is not expected to produce clinically meaningful inhibition of any CYP enzymes.

Pharmacodynamics

Limited PD data was provided and there was no PK/PD data. However, crisaborole is intended for topical administration and there could be technical difficulties in performing PK/PD studies as suggested by the clinical evaluator. The dermal tolerability studies were supportive of crisaborole and there was no indication of sensitisation. There was no clinically significant PD interaction with warfarin.

A thorough QT study in healthy adults was conducted in which crisaborole was applied to 60% of body surface area of subjects in the supratherapeutic dose group. No significant prolongation of the QTc interval was identified; however, systemic crisaborole exposure in the supratherapeutic dose group was lower than that in the maximal use pharmacokinetic trial. However, there was no evidence that crisaborole has a clinically meaningful effect on the QTc interval.

Dose selection

There were limited dose finding studies performed in patients with AD. These studies compared the 0.5% and 2% formulations and indicated greater efficacy for the 2% formulation; and greater efficacy for twice daily application compared to once daily. Studies were performed in patients with psoriasis with a 5% formulation that indicated better tolerability with the 2% formulation. This may have influenced the sponsor's choice of the 2% formulation.

Efficacy

Study AN2728-AD-301 and AN2728-AD-302

The sponsor submitted data from two pivotal trials, Studies AN2728-AD-301 and AN2728-AD-302 to establish the efficacy of their product in the treatment of mild to moderate AD. The trials were identical multi-centre, prospective, randomised, double blind, placebo controlled parallel group studies, conducted concurrently in the USA to evaluate the effect of crisaborole ointment, 2%, applied twice daily for 28 days.

The trials enrolled more than 1500 subjects aged 2 years of age and older with AD affecting at least 5% of the BSA and a score of mild (2) or moderate (3) on a five grade Investigator Static Global Assessment scale (ISGA) that rated erythema, induration/papulation, and oozing/crusting. Subjects were permitted to use a bland emollient on uninvolved skin '…but not on or overlapping the treatable AD involved areas'. Use of topical or systemic corticosteroids or topical calcineurin inhibitors was prohibited during the study. Subjects on stable regimens of oral antihistamines or inhaled corticosteroids were allowed to continue these treatments.

Subjects with any clinical significant medical disorder; unstable AD or any consistent requirement for high potency topical corticosteroids; significant or localised infections, history of use of biologics prior to study; anticipated concomitant use of systemic or topical therapies that might alter the course of AD or has undergone 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) were excluded.

Subjects were randomised 2:1 (crisaborole ointment, 2% applied twice daily for 28 days: vehicle applied twice daily for 28 days). After completing the treatment period, subjects scheduled a final safety evaluation for assessment of vital signs, adverse events and local tolerability.

Subjects continued to treat all areas which were identified on Day 1 'regardless of whether they become clinically clear prior to Day 29'. Subjects documented all applications in the Dosing Diary and applied any missed doses as soon as possible.

Investigator re-evaluated safety and efficacy parameters on Days 8, 15, 29. Safety assessments included physical examinations, vital sign measurements, AE reports, clinical laboratory testing (haematology, serum chemistry, and urinalysis), evaluation of concomitant medications, and assessment of local tolerability. Efficacy assessments included an evaluation of global severity of AD on five point ISGA scale, severity of pruritus on a four point scale and severity of signs of AD (erythema, induration/papulation, exudation, excoriation, and lichenification) on a four point scale.

Subjects were permitted to withdraw from the trial at any time for any reason and reasons were captured.

The primary efficacy variable was success in ISGA, defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a two grade improvement from Baseline.

- The primary efficacy endpoint was the proportion of subjects who achieved success in ISGA at Day 29 in the crisaborole treated group compared to the vehicle treated group.
- Secondary endpoints included:
  - the proportion of subjects with an ISGA score of Clear (0) or Almost Clear (1) at Day 29 in the crisaborole treated group compared to the vehicle treated group, and
  - time to success in ISGA in the crisaborole treated group compared to the vehicle treated group.
- Safety outcome measures were local tolerability; AEs; concomitant medication; clinical laboratory tests; height, weight and vital signs; ECGs; and physical examination

The majority of the subjects completed the trials (Studies AN2728-AD-301 and AN2728-AD-302). A greater proportion of subjects discontinued from the vehicle group (12.1 to 14.8%) than the crisaborole ointment, 2% group (5.9 to 6.0%). There was no major imbalance in baseline demographic characteristics.

The results of the primary and secondary endpoints are presented in Table 15 below.

