ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Staquis 20 mg/g ointment

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One g of ointment contains 20 mg of crisaborole.

Excipients with known effect

Propylene glycol, 90 mg/g of ointment

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ointment.

White to off-white ointment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Staquis is indicated for treatment of mild to moderate atopic dermatitis in adults and paediatric patients from 2 years of age with ≤ 40% body surface area (BSA) affected.

4.2 Posology and method of administration

Posology

Adults

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

The ointment should only be applied to affected skin areas up to a maximum of 40% BSA.

The ointment can be used on all skin areas except on the scalp. Use on the scalp has not been studied.

The ointment can be used twice daily for up to 4 weeks per treatment course. If any signs and/or symptoms persist, or new areas affected with atopic dermatitis appear, further treatment course(s) can be used as long as the application does not exceed 40% BSA (see section 5.1).

Use of the ointment should be discontinued if signs and/or symptoms on treated areas persist after 3 consecutive treatment courses of 4 weeks each or if the signs and/or symptoms worsen during treatment.

Paediatric population

For children and adolescents (2-17 years) the posology is the same as for adults.

The safety and efficacy of Staquis in children less than 2 years of age has not been established. No data are available.

Special populations

Hepatic impairment
Clinical studies in subjects with hepatic impairment have not been conducted. However, dosage adjustment is not expected to be necessary in subjects with mild to moderate hepatic impairment.

Renal impairment
Clinical studies in subjects with renal impairment have not been conducted. However, dosage adjustment is not expected to be necessary in this patient population.

Elderly
Atopic dermatitis is uncommonly observed in patients aged 65 years and over. Clinical studies of Staquis did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects (see section 5.1). However, dosage adjustment is not expected to be necessary in this patient population.

Method of administration

The ointment is for cutaneous use only.

The ointment is not for ophthalmic, oral, or intravaginal use (see section 4.4).

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

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

4.4 Special warnings and precautions for use

The ointment is not for ophthalmic, oral, or intravaginal use (see section 4.2). In cases of accidental exposure in the eyes or mucous membranes, the ointment should be thoroughly wiped off and/or rinsed with water.

Available data indicate that local skin reactions, such as burning or stinging, may be more likely to occur on sensitive skin areas (such as the face and neck).

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, Staquis should be discontinued immediately and appropriate therapy should be initiated.

Excipients with known effect

This medicine contains 90 mg propylene glycol in each gram of ointment.

4.5 Interaction with other medicinal products and other forms of interaction

Neither crisaborole nor its two 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).

Based on *in vitro* data, concomitant administration of Staquis and CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir) or CYP1A2 inhibitors (e.g., ciprofloxacin, fluvoxamine) can increase systemic crisaborole concentrations (see section 5.2).

Staquis has not been evaluated in combination with other cutaneous medicinal products used to treat mild to moderate atopic dermatitis and co-application on the same skin areas is not recommended. Emollients may be used on other areas of skin not affected by atopic dermatitis; co-application of emollients with Staquis on the same skin areas is not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of crisaborole in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Staquis during pregnancy.

Breast-feeding

Animal studies on milk excretion after topical application were not conducted. Staquis is systemically absorbed. It is unknown whether crisaborole or its metabolites or excipients are excreted in human milk following topical application of the ointment or has an effect on human milk production. The lack of clinical data during breast-feeding precludes a clear determination of the risk of Staquis to a breastfed infant. Therefore, because of the potential for adverse reactions in breastfed infants, Staquis should not be used in breast-feeding women.

Fertility

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

4.7 Effects on ability to drive and use machines

Staquis has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are application site reactions (6.0%), including application site pain, e.g., burning or stinging (4.4%). Generally, application site pain was noted early in the treatment period and was transient in nature, resolving spontaneously.

Tabulated list of adverse reactions

Adverse reactions are ranked under headings of frequency, with the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to

< 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 1: Adverse reactions

Immune system disorders	
Uncommon	Hypersensitivity
Skin and subcutaneous tissue disorders	
Uncommon	Urticaria contact
General disorders and administration site conditions	
Common	Application site reactions (e.g., application site pain[1], application site pruritus, application site dermatitis, application site erythema, application site irritation, application site urticaria)

[1] Refers to skin sensations such as burning or stinging.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdose following cutaneous administration is unlikely. If too much of the ointment has been applied, the excess can be wiped off.

