เอกสารกำกับยา

# STAQUIS™

## 1. NAME OF THE MEDICINAL PRODUCT

### 1.1. Product Name

STAQUIS

### 1.2. Strength

2% (20 mg/g)

### 1.3. Pharmaceutical Dosage Form

Ointment.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: crisaborole.

The medicinal product contains 2% crisaborole (w/w) in an ointment.

One gram of ointment contains 20 mg of crisaborole.

For the full list of excipients, see section **6.1 List of Excipients**.

## 3. PHARMACEUTICAL FORM

White to off-white ointment.

# 4. CLINICAL PARTICULARS

## 4.1. Therapeutic Indications

STAQUIS is indicated for topical treatment of mild to moderate atopic dermatitis in patients 3 months of age and older.

## 4.2. Posology and Method of Administration

### Posology

***Adults***

A layer of ointment is to be applied twice daily to affected areas.

STAQUIS can be used on all skin areas, including the face, neck, and intertriginous areas. The use of STAQUIS on the scalp has not been studied.

***Pediatric population***

For children and adolescents (3 months to 17 years of age) the posology is the same as for adults.

***Special populations***

Clinical trials with hepatic or renal impaired subjects have not been conducted. However, dosage adjustment is not expected to be necessary in subjects with mild to moderate hepatic impairment or in subjects with renal impairment.

Clinical studies of STAQUIS did not include sufficient numbers of subjects 65 years of age and over to determine whether they respond differently from younger subjects. However, dosage adjustment is not expected to be necessary in this patient population.

### Method of administration

STAQUIS is for topical use only and not for oral, ophthalmic, or intravaginal use.

STAQUIS has not been studied under occlusion. However, clinical experience available for use of the ointment under occlusion (i.e., diapers/nappies or clothing) has not shown the necessity for any dosage adjustment.

Patients should be instructed to wash their hands after applying STAQUIS, unless it is their hands that are being treated. If someone else applies STAQUIS to the patient, they too should wash their hands after application.

**4.3. Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section **6.1. List of Excipients**.

**4.4. Special Warnings and Precautions for Use**

STAQUIS is not for oral, ophthalmic, or intravaginal use. In cases of accidental exposure to these areas, the ointment should be thoroughly wiped off and/or rinsed with water.

**Hypersensitivity**

Hypersensitivity, including contact urticaria, has occurred in patients treated with STAQUIS. 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 immediately and initiate appropriate therapy.

**4.5. Interaction with Other Medicinal Products and Other Forms of Interaction**

Neither crisaborole nor its 2 main metabolites are expected to cause drug interactions by induction or inhibition of cytochrome P450 (CYP) enzymes based on *in vitro* and *in vivo* data (see section **5.2. Pharmacokinetic Properties**).

One of the 2 metabolites showed moderate inhibition of uridine diphosphate (UDP) glucuronosyltransferase (UGT) 1A9 and may result in a moderate increase in the concentrations of sensitive UGT1A9 substrates (see section **5.2. Pharmacokinetic Properties**).

## 4.6. Fertility, Pregnancy and Lactation

### Pregnancy

There is a limited amount of data from the use of STAQUIS in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at maternally non-toxic doses (see section **5.3. Preclinical Safety Data**). Because animal reproduction studies are not always predictive of the human response, as a precautionary measure, the mother's clinical benefit of STAQUIS along with any potential risk on the fetus should be considered.

### Breastfeeding

Animal studies on milk excretion after topical application were not conducted and the use of STAQUIS in breast feeding women has not been studied. STAQUIS is systemically absorbed. It is unknown whether crisaborole/metabolites are excreted in human milk following topical application of STAQUIS or the effects of the medicinal product on the breastfed infant or on human milk production. The lack of clinical data during lactation precludes a clear determination of the risk of STAQUIS to a breastfed infant. Therefore, the developmental and health benefits of breast feeding should be considered along with the mother's clinical need for STAQUIS and any potential adverse effects on the breastfed infant from STAQUIS or from the underlying maternal condition.

To avoid unintentional ingestion by the newborn, STAQUIS should not be applied to the breast.

### Fertility

Reproduction studies in male or female rats using oral administration of crisaborole revealed no effects on fertility (see section **5.3. Preclinical Safety Data**).

## 4.7. Effects on Ability to Drive and Use Machines

No studies with STAQUIS on the effect of the ability to drive or use machines have been performed, therefore STAQUIS has no known influence on the ability to drive or use machines.

