PT. PFIZER INDONESIA
Local Product Document

Generic Name: Abrocitinib
Trade Name: FREORLA
CDS Effective Date: March 29, 2024
Supersedes: April 13, 2023

1. NAME OF THE MEDICINAL PRODUCT

FREORLA 50 mg film-coated tablets
FREORLA 100 mg film-coated tablets
FREORLA 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FREORLA 50 mg film-coated tablets

Each film-coated tablet contains 50 mg abrocitinib

FREORLA 100 mg film-coated tablets

Each film-coated tablet contains 100 mg abrocitinib

FREORLA 200 mg film-coated tablets

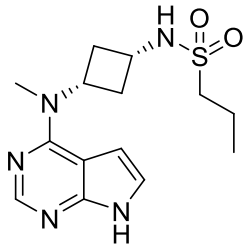
Each film-coated tablet contains 200 mg abrocitinib

Excipients with known effects

Each FREORLA 50 mg film-coated tablet contains 1.365 mg of lactose monohydrate.
Each FREORLA 100 mg film-coated tablet contains 2.73 mg of lactose monohydrate.
Each FREORLA 200 mg film-coated tablet contains 5.46 mg of lactose monohydrate.

For a full list of excipients, see Section 6.1

Structure of abrocitinib:



3. PHARMACEUTICAL FORM

Film-coated tablet.

FREORLA 50 mg film-coated tablets
Pink, oval tablet 10.50 mm long and 4.75 mm wide, debossed with “PFE” on one side and “ABR 50” on the other.

FREORLA 100 mg film-coated tablets
Pink, round tablet 9.00 mm in diameter, debossed with “PFE” on one side and “ABR 100” on the other.

FREORLA 200 mg film-coated tablets
Pink, oval tablet 18.42 mm long and 8.00 mm wide debossed with “PFE” on one side and “ABR 200” on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

FREORLA is indicated for the treatment of patients 12 years of age and older with moderate-to-severe atopic dermatitis, including the relief of pruritus, who have had an inadequate response to prescribed topical therapy or for whom these treatments are not advisable. FREORLA can be used with or without medicated topical therapies for atopic dermatitis.

4.2. Posology and method of administration

Treatment should be initiated and supervised by a healthcare professional experiences in the diagnosis and treatment of atopic dermatitis.

Posology

The recommended dose of FREORLA is 100 mg or 200 mg once daily, based on individual goal of therapy and potential risk for adverse reactions.

- A starting dose of 100 mg once daily is recommended for patients more than equal to 65 years of age. For other patients who may benefit from a starting dose of 100 mg (see Sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects). In

adolescents (12 years to 17 years of age), weighing 25 kg to < 59 kg, a starting dose of 100 mg once a day is recommended. If the patient does not respond adequately to 100 mg once daily, the dose can be increased to 200 mg once daily. In adolescents weighing at least 59 kg, a starting dose of 100 mg or 200 mg once daily may be appropriate.

- During treatment, the dose may be decreased or increased based on tolerability and efficacy. The lowest effective dose for maintenance should be considered. The maximum daily dose is 200 mg.

FREORLA can be used with or without medicated topical therapies for atopic dermatitis.

FREORLA should be taken orally once daily with or without food at approximately the same time each day.

Treatment with FREORLA should not be initiated in patients with a platelet count $<150 \times 10^3/mm^3$, an absolute lymphocyte count (ALC) $<0.5 \times 10^3/mm^3$, an absolute neutrophil count (ANC) $<1 \times 10^3/mm^3$ or who have a hemoglobin value <8 g/dL (see Section 4.4).

Discontinuation of treatment should be considered in patient who show no evidence of therapeutic benefit after 24 weeks.

Laboratory monitoring

Table 1. Laboratory Measures and Monitoring Guidance

Laboratory measure	Monitoring guidance	Action
Complete blood count including Platelet count, Absolute Lymphocyte Count (ALC), Absolute Neutrophil Count (ANC) and Haemoglobin (Hb)	Before treatment initiation, 4 weeks after initiation and thereafter according to routine patient management.	Platelets: Treatment should be discontinued if platelet counts are $<50 \times 10^3/mm^3$.
		ALC: Treatment should be interrupted if ALC is $< 0.5 \times 10^3/mm^3$ and may be restarted once ALC returns above this value. Treatment should be discontinued if confirmed.
		ANC: Treatment should be interrupted if ANC is $< 1 \times 10^3/mm^3$ and may be restarted once ANC returns above this value.
		Hb: Treatment should be interrupted if Hb is < 8 g/dL and may be restarted once Hb returns above this value.
Lipid parameters	Before treatment initiation, 4 weeks after initiation and thereafter according to the patient's risk for	Patients should be monitored according to clinical guidelines for hyperlipidemia.

	cardiovascular disease and clinical guidelines for hyperlipidaemia.	

Missed doses
If a dose is missed, patients should be advised to take the dose as soon as possible unless it is less than 12 hours before the next dose, in which case the patient should not take the missed dose. Thereafter, resume dosing at the regular scheduled time.

Dose interruption
If a patient develops a serious infection, sepsis or opportunistic infection, consider interruption of FREORLA until the infection is controlled should be considered (see Section 4.4).

Interruption of dosing may be needed for management of laboratory abnormalities as described in Table 2 (see Section 4.4).

Drug-drug interactions
In patients receiving dual strong inhibitors of CYP2C19 and moderate inhibitors of CYP2C9, or strong inhibitors of CYP2C19 alone (e.g. fluvoxamine, fluconazole, fluoxetine and ticlopidine), the recommended dose should be reduced by half to 100 mg or 50 mg once daily. Treatment is not recommended concomitantly with moderate or strong inducers of CYP2C19/CYP2C9 enzymes (e.g. rifampicin, apalutamide, efavirenz, enzalutamide, phenytoin).

Special populations

Renal impairment
No dose adjustment is required in patients with mild renal impairment, i.e., estimated glomerular filtration rate (eGFR) of 60 to <90 mL/min. In patients with moderate (eGFR 30 to less than 60 mL/min) renal impairment, the recommended dose of abrocitinib should be reduced by half to 100 mg or 50 mg once daily. In patients with severe (eGFR less than 30 mL/min) renal impairment, 50 mg once daily is the recommended starting dose. The maximum daily dose is 100 mg. The use of FREORLA has not been studied in patients with end-stage renal disease (ESRD) on renal replacement therapy.

Hepatic impairment
No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. FREORLA has not been studied in patients with severe (Child Pugh C) hepatic impairment (see Section 5.2).

Elderly population
The recommended starting dose for patients aged 65 years or more is 100 mg once daily.

Pediatric population
The safety and efficacy of FREORLA in pediatric patients under 12 years of age have not yet been established. No data are available.

Method of administration

FREORLA is to be taken orally once daily with or without food at approximately the same time each day.

In patients who experience nausea while taking FREORLA, taking with food may improve nausea.

Swallow FREORLA tablets whole and intact with water. Do not crush, split, or chew FREORLA tablets.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed.
- Active serious systemic infections, including tuberculosis (TB).
- Severe hepatic impairment.
- Pregnancy and breast-feeding.

4.4. Special warnings and precautions for use

Infections/serious infections

Serious infections have been reported in patients receiving FREORLA. The most frequent serious infections in clinical studies were herpes simplex, herpes zoster, and pneumonia (see Section 4.8).

Treatment must not be initiated in patients with an active, serious systemic infections.

Risks and benefits of treatment prior to initiating abrocitinib should be considered for patients:
- with chronic or recurrent infection
- who have been exposed to TB
- with a history of a serious or an opportunistic infection
- who have resided or travelled in areas of endemic TB or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with FREORLA. A patient who develops a new infection during treatment with FREORLA should undergo prompt and complete diagnostic testing and appropriate antimicrobial therapy should be initiated. The patient should be closely monitored and FREORLA therapy should be interrupted if the patient is not responding to standard therapy.

Tuberculosis
Tuberculosis was observed in clinical studies with abrocitinib. Patients should be screened for tuberculosis (TB) before starting FREORLA therapy and consider yearly screening for patients in highly endemic areas for TB. FREORLA should not be given to patients with active TB. For patients with a new diagnosis of latent TB or prior untreated latent TB, preventive therapy for latent TB should be started prior to initiation of FREORLA.

Viral reactivation
Viral reactivation, including herpes virus reactivation (e.g., herpes zoster, herpes simplex), was reported in clinical studies (see Section 4.8). The rate of herpes zoster infections was higher in patients who were treated with 200 mg, 65 years of age and older, with a medical history of herpes zoster, with a confirmed ALC $<1 \times 10^3/mm^3$ prior to the event and patients with severe atopic dermatitis at baseline (see Section 4.8). If a patient develops herpes zoster, temporary interruption of treatment should be considered until the episode resolves.

Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy and during therapy with FREORLA. Patients with evidence of active hepatitis B or hepatitis C (positive hepatitis C PCR) infection were excluded from clinical studies (see Section 5.2). Patients who were hepatitis B surface antigen negative, hepatitis B core antibody positive, and hepatitis B surface antibody positive had testing for hepatitis B virus (HBV) DNA. Patients who had HBV DNA above the lower limit of quantification (LLQ) were excluded. Patients who had HBV DNA negative or below LLQ could initiate treatment with FREORLA; such patients had HBV DNA monitored. If HBV DNA is detected, a liver specialist should be consulted.

Vaccination

No data are available on the response to vaccination in patients receiving abrocitinib. Use of live, attenuated vaccines should be avoided during or immediately prior to treatment. Prior to initiating FREORLA, it is recommended that patients be brought up to date with all immunizations, including prophylactic herpes zoster vaccinations, in agreement with current immunization guidelines.

Venous thromboembolism

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving Janus kinase (JAK) inhibitors including FREORLA (see Section 4.8). FREORLA should be used with caution in patients at high risk for DVT/PE. Risk factors that should be considered in determining the patient's risk for DVT/PE include older age, obesity, a medical history of DVT/PE, prothrombotic disorder, use of combined hormonal contraceptives or hormone replacement therapy, patients undergoing major surgery, or prolonged immobilization. If clinical features of DVT/PE occur, FREORLA treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.