In cases of accidental ophthalmic, oral mucosa, or intravaginal exposure, the ointment should be thoroughly wiped off and/or rinsed with water (see sections 4.2 and 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatological preparations, agents for dermatitis, excluding corticosteroids, ATC code: D11AH06

Mechanism of action

Crisaborole is an anti-inflammatory benzoxaborole phosphodiesterase-4 (PDE4) inhibitor that suppresses secretion of certain cytokines, such as tumour necrosis factor-α (TNF-α), interleukins (IL-2, IL-4, IL-5), and interferon gamma (IFNγ), 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 and safety

Two multicentre, randomised, double-blind, parallel-group, vehicle-controlled trials (Trials 1 and 2), identical in design, included a total of 1,522 subjects 2 to 79 years of age. 61.9% of subjects were 2-11 years old, 24.4% of subjects were 12-17 years old, 13.3% of subjects were 18-64 years old, and 0.5% of subjects were 65 years of age or older; the number of subjects ≥ 18 years of age was limited. The treatable BSA ranged from 5% to 95% (mean = 18.3%, standard deviation [SD] = 17.8%; 9.6% of subjects had > 40% treatable BSA); the trials did not include sufficient numbers of subjects with > 40% treatable BSA to determine the safety and efficacy of Staquis in this subpopulation. 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 randomised 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 safety and efficacy of Staquis on sensitive skin areas (such as the face and neck) compared to nonsensitive skin areas (such as the arms and legs) were not separately assessed in the clinical trials.

Efficacy results from the two trials are summarised in Tables 2 and 3. The Kaplan-Meier plots for the time to achieve an ISGA score of Clear or Almost Clear with at least a 2-grade improvement from baseline are provided in Figures 1 and 2. The log-rank test p-values for both trials were < 0.001.

Table 2: Efficacy outcomes in subjects with mild to moderate atopic dermatitis

	Trial 1		**Trial 2**	
	Staquis (N = 503)	**Vehicle (N = 256)**	**Staquis (N = 513)**	**Vehicle (N = 250)**
ISGA score of Clear or Almost Clear with at least a 2-grade improvement from baseline at Day 29	32.8%	25.4%	31.4%	18.0%
95% CI[a]	(28.6, 37.0)	(19.9, 30.9)	(27.3, 35.5)	(13.2, 22.9)
p-value	0.038[b]		< 0.001[b]	
ISGA of Clear or Almost Clear at Day 29	51.7%	40.6%	48.5%	29.7%
95% CI[a]	(47.2, 56.1)	(34.4, 46.8)	(44.1, 52.9)	(23.9, 35.5)
p-value	0.005[b]		< 0.001[b]	

