Taiwan Food and Drug Administration

Assessment Report

Trade Name：適健膚外用軟膏/STAQUIS Topical Ointment

Active Ingredient：Crisaborole

License Number：MOHW-PI 027999

Applicant：美商惠氏藥廠(亞洲)股份有限公司台灣分公司

Approval Date：2021/01/14

Indication：
適用於 2 歲(含)以上患有輕度至中度異位性皮膚炎病人的外用治療。

STAQUIS is indicated for topical treatment of mild to moderate atopic dermatitis in adults and pediatric patients 2 years of age and older.

1. Background Information

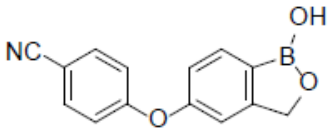
Trade Name	STAQUIS Topical Ointment
Active Ingredient(s)	Crisaborole
Applicant	美商惠氏藥廠(亞洲)股份有限公司台灣分公司
Dosage Form & Strengths	軟膏劑 每克(2%)含有 20 mg crisaborole
Indication	適用於 2 歲(含)以上患有輕度至中度異位性皮膚炎病人的外用治療。 STAQUIS is indicated for topical treatment of mild to moderate atopic dermatitis in adults and pediatric patients 2 years of age and older.
Posology	每日兩次在患處塗上薄薄一層的適健膚。適健膚僅供外用，不適用於眼睛、口服或陰道內之使用。 Apply a thin layer of STAQUIS twice daily to affected areas. STAQUIS is for topical use only and not for ophthalmic, oral, or intravaginal use.
Pharmacological Category ATC Code	D11AH06

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, crisaborole, is chemically designated as 5-(4-cyanophenoxy)-1, 3-dihydro-1-hydroxy-[2,1]-benzoxaborole and has the following structure:



It is a white to pale yellow powder. The molecular formula and the molecular weight are $C_{14}H_{10}BNO_3$ and 251.1 g/mol, respectively. It is freely soluble in common organic solvents such as isopropyl alcohol and propylene glycol, and insoluble in water.

Adequate information of characterization of the drug substance has been provided. The structure of crisaborole is confirmed by elemental analysis, UV/VIS spectrum, IR spectrum, mass spectrum and nuclear magnetic resonance spectrum.

The specification for drug substance includes tests for appearance, identification, assay, impurities, residual solvents, loss on drying and polymorph.

2.1.2 Drug product

The drug product contains 2% crisaborole (w/w) in a petrolatum-based, white to off-white ointment and is for topical use. All excipients used in the drug product are well known pharmaceutical ingredients and their quality is compliant with compendial monographs.

Adequate release specifications have been presented for the drug product. The analytical methods are adequately described and appropriately validated.

Stability studies of the drug product under long term conditions (25°C/60% RH) and accelerated conditions (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

The pharmacology studies demonstrated that crisaborole is a competitive PDE-4 inhibitor that binds to receptors on, and activity in, many immune cell types. It has relative specificity for PDE-4, with 55–350 nM potency (based on IC50), and lower activity versus other PDE enzymes, ranging from inactive to mid-micromolar potency. Crisaborole binds to the PDE-4 active site in a cAMP-competitive manner. The boron atom in the crisaborole molecule is essential for PDE-4 binding and inhibition. In vitro and in vivo studies demonstrated that crisaborole could inhibit inflammation and the secretion of specific cytokines, some of which are critical in AD pathophysiology.

2.2.2 Toxicological Studies

The repeated-dose toxicology studies demonstrated that administration of crisaborole by both the dermal and oral routes at plasma exposures up to 11 times that in humans did not result in significant toxicity relevant to its use in humans.

Crisaborole was not genotoxic in a standard battery of genetic toxicology assays. In 2-year carcinogenicity studies, no evidence of crisaborole-induced tumors was observed in mice dosed dermally with crisaborole topical ointment, 7%. In an oral carcinogenicity study in rats, a drug-related increased incidence of benign granular cell tumors of the female reproductive tract was observed; however, this finding’s clinical relevance is unknown.