Table 15: Primary and secondary endpoints of Phase III studies

	Study AN2728-AD-301			Study AN2728-AD-302		
Endpoints	Staquis N = 503	Vehicle N = 256	P-value	Staquis N = 513	Vehicle N = 250	P-value
Primary: Success in ISGA	32.8%	25.4%	0.038	31.4%	18.0%	< 0.001
Secondary:						
ISGA 0 or 1	51.7%	40.6%	0.005	48.5%	29.7%	< 0.001

Time to success could not be calculated because fewer than 50% of subjects achieved success in (as defined by) ISGA.

In both trials, crisaborole was statistically superior (p-values < 0.05) to vehicle for the primary endpoint, and also for the secondary endpoint ISGA 0 or 1.

Exploratory variables supporting primary/secondary endpoints were analysed:

- Median time to improvement in pruritus was 1.32 days for crisaborole and 1.87 for vehicle, $p < 0.001$ in Study AN2728-AD-301; and 1.41 days for crisaborole and 1.54 for vehicle, $p = 0.425$ in Study AN2728-AD-302.
- There was improvement from Day 8 in all of the symptoms of AD, with greater improvement in the crisaborole group (both Studies AN2728-AD-301 and AN2728-AD-302).
- The change from Baseline was greater for crisaborole than vehicle for all the individual signs except induration/papulation (both Studies AN2728-AD-301 and AN2728-AD-302).

- Mean (SD) change from Baseline in treatable %BSA was –8.2 (12.83) % and –5.8 (12.79) in Study AN2728-AD-301 and –6.7 (12.22) % and –3.1 (11.07)% for vehicle in Study AN2728 AD 302.
- Quality of life instruments: crisaborole subjects experienced greater reductions in mean score from Baseline/Day 1 to Day 29 than vehicle subjects in both studies.

In the Integrated Summary of Efficacy the difference in success rate between crisaborole 2% ointment and vehicle was 10.3% of patients. Overall, the difference between crisaborole and vehicle in success in improvement in pruritus at Day 29 was 10% of patients. This indicates a number needed to treat of 10. Improvement in pruritus score was demonstrated from Day 8 and increased through to Day 29. The median time to improvement in pruritus was 5.0 days earlier with crisaborole. The difference in improvement in treatable %BSA for crisaborole compared to vehicle was –3%. Improvements in AD were measurable from Day 8 of treatment and increased to Day 29.

Additional efficacy studies

- Study AN2728-AD-102 indicated similar benefit in the different age groups, and benefit for all the symptoms of AD.
- Study AN2898-AD-202 (all Australian sites) indicated benefit in adults with AD, using the ADSI as the main outcome measure. Success rates using the ADSI were greater than in the subsequent pivotal studies using the ISGA.
- Study AN2728-AD- 203 was an exploratory study indicating potential benefit for crisaborole 2% ointment.
- Study AN2728-AD-204 (nearly half were Australian sites) was a dose finding study in adolescents with AD and found the greatest efficacy was with the crisaborole 2% formulation applied twice daily.

Safety

Overall the safety profile of crisaborole ointment, 2% was reasonably well characterised in the population with mild to moderate AD. The sponsor evaluated the local and systemic safety of their product in an adequate number of subjects to identify relevant safety issues.

The primary source of data for the evaluation of long term safety was Study AN2728-AD-303. Eligible subjects included males and females aged 2 years and older that completed the pivotal efficacy trials (Studies AN2728-AD-301 and AN2728-AD-302) without any study drug related safety issues.

The overall safety database in AD, based on subjects with AD who received crisaborole at concentrations from 0.3 to 5%, includes data from 1340 subjects, of whom 1293 were exposed to crisaborole 2% twice daily and 1150 of whom were < 17 years of age. The primary safety database for AD, comprised of pooled data from the Phase III trials, includes data from 1012 subjects who received crisaborole and 499 subjects who received vehicle.

No deaths were reported during the development program. SAEs were reported in 9 subjects (8 crisaborole and 1 vehicle) during the pivotal trials and 7 subjects during the long term safety study. Only one of which could have been related to treatment: application site infection. Overall adverse event rates were similar across study arms. The most frequently reported adverse reaction was application site pain.

There were occasional reports of elevated hepatic transaminases, one with associated hyperbilirubinaemia. There were no other clinically significant abnormalities in clinical chemistry. There were occasional reports of haematological abnormalities that were attributable to intercurrent illness or to atopic conditions.

There were few serious cutaneous reactions. One volunteer discontinued because of urticaria. There were several skin and/or soft tissue infections that would be consistent with AD. There was one drug eruption, reported as a SAE, and attributed to penicillin. The risk for hypersensitivity reactions, including contact urticaria, is addressed in labelling.

Risk management plan

The RMP evaluator has noted that the summary of safety concerns and proposed additional pharmacovigilance activities were amended during the evaluation process and these are now acceptable.

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised in Table 14 (above).