Malignancy (including non-melanoma skin cancers)

Malignancies, including non-melanoma skin cancer (NMSC), were observed in clinical studies with FREORLA. Clinical data are insufficient to assess the potential relationship of exposure to FREORLA and the development of malignancies. Long-term safety evaluations are ongoing.

The risks and benefits of FREORLA treatment should be considered prior to initiating in patients with a known malignancy other than a successfully treated NMSC or cervical cancer in situ or when considering continuing FREORLA therapy in patients who develop a malignancy. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Hematologic abnormalities

Confirmed ALC $<0.5 \times 10^3/mm^3$ and platelet count $<50 \times 10^3/mm^3$ were observed in less than 0.5% of patients in clinical studies (see Section 4.8). Treatment with FREORLA should not be initiated in patients with a platelet count $<150 \times 10^3/mm^3$, an ALC $<0.5 \times 10^3/mm^3$, an ANC $<1 \times 10^3/mm^3$ or who have a hemoglobin value <8 g/dL (see Section 4.2). Complete blood count should be monitored 4 weeks after initiation of therapy with FREORLA and thereafter according to routine patient management (see Table 1 in Section 4.2)..

Lipids

Dose-dependent increase in blood lipid parameters were reported in patients treated with FREORLA (see Section 4.8). Lipid parameters should be assessed approximately 4 weeks following initiation of FREORLA therapy and thereafter patients should be managed according to clinical guidelines for hyperlipidemia. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined. Patients with abnormal lipid parameters should be further monitored and managed according to clinical guidelines, due to the known cardiovascular risks associated with hyperlipidaemia. In patients with a high burden of cardiovascular risk factors, the risks and benefits of abrocitinib compared to that of other available therapies for atopic dermatitis should be considered. If abrocitinib is chosen, interventions to manage lipid concentrations should be implemented according to clinical guidelines.

Major Adverse Cardiovascular Events

Major adverse cardiovascular events were reported in clinical trials of FREORLA for atopic dermatitis (See section 4.8)

In a large, randomized, postmarketing safety trial of another JAK inhibitor in (Rheumatoid Arthritis) RA subjects 50 years of age and older with at least one cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke was observed with the JAK inhibitor compared to those treated with TNF blockers. FREORLA is not approved for use in RA. Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with FREORLA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue FREORLA in patients that have experienced a myocardial infarction or stroke.

Mortality In a large, randomized, post marketing safety trial of another JAK inhibitor in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed in subjects treated with the JAK inhibitor compared with TNF blockers. FREORLA is not approved for use in RA. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with FREORLA.

Immunosuppressive conditions or medicinal products: Patients with immunodeficiency disorders or a first-degree relative with a hereditary immunodeficiency were excluded from clinical studies and no information on these patients is available. Combination with biologic immunomodulators, potent immunosuppressants such as ciclosporin or other Janus kinase (JAK) inhibitors has not been studied. Their concomitant use with abrocitinib is not recommended as a risk of additive immunosuppression cannot be excluded.

Elderly: The safety profile observed in elderly patients was similar to that of the adult population with the following exceptions : a higher proportion of patients 65 years of age and older discontinued from clinical studies and were more likely to have serious adverse reactions compared to younger patients : patients 65 years and older were more likely to develop low platelet and ALC values; the incidence rate of herpes zoster in patients 65 years of age and older was higher than that of younger patients. There are limited data in patients above 75 years of age.

Excipients: Lactose monohydrate: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5. Interaction with other medicinal products and other forms of interaction

Potential for other medicines to affect pharmacokinetics of FREORLA

Abrocitinib is metabolized predominantly by CYP2C19 and CYP2C9 enzymes, and to a lesser extent by CYP3A4 and CYP2B6 enzymes, and its active metabolites are renally excreted and are substrates of the organic anion transporter 3 (OAT3). Therefore, exposures of abrocitinib and/or its active metabolites may be affected by medicinal products that inhibit or induce these enzymes and transporter. Dose adjustments, as appropriate, are outlined in section 4.2.

Coadministration with CYP2C19/CYP2C9 inhibitors
When FREORLA 100 mg was administered concomitantly with fluvoxamine (a strong CYP2C19 and moderate CYP3A inhibitor) or fluconazole (a strong CYP2C19, moderate

CYP2C9 and CYP3A inhibitor), the extent of exposure of abrocitinib active moiety increased by 91% and 155%, respectively, compared with administration alone.

Coadministration with CYP2C19/CYP2C9 inducers
Administration of FREORLA 200 mg after multiple dosing with rifampin, a strong inducer of CYP enzymes, resulted in reduction of abrocitinib active moiety exposures by approximately 56%. Based on the results of PBPK analysis, moderate induction of CYP enzymes reduces the exposure of abrocitinib active moiety by 44%.

Coadministration with OAT3 inhibitors
When FREORLA 200 mg was administered concomitantly with probenecid, an OAT3 inhibitor, abrocitinib active moiety exposures increased by approximately 66%. This is not clinically significant, and a dose adjustment is not needed.

Co-administration with products which increase gastric pH
The effect of elevating gastric pH on abrocitinib active moiety exposures is not clinically significant and dose adjustment is not needed.

When abrocitinib 200 mg was administered concomitantly with famotidine 40 mg, an H2-receptor antagonist, the peak and extent of abrocitinib active moiety exposures decreased by approximately 82% and 20% respectively. The effect of elevating gastric pH with antacids, or proton pump inhibitors (omeprazole) on the pharmacokinetics of abrocitinib has not been studied and may reduce the absorption of abrocitinib in a manner similar to that seen with famotidine.

<u>Potential for FREORLA to affect pharmacokinetics of other medicines</u>

No clinically significant effects of FREORLA were observed in drug interaction studies with oral contraceptives (e.g., ethinyl estradiol/levonorgestrel), or with substrates of BCRP and OAT3 (e.g., rosuvastatin), MATE1/2K (e.g., metformin), CYP3A4 (e.g., midazolam), CYP1A2 (e.g., caffeine) and CYP2B6 (e.g., efavirenz). *In vitro*, abrocitinib is an inhibitor of P-glycoprotein (P-gp). Coadministration of dabigatran etexilate (a P-gp substrate), with a single dose of FREORLA 200 mg increased dabigatran AUC_{inf} and C_{max} by approximately 53% and 40%, respectively, compared with administration alone. Caution should be exercised for concomitant use of abrocitinib with dabigatran. The effect of abrocitinib on the pharmacokinetics of other P-gp substrates has not been evaluated. Caution should be exercised as the levels of P-gp substrates with a narrow therapeutic index, such as digoxin, may increase.

In vitro, abrocitinib is an inhibitor of CYP2C19 enzyme. Coadministration of abrocitinib 200 mg once daily with omeprazole 10 mg single dose increased the AUC_{inf} and C_{max} of omeprazole by approximately 189% and 134%, respectively, indicating that abrocitinib is a moderate inhibitor of CYP2C19 enzyme. Caution should be exercised when using abrocitinib concomitantly with narrow therapeutic index medicines that are primarily metabolized by CYP2C19 enzyme (e.g., S-mephenytoin, clopidogrel).

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

Women of reproductive potential should be advised to use effective contraception during treatment and for 1 month following the final dose of FREORLA. Consider pregnancy planning and prevention for females of reproductive potential.

Pregnancy

The limited human data on use of FREORLA in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage. In embryo-fetal development studies, oral administration of FREORLA to pregnant rats during organogenesis resulted in fetotoxicity at exposures equal to 17 times the unbound AUC at the maximum recommended human dose (MRHD) of 200 mg once daily. In embryo-fetal development studies, oral administration of FREORLA to pregnant rabbits did not result in fetotoxicity at exposures equal to 4 times the unbound AUC at the MRHD of 200 mg. In a pre- and postnatal development study in pregnant rats, FREORLA oral administration during gestation and through lactation resulted in lower postnatal survival and lower offspring body weights at exposures greater than or equal to 11 times the unbound AUC at the MRHD of 200 mg once daily (see Section 5.3). FREORLA is contraindicated during pregnancy.

Breastfeeding

There are no data on the presence of FREORLA in human milk, the effects on the breastfed infant, or the effects on milk production. FREORLA was secreted in milk of lactating rats. A risk to newborns/infants cannot be excluded and FREORLA is contraindicated during breast-feeding.

Fertility

Based on the findings in rats, oral administration of FREORLA may result in temporary reduced fertility in females of reproductive potential. These effects on female rat fertility were reversible 1 month after cessation of FREORLA oral administration (see Section 5.3).

4.7. Effects on ability to drive and use machines

FREORLA has no or negligible sedating effect. However, patients who experience dizziness after the intake of abrocitinib should refrain from driving or using machines until the dizziness resolves.

4.8. Undesirable effects

Summary of safety profile

The most commonly reported adverse reactions (ARs) occurring in ≥2% of patients treated with FREORLA in placebo-controlled studies were nausea (15.1%), headache (7.9%), acne (4.8%),

herpes simplex (4.2%), vomiting (3.5%), dizziness (3.4%), blood creatine phosphokinase increased (3.1%), and abdominal pain upper (2.2%). The most frequent serious adverse reactions in atopic dermatitis patients were infections (see Section 4.4).

Tabulated list of adverse reactions

A total of 3848 patients were treated with FREORLA in clinical studies in atopic dermatitis; among them 3050 patients (representing 5166 patient-years of exposure) were integrated for safety analysis, 2013 patients with at least 48 weeks of exposure. The integrated safety analysis included 1997 patients receiving a constant dose of FREORLA 200 mg and 1053 patients receiving a constant dose of 100 mg.[37] Five placebo-controlled studies were integrated (703 patients on 100 mg once daily, 684 patients on 200 mg once daily and 438 patients on placebo) to evaluate the safety of FREORLA in comparison to placebo for up to 16 weeks.