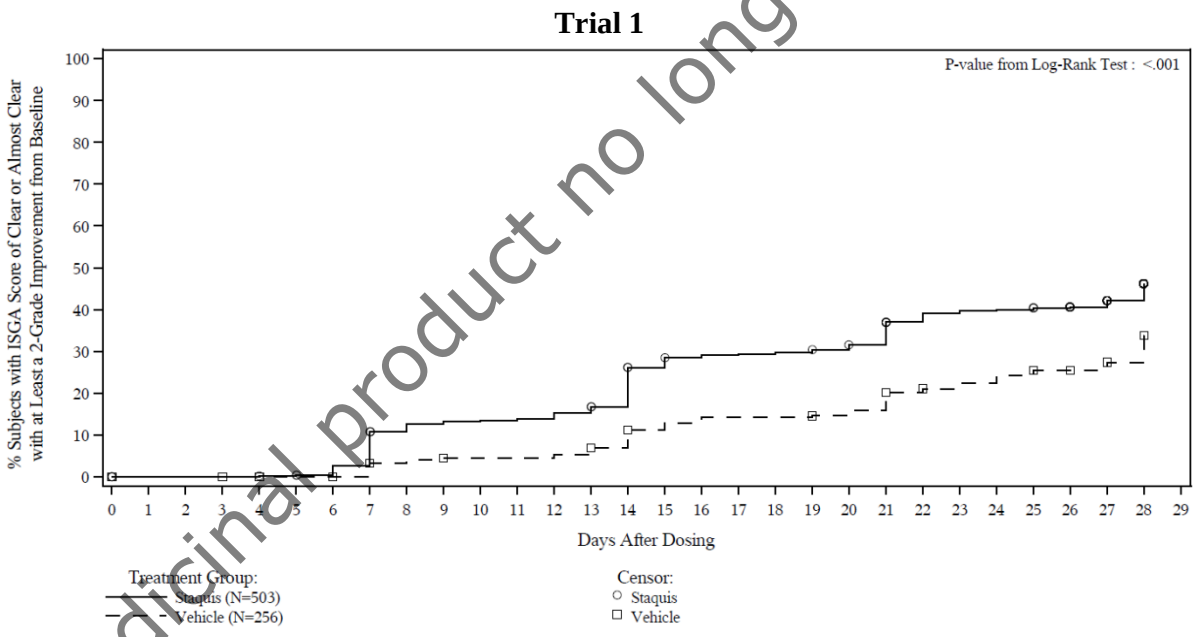
[a] Confidence Interval (CI) from normal approximation.
[b] p-value from a logistic regression (with Firth option) test with factors of treatment group and analysis centre after adjusted for multiple imputation.

Table 3: Post-hoc efficacy outcomes in subjects with mild to moderate atopic dermatitis with ≤ 40% BSA affected

	Trial 1		Trial 2	
	Staquis (N = 446)	**Vehicle (N = 231)**	**Staquis (N = 465)**	**Vehicle (N = 234)**
ISGA score of Clear or Almost Clear with at least a 2-grade improvement from baseline at Day 29	34.1%	25.5%	32.6%	18.8%
95% CI[a]	(29.7, 38.6)	(19.7, 31.3)	(28.3, 36.9)	(13.7, 24.0)
p-value	0.022[b]		<0.0001[b]	
ISGA of Clear or Almost Clear at Day 29	53.8%	41.9%	51.0%	30.9%
95% CI[a]	(49.1, 58.5)	(35.3, 48.4)	(46.4, 55.6)	(24.8, 37.0)
p-value	0.0041[b]		<0.0001[b]	

[a] Confidence Interval (CI) from normal approximation.
[b] p-value from a logistic regression (with Firth option) test with factors of treatment group and analysis centre after adjusted for multiple imputation.

Figure 1: Kaplan-Meier plot of Time to ISGA score of Clear or Almost Clear with at least a 2-grade improvement from baseline for subjects with mild to moderate atopic dermatitis