Reproductive toxicology studies demonstrated that crisaborole was neither a teratogen nor a reproductive toxicant. There were no significant effects when crisaborole was administered orally to juvenile rats and topically to juvenile minipigs. Crisaborole did not show skin

sensitization activity in the mouse local lymph node assay.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The PK of crisaborole were investigated in 33 pediatric subjects 2 to 17 years of age with mild to moderate atopic dermatitis and a mean ± SD body surface area (BSA) involvement of 49 ± 20% (range 27% to 92%). In this study, subjects applied approximately 3 mg/cm^2 of crisaborole ointment (dose range was approximately 6 g to 30 g per application) twice daily for 8 days.

Plasma concentrations were quantifiable in all the subjects. The mean ± SD C_{max} and AUC_{0-12} for crisaborole on Day 8 were 127±196 ng/mL and 949±1240 ng•h/mL, respectively. Systemic concentrations of crisaborole were at steady state by Day 8. Based on the ratios of AUC_{0-12} between Day 8 and Day 1, the mean accumulation factor for crisaborole was 1.9.

Crisaborole is 97% bound to human plasma proteins based on *in vitro* study.

Crisaborole is substantially metabolized into inactive metabolites. The major metabolite 5-(4-cyanophenoxy)-2-hydroxyl benzylalcohol (metabolite 1；AN7602), is formed via hydrolysis; this metabolite is further metabolized into downstream metabolites, among which 5-(4-cyanophenoxy)-2-hydroxyl benzoic acid (metabolite 2；AN8323), formed via oxidation, is also a major metabolite.

PK of metabolites 1 and 2 were assessed in the PK study described above and the systemic concentrations were at or near steady state by Day 8. Based on the ratios of AUC_{0-12} between Day 8 and Day 1, the mean accumulation factors for metabolites 1 and 2 were 1.7 and 6.3, respectively.

Renal excretion of metabolites is the major route of elimination.

2.3.2 Interaction Studies

In vitro studies using human liver microsomes indicated that under the conditions of clinical use, crisaborole and metabolite 1 are not expected to inhibit cytochrome P450 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4. *In vitro* human liver microsomes studies for metabolite 2 showed that it did not inhibit activities of CYP2C19, 2D6, and 3A4; was a weak inhibitor of CYP1A2 and 2B6; and a moderate inhibitor of CYP2C8 and 2C9. The most sensitive enzyme, CYP2C9, was further investigated in a clinical trial using warfarin as a CYP2C9 substrate. The results of this study showed no drug interaction potential.

In vitro studies in human hepatocytes showed that under the conditions of clinical use,

crisaborole and metabolites 1 and 2 are not expected to induce CYP enzymes.

2.3.3 Special Populations

Clinical studies of crisaborole did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. Clinical studies in subjects with hepatic or renal impairment have not been conducted. Considering topical use and low systemic exposure, dose adjustment is not expected to be necessary in subjects with mild to moderate hepatic impairment and renal impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

This NDA of Staquis (crisaborole) topical ointment 2% was indicated for the treatment of mild to moderate atopic dermatitis in patients 2 years of age and older. For the claimed indication, the sponsor submitted data from two identically-designed, randomized, multi-center, vehicle-controlled, Phase III studies (Studies [AN2728-AD-301] and [AN2728-AD-302]).

For both studies, the primary efficacy endpoint was the proportion of subjects achieving success in Investigator's Static Global Assessment (ISGA) at Day 29, where success in ISGA was defined as an ISGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. The protocol specified the following two secondary efficacy endpoints: the proportion of subjects with an ISGA score of 0 (clear) or 1 (almost clear) at Day 29 and the time to success in ISGA.

Two trials treated a total of 1522 subjects 2 to 79 years of age (86.3% of subjects were 2 to 17 years of age) with a 5% to 95% treatable body surface area. At baseline, 38.5% of the subjects had an ISGA score of 2 (mild), and 61.5%had an ISGA score of 3 (moderate), in the overall assessment of atopic dermatitis (erythema, induration/papulation, and oozing/crusting) on a severity scale of 0 to 4.