Table 2. Adverse reactions for FREORLA

System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ⩾1/1,000 to <1/100**
Infections and infestations		Herpes simplex[a] Herpes zoster[b]	Pneumonia
Blood and lymphatic system disorders		Thrombocytopenia	Lymphopenia
Metabolism and nutrition disorders			Hyperlipidaemia[c]
Nervous system disorders		Headache Dizziness	
Vascular disorders			Venous thromboembolism[d]
Gastrointestinal disorders	Nausea	Vomiting Abdominal pain upper	
Skin and subcutaneous tissue disorders		Acne	
Investigations		Blood creatine phosphokinase increased	

a. Herpes simplex includes oral herpes, ophthalmic herpes simplex, genital herpes, and herpes dermatitis.
b. Herpes zoster includes ophthalmic herpes zoster.
c. Hyperlipidaemia included dyslipidaemia and hypercholesterolaemia.
d. Venous thromboembolism includes pulmonary embolism and deep vein thrombosis.

Description of selected adverse reactions

Infections
In placebo-controlled studies, for up to 16 weeks, overall infections have been reported in 27.4% of patients treated with placebo and in 34.9% and 34.8% of patients treated with FREORLA 100 mg and 200 mg, respectively. Most infections were mild or moderate.

The percentage of patients reporting infection-related adverse reactions in the 200 mg and 100 mg groups compared to placebo were : herpes simplex (4.2% and 2.8% versus 1.4%), herpes zoster (1.2% and 0.6% versus 0%), pneumonia (0.1% and 0.1% versus 0%). Herpes simplex was more frequent in patients with a history of herpes simplex or eczema herpeticum. Most of the herpes zoster events involved a single dermatome and were non-serious.

Most opportunistic infections were cases of herpes zoster (0.61 per 100 patient-years in the abrocitinib 100 mg group and 1.23 per 100 patient-years in the abrocitinib 200 mg group), most of which were non-serious multidermatomal cutaneous infections. Among all patients treated in clinical studies with consistent dosing regimens of either abrocitinib 100 mg or 200 mg, including the long-term extension study, the incidence rate of herpes zoster in patients treated with abrocitinib 200 mg (4.36 per 100 patient-years) was higher than that of patients treated with 100 mg (2.61 per 100 patient-years). Incidence rates for herpes zoster were also higher for patients 65 years of age and older (HR 1.76), patients with a medical history of herpes zoster (HR 3.41), patients with severe atopic dermatitis at baseline (HR 1.17), and a confirmed ALC < 1.0×10^3 /mm^3 prior to the event of herpes zoster (HR 2.18) (see section 4.4)

In placebo-controlled studies, for up to 16 weeks, the rate of serious infections was 1.81 per 100 patient-years in patients treated with placebo, 3.32 per 100 patient-years in patients treated with 100 mg, and 1.12 per 100 patient-years in patients treated with 200 mg. Among all patients treated in clinical studies with consistent dosing regimens of either FREORLA 100 mg or 200 mg, including the long the rate of serious infections was 2.20 per 100 patient-years in the FREORLA 100 mg group and 2.48 per 100 patient-years in the FREORLA 200 mg group. The most commonly reported serious infections were herpes simplex, herpes zoster, and pneumonia (see Section 4.4).

Opportunistic infections
Most opportunistic infections were non-serious cases of multidermatomal cutaneous herpes zoster. Among all patients treated in clinical studies with consistent dosing regimens of either FREORLA 100 mg or 200 mg, including the long-term extension study, the rate of opportunistic infections was 0.70 per 100 patient-years in the FREORLA 100 mg group and 0.96 per 100 patient-years in the FREORLA 200 mg group. Most cases of opportunistic herpes zoster were mild or moderate.

Venous thromboembolism
Among all patients treated in clinical studies with consistent dosing regimen of either FREORLA 100 mg or 200 mg, including the long-term extension study, the rate of PE was 0.05 per 100 patient-years in the FREORLA 100 mg group and 0.21 per 100 patient-years in the

FREORLA 200 mg group. The rate of DVT was 0.05 per 100 patient-years in the FREORLA 100 mg group and 0.06 per 100 patient-years in the FREORLA 200 mg group (see Section 4.4).

Thrombocytopenia
In placebo-controlled studies, for up to 16 weeks, treatment with FREORLA was associated with a dose-related decrease in platelet count. Maximum effects on platelets were observed within 4 weeks, after which the platelet count returned towards baseline despite continued therapy. Confirmed platelet counts of $<50 \times 10^3/mm^3$ were reported in 0.1% of patients exposed to FREORLA 200 mg, 0 patients treated with FREORLA 100 mg or placebo. Among all patients treated in clinical studies with consistent dosing regimens of either FREORLA 100 mg or 200 mg, including the long-term extension study, the rate of confirmed platelet counts of $<50 \times 10^3/mm^3$ was 0.22 per 100 patient-years for 200 mg and 0 per 100 patient-years for 100 mg, most occurring at Week 4. Patients 65 years of age and older had a higher rate of platelet counts $<75 \times 10^3/mm^3$ (see Section 4.4). There were no adolescent patients who developed platelet counts $<75 \times 10^3/mm^3$.

Lymphopenia
In placebo-controlled studies, for up to 16 weeks, confirmed ALC $<0.5 \times 10^3/mm^3$ occurred in 2 patients (0.3%) treated with FREORLA 200 mg and 0 patients treated with FREORLA 100 mg or placebo. Both cases occurred in the first 4 weeks of exposure. Among all patients treated in clinical studies with consistent dosing regimens of either FREORLA 100 mg or 200 mg, including the long-term extension, the rate of confirmed ALC $<0.5 \times 10^3/mm^3$ was 0.40 per 100 patient-years for 200 mg and 0 per 100 patient-years for 100 mg, the highest rate was observed in patients 65 years of age and older (see Section 4.4). There were no adolescent patients who developed an ALC $<0.5 \times 10^3/mm^3$.

Lipid elevations
In placebo-controlled studies, for up to 16 weeks, there was a dose-related percent increase in low-density lipoprotein cholesterol (LDL-c), total cholesterol, and high-density lipoprotein cholesterol (HDL-c) relative to placebo at Week 4 which remained elevated through the final visit in the treatment period. The median % change in LDL-c at Week 4 was 9.1%, 4.9% and -2.8% in patients exposed to 200 mg, 100 mg and placebo, respectively. The median % change in HDL-c at Week 4 was 20.0%, 12.1%, and 0% in patients exposed to 200 mg, 100 mg and placebo, respectively. Events related to hyperlipidemia occurred in 0.4% of patients exposed to FREORLA 100 mg, 0.6% of patients exposed to 200 mg, and 0% of patients exposed to placebo (see Section 4.4).

Creatine phosphokinase elevations (CPK)
In placebo-controlled studies, for up to 16 weeks, events of blood CPK increased (>5 × ULN) were reported in 3.8% of patients treated with 200 mg, 1.8% of patients treated with 100 mg of FREORLA and 1.8% of patients treated with placebo. Most elevations were transient, and none led to discontinuation.

Nausea

Nausea was most frequent in the first week of FREORLA therapy and generally resolved with continued therapy. The median duration of nausea was 15 days. Most of the cases were mild to moderate in severity.

In placebo-controlled studies, for up to 16 weeks, nausea was reported in 1.8% of patients treated with placebo and in 6.3% and 15.1% of patients treated with 100 mg and 200 mg, respectively. Discontinuation due to nausea occurred in 0.4% of patients treated with abrocitinib. Among patients with nausea, 63.5% of patients had onset of nausea in the first week of therapy.

Major Adverse Cardiovascular Events

In the placebo-controlled trials, for up to 16 weeks, major adverse cardiovascular event (MACE) was reported in 1 subject (0.6 per 100 patient-years) treated with FREORLA 100 mg. In all 5 clinical trials, including the long-term extension trial, MACE was reported in 1 patient (0.1 per 100 patient-years) treated with FREORLA 100 mg and 2 subjects (0.3 per 100 patient-years) treated with FREORLA 200 mg.

Pediatric population

The pharmacokinetics, safety and efficacy of FREORLA in pediatric patients under 12 years of age have not yet been established.

A total of 635 adolescent patients (12 to less than 18 years of age) were treated with abrocitinib in clinical studies in atopic dermatitis representing 1326.1 patient-years of exposure. The safety profile observed in adolescents in atopic dermatitis clinical studies was similar to that of the adult population.

Elderly population

A total of 145 patients 65 years of age and older were enrolled in FREORLA studies. The safety profile observed in elderly patients was similar to that of the adult population overall. A higher proportion of patients 65 years of age and older discontinued from clinical studies compared to younger patients. Among all patients exposed to FREORLA including the long-term extension study, confirmed ALC $<0.5 \times 10^3/mm^3$ occurred only in patients 65 years of age and older. A higher proportion of patients 65 years of age and older had platelet counts $<75 \times 10^3/mm^3$. The incidence rate of herpes zoster in patients 65 years of age and older treated with FREORLA (7.40 per 100 patient-years) was higher than that of patients 18 to less than 65 years of age (3.44 per 100 patient-years) and less than 18 years of age (2.12 per 100 patient-years). There is limited data in patients above 75 years of age.

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:
Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif

Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR

PT Pfizer Indonesia
Email: IDN.AEReporting@pfizer.com
Website: www.pfizersafetyreporting.com

4.9. Overdose

FREORLA was administered in clinical studies up to a single oral dose of 800 mg. There is no experience with overdose of FREORLA. There is no specific antidote for overdose with FREORLA. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Treatment should be symptomatic and supportive.

Pharmacokinetic data up to and including a single oral dose of 800 mg in healthy adult volunteers indicate that more than 90% of the administered dose is expected to be eliminated within 48 hours.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Mechanism of action

FREORLA is a Janus kinase (JAK) 1 inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Inhibition of JAK1 modulates the signaling pathway by preventing the phosphorylation and activation of STATs.

In biochemical assay, FREORLA has selectivity for JAK1 over the other 3 JAK isoforms JAK2 (28-fold), JAK3 (>340-fold) and tyrosine kinase 2 (TYK 2, 43-fold). In cellular settings, it preferentially inhibits cytokine-induced STAT phosphorylation by signaling pairs involving JAK1, and spares signaling by JAK2/JAK2 or JAK2/TYK2 pairs. The relevance of selective enzymatic inhibition of specific JAK enzymes to clinical effect is not currently known.

Pharmacodynamic effects

Treatment with FREORLA was associated with dose-dependent reduction in serum markers of inflammation, including high sensitivity C-reactive protein (hsCRP), interleukin-31 (IL-31) and

thymus and activation-regulated chemokine (TARC). These changes returned to near baseline within 4 weeks of drug discontinuation.