The sponsor agreed to the recommendations regarding 'missing information' and confirms that routine pharmacovigilance includes collection of ethnicity data, when reported, in the safety database. The sponsor also added the statement regarding the lack of clinical evidence in long term use in the PI. Wording of conditions of registration has been explained below.

- The sponsor has proposed routine pharmacovigilance for all safety concerns.
- The sponsor has proposed additional pharmacovigilance activities which include one postmarketing study and one animal study to further characterise the use of crisaborole in patients less than 2 years of age. The EMA has recommended a Paediatric Investigation Plan which should also be included as additional pharmacovigilance in the RMP/ASA.
- The sponsor has proposed routine risk minimisation for all safety concerns.
- No additional risk minimisation activities are proposed which is acceptable as the CMI has been updated to provide instructions regarding application of the ointment.

The RMP may need to be amended to include depression, suicidal ideation and weight loss as class effect and therefore should be closely monitored in the postmarketing activities.

Risk-benefit analysis

Delegate's considerations

Overall, thePK of crisaborole 2% ointment is well characterised in the clinical program without posing any substantial issues. Drug-drug interaction studies did not detect any clinically significant interactions. Crisaborole has no clinically significant impact on cardiac repolarisation. Better tolerability with the 2% formulation possibly influenced the selection of dose.

Both the pivotal Phase III efficacy studies were well designed and conducted to support the use of crisaborole 2% ointment, for the topical treatment of mild to moderate AD. In the pivotal studies, the formulation used was that proposed for marketing in Australia, and the dosing regimen and administration instructions was the same as that in the proposed PI and CMI. Crisaborole ointment, 2% was statistically superior to vehicle ointment on the primary and secondary efficacy endpoint in both trials.

Overall, the difference in success rate between crisaborole 2% ointment and vehicle was 7.4% (Study AN2728-AD-301) and 13.4% (Study AN2728-AD-302) of patients. The difference in proportion of patients with ISGA of Clear or Almost Clear at Day 29 was 11.1% (Study AN2728-AD-301) and 18.8% (Study AN2728-AD-302). Crisaborole improved all the symptoms of AD, compared with vehicle. In addition, a greater

proportion of subjects in the crisaborole arm experienced improvement in all signs and symptoms of AD at Day 29 than subjects in the vehicle arm.

Due to lack of direct head to head comparison data with TCSs or TCIs, optimal use of crisaborole 2% ointment in the treatment of mild to moderate AD is not clear.

Although crisaborole is a new molecular entity, it is not first in class. The route of administration for crisaborole is topical, whereas the other products in the PDE4 class are oral dosage forms (roflumilast and apremilast). The safety profile of crisaborole ointment, 2% was relatively well characterised in the population aged 2 years or more with mild to moderate AD. There were no deaths and no serious adverse events that were attributed to the study product. The only adverse reaction observed in greater than 1% of subjects compared with vehicle was application site pain.

However, uncertainty still remains in areas of depression, suicidal ideation and weight loss as safety concern. All of these events are included in the Warnings and Precautions sections of labelling for the approved, orally administered phosphodiesterase inhibitors such as roflumilast and apremilast. Safety studies lacked validated instrument to detect the signal of depression, suicidal ideation and weight loss. Although oral administration of PDE4 inhibitors has greater anticipated exposure than a topical product, the occurrence of these potential class effects needs to be monitored carefully in future clinical trials of crisaborole ointment and postmarketing surveillance.

Although, the overall benefits of crisaborole 2% ointment in mild to moderate AD are modest, addition of a therapeutic option (with appropriate safety labelling) with clinically meaningful benefit to the population with AD seems reasonable. The approval of crisaborole 2% ointment may provide an alternative for patients who are unresponsive to the currently available treatment options (TCS and TCI) or unable to use them based on their adverse event profile.

Deficiencies of the data

- No studies with proprietary emollients as comparator.
- No studies with TCS as comparator.
- No studies with TCI as comparator.
- No studies in combination therapy.
- Depression, suicidal ideation and weight loss; class effect safety data.

The efficacy data only cover a duration of therapy of 4 weeks. There are no long term efficacy data, and it is not clear whether response to crisaborole is maintained over time. There were also no data assessing for rebound phenomena.

Delegate's preliminary assessment and proposed action

Overall crisaborole is approvable as the quality, nonclinical and clinical evaluators (subjected to product information changes) have all recommended approval. The Delegate considers that sufficient data and justification have been provided to support the registration of crisaborole on quality, safety and efficacy grounds for the treatment of patients with mild to moderate AD.

Request for ACM advice

The Committee is requested to provide advice on the following specific issues:

1. What are the ACM's views on the efficacy and to what extent is there sufficient clinical trial evidence to support the proposed indication for crisaborole? Should crisaborole 2% ointment be used as first line agent for AD or considered after TCS or TCI?