## 4.8. Undesirable Effects

The most common adverse drug reactions from completed STAQUIS clinical trials (Trials 1 and 2) were application site reactions (5.6% and 3.6% for STAQUIS and vehicle groups, respectively) and most were classified as mild. Of these drug-related application site reactions, application site pain (e.g., burning or stinging) was the only adverse drug reaction that showed a clinically relevant difference in rates between the treatment groups (4.4% and 1.2% for STAQUIS and vehicle groups, respectively). Generally, application site pain was noted early in the treatment period and was transient in nature, resolving spontaneously.

**Table 1: Adverse Drug Reactions**

| System Organ Class | Adverse Drug Reactions |
|---|---|
| General disorders and administration site conditions | Application site reactions (e.g., application site pain*, application site pruritus) |

* Refers to skin sensations such as burning or stinging

**Pediatric clinical trial**

In a multicenter, open-label, uncontrolled trial, 137 pediatric subjects aged 3 months to less than 2 years were treated with STAQUIS twice daily for 4 weeks. Overall, the safety profile of STAQUIS in this age group was consistent with that of Trials 1 and 2 in subjects 2 years of age and older.

### 4.9. Overdose

There has been no experience of overdose with STAQUIS. Overdose following topical administration is unlikely. If too much STAQUIS has been applied, the excess can be wiped off.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic Properties

**Mechanism of action**

Crisaborole is an anti-inflammatory benzoxaborole phosphodiesterase-4 (PDE4) inhibitor that suppresses the secretion of certain cytokines, such as tumor necrosis factor-$\alpha$ (TNF-$\alpha$), interleukins (IL-2, IL-4, IL-5), and interferon gamma (IFN$_\gamma$), and improves skin barrier function as measured by transepidermal water loss (TEWL). Crisaborole applied on atopic dermatitis lesions

of patients reduces expression of atopic inflammation associated chemokines including CCL17, CCL18, and CCL22.

**Clinical efficacy**

Two multicenter, randomized, double-blind, parallel-group, vehicle-controlled trials (Trials 1 and 2), which were identical in design, included a total of 1,522 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 (BSA). At baseline (pooled study data), 38.5% of the subjects had an Investigator's Static Global Assessment (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.

In both trials, subjects were randomized 2:1 to receive STAQUIS or vehicle applied twice daily for 28 days. The primary efficacy endpoint was the proportion of subjects at Day 29 who achieved an ISGA grade of Clear (score of 0) or Almost Clear (score of 1) with at least a 2-grade improvement from baseline, comparing STAQUIS-treated subjects to vehicle-treated subjects. In both trials, a statistically significantly greater percentage of subjects achieved this endpoint in the STAQUIS-treated group compared with the vehicle-treated group.

The secondary efficacy endpoints were the proportion of subjects at Day 29 with an ISGA grade of Clear or Almost Clear and the time to achieve an ISGA grade of Clear or Almost Clear with at least a 2-grade improvement from baseline. The proportion of subjects achieving an ISGA score of Clear or Almost Clear at Day 29 in the STAQUIS-treated group compared to the vehicle-treated group was statistically significantly higher. STAQUIS-treated subjects showed a statistically significantly shorter time to achieve an ISGA grade of Clear or Almost Clear with at least a 2-grade improvement from baseline than vehicle-treated subjects by the log-rank test for each study.

Efficacy results from the two trials are summarized in **Table 2**.

**Table 2: Efficacy Outcomes in Subjects with Mild to Moderate Atopic Dermatitis at Day 29**

| | Trial 1 | | Trial 2 | |
|---|---|---|---|---|
| | **STAQUIS (N=503)** | **Vehicle (N=256)** | **STAQUIS (N=513)** | **Vehicle (N=250)** |
| **ISGA**[a] | 32.8% | 25.4% | 31.4% | 18.0% |
| **p-value** | 0.038[b] | | <0.001[b] | |
| **ISGA of Clear or Almost Clear**[c] | 51.7% | 40.6% | 48.5% | 29.7% |
| **p-value** | 0.005[d] | | <0.001[d] | |
| **Time to ISGA**[a,e] | NC[f] | NC[f] | NC[f] | NC[f] |
| **p-value** | <0.001[g] | | <0.001[g] | |

[a] Defined as an ISGA score of Clear or Almost Clear with at least a 2-grade improvement from baseline.

[b] p-value from a logistic regression (with Firth option) test with factors of treatment group and analysis center. Trial 1 estimates from logistic regression are 29.1% and 22.0% for STAQUIS and vehicle, respectively. Trial 2 estimates from logistic regression are 26.5% and 14.2% for STAQUIS and vehicle, respectively. Values were adjusted for multiple imputation.

[c] At least a 2-grade improvement from baseline was not required.