Mean absolute lymphocyte count increased by 2 weeks after starting treatment with abrocitinib and returned to baseline by Month 9 of treatment. Most patients maintained an ALC within the reference range. Treatment with abrocitinib was associated with a dose-related increase in B cell counts and a dose-related decrease in NK cell counts. The clinical significance of these changes in B cell and NK cell counts is unknown

Clinical efficacy and safety

The efficacy and safety of FREORLA as monotherapy and in combination with background medicated topical therapies over 12-16 weeks were evaluated in 1616 patients in 3 pivotal randomized, double-blind, placebo-controlled studies (MONO-1, MONO-2, and COMPARE). In addition, the efficacy and safety of FREORLA in monotherapy over 52 weeks (with the option of rescue treatment in flaring patients) was evaluated in 1233 patients in a Phase 3 induction, randomized withdrawal, double-blind, placebo-controlled study (REGIMEN). The patients in these 4 studies were 12 years of age and older with moderate-to-severe atopic dermatitis as defined by Investigator's Global Assessment (IGA) score ≥3, Eczema Area and Severity Index (EASI) score ≥16, body surface area (BSA) involvement ≥10%, and Peak Pruritus Numerical Rating Scale (PP-NRS) ≥4 at the baseline visit prior to randomization. Patients who had a prior inadequate response or for whom topical treatments were medically unadvisable, or who had received systemic therapies were eligible for inclusion.

All patients who completed the parent studies were eligible to enroll into the long-term extension study EXTEND.

Clinical response
Treatment with FREORLA 100 mg or 200 mg once daily as monotherapy or in combination with background medicated topical therapy resulted in improvement in objective signs of atopic dermatitis and patient-reported pruritus.

Baseline characteristics
In the placebo-controlled studies (MONO-1, MONO-2, COMPARE) and the open label induction, randomized withdrawal study (REGIMEN) across all treatment groups 41.4% to 51.1% were female, 59.3% to 77.8% were Caucasian, 15.0% to 33.0% were Asian and 4.1% to 8.3% were Black, and the mean age was 32.1 to 37.7 years. In these studies, 32.2% to 40.8% had a baseline IGA of 4 (severe atopic dermatitis), and 41.4% to 59.5% of patients had received prior systemic treatment for atopic dermatitis. The baseline mean EASI score ranged from 28.5 to

30.9, the baseline PP-NRS ranged from 7.0 to 7.3 and the baseline Dermatology Life Quality Index (DLQI) ranged from 14.4 to 16.0.

Monotherapy studies
In both pivotal monotherapy studies (MONO-1, MONO-2), the proportion of patients who achieved IGA and/or EASI-75 response was significantly higher in patients who received FREORLA 100 mg or 200 mg once daily compared with placebo at Week 12 (see Table 5).

A significantly higher proportion of patients who achieved PP-NRS4 (defined as an improvement of ≥4 points in the severity of PP-NRS) with FREORLA 100 mg or 200 mg once daily compared with placebo was observed as soon as Week 2 and persisting through Week 12. Higher proportions of patients achieved PP-NRS4 with FREORLA 100 mg or 200 mg once daily compared with placebo by Day 6 and Day 3 (2 days after the first dose), respectively (see Table 3).

Table 3. Efficacy results of FREORLA monotherapy at Week 12

	MONO-1			**MONO-2**		
	FRE			**FRE**		
	200 mg QD N=154	**100 mg QD N=156**	**Placebo N=77**	**200 mg QD N=155**	**100 mg QD N=158**	**Placebo N=78**
	% Responders (95% CI)					
IGA 0 or 1[a]	43.8[g] (35.9, 51.7)	23.7[e] (17.0, 30.4)	7.9 (1.8, 14.0)	38.1[g] (30.4, 45.7)	28.4[f] (21.3, 35.5)	9.1 (2.7, 15.5)
EASI-50[b]	75.8[k] (69.0, 82.6)	57.7[k] (49.9, 65.4)	22.4 (13.0, 31.7)	79.9[k] (73.5, 86.2)	68.4[k] (61.1, 75.7)	19.5 (10.6, 28.3)
EASI-75[b]	62.7[g] (55.1, 70.4)	39.7[g] (32.1, 47.4)	11.8 (4.6, 19.1)	61.0[g] (53.3, 68.7)	44.5[g] (36.7, 52.3)	10.4 (3.6, 17.2)
EASI-90[b]	38.6[k] (30.8, 46.3)	18.6[i] (12.5, 24.7)	5.3 (0.2, 10.3)	37.7[k] (30.0, 45.3)	23.9[k] (17.2, 30.6)	3.9 (0.0, 8.2)
EASI-100[b]	13.1[i] (7.7, 18.4)	6.4[h] (2.6, 10.3)	0 (0.0, 4.7)	7.1[h] (3.1, 11.2)	5.2[h] (1.7, 8.6)	0 (0.0, 4.7)
PP-NRS4[c,d]	57.2[g] (48.8, 65.6)	37.7[f] (29.2, 46.3)	15.3 (6.6, 24.0)	55.3[g] (47.2, 63.5)	45.2[g] (37.1, 53.3)	11.5 (4.1, 19.0)
PP-NRS (0 or 1)	35.4[k] (27.2, 43.6)	21.1[i] (13.9, 28.4)	3.2 (0.0, 7.5)	32.4[k] (24.5, 40.2)	21.3[i] (14.5, 28.0)	5.5 (0.3, 10.7)

Table 3. Efficacy results of FREORLA monotherapy at Week 12

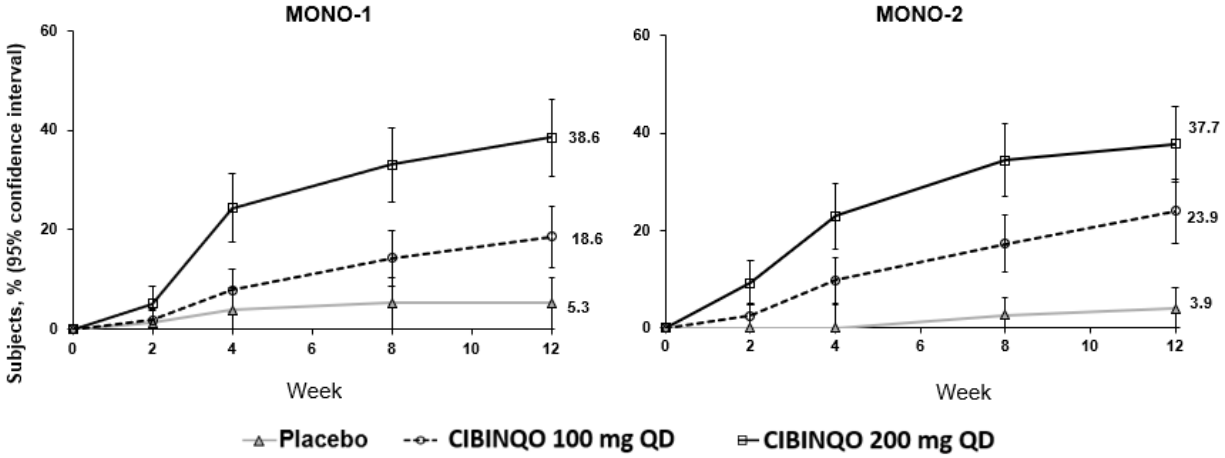
	MONO-1			MONO-2		
	FRE			FRE		
	200 mg QD N=154	100 mg QD N=156	Placebo N=77	200 mg QD N=155	100 mg QD N=158	Placebo N=78
	% Change from baseline (95% CI)					
LSM EASI	-73.5[k] (-79.1, -68.0)	-57.5[k] (-63.1, -51.9)	-28.4 (-36.5, -20.3)	-73.3[k] (-79.7, -66.9)	-60.0[k] (-66.5, -53.6)	-28.6 (-38.4, -18.8)
LSM PP-NRS	-56.5[k] (-63.6, -49.5)	-39.5[i] (-46.7, -32.3)	-19.5 (-30.0, -9.0)	-56.9[k] (-64.0, -49.8)	-43.5[j] (-50.7, -36.3)	-20.8 (-31.6, -9.9)
LSM SCORAD	-55.1[k] (-60.1, -50.2)	-41.5[k] (-46.5, -36.5)	-21.6 (-28.7, -14.5)	-56.2[k] (-61.2, -51.1)	-45.8[k] (-50.9, -40.7)	-22.7 (-30.4, -15.1)
	Change from baseline (95% CI)					
LSM PSAAD	-3.2[g] (-3.6, -2.8)	-2.2[e] (-2.6, -1.9)	-1.1 (-1.7, -0.6)	-3.0[g] (-3.3, -2.7)	-2.4[g] (-2.8, -2.1)	-0.8 (-1.3, -0.3)

Abbreviations: FRE=FREORLA; CI=confidence interval; EASI=Eczema Area and Severity Index; LSM=least squares mean; IGA=Investigator Global Assessment; N=number of patients randomized; PP-NRS=Peak Pruritus Numerical Rating Scale; PSAAD=Pruritus and Symptoms Assessment for Atopic Dermatitis; QD=once daily; SCORAD=SCORing Atopic Dermatitis.

a. IGA responders were patients with IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥ 2 points.
b. EASI-50, -75, -90 and -100 responders were patients with ≥50%, ≥75%, ≥90%, and ≥100% improvement, respectively in EASI, from baseline.
c. The proportion of PP-NRS4 responders was also significantly higher with FREORLA 200 mg and 100 mg once daily than placebo at Week 2, Week 4, and Week 8 in both MONO-1 and MONO-2.
d. PP-NRS4 responders were patients with ≥4-point improvement in PP-NRS from baseline.
e. Multiplicity-controlled p <0.01 versus placebo.
f. Multiplicity-controlled p <0.001 versus placebo.
g. Multiplicity-controlled p <0.0001 versus placebo.
h. Nominal p <0.05 versus placebo.
i. Nominal p <0.01 versus placebo.
j. Nominal p <0.001 versus placebo.
k. Nominal p <0.0001 versus placebo.