2. Does the ACM consider appropriate to restrict the use to short term (up to 28 days)?
3. Does the the ACM consider that the safety of crisaborole in the proposed new indication is sufficiently well characterised and communicated in the PI? Is there a need for class effect warnings on depression, suicidal ideation and weight loss in the PI?

The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Optimal use of Staquis

> *The Delegate has sought advice from the ACM, as to whether Staquis should be used as first line agent for AD or considered after topical corticosteroids (TCSs) or topical calcineurin inhibitors (TCIs); and states that the optimal use of Staquis is not clear.*

The therapeutic effect of crisaborole as a monotherapy to treat AD was confirmed by the results of 2 identically designed randomised, double blind, vehicle controlled, Phase III registration studies (Studies AN2728-AD-301 and AN2728-AD-302). When evaluated both individually and collectively, the success achieved in the primary, secondary, and other endpoints provides robust, clinically meaningful evidence of the efficacy of crisaborole. Benefits include an overall reduction in the severity of AD with rapid improvement in pruritus, reduction of signs of AD (erythema, induration/papulation, exudation, excoriation, and lichenification), decreases in BSA involvement and meaningful improvements in quality of life for both patients and caregivers. In the pooled population, 58.9% and 54.3% of subjects in the crisaborole and vehicle groups, respectively, were defined as treatment naïve and 40.0% and 44.5% of subjects in the crisaborole and vehicle groups, respectively, had prior corticosteroid use. Crisaborole efficacy was similar in treatment naïve and treatment experienced groups.

There are no demonstrated safety concerns with crisaborole that would warrant placement later in the line of therapy. The safety findings in the crisaborole AD program did not include evidence of cutaneous reactions at the application site (for example, atrophy, telangiectasia or hypopigmentation as have been described with the use of TCSs). There was no signal for immunosuppression, including no evidence for increased risk of serious infections or malignancies, consistent with results of nonclinical safety studies. Furthermore, the safety profile of crisaborole was not consistent with the adverse reactions reported with systemically administered small molecule PDE4 inhibitors, such as gastrointestinal disorders, psychiatric disorders (specifically, depression and SIB), serious infection, malignancy, and major adverse cardiac events.

Based on its favourable safety and efficacy profile, crisaborole addresses a medical need by avoiding serious local and/or systemic toxicity that can occur with the available therapies (TCSs and TCIs) while relieving the signs and symptoms related to AD patients aged 2 years and older. Furthermore, we wish to point out that there is a lack of EU regulatory guidance requiring head-to-head comparisons. Dupixent (dupilumab) safety and efficacy was evaluated in 3 double blind placebo controlled studies. While Dupixent is for severe AD, head-to-head trials were not required in order to determine its place in therapy.

The pivotal trials included both subjects who were treatment naïve and treatment experienced (with TCSs and/or TCIs). Crisaborole efficacy was similar in both groups. Furthermore, there are no demonstrated safety concerns with crisaborole that would necessitate placement later in the line of therapy. Therefore, the decision to use first or second line should be up to the discretion of the treating clinician, based on the patient's individual condition and requirements.

Long term safety and efficacy

> *The Delegate has sought the advice of ACM regarding possible restriction of Staquis use to 28 days, citing the lack of data to assess long term safety and efficacy or the potential for rebound phenomena, and that it was not clear whether efficacy would be maintained over time.*

Study AN2728-AD-303 was an open label, single arm, long term safety study in subjects who completed Study AN2728-AD-301 or Study AN2728-AD-302 without safety issues that precluded further treatment with crisaborole in the opinion of the Investigator and who met the study inclusion/exclusion criteria. The objective of the study was to evaluate the long term safety of open label treatment with crisaborole ointment in children, adolescents, and adults (ages 2 years and older) with mild to moderate AD. Subjects participated in the study for up to 48 weeks (twelve 28 day treatment cycles).

No predefined efficacy analysis was conducted for the study. The ISGA score was the only efficacy assessment recorded during the study, and was utilised by Investigators to determine whether the subject would receive crisaborole (on-treatment) or no study drug (off-treatment) at the beginning of each cycle. Ad hoc efficacy analyses have been conducted to assess the treatment effect over time by analysing the ISGA response over time.

Study AN2728-AD-303 mean baseline ISGA score was assessed 6.7 days (mean; range 1 to 18 days) after the Day 29 assessment in the pivotal Studies AN2728-AD-301 and AN2728-AD-302. Between Day 29 of Studies AN2728-AD-301 and AN2728-AD-302 and the baseline assessment of Study AN2728-AD-303, the use of bland emollient(s) was permitted to manage dry skin in the areas surrounding, but not on or overlapping, the treatable AD involved areas. The majority (84.5%) of the subjects in Study AN2728-AD-303 had an ISGA score of 2 (mild) or 3 (moderate) at the Baseline of Study AN2728-AD-303.