Table 2.4.1-1 presents the results of the primary and secondary efficacy endpoints. In both trials, crisaborole ointment, 2% was statistically superior (p-value $\leqq$ 0.038) to vehicle ointment for all endpoints presented in Table 2.4.1-1.

Table 2.4.1-1 Efficacy results at Day 29 (ITT, MI[(1)])

Endpoints	Study [AN2728-AD-301]			Study [AN2728-AD-302]		
	Crisaborole (N = 503)	Vehicle (N = 256)	p-value	Crisaborole (N =513)	Vehicle (N = 250)	p-value
Primary endpoint: Success in ISGA[(2)]	32.8%	25.4%	0.038[(3)]	31.4%	18.0%	< 0.001[(3)]

Key secondary endpoints:						
-ISGA score of Clear or Almost Clear	51.7%	40.6%	0.005[3]	31.4%	18.0%	< 0.001[3]
-Time to success in ISGA[2]	NC[4]	NC	< 0.001[5]	NC	NC	< 0.001[5]

(1) Missing data was imputed using multiple imputation (MI). The values displayed are the average over the 140 imputed datasets for Trial 301 and the 135 datasets for Trial 302.
(2) Success is defined as an ISGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement at baseline.
(3) P-value from a logistic regression (using Firth's Penalized Likelihood) with treatment and analysis center as factors.
(4) Median time to success in ISGA could not be calculated because fewer than 50% of subjects achieved success in ISGA.
(5) P-value based on a log-rank test.

In conclusion, efficacy findings from the two pivotal Phase III trials (Studies [AN2728-AD-301] and [AN2728-AD-302]) are sufficient to support the efficacy of crisaborole ointment, 2% for the treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.

2.4.2 Safety Results

In two double-blind, vehicle-controlled clinical trials, 1012 subjects 2 to 79 years of age with mild to moderate atopic dermatitis were treated with crisaborole topical ointment 2% twice daily for 4 weeks. The adverse reaction reported by ≥1% of crisaborole topical ointment 2% -treated subjects is showed in Table 1.

Table 1 Adverse Reaction Occurring in ≧1% of Subjects in Atopic Dermatitis Trials through Week 4

Adverse Reaction	Crisaborole N=1012 n (%)	Vehicle N=499 n (%)
Application site pain	45 (4)	6 (1)

Hypersensitivity reactions, including contact urticaria, have occurred in patients treated with crisaborole ointment. Hypersensitivity should be suspected in the event of severe pruritus, swelling and erythema at the application site or at a distant site. If signs and symptoms of hypersensitivity occur, discontinue Staquis (crisaborole) topical ointment 2% immediately and initiate appropriate therapy.

Overall, the reported AEs were not atypical or unexpected for the enrolled patient population. In general, the safety profile of cisaborole was tolerable based on available data.

2.5 Bridging Study Evaluation

After applying 3 mg/cm^2 crisaborole BID topical use in target AD patients, the C_{max} and $AUC_{0\text{-}12hr}$ of crisaborole on Day 8 in Japanese patients (N=9) was 1.46-fold and 1.31-fold in Caucasian patients (N=34).

Considering the high inter-subject variation of crisaborole via topical route (about 50~150%) and the metabolism pathway of crisaborole was via hydrolysis and oxidation, with limited influence by genetic polymorphism, crisaborole is none to minimally ethnically sensitive from PK aspect.

In AN2728-AD-301 and AN2728-302, only 52 Asians were enrolled. Although the effect size seems less in Asians, the efficacy trend was showed. The safety profile of crisaborole in Asians was similar to the overall population. The most common adverse reaction is application site pain, which is mostly mild in intensity.

In conclusion, based on the characteristics of crisaborole (local application with limited systemic exposure), available PK and clinical information, the waiver of bridging study is recommended.

2.6 Conclusion

Based on the assessment on the CMC, PT, PK, Clinical and Statistical information provided by the sponsor, the approval of Staquis (crisaborole) ointment 2% for the treatment of mild to moderate atopic dermatitis in patients 2 years of age and older is recommended.

3. Post-Marketing Requirements

Routine pharmacovigilance is applicable.