Trial 2

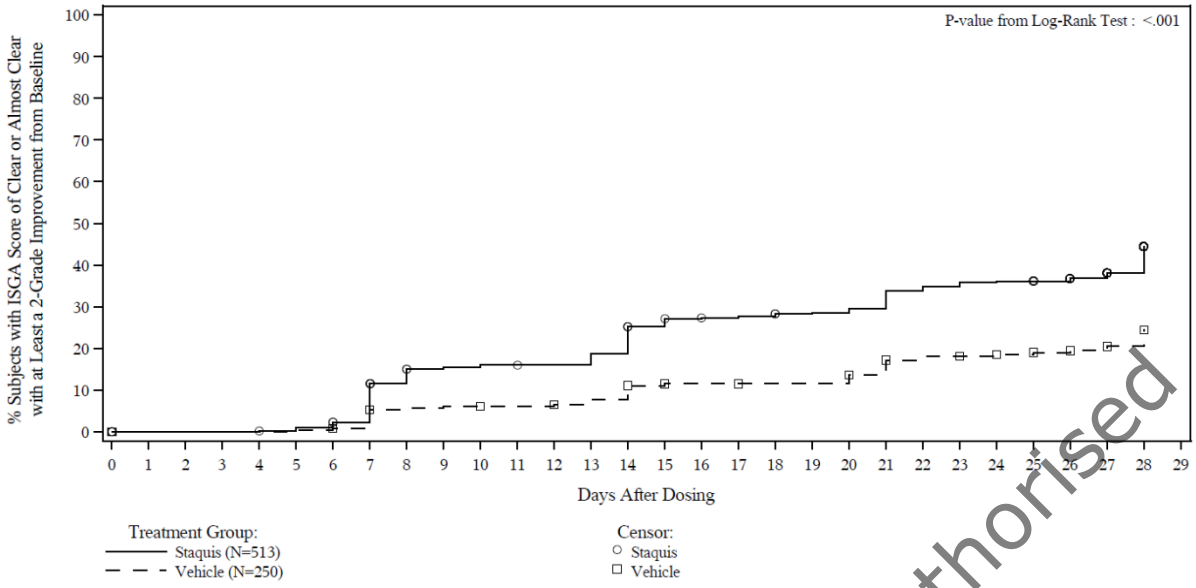
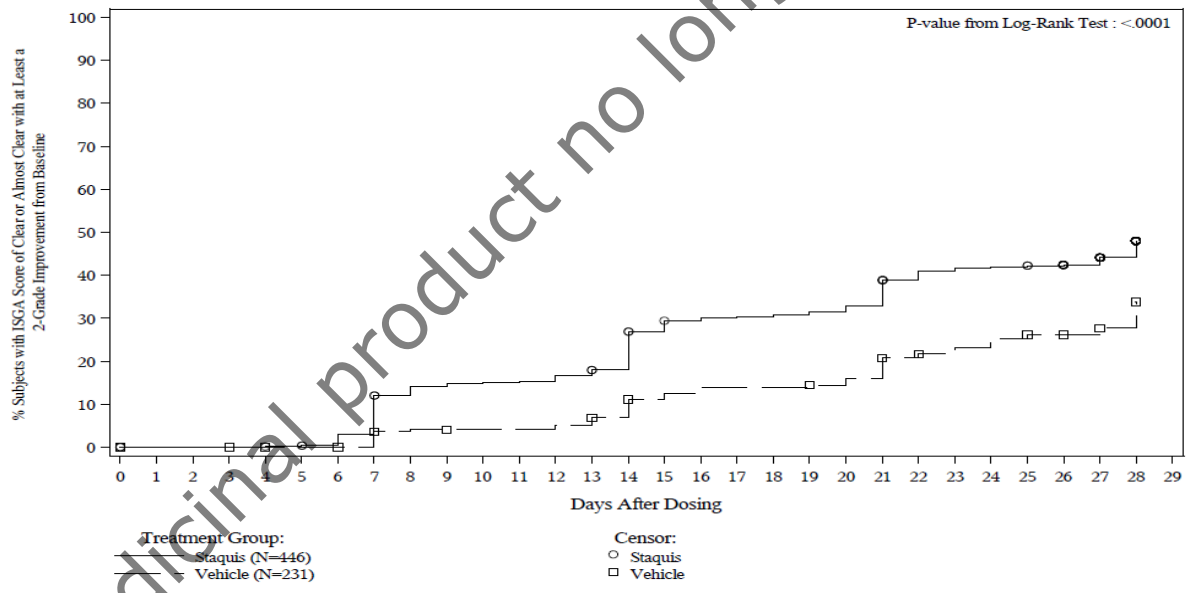
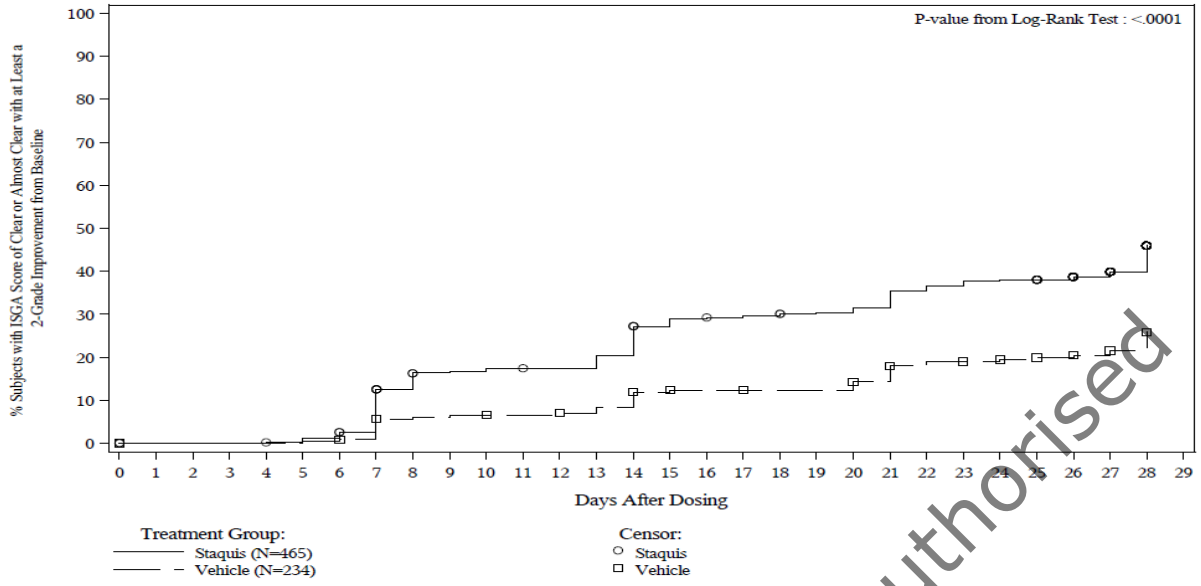