The proportion of subjects with an ISGA Clear (score of 0) or Almost Clear (score of 1) response improved over time, with 55% of subjects achieving a response of ISGA Clear or Almost Clear at Week 48. This assessment of efficacy in the long term extension Study AN2728-AD-303 shows that clinical benefit as assessed by ISGA was sustained with long term intermittent treatment with crisaborole ointment.

Regarding rebound phenomena, in the current AD literature there is no formal definition of rebound and in the Phase III registration studies (Studies AN2728-AD-301, AN2728-AD-302 and AN2728-AD-303) this was not specifically investigated or formally defined in the study protocols. In order to address the question, the sponsor has defined rebound as worsening of AD that is greater than the Baseline severity in Studies AN2728-AD-301 and AN2728-AD-302. For subjects with Mild ISGA at Baseline, following cessation of treatment, 21.05% had a score of Moderate for crisaborole compared with 24.00% in vehicle at Baseline in Study AN2728-AD-303. For subjects with a Moderate ISGA at Baseline, following cessation of treatment, 3.59% had a score of Severe for crisaborole compared with 3.64% in vehicle at Baseline in Study AN2728-AD-303. Since the incidence of rebound (as defined for this analysis) was similar for crisaborole and vehicle, these data do not show evidence of a rebound phenomenon with cessation of crisaborole therapy.

AEs that were reported following the end of treatment (after the Day 29 clinic visit) in Studies AN2728-AD-301 and AN2728-AD-302, that might indicate potential rebound effects were rare and are summarised here. In Study AN2728-AD-301 only 3 of 502 subjects (0.6%) who had received crisaborole reported AEs reflecting worsening AD symptoms (1 dermatitis atopic, 2 eczema). Among the 252 subjects who had received vehicle, none experienced an AE potentially related to worsening AD symptoms. In Study AN2728-AD-302, 2/510 subjects (0.4%) who had received crisaborole reported AEs reflecting worsening AD symptoms (1 each of dermatitis atopic and eczema). Among 247

subjects who had been treated with vehicle, none reported an AE potentially related to worsening AD symptoms. Furthermore, no events of 'Rebound effect' were reported in any of the Phase III studies.

A postmarketing review was conducted to identify cases of rebound effect, cumulatively through 31 August 2018 (data on file). The review included events coded to Medical Dictionary for Regulatory Activities (MedDRA) (version 21.0) Preferred Terms: Rebound effect, Rebound atopic dermatitis, Rebound eczema, and Rebound psoriasis. One case of Rebound eczema was identified which describes a patient that stopped using the product on his face and the 'eczema came back.' An inconsistency in coding is noted; and this case does not describe rebound as no report of worsening or increased severity of the recurrence of disease was described.

In conclusion, the long term extension Study AN2728-AD-303 provides clinical trial evidence of a favourable safety profile and sustained efficacy with crisaborole treatment; and it is unlikely cessation of crisaborole treatment would lead to a rebound phenomenon.

Depression, suicidal ideation and weight loss as potential safety risks

> *The Delegate has asked the ACM's advice regarding the need for class effect warning on depression, suicidal ideation and weight loss in the PI, and whether the RMP required amending to include these as class effect warning and for them to be closely monitored in future clinical trials and postmarketing surveillance.*

The sponsor does not propose that suicidal ideation or behaviour (SIB), depression or weight loss be included in the summary of safety concerns for the RMP and does not believe that a warning in the PI is warranted or supported by the existing clinical data. These events will be assessed as a part of routine pharmacovigilance and in any (age appropriate) planned/ongoing crisaborole clinical studies.

The systemic exposures of crisaborole ointment under maximal use conditions are unlikely to achieve levels necessary to produce systemic pharmacologic effects of PDE4 inhibition. The limited systemic exposure to the PDE4 inhibitory effects of crisaborole, coupled with PDE4 inactivity of its metabolites, the low unbound crisaborole systemic concentration to inhibitory constants' (Ki) ratio, and the low fractional enzyme to inhibition ratio for the various PDE4 isoforms, lead to a safety profile different from that of systemically administered small molecule PDE4 inhibitors. The level of PDE4 enzyme inhibition at therapeutic doses of systemic agents, apremilast or roflumilast, is substantially greater than that achieved in crisaborole treated patients. Furthermore, nausea and other gastrointestinal related side effects are among the most commonly reported side effects associated with systemic PDE4 inhibitors. Compared with apremilast and roflumilast, crisaborole under maximal use conditions, was not associated with gastroinetestinal toxicity events, which are known signs of systemic PDE4 inhibitor toxicity. Thus, these data further support that crisaborole, even under maximal use conditions, does not produce systemically active PDE4 inhibition, and it should not, therefore, be considered a member of the systemic PDE4 inhibitor class.