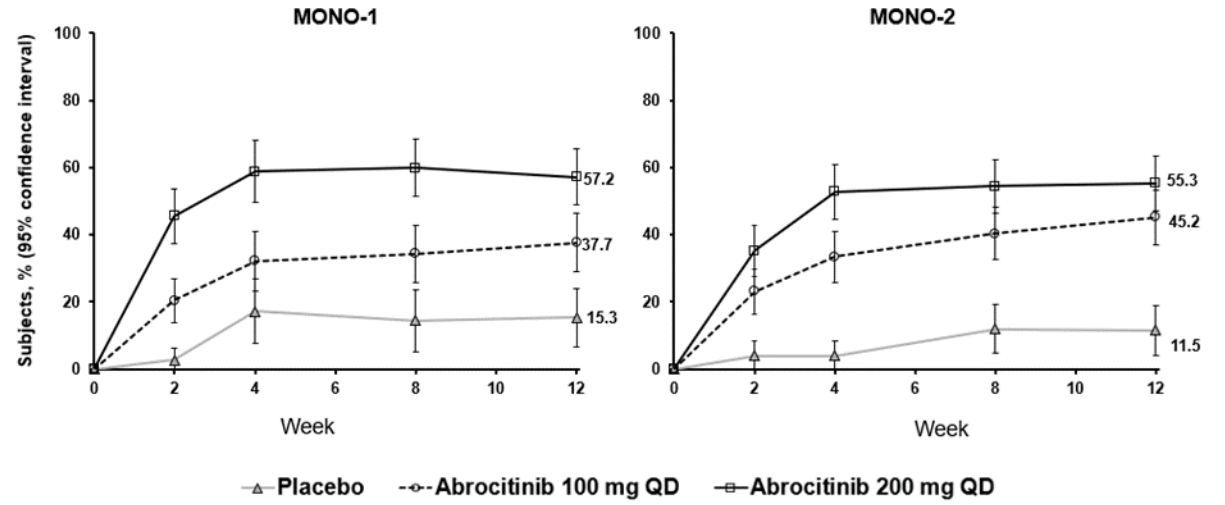
The proportion of patients who achieved EASI-90 or PP-NRS4 over time in studies MONO-1 and MONO-2 are shown in Figures 1 and 2.

Figure 1. Proportion of patients who achieved EASI-90 over time in MONO-1 and MONO-2



Abbreviations: EASI=Eczema Area and Severity Index; QD=once daily.
PP-NRS4 responders were patients with ⩾4-point improvement in Peak Pruritis Numerical Rating Scale (PP-NRS) from baseline.

Figure 2. Proportion of patients who achieved PP-NRS4 over time in MONO-1 and MONO-2



Abbreviations: PP-NRS=Peak Pruritus Numerical Rating Scale; QD=once daily.
PP-NRS4 responders were patients with ⩾4-point improvement in Peak Pruritis Numerical Rating Scale (PP-NRS) from baseline.

Treatment effects in subgroups (e.g., weight, age, sex, race and prior systemic immunosuppressant treatment) in MONO-1 and MONO-2 were consistent with the results in the overall study population.

Combination therapy study

In the pivotal combination therapy study (COMPARE), the proportion of patients who achieved IGA or EASI-75 response was significantly higher in patients who received FREORLA 100 mg or 200 mg once daily compared with placebo at Week 12 (see Table 4).

The proportions of patients achieving PP-NRS4 with FREORLA 100 mg and 200 mg once daily were significantly higher than placebo by Day 9 and Day 4, respectively, and remained significantly higher than placebo with both FREORLA doses at Week 2 and Week 16.

The proportion of patients achieving PP-NRS4 with FREORLA 200 mg once daily was significantly higher than dupilumab as early as Day 4 and remained significantly higher than dupilumab at Week 2. The proportion of patients achieving PP-NRS4 was similar between FREORLA 100 mg once daily and dupilumab at Week 2.

Table 4. Efficacy results of FREORLA with concomitant topical therapy

	Week 2				**Week 12**				**Week 16**			
	FRE				**FRE**				**FRE**			
	200 mg N=226	**100 mg N=238**	**PBO N=131**	**DUP N=243**	**200 mg N=226**	**100 mg N=238**	**PBO N=131**	**DUP N=243**	**200 mg N=226**	**100 mg N=238**	**PBO N=131**	**DUP N=243**
	% Responders											
IGA 0 or 1[a]	18.4[i]	15.2[h]	6.3	4.7	48.4[e]	36.6[e]	14.0	36.5	47.5[e]	34.8[e]	12.9	38.8
EASI-50[b]	60.5[j]	53.1[j]	21.9	35.7	86.3[j]	75.3[j]	52.7	80.9	87.3[j]	81.2[j]	57.3	84.1
EASI-75[b]	30.0[j]	25.4[i]	10.9	14.0	70.3[e]	58.7[e]	27.1	58.1	71.0[e]	60.3[e]	30.6	65.5
EASI-90[b]	11.2[h]	8.3[g]	2.3	2.6	46.1[j]	36.6[j]	10.1	34.9	48.9[j]	38.0[j]	11.3	38.8
EASI-100[b]	4.5[g]	1.3	0	0.4	12.3[i]	8.1[h]	1.6	6.6	13.6[h]	12.7[h]	4.0	5.2
PP-NRS4[c]	49.1[e,f]	31.8[d]	13.8	26.4	63.1[j]	47.5[i]	28.9	54.5	62.8[j]	47.0[h]	28.7	57.1
PP-NRS (0 or 1)	15.0[h]	8.9	4.6	4.6	36.9[j]	21.1[i]	7.4	24.9	32.0[i]	24.7[g]	11.7	24.2
	% Change from baseline											
LSM EASI	-54.6[j]	-49.3[j]	-21.2	-38.8	-80.6[j]	-73.8[j]	-47.7	-75.4	-83.2[j]	-75.2[j]	-53.8	-80.2

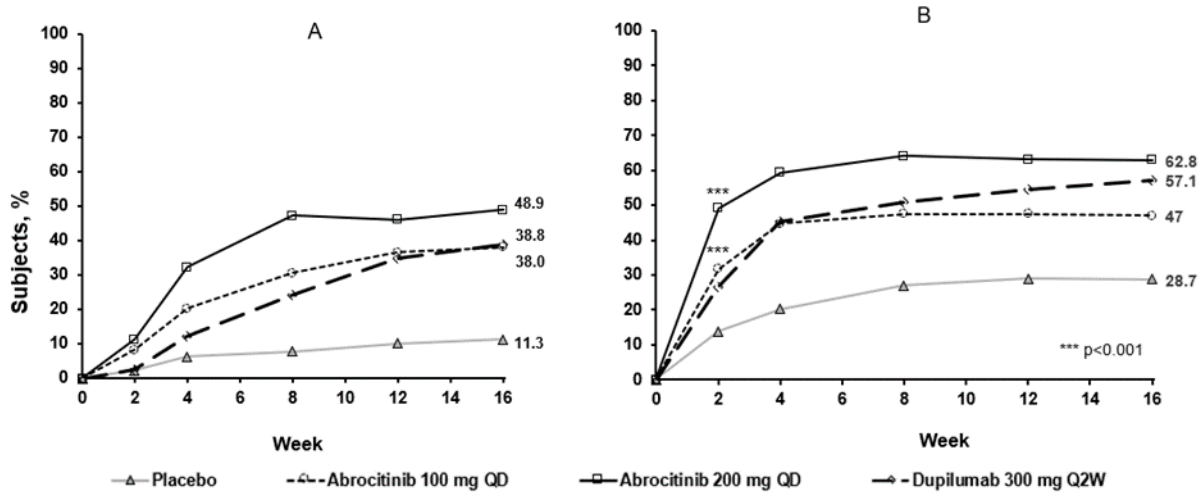
LSM PP-NRS	-45.6[j]	-35.5[j]	-19.5	-29.3	-63.3[j]	-48.2[j]	-30.4	-54.8	-64.1[j]	-49.1[j]	-30.3	-58.5
LSM SCORAD	-41.7[j]	-34.6[j]	-18.1	-27.7	-65.2[j]	-54.2[j]	-33.5	-58.4	-65.4[j]	-55.6[j]	-38.8	-61.9
	Change from baseline											
LSM PSAAD	-2.3[j]	-1.8[j]	-0.9	-1.6	-3.6[j]	-2.7[j]	-1.6	-3.2	-3.6[j]	-2.8[j]	-1.7	-3.4

Abbreviations: FRE=FREORLA; DUP=dupilumab; EASI=Eczema Area and Severity Index; LSM=least squares mean; N=number of patients randomized; PBO=placebo; PP-NRS=Peak Pruritus Numerical Rating Scale; PSAAD=Pruritus and Symptoms Assessment for Atopic Dermatitis; SCORAD=SCORing Atopic Dermatitis.

a. IGA responders were patients with IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥ 2 points.
b. EASI-50, -75, -90 and -100 responders were patients with ≥50%, ≥75%, ≥90% and ≥100% improvement in EASI, respectively, from baseline.
c. PP-NRS4 responders were patients with ≥4-point improvement in PP-NRS from baseline.
d. Multiplicity-controlled p <0.001 vs. placebo
e. Multiplicity-controlled p <0.0001 vs. placebo
f. Multiplicity-controlled p <0.0001 vs. dupilumab. Statistical comparison between either abrocitinib dose and dupilumab was only performed on the proportion of patients achieving PP-NRS4 at Week 2.
g. Nominal p <0.05 vs. placebo
h. Nominal p <0.01 vs. placebo
i. Nominal p <0.001 vs. placebo
j. Nominal p <0.0001 vs. placebo

The proportion of patients who achieved EASI-90 or PP-NRS4 over time in COMPARE are shown in Figure 3.

Figure 3. Proportion of patients who achieved A) EASI-90 and B) PP-NRS4 over time in COMPARE



Abbreviations: EASI=Eczema Area and Severity Index; PP-NRS=Peak Pruritus Numerical Rating Scale; QD=once daily; Q2W=every 2 weeks.
EASI-90 was based on EASI ≥90% improvement from baseline.
PP-NRS4 response was based on achieving at least 4 points improvement in the severity of Peak Pruritus Numerical Rating Scale (PP-NRS).