Figure 2: Post-hoc Kaplan-Meier plot of Time to ISGA score of Clear or Almost Clear with at least a 2-grade improvement from baseline for subjects with mild to moderate atopic dermatitis with ≤ 40% BSA affected

Trial 1



Trial 2



The pooled primary efficacy results by race category are summarised in Table 4.

Table 4: Summary of subjects achieving ISGA score of Clear or Almost Clear with at least a 2-grade improvement from baseline at Day 29 by race category – Trial 1 and 2 pooled

	Staquis (N = 1016)		Vehicle (N = 506)	
Race Category	**n**	**Rate**	**n**	**Rate**
American Indian or Alaska Native	11	18.0%	5	0.0%
Asian	52	17.7%	27	13.4%
Black or African American	285	32.1%	139	24.6%
Native Hawaiian or Other Pacific Islander	7	42.9%	8	17.0%
White	617	33.5%	306	22.3%
Other	44	31.9%	21	16.3%

N = Number of subjects in each treatment group
n = Number of subjects in each sub-group category by treatment group

One multicentre, single-arm, open-label long-term safety trial (Trial 3) included a total of 517 subjects 2 to 72 years of age (59.6% of subjects were 2-11 years old, 28.2% of subjects were 12-17 years old, 11.8% of subjects were 18-64 years old, and 0.4% of subjects were 65 years of age or older) with a 5% to 95% treatable BSA. Subjects at participating investigator sites (a subset of sites that participated in Trials 1 and 2) who completed Trials 1 or 2 without safety events that precluded further treatment with Staquis were eligible.

Subjects participated in the study in 28-day treatment courses for up to 48 weeks. Subjects received Staquis for a variable number of treatment courses intermittently based on disease severity as determined by the ISGA at the beginning of each 28-day treatment course: subjects received open-label treatment with Staquis twice daily (on-treatment when ISGA was Mild or worse [≥ 2]) or no treatment (off-treatment when the ISGA was Clear [0] or Almost Clear [1]). Discontinuation from

the study was to occur if there was no improvement in the subject's ISGA after 3 consecutive treatment courses of treatment with Staquis.

Trial 3 did not include an efficacy endpoint; Staquis efficacy response based on ISGA determined the extent of intermittent use of Staquis for up to 48 weeks. Overall, subjects received a mean of 6.2 on-treatment courses (out of a possible 13 on-treatment courses including the 28-day treatment period in Trials 1 or 2). The mean number of consecutive on-treatment courses was 3.6 and the mean number of consecutive off-treatment courses was 2.5.