Suicidal ideation and behaviour (SIB), and depression

Published evidence demonstrates that adolescents and adults with AD are at increased risk of SIB and depression.

Narratives for all SAEs related to depression and SIBs were provided in the submission. The crisaborole reported incidence rate of these events is low and is lower than the background epidemiologic data. Of note, there were no TEAEs of depression, suicidal ideation, or suicidal attempt reported in subjects aged 2 to 4 years, 5 to 11 years, or ≥ 18 years. All events occurred in adolescents, a population with a high background prevalence of SIB compared to adults. As noted in the narratives, all 4 subjects who experienced SAEs of depression and/or suicidal ideation or behaviour were adolescents, who are at greater

risk for these events compared to other age groups. Moreover, all had relevant risk factors for these events such as life circumstances or medical histories that included psychiatric disorders. In all cases, the SAEs were assessed as not related to study drug and therefore, study drug was not stopped.

Occurrences of SAEs for depression or SIB do not appear to be a result of greater exposure to crisaborole. In the Studies AN2728-AD-301 and AN2728-AD-302, the mean Baseline %BSA was 18%; whereas, in the four subjects who experienced SAEs of depression/suicidal ideation, the Baseline %BSA was less than 15% and in three of the four cases less than 10%. It is highly unlikely that in these cases, the levels of systemic exposure could have caused meaningful PDE4 inhibition and led to systemic effects, including CNS effects.

Crisaborole Phase III psychiatric adverse event data

Rates of SIB and depression events in the Phase III studies for crisaborole treated subjects were compared to rates of these events in vehicle treated subjects applying Fisher's exact test to Studies AN2728-AD-301, AN2728-AD-302 and the pooled analysis of Studies AN2728-AD-301 and AN2728-AD-302. There were no statistically significant differences between the treatment groups for suicidal ideation and suicide attempt ($p = 1.0000$ in Studies AN2728-AD-301, AN2728-AD-302 and the pooled analysis). Similarly, there were no statistically significant differences between treatment groups for suicidal ideation, suicide attempt, and depression ($p = 0.5544$ for Study AN2728-AD-301, $p = 1.0000$ for Study AN2728-AD-302, and $p = 0.3089$ for the pooled analysis). For further detail on Psychiatric Disorders in the Phase III studies see original submission.

Gastrointestinal effects are recognised signs of systemic PDE4 inhibitor toxicity. It should be noted that in an open label, systemic exposure study to assess safety and pharmacokinetics of crisaborole (Study AN2728-AD-102), no such gastrointestinal effects were observed under maximal use conditions through the 28 day duration of the trial.

Crisaborole post marketing (PM) psychiatric disorder data

To identify cases of psychiatric disorders, specifically suicidal ideation/suicidal behaviour and depression, PM cases cumulative through 31 August 2018 were searched for events coded to MedDRA (version 21.0) preferred terms within the Standardised MedDRA Queries (SMQ) Depression and suicide/self-injury (narrow terms). A total of 2 cases were identified, both coding to the preferred term Depression, which represents < 0.1% of PM cases. The first cases involved a 62 year old female who reported 'anxiety and depression' and was taking citalopram and zolpidem; whether anxiety and depression were reported in the context of pre-existing medical history or AEs was not specified. This case lacked the necessary information (for example, medical history, concomitant medications, therapy dates, event onset dates, and event outcomes) for meaningful medical assessment of association. The second case involved a 71 year old female who received crisaborole for eczema. The patient 'experienced itching, so she was depressed.' Additionally, it was reported that the patient's dog had died 2 weeks earlier and she had become more stressed. No action was taken with crisaborole and the outcome of the depression was unknown. This case did not report a medically confirmed diagnosis of depression and was based on the patient's use of the term of depression to describe how she felt due to another event that she experienced.

No new safety information with regard to crisaborole and SIB and depression was identified upon review of PM cases.

Weight loss

No AEs of weight loss occurred in any of the short term or long term Phase III trials (Studies AN2728-AD-301, AN2728-AD-302or AN2728-AD-303). A PM review was also conducted to identify cases of weight loss, cumulatively through 31 August 2018. The

search included events coded to MedDRA (version 21.0) preferred term Weight decreased. One case was identified. This case involved a 71 year old female patient with a history of abnormal blood pressure and thyroid disorder. The patient's weight was 215 pounds and the last time she was weighed, she lost weight but she did not know exactly how much. Crisaborole treatment continued and the outcome of the event was unknown.