[d] p-value from a logistic regression (with Firth option) test with factors of treatment group and analysis center. Trial 1 estimates from logistic regression are 49.0% and 37.7% for STAQUIS and vehicle, respectively. Trial 2 estimates from logistic regression are 45.2% and 25.5% for STAQUIS and vehicle, respectively. Values were adjusted for multiple imputation.

[e] Medians computed using Kaplan-Meier methods.

[f] The median time to achieve an ISGA grade of Clear or Almost Clear with at least a 2-grade improvement from baseline could not be calculated (NC), as fewer than 50% of subjects achieved an ISGA grade of Clear or Almost Clear with at least a 2-grade improvement from baseline.

[g] p-value from log-rank test.

In both clinical trials (Trial 1 and 2), the signs (erythema, induration/papulation, exudation, excoriation, and lichenification) and a symptom (pruritus) of atopic dermatitis were assessed.

The proportion of subjects with improvement in signs of atopic dermatitis (defined as None [0] or Mild [1] with at least a 1-grade improvement from baseline on a 4 point scale) at Day 29 was greater in STAQUIS-treated subjects than vehicle-treated subjects for all 5 clinical signs of atopic dermatitis. In Trial 2, all 5 clinical signs of atopic dermatitis were statistically significantly improved. In Trial 1, statistical significance was achieved for erythema, exudation, and excoriation. Results

for each trial are summarized in **Table 3**.

**Table 3: Proportion of Subjects Achieving Improvement[a] in Signs of Atopic Dermatitis at Day 29**

| | Trial 1 | | | Trial 2 | | |
|---|---|---|---|---|---|---|
| | **STAQUIS (N=503)** | **Vehicle (N=256)** | **p-value[b]** | **STAQUIS (N=513)** | **Vehicle (N=250)** | **p-value[b]** |
| **Erythema** | 62.8% | 46.1% | <0.001 | 54.9% | 33.9% | <0.001 |
| **Induration/Papulation** | 57.7% | 54.8% | 0.375 | 51.9% | 40.2% | 0.005 |
| **Exudation** | 41.0% | 33.3% | 0.027 | 38.1% | 27.2% | 0.004 |
| **Excoriation** | 63.0% | 51.8% | 0.004 | 57.2% | 44.2% | 0.001 |
| **Lichenification** | 51.7% | 46.5% | 0.128 | 51.4% | 35.3% | <0.001 |

[a] Defined as None or Mild with at least a 1-grade improvement from baseline.

[b] p-value from Cochran-Mantel-Haenszel (CMH) test stratified by analysis center.

The proportion of subjects achieving improvement in pruritus, defined as achieving a weekly mean Severity of Pruritus Scale (SPS) score of $\leq$1 with at least a 1-point improvement from baseline on a severity scale of 0 to 3, was assessed at each scheduled study visit. A statistically significantly higher proportion of subjects achieving improvement in pruritus was observed with STAQUIS treated subjects compared to vehicle treated subjects at Week 4, as summarized in **Table 4**.

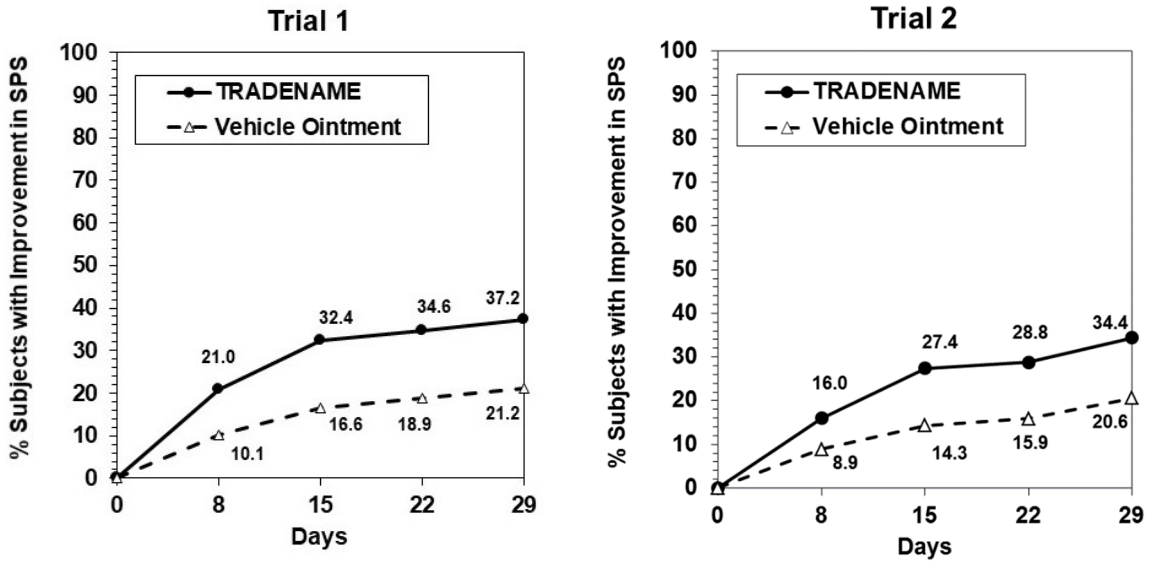
**Table 4: Improvement in the Severity of Pruritus Scale (SPS) in Subjects with Mild to Moderate Atopic Dermatitis at Week 4**