QT study results

Results from a thorough QT study of Staquis applied to 60% BSA in healthy volunteers did not demonstrate QT prolongation. Although healthy volunteers had lower crisaborole concentrations compared to patients with atopic dermatitis, clinical studies of Staquis did not identify any cardiac effects including prolongation of QT interval.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Staquis in one or more subsets of the paediatric population for the treatment of atopic dermatitis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics (PK) of Staquis were investigated in 33 paediatric subjects 2 to 17 years of age with mild to moderate atopic dermatitis and a mean ± 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 exposure (C_{max} and AUC_{0-12}) of crisaborole and its main metabolites increased with increasing % BSA treated.

The studies were performed with a different formulation of crisaborole which, unlike Staquis, contained butylhydroxytoluene (BHT). *In vitro* permeation testing (IVPT) was performed in intact skin to support therapeutic equivalence between the BHT-containing and the no-added BHT formulations. Although the results were inconclusive and highly variable, a possible slight increase in permeation is not expected to influence the benefit-risk profile of the product in patients with up to 40% BSA affected to a clinically relevant extent.

Distribution

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

Biotransformation and elimination

Crisaborole is substantially metabolised into inactive metabolites. The main metabolite 5-(4-cyanophenoxy)-2-hydroxyl benzylalcohol (metabolite 1), is formed via multiple CYP enzymes including CYP3A4, 1A2 and hydrolysis; this metabolite is further metabolised 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. The mean ± SD C_{max} and AUC_{0-12} for metabolite 2 on Day 8 were 1850 ± 1830 ng/mL and 18200 ± 18100 ng*h/mL, respectively. Renal excretion of metabolites is the major route of elimination. Approximately 25% of the radiolabelled dose was absorbed and predominantly excreted in the urine.

Drug interactions

Potential for crisaborole to influence the PK of other medicinal products
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.

Based on *in vitro* data, crisaborole is metabolised to some extent (<30%) via CYP3A4 and CYP1A2. Concomitant administration of Staquis and potent CYP3A4 or CYP1A2 inhibitors may result in increases in crisaborole systemic exposure.

In vitro studies showed that crisaborole and metabolite 1 did not inhibit the activities of uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1, 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, such as propofol. A clinically relevant interaction between metabolite 2 and propofol is not anticipated due to the posology and method of administration of propofol (intravenous infusion or injection with titration to clinical effect for anaesthesia or sedation). Drug interaction studies with sensitive UGT1A9 substrates have not been conducted.

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 from studies conducted *in vitro* or *in vivo* by the oral and dermal routes of administration reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, juvenile toxicity, or toxicity to reproduction and development.

A drug-related increased incidence of benign granular cell tumours in the uterus with cervix and vagina (combined) was noted in crisaborole-treated female rats at oral doses approximately 2 times the mean human systemic exposure in maximum use conditions. The clinical relevance of this finding is unknown, however given the tumour type and benign status in a single species and single sex, the relevance to humans is considered to be low.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Paraffin, white soft
Propylene glycol (E 1520)
Glycerol monostearate 40-55 (Type I)
Paraffin, hard
Sodium calcium edetate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

After first opening the container: 1 year.

6.4 Special precautions for storage

Do not store above 25 ºC. Do not freeze.

Keep the tube tightly closed.

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. The exterior layer of the tube consists of seven layers (low-density polyethylene, white high-density polyethylene, high-density polyethylene, low-density polyethylene, ethylene-acrylic acid, foil, and ethylene-acrylic acid). The inner lining consists of linear low-density polyethylene.

Tubes of 2.5 g, 30 g, 60 g, and 100 g. Six tubes per carton for the 2.5 g tubes. One tube per carton for the 30 g, 60 g, and 100 g tubes.

Not all tube sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1421/001
EU/1/19/1421/002
EU/1/19/1421/003
EU/1/19/1421/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 March 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.