Conclusion

In summary, topical crisaborole is unlikely to achieve systemic exposures resulting in inhibition of PDE4 that would produce any systemic pharmacologic effects, including those affecting the central nervous system (CNS). The following points summarise the rationale for not including SIB and depression as potential risks for AD patients using crisaborole:

1. No statistically significant differences between the treatment groups for suicidal ideation, suicide attempt, and depression in the Phase III studies
2. Unrelated causality for the SIB events due to confounding factors (relevant concomitant medications and medical history, or no temporal relationship)
3. No association with high treated %BSA making it highly unlikely that the low levels of systemic exposure may have caused any systemic effects on the CNS in these subjects; and,
4. No other psychiatric disorder signals in the Phase III studies (for example, insomnia and anxiety).

The safety events such as SIB which are associated with oral systemic PDE4 inhibitors such as apremilast and roflumilast will be continuously monitored and evaluated as a part of routine pharmacovigilance and in any (age appropriate) planned/ongoing crisaborole clinical studies.

Details included in clinical trials section of the PI

> *The Delegate has requested the removal from the PI of all information relating to exploratory endpoints from the clinical trials.*

AD is described using clinical signs and symptoms of erythema, induration/papulation, exudation, excoriation, lichenification, and pruritus; each of which may have different levels of intensity over time depending on the acute or chronic nature of lesions. The response of each of these clinical signs and symptoms to crisaborole treatment provides patients, caregivers, and clinicians with valuable additional insights into the benefits of crisaborole across all clinical characteristics of AD. Removal of these data from the PI would substantially diminish the value of the Clinical Trials section of the PI to the prescribing clinician. For these reasons, the sponsor believes that these important endpoints should be retained in the PI as it can only improve the clinician's decision making process regarding the suitability of Staquis for their patient. This issue is discussed further in sponsor's comments on PI (not included here as it is beyond the scope of the AusPAR).

Absence of specific clinical studies in the dossier submitted

> *The Delegate has cited the following as data deficiencies: No comparator studies against proprietary emollients, TCS or TCI, and no studies in combination therapy.*

The sponsor notes there is no EU guidance that requires a head-to-head comparison with existing therapies. Crisaborole was compared to vehicle in the Phase III Studies AN2728-AD-301 and AN2728-AD-302. The proprietary vehicle had therapeutic benefit due to its emollient properties, and this benefit was significantly improved upon by the addition of the active drug substance, crisaborole.

The sponsor does not have efficacy data for crisaborole in combination with other treatments for AD. Rescue treatment was allowed in the long term extension study (Study AN2728-AD-303) based solely on Investigator's judgment, but it was not permitted in combination with crisaborole.

In conclusion, crisaborole would be expected to demonstrate superior efficacy over proprietary emollients and similar efficacy to the TCI, pimecrolimus, in mild to moderate AD. Of equal or greater importance, the safety profile of crisaborole is favourable compared to the well-established side effects of TCSs and TCIs for patients 2 years and older as described.

Conclusion

The data submitted by the sponsor demonstrate that Staquis would be a useful addition to the available options in treating AD. The sponsor looks forward to a favourable consideration of their application to register Staquis for the topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.

Advisory Committee Considerations[23]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Staquis, ointment in sizes of 30 g, 60 g, 100 g, and 2.5 g x 6, containing 2% w/w of crisaborole, to have an overall positive benefit-risk profile for the amended indication.

The indication presented to the ACM was:

> *Staquis is indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.*

The ACM recommended the amended indication:

> *Staquis is indicated for **short term** topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.*

In providing this advice the ACM noted the following:

- Study AN2728-AD-301 and Study AN2728-AD-302 were Phase III, multicentre, randomised, double blind, vehicle controlled efficacy and safety studies of crisaborole 2% in children, adolescents and adults with AD. The primary efficacy outcome measure was the proportion of subjects achieving success in ISGA at Day 29 in the crisaborole treated group compared to the vehicle treated group. The studies demonstrated that crisaborole improved symptoms of AD compared to vehicle.
- The ointment vehicle contains non-paraffin excipients which are irritants and propylene glycol (9%) which is also a sensitiser. As crisaborole was being compared to

[23] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and postmarket functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and postmarket advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

a vehicle that may be an irritant, the magnitude of benefit is uncertain. Comparison with an emollient of white soft paraffin and synthetic paraffin would be informative.

- Crisaborole has been approved for registration in the US and Canada. It is currently under review in the EU.

The ACM also advised that:

- the sponsor should be requested to provide further information regarding the use of excipients such as propylene glycol (a known sensitiser) in the placebo and the effect on the ISGA score.
- the sponsor should be requested to provide paediatric data broken down by age subsets in the Periodic Safety Update Reports.