| | Trial 1 | | | Trial 2 | | |
|---|---|---|---|---|---|---|
| | **STAQUIS (N=363)** | **Vehicle (N=170)** | **p-value** | **STAQUIS (N=363)** | **Vehicle (N=165)** | **p-value** |
| **Improvement in SPS** | 37.2% | 21.2% | p<0.001 | 34.4% | 20.6% | p<0.001 |

Improvement in SPS is defined as achieving a weekly mean Severity of Pruritus Scale (SPS) score of $\leq$1 with at least a 1-point improvement from baseline.

The pruritus improvement rates over time are presented in **Figure 1**.

**Figure 1: Improvement in SPS Over Time in Subjects with Mild to Moderate Atopic Dermatitis**




Improvement in SPS is defined as achieving a weekly mean Severity of Pruritus Scale (SPS) score of ≤1 with at least a 1-point improvement from baseline.

The time to improvement in pruritus was defined as time to achieve a daily mean SPS score of ≤1 with at least a 1-point improvement from baseline. In Trial 1 and Trial 2, STAQUIS-treated subjects had a statistically significant shorter median time to improvement than vehicle-treated subjects. In Trial 1, STAQUIS-treated subjects achieved improvement in pruritus symptoms with a median of 4 days versus 9 days for vehicle-treated subjects (p=0.0008). In Trial 2, STAQUIS-treated subjects achieved improvement in pruritus symptoms with a median of 5 days versus 9 days for vehicle-treated subjects (p=0.0042).

In the pooled clinical trials (Trial 1 and 2), the STAQUIS-treated group showed a greater reduction in mean treatable percent BSA affected with atopic dermatitis (-7.4% from a baseline of 18.3%) than the vehicle-treated group (-4.4% from a baseline of 18.1%) at Day 29.

In a multicenter, open-label, uncontrolled trial, 137 pediatric subjects aged 3 months to less than 2 years were treated with STAQUIS twice daily for 4 weeks. Efficacy was considered an exploratory objective in this study. At Baseline, 38.0% of the subjects had an ISGA score of 2 (Mild), and 61.3% had an ISGA score of 3 (Moderate). At Day 29, 30.2% of subjects achieved an ISGA grade of Clear (score of 0) or Almost Clear (score of 1) with at least a 2-grade improvement. In addition, 47.3% of subjects had achieved an ISGA grade of Clear or Almost Clear. Mean treatable percent BSA affected with atopic dermatitis decreased from 28.1% at Baseline to 12.4% at Day 29. The results on ISGA and treatable percent BSA were comparable to those observed among

STAQUIS-treated subjects in Trials 1 and 2.

## 5.2. Pharmacokinetic Properties

### Absorption

The pharmacokinetics (PK) of STAQUIS were investigated in 33 pediatric subjects 2 to 17 years of age with mild to moderate atopic dermatitis and a mean ± standard deviation (SD) BSA involvement of 49 ± 20% (range 27% to 92%). In this study, subjects applied approximately 3 mg/cm$^2$ of STAQUIS ointment (dose range was approximately 6 g to 30 g per application) twice daily for 8 days. Plasma concentrations were quantifiable in all subjects. The mean ± SD maximum plasma concentration ($C_{max}$) and area under the concentration time curve from 0 to 12 hours post dose ($AUC_{0-12}$) 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. Systemic levels of crisaborole and its main metabolites were similar between age cohorts of 2 to 5 years, 6 to 11 years, and 12 to 17 years.

For subjects 3 months of age and older, the systemic exposures ($AUC_{0-12}$ and $C_{max}$) to crisaborole are comparable with no clinically significant differences at similar treated BSA.

### Distribution

Based on an *in vitro* study, crisaborole is 97% bound to human plasma proteins.