Patients who received dupilumab and subsequently enrolled in EXTEND were randomized to either FREORLA 100 mg or 200 mg once daily upon entering EXTEND. Among responders to dupilumab in COMPARE, the majority maintained response 12 weeks after switching to

FREORLA [77% and 86% for IGA (0 or 1) response, and 90% and 96% for EASI-75 with 100 mg once daily or 200 mg once daily, respectively]. Among non-responders to dupilumab in COMPARE, a substantial proportion of patients achieved response 12 weeks after switching to FREORLA [34% and 47% for IGA (0 or 1) response, and 68% and 80% for EASI-75 with 100 mg once daily or 200 mg once daily, respectively].

Treatment effects in subgroups (e.g., weight, age, sex, race, and prior systemic immunosuppressant treatment) in COMPARE were consistent with the results in the overall study population.

Late-onset efficacy
Eligible patients who completed the full treatment period of a qualifying parent study (e.g., MONO-1, MONO-2, COMPARE) were considered for enrollment in the long-term extension study EXTEND, which allows patients to extend FREORLA treatment for at least 92 weeks or until availability of commercial product in their country. In EXTEND, patients received FREORLA with or without background medicated topical therapy Patients who were previously randomized to FREORLA 100 mg or 200 mg once daily in qualifying studies continued the same dose in EXTEND as in the parent study, and the blind was maintained. Patients not previously randomized to FREORLA in a qualifying parent study were randomized to either FREORLA 100 mg or 200 mg once daily upon entering EXTEND.

Among patients who did not achieve IGA (0 or 1) response after 12 weeks of FREORLA treatment and entered EXTEND, 14% and 25% of patients continuing FREORLA 100 mg once daily in EXTEND achieved IGA (0 or 1) response by Week 16 and Week 24 (with 4 and 12 additional weeks of treatment), respectively, and 19% and 29% of patients continuing FREORLA 200 mg once daily achieved IGA response by Week 16 and Week 24, respectively (based on observed data). Among patients who did not achieve EASI-75 after 12 weeks of FREORLA treatment and entered EXTEND, 32% and 50% of patients continuing FREORLA 100 mg once daily in EXTEND achieved EASI-75 by Week 16 and Week 24 (with 4 and 12 additional weeks of treatment), respectively, and 33% and 57% of patients continuing FREORLA 200 mg once daily achieved EASI-75 response by Week 16 and Week 24, respectively (based on observed data).

Patients who received dupilumab in the COMPARE study and subsequently entered EXTEND were randomized to either 100 mg or 200 mg of abrocitinib once daily upon entering EXTEND. Among non-responders to dupilumab, a substantial proportion of patients achieved response 12 weeks after switching to abrocitinib [34% and 47% for IGA (0 or 1) response, and 68% and 80% for EASI-75 with 100 mg once daily or 200 mg once daily, respectively].

Long-term efficacy
Among patients who achieved response at Week 12 of a qualifying parent study and entered EXTEND, the majority of patients maintained their response at Week 96 of cumulative FREORLA treatment for both doses of FREORLA [64% and 72% for IGA (0 or 1) response,

87% and 90% for EASI-75, and 75% and 80% for PP-NRS4 with 100 mg once daily and 200 mg once daily, respectively (based on observed data)].

Health related outcomes

Treatment with either dose of FREORLA as monotherapy resulted in significantly improved patient-reported outcomes at 12 weeks compared with placebo (see Table 5). A significantly larger proportion of the FREORLA groups had clinically meaningful reductions in Dermatology Life Quality Index (DLQI) total scores (defined as a 4-point improvement) from baseline to Week 12 compared with placebo. FREORLA groups also had a significantly larger proportion of patients who reported "no effect" of their disease on their quality of life (as measured by a DLQI score of 0 or 1).

Both groups significantly improved patient-reported atopic dermatitis symptoms and sleep disruption as measured by the Patient Oriented Eczema Measure (POEM), Night Time Itch Scale (NTIS), and SCORing Atopic Dermatitis (SCORAD) sleep loss subscale. In addition, anxiety and depression symptoms as measured by the Hospital Anxiety and Depression Scale (HADS) total score were significantly reduced in the FREORLA groups compared with placebo at 12 weeks.

Table 5. Additional endpoint results with FREORLA monotherapy at Week 12

	MONO-1			**MONO-2**		
	FRE			**FRE**		
	200 mg QD N=154	**100 mg QD N=156**	**Placebo N=77**	**200 mg QD N=155**	**100 mg QD N=158**	**Placebo N=78**
LSM SCORAD (sleep loss subscale)						
Baseline median (SD)	5.9	6.0	6.5	6.2	6.2	5.7
Change from baseline (95% CI)	-3.7[d] (-4.2, -3.3)	-2.9[c] (-3.4, -2.5)	-1.6 (-2.2, -1.0)	-3.8[d] (-4.2, -3.4)	-3.0[a] (-3.4, -2.6)	-2.1 (-2.7, -1.5)
NTIS >4-point improvement						
% responders	n/a	n/a	n/a	57.0[d]	42.7[d]	12.7
DLQI						
0 or 1, % responders	31.9[b]	20.2	12.1	26.6[c]	20.3[b]	5.7
≥4 point improvement, % responders	72.6[c]	67.2[b]	43.6	78.1[d]	73.3[d]	32.3
LSM DLQI						
Baseline mean (SD)	14.6 (6.8)	14.6 (6.5)	13.9 (7.3)	14.8 (6.0)	15.4 (7.3)	15.0 (7.1)
Change from baseline (95% CI)	-9.1[d] (-10.3, -8.0)	-7.0[b] (-8.1, -5.8)	-4.2 (-5.9, -2.5)	-9.8[d] (-10.7, -8.8)	-8.3[d] (-9.3, -7.3)	-3.9 (-5.3, -2.4)
CDLQI						
≥2.5 point improvement, % responders	83.9[a]	73.3	53.3	93..3[c]	56.3[a]	12.5
LSM-CDLQI						
Baseline mean (SD)	13.2 (5.5)	11.7 (6.6)	13.6 (7.0)	12.9 (5.7)	13.8 (5.8)	10.1 (3.8)
Change from baseline (95% CI)	-7.5[a] (-8.9, -6.0)	-6.4 (-7.9, -5.0)	-3.9 (-6.1, -1.7)	-9.7[b] (-12.1, -7.4)	-4.8 (-7.2, -2.5)	-2.7 (-6.1, 0.8)
LSM POEM						
Baseline mean (SD)	19.6 (5.9)	19.5 (6.5)	19.9 (6.1)	19.7 (5.7)	20.9 (5.7)	19.2 (5.5)
Change from baseline (95% CI)	-10.6[d] (-11.8, -9.4)	-6.8[b] (-8.0, -5.6)	-3.7 (-5.5, -1.9)	-11.0[d] (-12.1, -9.8)	-8.7[d] (-9.9, -7.5)	-3.6 (-5.3, -1.9)

Table 5. Additional endpoint results with FREORLA monotherapy at Week 12

	MONO-1			MONO-2		
	FRE			FRE		
	200 mg QD N=154	100 mg QD N=156	Placebo N=77	200 mg QD N=155	100 mg QD N=158	Placebo N=78
LSM HADS (anxiety)						
Baseline mean (SD)	5.6 (4.0)	5.9 (4.1)	6.0 (4.0)	5.9 (3.9)	5.5 (4.2)	6.0 (3.7)
Change from baseline	-2.1[b]	-1.6	-1.0	-1.7[a]	-1.6[a]	-0.6
(95% CI)	(-2.5, -1.6)	(-2.0, -1.1)	(-1.7, -0.4)	(-2.2, -1.2)	(-2.1, -1.1)	(-1.3, 0.2)
LSM HADS (depression)						
Baseline mean (SD)	4.2 (3.7)	4.1 (3.7)	3.9 (3.5)	4.0 (3.7)	4.1 (4.0)	4.4 (3.3)
Change from baseline	-1.8[d]	-1.4[b]	-0.2	-1.4[d]	-1.0[c]	0.3
(95% CI)	(-2.2, -1.4)	(-1.8, -0.9)	(-0.8, 0.4)	(-1.8, -1.0)	(-1.5, -0.6)	(-0.3, 0.9)

Abbreviations: FRE=FREORLA; CDLQI=Child Dermatology Life Quality Index; CI=confidence interval; DLQI=Dermatology Life Quality Index; HADS=Hospital Anxiety and Depression Scale; LSM=least squares mean; N=number of patients randomized; n/a= not available; NTIS=Night Time Itch Scale Severity; POEM=Patient Oriented Eczema Measure; QD=once daily; SCORAD=SCORing Atopic Dermatitis.

a. Nominal p <0.05 versus placebo.
b. Nominal p <0.01 versus placebo.
c. Nominal p <0.001 versus placebo.
d. Nominal p <0.0001 versus placebo.

In COMPARE, a significantly larger proportion of the FREORLA groups had clinically meaningful reductions in DLQI total scores (defined as a 4-point improvement) from baseline to Week 12 compared with placebo (see Table 6). FREORLA groups also had a significantly larger proportion of patients who reported “no effect” of their disease on their quality of life (as measured by a DLQI score of 0 or 1).

Both groups significantly improved patient-reported atopic dermatitis symptoms and sleep disruption as measured by the POEM and SCORAD sleep loss subscale, respectively. In addition, anxiety and depression symptoms as measured by the HADS total score were significantly reduced in the FREORLA groups compared with placebo at 12 weeks.