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration and specifically advised the following:

- Inclusion in the Black Triangle Scheme to support extra clinical vigilance.
- The safety information on suicidal ideation, depression and weight loss should be incorporated into the PI, with details of the missing safety data and populations excluded from studies.

Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the PI and CMI.

Specific Advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. What are the ACM's views on the efficacy and to what extent is there sufficient clinical trial evidence to support the proposed indication for crisaborole? Should crisaborole 2% ointment be used as first line agent for AD or considered after TCS or TCI?

The ACM considered that there was sufficient evidence to support efficacy of crisaborole in AD, however noted that it was uncertain how this would translate in clinical practice given: the lack of comparative data with established therapies such as emollients, topical corticosteroids, or topical calcineurin inhibitors; no study in combination therapy; and no long term efficacy data beyond four weeks.

The ACM noted that there was no data presented to enable an assessment of place in therapy, or to preclude use as a first-line agent. The safety profile of crisaborole suggests low risk in first-line use.

The ACM also considered that in the absence of comparative efficacy data, the clinical place of crisaborole is uncertain, and may become better established with greater clinician experience.

2. Does the ACM consider appropriate to restrict the use to short term (up to 28 days)?

The ACM advised that it would be appropriate to restrict use of crisaborole to 28 days, consistent with the absence of clinical evidence beyond this period, and to include at the minimum a reference to 'short term' use in the indication.

The ACM considered that the principles of AD management encourage titration of active treatments. Clinical assessment and cessation of treatment with crisaborole after 28 days

would be appropriate, and if successful clearance is not achieved by that time then other active treatment options would need to be considered. After disease severity is reduced, long term maintenance and background management would be appropriate.

3. ***Does the the ACM consider that the safety of crisaborole in the proposed new indication is sufficiently well characterised and communicated in the PI? Is there a need for class effect warnings on depression, suicidal ideation and weight loss in the PI?***

The ACM considered that the safety of crisaborole was well characterised within the parameters of the studies presented and was mostly sufficiently communicated in the PI.

The ACM was of the view that a class effect warning on depression, suicidal ideation and weight loss should be included in the PI, particularly considering that the available safety data only extends to approximately one year and signals for these events may not have been detected within the limits of the submitted studies. Further, the ACM noted that there was significant systemic bioavailability (25%) from topical application, therefore monitoring for possible class effects is warranted.

The ACM noted that inclusion in the Black Triangle Scheme would support extra clinical vigilance.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Post ACM negotiations

Sponsor response to ACM recommendations

On 24 January 2019, the sponsor provided a response to the TGA regarding the ACM recommendations, including amendment of the proposed indication and PI changes. The sponsor does not agree with the delegate's proposal to add the word 'short term' to the indication. 'Short term' is an arbitrary, undefined period and is, therefore, an uninformative, vague and redundant term. There are no recognised safety concerns associated with the continuous use of Staquis for up to 4 weeks. However, the inclusion of the words 'short term' into the indication would create the implication that there is a safety concern with the use of the medicine for extended periods. Of note, topical corticosteroids, which do have clearly identified safety concerns associated with use as short as 2 weeks, do not include such wording in their indication.

The TGA's form for providing product information makes no mention of any need to describe the duration of use in the Indications section. It explains that the specific therapeutic uses should:

- be stated clearly and concisely
- define the target disease or condition
- distinguish between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and diagnostic indications.

Details regarding the duration of use are more appropriately located under Section 4.2 'Dose and Method of Administration', which is located directly after the Indication section. It includes the statements 'Staquis can be used continuously for up to 28 days per treatment course. The efficacy for continuous use beyond 28 days has not been studied in a controlled trial.' It also states that multiple treatment courses have been studied in a trial for up to 48 weeks, presenting no safety issues with intermittent use over this period. The

sponsor believes that this provides adequate qualification as to the appropriate maximum duration of continuous use of Staquis.

The sponsor provided a response to other changes to the PI recommended by the ACM; however, these are beyond the scope of this AusPAR.

Delegate review of Sponsor response

On 30 January 2019, the Delegate accepted the sponsor's response and agreed to remove the words 'short term' from the indication.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Staquis crisaborole 2% w/w ointment tube, indicated for:

> *Staquis is indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.*

Specific conditions of registration applying to these goods

- Staquis (crisaborole) is to be included in the Black Triangle Scheme. The PI and CMI for Staquis must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Staquis EU-Risk Management Plan (RMP) (version 1.0, dated 26 May 2017, data lock point 30 November 2016), with Australian Specific Annex (version 2.0, dated 1 June 2018, data lock point 30 November 2016), included with submission PM-2017-03748-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Staquis approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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