### Biotransformation and elimination

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

**Drug interactions**

***Potential for crisaborole to influence the PK of other drugs***

*In vitro* studies using human liver microsomes indicated that under the conditions of clinical use, crisaborole and metabolite 1 are not expected to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 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 indicate that under the condition of clinical use, crisaborole and metabolites 1 and 2 are not expected to induce CYP enzymes.

*In vitro* studies showed that crisaborole and metabolite 1 did not inhibit the activities of UGT1A1, 1A4, 1A6, 1A9, 2B7, and 2B15. Metabolite 2 did not inhibit UGT1A4, 1A6, 2B7, and 2B15. Metabolite 2 showed weak inhibition of UGT1A1, however, no clinically significant drug interactions are expected between crisaborole (and its metabolites) and UGT1A1 substrates at therapeutic concentrations. Metabolite 2 showed moderate inhibition of UGT1A9 and may result in a moderate increase of the concentrations of sensitive UGT1A9 substrates.

*In vitro* studies indicate that under the condition of clinical use, crisaborole and metabolites 1 and 2 are not expected to cause clinically significant interactions with substrates of transporters such as P-glycoprotein, breast cancer resistance protein (BCRP) and organic anionic or cationic transporters.

**5.3. Preclinical Safety Data**

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenicity, juvenile toxicity, or toxicity to reproduction and development.

The repeated-dose toxicology studies demonstrated that administration of crisaborole by both the

dermal and oral routes in mice, rats, and minipigs at plasma exposures up to 11 times that in humans did not result in significant toxicity relevant to its use in humans.

Crisaborole revealed no evidence of mutagenic or clastogenic potential based on the results of two *in vitro* genotoxicity tests (Ames assay and human lymphocyte chromosomal aberration assay) and one *in vivo* genotoxicity test (rat micronucleus assay).

In an oral carcinogenicity study in Sprague-Dawley rats, oral doses of 30, 100, or 300 mg/kg/day crisaborole were administered once daily. A crisaborole related increased incidence of benign granular cell tumors in the uterus with cervix and vagina (combined) was noted in 300 mg/kg/day crisaborole-treated female rats (2 times the maximum recommended human dose (MRHD) on an area under the curve (AUC) comparison basis). The clinical relevance of this finding is unknown, however given the tumor type and benign status in a single species and single sex, the relevance to humans is considered to be low.

In a dermal carcinogenicity study in CD-1 mice, topical doses of 2%, 5%, or 7% crisaborole ointment were administered once daily. No crisaborole related neoplastic findings were noted at topical doses up to 7% crisaborole ointment (1 time the MRHD on an AUC comparison basis).

Crisaborole was not found to be a reproductive toxicant nor a teratogen in reproductive toxicology studies at maternally non-toxic doses that examined effects on fertility, embryo-fetal development, and the F1 generation. Maternal toxicity in rats (associated with decreased fetal body weight and delayed skeletal ossification) but no crisaborole-related fetal malformations were noted after oral administration of crisaborole during organogenesis at doses up to 600 mg/kg/day (13 times the MRHD on an AUC comparison basis). Crisaborole did not cause adverse effects to the fetus at oral doses up to the highest dose tested of 100 mg/kg/day in pregnant rabbits administered during the period of organogenesis (2 times the MRHD on an AUC comparison basis).

In a rat prenatal/postnatal development study, crisaborole did not have any adverse effects on fetal development at doses up to 300 mg/kg/day (3 times the MRHD on an AUC comparison basis). Maternal toxicity was produced at the high dose of 600 mg/kg/day in pregnant rats and was associated with findings of stillbirths, pup mortality, and reduced pup weights.

No effects on fertility were observed in male or female rats that were administered oral doses up to 600 mg/kg/day crisaborole (13 times the MRHD on an AUC comparison basis) prior to and

during early pregnancy.

Juvenile rat and minipig studies did not reveal any relevant findings suggestive of a specific risk for use in the pediatric population.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of Excipients

White Petrolatum
Propylene Glycol
Mono- and Di-glycerides
Paraffin
Butylated Hydroxytoluene
Edetate Calcium Disodium

### 6.2. Incompatibilities

Not applicable.

### 6.3. Shelf Life

Please see details on the carton.

### 6.4. Special Precautions for Storage

This product does not have any special storage restrictions.

### 6.5. Nature and Contents of Container

Multi-layered laminate tube with a high density polyethylene tube head with a peel seal, and a white polypropylene cap closure.

Tubes of 2.5 and 30 grams.

## 7. MARKETING AUTHORIZATION HOLDER

Pfizer (Thailand) Limited

## 8. MARKETING AUTHORIZATION NUMBERS

## 9. DATE OF AUTHORIZATION

## 10. DATE OF REVISION OF THE TEXT

15 June 2021