Table 6 Additional endpoint results with FREORLA in combination with medicated topical therapies at Week 12

	COMPARE		
	FRE		
	200 mg QD + Topical N=226	100 mg QD + Topical N=238	Placebo + Topical N=131
LSM SCORAD (sleep loss subscale)			
Baseline mean values	6.4	6.1	6.0
Change from baseline	-4.6[d]	-3.7[d]	-2.4
(95% CI)	(-4.9, -4.3)	(-4.0, -3.4)	(-2.8, -2.0)
NTIS >4-point improvement			
% responders	64.3[d]	54.0[c]	34.4
DLQI			
0 or 1, % responders	29.7%[d]	21.9%[b]	8.6%
≥4 point improvement, % responders	86.4%[d]	74.7%[c]	56.5%
LSM DLQI			
Baseline mean (SD)	16.3 (6.6)	15.5 (6.4)	15.2 (6.9)
Change from baseline	-11.0[d]	-8.7[d]	-6.2
(95% CI)	(-11.7, -10.3)	(-9.4, -8.0)	(-7.1, -5.3)

Table 6 Additional endpoint results with FREORLA in combination with medicated topical therapies at Week 12

	COMPARE		
	FRE		
	200 mg QD + Topical N=226	100 mg QD + Topical N=238	Placebo + Topical N=131
LSM POEM			
Baseline mean (SD)	21.5 (5.3)	20.9 (5.5)	20.4 (6.1)
Change from baseline	-12.6[d]	-9.6[d]	-5.1
(95% CI)	(-13.6, -11.7)	(-10.5, -8.6)	(-6.3, -3.9)
LSM HADS (anxiety)			
Baseline mean (SD)	5.5 (3.8)	5.3 (3.9)	5.3 (3.9)
Change from baseline	-1.6[c]	-1.2[a]	-0.4
(95% CI)	(-2.0, -1.2)	(-1.5, -0.8)	(-0.9, 0.1)
LSM HADS (depression)			
Baseline mean (SD)	3.9 (3.4)	4.0 (3.3)	4.1 (3.7)
Change from baseline	-1.6[d]	-1.3[c]	-0.3
(95% CI)	(-1.9, -1.2)	(-1.6, -0.9)	(-0.7, 0.2)

Abbreviations: FRE=FREORLA; DLQI=Dermatology Life Quality Index; HADS=Hospital Anxiety and Depression Scale; LSM=least squares mean; NTIS=Night Time Itch Scale Severity; POEM=Patient Oriented Eczema Measure; QD=once daily; SCORAD=SCORing Atopic Dermatitis; SD=standard deviation.

a. Nominal p <0.05 versus placebo.
b. Nominal p <0.01 versus placebo.
c. Nominal p <0.001 versus placebo.
d. Nominal p <0.0001 versus placebo.

Pediatric population

The efficacy and safety of FREORLA as monotherapy was evaluated in 2 Phase 3 randomized, double-blind, placebo-controlled studies (MONO-1, MONO-2) which included 124 patients who were 12 to less than 18 years of age. The efficacy and safety were also evaluated in open label induction, randomized withdrawal study (REGIMEN) which included 246 patients who were 12 to less than 18 years of age. In these studies, the results in the adolescent subgroup were consistent with the results in the overall study population.

The efficacy and safety of FREORLA in combination with background medicated topical therapy was evaluated in the Phase 3 randomized, double-blind, placebo-controlled study TEEN. The study included 285 patients who were 12 to less than 18 years of age with moderate-to-severe atopic dermatitis as defined by IGA score ≥3, EASI score ≥16, BSA involvement ≥10%, and PP-NRS ≥ 4 at the baseline visit prior to randomization. Patients who had a prior inadequate response or who had received systemic therapy, were eligible for inclusion.

Baseline characteristics

In TEEN, across all treatment groups 49.1% were female, 56.1% were Caucasian, 33.0% were Asian and 6.0% were Black patients. The median age was 15 years and the proportion of patients with severe atopic dermatitis (IGA of 4) was 38.6%.

Table 8. Adolescent efficacy results of FREORLA in TEEN

	TEEN[d]		
	FRE		PBO
	200 mg QD	100 mg QD	

	N=94	N=95	N=96
IGA 0 or 1[a] % responders (95% CI)	46.2[e] (36.1, 56.4)	41.6[e] (31.3, 51.8)	24.5 (15.8, 33.2)
EASI-75[b] % responders (95% CI)	72.0[e] (62.9, 81.2)	68.5[e] (58.9, 78.2)	41.5 (31.5, 51.4)
PP-NRS4[c] % responders (95% CI)	55.4[e] (44.1, 66.7)	52.6 (41.4, 63.9)	29.8 (20.0, 39.5)

Abbreviations: FRE=FREORLA; CI=confidence interval; EASI=Eczema Area and Severity Index; IGA=Investigator Global Assessment; N=number of patients treated; PBO=placebo; PP-NRS=Peak Pruritus Numerical Rating Scale; QD=once daily.

a. IGA responders were patients with IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points.

b. EASI-75 responders were patients with ⩾75% improvement in EASI from baseline.

c. PP-NRS4 responders were patients with ⩾4-point improvement in PP-NRS from baseline.

d. FREORLA used in combination with medicated topical therapy.

e. Statistically significant with adjustment for multiplicity versus placebo.

Among adolescent patients who achieved response after 12 weeks of treatment and entered long-term extension study EXTEND, the majority of patients maintained their response at Week 96 of cumulative treatment for both doses of abrocitinib [62% and 78%, for IGA (0 or 1) response, 89% and 93% for EASI-75, and 77% and 76% for PP-NRS4] with 100 mg and 200 mg once daily, respectively.

Among adolescent patients who did not achieve response after 12 weeks of treatment and entered EXTEND, a proportion of patients achieved late-onset response by Week 24 (from baseline) of continued treatment with both doses of abrocitinib [34% and 28% for IGA (0 or 1) response, and 41% and 55% for EASI-75] with 100 mg and 200 mg once daily, respectively.

Open label induction, randomized withdrawal study (REGIMEN)
A total of 1,233 patients received open label FREORLA. Seven-hundred ninety-eight (798) induction responders were randomized to 200 mg or 100 mg of medicinal product or placebo.

Continuous treatment (200 mg continuous) and induction-maintenance treatment (200 mg for 12 weeks followed by 100 mg) prevented flare with 81.1% and 57.4% probability, respectively, versus 19.1% among patients who withdrew treatment (randomized to placebo) after 12 weeks of induction. Three-hundred fifty-one (351) patients including 16.2% of 200 mg, 39.2% of 100 mg and 76.4% of placebo patients received rescue medication of 200 mg FREORLA in combination with topical therapy.

Table 9. Efficacy results of FREORLA in REGIMEN

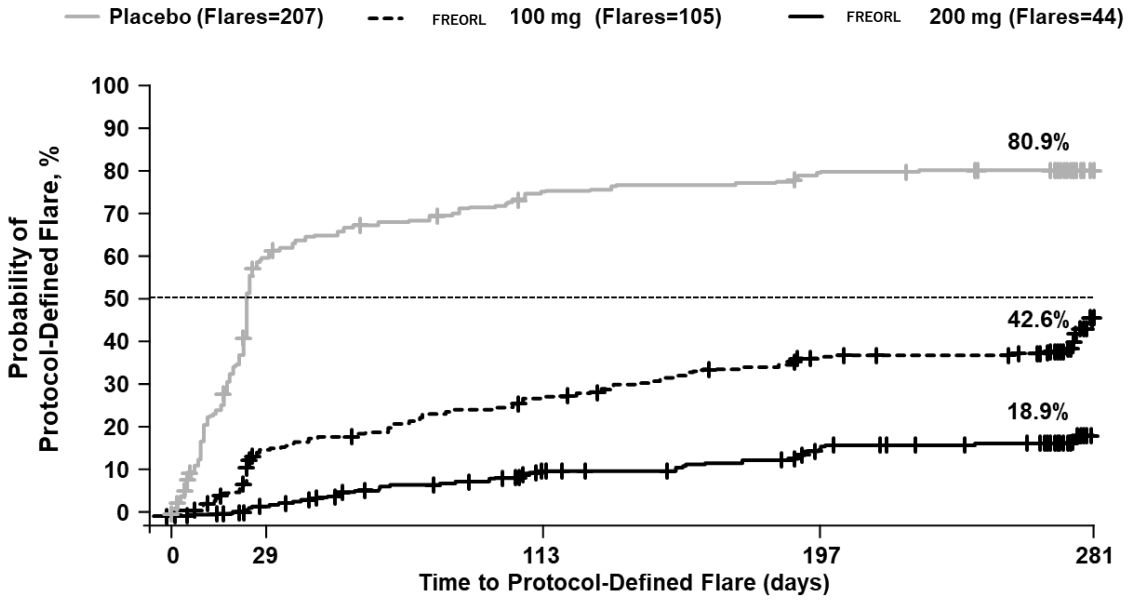
	FRE monotherapy Open label induction, Week 12 200 mg N=1233
IGA 0 or 1[a] % responders (95% CI)	65.9 (63.3, 68.6)
EASI-75[b] % responders (95% CI)	75.6 (73.1, 78.0)
PP-NRS 4-point improvement[c]	68.3 (65.3, 71.3)

% responders (95% CI)	

Abbreviations: FRE=FREORLA; CI=confidence interval; EASI=Eczema Area and Severity Index; IGA=Investigator Global Assessment; N=number of patients randomized; PP-NRS=Peak Pruritus Numerical Rating Scale.

a. IGA responders were patients with IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points.
b. EASI-75 responders were patients with ≥75% improvement in EASI from baseline.
c. PP-NRS4 responders were patients with ≥4-point improvement in PP-NRS from baseline.

Figure 4. Time to protocol-defined flare



FREORLA used in monotherapy
Protocol-defined flare=A loss of at least 50% of the EASI response at Week 12 and an IGA score of 2 or higher.
Multiplicity-controlled p <0.0001 200 mg versus placebo; 100 mg versus placebo; 200 mg versus 100 mg.

A multivariate analysis was performed to identify predictors of successfully decreasing the dose from 200 mg to 100 mg and remaining flare-free for at least 12 weeks after the dose decrease. In that analysis, patients who had not received prior systemic agents (OR 1.8, 95% CI: 1.2, 2.6) and patients who had ⩽50% BSA involvement before starting abrocitinib (OR 1.8, 95% CI: 1.2, 2.6) were almost twice as likely to remain protocol-defined flare-free than those who had received prior systemic agents and who had >50% BSA involvement.

