ABROCITINIB

CIBINQO

50 mg, 100 mg, 200 mg Film-Coated Tablet
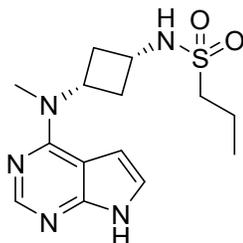
℞

1.0 PHARMACOLOGIC CATEGORY

Agent for Dermatitis (Janus Kinase Inhibitor)

2.0 DESCRIPTION

Structure of Abrocitinib:

Abrocitinib (Cibinqo) 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.

Abrocitinib (Cibinqo) 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.

Abrocitinib (Cibinqo) 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.

3.0 FORMULATION/ COMPOSITION

Abrocitinib (Cibinqo) 50 mg film-coated tablets:
Each film-coated tablet contains 50 mg abrocitinib

Abrocitinib (Cibinqo) 100 mg film-coated tablets:
Each film-coated tablet contains 100 mg abrocitinib

Abrocitinib (Cibinqo) 200 mg film-coated tablets:
Each film-coated tablet contains 200 mg abrocitinib

Excipients with known effects:
Each Abrocitinib (Cibinqo) 50 mg film-coated tablet contains 1.365 mg of lactose monohydrate.

Each Abrocitinib (Cibinqo) 100 mg film-coated tablet contains 2.73 mg of lactose monohydrate.

Each Abrocitinib (Cibinqo) 200 mg film-coated tablet contains 5.46 mg of lactose monohydrate.

4.0   CLINICAL PARTICULARS

4.1   Therapeutic Indications

Abrocitinib (Cibinqo) 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. Abrocitinib (Cibinqo) can be used with or without medicated topical therapies for atopic dermatitis.

4.2   Dosage and Method of Administration

Posology

The recommended dose of Abrocitinib (Cibinqo) is either 100 mg or 200 mg once daily. For most patients, 200 mg is the recommended starting dose. A dose of 100 mg once daily is the recommended starting dose for patients aged ≥65 years, and for those who have risk factors for developing an adverse reaction to Abrocitinib or those who are less likely to tolerate the adverse reactions (see **Sections 4.4 Special Warnings and Precautions for Use** and **4.8 Undesirable Effects**). 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.

Abrocitinib (Cibinqo) can be used with or without medicated topical therapies for atopic dermatitis.

Treatment initiation
Treatment with Abrocitinib (Cibinqo) should not be initiated in patients with a platelet count $<150 \times 10^3/\text{mm}^3$, an absolute lymphocyte count (ALC) $<0.5 \times 10^3/\text{mm}^3$, an absolute neutrophil count (ANC) $<1 \times 10^3/\text{mm}^3$ or who have a hemoglobin value <8 g/dL (see **Section 4.4 Special Warnings and Precautions for Use**).

Dose interruption
If a patient develops a serious infection, sepsis or opportunistic infection, consider interruption of Abrocitinib (Cibinqo) until the infection is controlled should be considered (see **Section 4.4 Special Warnings and Precautions for Use**).

Interruption of dosing may be needed for management of laboratory abnormalities as described in Table 1 (see **Section 4.4 Special Warnings and Precautions for Use**).

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.

Drug-drug interactions
When recommended dose is 100 mg or 200 mg Abrocitinib (Cibinqo) once daily, dose should be reduced by 50% to 50 mg or 100 mg once daily, respectively, in patients taking strong inhibitors of cytochrome P450 (CYP) 2C19 (e.g., fluvoxamine, fluconazole). The use of Abrocitinib (Cibinqo) is not recommended concomitantly with moderate or strong inducers of CYP2C19/CYP2C9 enzymes (e.g., rifampin, apalutamide, efavirenz, enzalutamide, phenytoin) (see **Section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

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 <60 mL/min) renal impairment, the recommended dose of Abrocitinib (Cibinqo) should be reduced by half to 100 mg or 50 mg once daily (see **Section 5.2 Pharmacokinetic Properties**).

In patients with severe (eGFR <30 mL/min) renal impairment, 50 mg once daily is the recommended starting dose. The maximum daily dose is 100 mg (see **Section 5.2 Pharmacokinetic Properties**).

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

Elderly population
The recommended starting dose for patients ≥65 years of age is 100 mg once daily (see **Section 4.4 Special Warnings and Precautions for Use**).

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

Method of administration

Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo), taking with food may

improve nausea.

Swallow Abrocitinib (Cibinqo) tablets whole and intact with water. Do not crush, split, or chew Abrocitinib (Cibinqo) tablets.