5.2. Pharmacokinetic properties

Absorption

Effect of Food
Abrocitinib is well-absorbed with over 91% extent of oral absorption and absolute oral bioavailability of approximately 60%. The oral absorption of abrocitinib is rapid and peak plasma concentrations and reached within 1 hour. Steady-state plasma concentrations of abrocitinib are achieved within 48 hours after once daily administration. Both C_{max} and AUC of abrocitinib increased dose proportionally up to 400 mg. Coadministration of FREORLA with a

high-fat meal had no clinically relevant effect on abrocitinib exposures (AUC and C_{max} increased by approximately 26% and 29%, respectively, and T_{max} was prolonged by 2 hours). In clinical studies, FREORLA was administered without regard to food (see Section 4.2).

Distribution

After intravenous administration, the volume of distribution of FREORLA is about 100 L. Approximately 64%, 37% and 29% of circulating abrocitinib and its active metabolites M1 and M2, respectively, are bound to plasma proteins. Abrocitinib and its active metabolites distribute equally between red blood cells and plasma.

Metabolism

The metabolism of abrocitinib is mediated by multiple CYP enzymes, CYP2C19 (~53%), CYP2C9 (~30%), CYP3A4 (~11%) and CYP2B6 (~6%). In a human radiolabeled study, abrocitinib was the most prevalent circulating species, with 3 polar mono-hydroxylated metabolites identified as M1 (3-hydroxypropyl), M2 (2-hydroxypropyl), and M4 (pyrrolidinone pyrimidine). Of the 3 metabolites in circulation, M1 and M2 have similar JAK inhibitory profiles as abrocitinib, while M4 was pharmacologically inactive. The pharmacologic activity of FREORLA is attributable to the unbound exposures of parent molecule (~60%) as well as M1 (~10%) and M2 (~30%) in systemic circulation. The sum of unbound exposures of abrocitinib, M1 and M2, each expressed in molar units and adjusted for relative potencies, is referred to as the abrocitinib active moiety.

In vitro, abrocitinib or its metabolites were not significant inhibitors or inducers of CYP enzymes (CYP2C8, CYP2C9 and CYP2D6) or of uridine diphosphate glucuronyltransferases (UGTs) (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7). Abrocitinib or its metabolites at clinically meaningful concentrations are not inhibitors of organic anion transporter (OAT)3, organic cation transporter (OCT)1, multidrug and toxin compound extrusion protein (MATE)1/2K and breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1/1B3, bile salt export pump (BSEP), OAT1 or OCT2.

Elimination

The elimination half-life of abrocitinib is about 5 hours. FREORLA is eliminated primarily by metabolic clearance mechanisms, with less than 1% of the dose excreted in urine as unchanged drug. The metabolites of abrocitinib, M1, M2 and M4 are excreted predominantly in urine, and are substrates of OAT3 transporter.

Special populations

Body Weight, Gender, Genotype, Race, and Age
Body weight, gender, CYP2C19/2C9 genotype, race, and age did not have a clinically meaningful effect on FREORLA exposure (see Section 4.2).

Adolescents (12 to less than 18 years of age)
Based on population pharmacokinetic analysis, there was no clinically significant difference in mean FREORLA steady-state exposures in adolescent patients compared to adults at their typical body weights.

Pediatric (under 12 years of age)
The pharmacokinetics of FREORLA in pediatric patients under 12 years of age have not yet been established (see Section 4.2).

Renal impairment

In a renal impairment study, patients with severe (eGFR <30 mL/min) and moderate (eGFR 30 to <60 mL/min) renal impairment had approximately 191% and 110% increase in active moiety AUC_{inf}, respectively, compared to patients with normal renal function (eGFR ≥90 mL/min; see Section 4.2). Pharmacokinetics of abrocitinib have not been determined in patients with mild renal impairment, however, based on the results observed in other groups, an increase of up to 70% in active moiety exposure is expected in patients with mild renal impairment (eGFR 60 to <90 mL/min). The increase of up to 70% is not clinically meaningful as the efficacy and safety of abrocitinib in atopic dermatitis patients with mild renal impairment (n=756) was comparable to the overall population in Phase 2 and 3 clinical studies. Based on these results, a clinically significant increase in abrocitinib active moiety is not expected in patients with mild renal impairment (creatinine clearance 60 to <90 mL/min). The eGFR in individual patients was estimated using Modification of Diet in Renal Disease (MDRD) formula.

FREORLA has not been studied in patients with ESRD on renal replacement therapy (see Section 4.2). In Phase 3 clinical studies, FREORLA was not evaluated in patients with atopic dermatitis with baseline creatinine clearance values less than 40 mL/min.

Hepatic impairment

Patients with mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment had approximately 4% decrease and 15% increase in active moiety AUC_{inf}, respectively, compared to patients with normal hepatic function. These changes are not clinically significant, and no dose adjustment is required in patients with mild or moderate hepatic impairment (see Section 4.2). In clinical studies, FREORLA was not evaluated in patients with severe (Child Pugh C) hepatic impairment, or in patients screened positive for active hepatitis B or hepatitis C.

5.3 Preclinical safety data

Genotoxicity

FREORLA is not mutagenic in the bacterial mutagenicity assay (Ames assay). Although FREORLA is aneugenic in the in vitro TK6 micronucleus assay, FREORLA is not aneugenic or clastogenic based on the results of the in vivo rat bone marrow micronucleus assay.

Carcinogenicity

No evidence of tumorigenicity was observed in the 6-month Tg.rasH2 mice administered FREORLA at oral doses up to 75 mg/kg/day and 60 mg/kg/day in female and male mice, respectively. In the 2-year oral carcinogenicity study, FREORLA resulted in statistically higher incidence of benign thymomas in female rats at exposures greater than or equal to 2.8 times the unbound human AUC at the MRHD of 200 mg. No evidence of FREORLA-related tumorigenicity was observed following oral FREORLA administration in female rats at exposures equal to 0.6 times the unbound human AUC at the MRHD of 200 mg or in male rats at exposures equal to 14 times the unbound human AUC at the MRHD of 200 mg.

Reproductive and developmental toxicity

FREORLA had no effects on rat male fertility or spermatogenesis at doses up to 70 mg/kg/day at exposures equal to 26 times the unbound human AUC at the MRHD of 200 mg. FREORLA resulted in effects on rat female fertility (lower fertility index, corpora lutea, and implantation sites) at exposures equal to 29 times the unbound human AUC at the MRHD of 200 mg and higher postimplantation loss at exposures greater than or equal to 11 times the unbound human AUC at the MRHD of 200 mg. The effects on female fertility in rats reversed 1 month after cessation of FREORLA administration. No effects on female fertility were noted at exposures equal to 2 times the unbound human AUC at the MRHD of 200 mg.

No fetal malformations were observed in embryo-fetal development studies in rats or rabbits. In an embryo-fetal development study in pregnant rabbits, oral administration of FREORLA during gestation days 7 to 19 had no effects on embryo-fetal survival or fetal morphological development at exposures equal to 4 times the unbound human AUC at the MRHD of 200 mg. FREORLA resulted in increased incidence of delayed ossification of the forelimb phalanges at exposures equal to 4 times the unbound human AUC at the MRHD of 200 mg.

In an embryo-fetal development study in pregnant rats, oral administration of FREORLA during gestation days 6 to 17 resulted in increased embryo-fetal lethality at exposures equal to 17 times the unbound human AUC at the MRHD of 200 mg. No embryo-fetal lethality was observed in pregnant rats orally dosed with FREORLA during organogenesis at exposures equal to 11 times the unbound human AUC at the MRHD of 200 mg. FREORLA resulted in increased incidences of skeletal variations of short 13th ribs at exposures greater than or equal to 11 times the unbound human AUC at the MRHD of 200 mg and reduced ventral processes, thickened ribs, and unossified metatarsals at exposures equal to 17 times the unbound human AUC at the MRHD of 200 mg. No skeletal variations were noted in rats at exposures equal to 2.4 times the unbound human AUC at the MRHD of 200 mg.

In a pre- and postnatal development study in pregnant rats, oral administration of FREORLA during gestation day 6 through lactation day 21 resulted in dystocia with prolonged parturition and lower offspring body weights at exposures greater than or equal to 11 times the unbound human AUC at the MRHD of 200 mg and lower postnatal survival at exposures equal to 17 times the unbound human AUC at the MRHD of 200 mg. No maternal or developmental

toxicity was observed in either dams or offspring at exposures equal to 2.4 times the unbound human AUC at the MRHD of 200 mg.

Administration of abrocitinib to juvenile rats beginning on postnatal Day 21 and older (comparable to a 2-year-old human and older) was not associated with microscopic or macroscopic bone findings. Administration of abrocitinib to juvenile rats beginning on postnatal Day 10 (comparable to a 3-month-old human infant) resulted in adverse microscopic and macroscopic bone findings, including malrotated paws, fractures, and/or femoral head abnormalities.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core

Microcrystalline cellulose
Dibasic calcium phosphate anhydrous
Sodium starch glycolate
Magnesium stearate

Film-coat

Hypromellose (E464)
Titanium dioxide (E171)
Lactose monohydrate
Macrogol
Triacetin (E1518)
Iron red oxide (E172)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store below 30ºC. Keep in original package.

6.5. Nature and contents of container

FREORLA 50 mg film-coated tablets

Polyvinylidene chloride (PVDC) blister with aluminium foil lidding film containing 7 film-coated tablets. Each pack contains 14 film-coated tablets.

FREORLA 100 mg film-coated tablets

Polyvinylidene chloride (PVDC) blister with aluminium foil lidding film containing 7 film-coated tablets. Each pack contains 14 film-coated tablets.

FREORLA 200 mg film-coated tablets

Polyvinylidene chloride (PVDC) blister with aluminium foil lidding film containing 7 film-coated tablets. Each pack contains 14 film-coated tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Manufactured by:
Pfizer Manufacturing Deutschland GmbH
Freiburg Im Breisgau
Germany

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia

8. MARKETING AUTHORISATION NUMBER(S)

FREORLA® 50 mg film-coated tablets, Box, 2 blister @ 7 film coated tablets; Reg. No.: DKI2358501917A1.
FREORLA® 100 mg film-coated tablets, Box, 2 blister @ 7 film coated tablets; Reg. No.: DKI2358501917B1.
FREORLA® 200 mg film-coated tablets, Box, 2 blister @ 7 film coated tablets; Reg. No.: DKI2358501917C1.

HARUS DENGAN RESEP DOKTER

9. DATE OF REVISION OF THE TEXT

11/2025