4.3 Contraindications

- Active serious systemic infections, including tuberculosis (TB) (see **Section 4.4 Special Warnings and Precautions for Use**).
- Severe hepatic impairment (see **Section 4.2 Dosage and Method of Administration**).
- Pregnancy and breast-feeding (see **Section 4.6 Fertility, Pregnancy and Lactation**).

4.4 Special Warnings and Precautions for Use

<u>Serious infections</u>

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

The risks and benefits of treatment with Abrocitinib (Cibinqo) should be carefully 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 Abrocitinib (Cibinqo). A patient who develops a new infection during treatment with Abrocitinib (Cibinqo) should undergo prompt and complete diagnostic testing and appropriate antimicrobial therapy should be initiated. The patient should be closely monitored and Abrocitinib (Cibinqo) therapy should be interrupted if the patient is not responding to standard therapy.

Tuberculosis
Tuberculosis was observed in clinical studies with Abrocitinib (Cibinqo). Patients should be screened for tuberculosis (TB) before starting Abrocitinib (Cibinqo) therapy and consider yearly screening for patients in highly endemic areas for TB. Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo).

Viral reactivation
Viral reactivation, including herpes virus reactivation (e.g., herpes zoster, herpes simplex), was reported in clinical studies (see **Section 4.8 Undesirable Effects**). 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 $<1 \times 10^3/\text{mm}^3$ prior to the event and patients with severe atopic dermatitis at baseline (see **Section 4.8 Undesirable Effects**). If a patient develops herpes zoster, temporary interruption of treatment may 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 Abrocitinib (Cibinqo). Patients with evidence of active hepatitis B or hepatitis C (positive hepatitis C PCR) infection were excluded from clinical studies (see **Section 5.2 Pharmacokinetic Properties**). 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 Abrocitinib (Cibinqo); such patients had HBV DNA monitored. If HBV DNA is detected, a liver specialist should be consulted.

<u>Vaccination</u>

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

<u>Thrombotic events including pulmonary embolism</u>

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving Janus kinase (JAK) inhibitors including Abrocitinib (see **Section 4.8 Undesirable Effects**). Abrocitinib (Cibinqo) 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, Abrocitinib (Cibinqo) treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.

<u>Malignancy (including non-melanoma skin cancers)</u>

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

The risks and benefits of Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 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 Undesirable Effects**). Treatment with Abrocitinib (Cibinqo) 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 Dosage and Method of Administration**). Complete blood count should be monitored 4 weeks after initiation of therapy with Abrocitinib (Cibinqo) and thereafter according to routine patient management (see Table 1).

Lipids

In patients with a high burden of cardiovascular risk factors, including hyperlipidemia, the risks and benefits of Abrocitinib compared to that of other available therapies for atopic dermatitis should be considered. Dose dependent increase in blood lipid parameters were reported in patients treated with Abrocitinib (Cibinqo) (see **Section 4.8 Undesirable Effects**). Lipid parameters should be assessed approximately 4 weeks following initiation of Abrocitinib (Cibinqo) therapy and thereafter according to their risk for cardiovascular disease (see Table 1). 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 hyperlipidemia. If Abrocitinib (Cibinqo) is chosen interventions to manage lipid concentrations should be implemented according to clinical guidelines.

Laboratory monitoring

Table 1.   Laboratory monitoring guidance

Laboratory measures	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.

Table 1. **Laboratory monitoring guidance**

Laboratory measures	Monitoring guidance	Action
		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 cardiovascular disease and clinical guidelines for hyperlipidemia.	Patients should be monitored according to clinical guidelines for hyperlipidemia.

Elderly

A total of 173 patients 65 years of age and older were enrolled in Abrocitinib (Cibinqo) studies. 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 events 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 (see **Section 4.8 Undesirable Effects**). There are limited data in patients above 75 years of age.

4.5   Interaction with Other Medicinal Products and Other Forms of Interaction

Potential for other medicines to affect pharmacokinetics of Abrocitinib (Cibinqo)

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 strongly inhibit or induce CYP2C19 or CYP2C9 or inhibit the OAT3 transporter. Dose adjustments, as appropriate, based on these results are outlined in **Section 4.2 Dosage and Method of Administration.**

Coadministration with CYP2C19/CYP2C9 inhibitors
When Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 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.

<u>Coadministration with products which increase gastric pH</u>

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 Abrocitinib (Cibinqo) to affect pharmacokinetics of other medicines</u>

No clinically significant effects of Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo). Consider pregnancy planning and prevention for females of reproductive potential.

Pregnancy

The limited human data on use of Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 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, Abrocitinib (Cibinqo) 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 Preclinical Safety Data**). Abrocitinib (Cibinqo) should not be used during pregnancy unless clearly necessary.

Breastfeeding

There are no data on the presence of Abrocitinib (Cibinqo) in human milk, the effects on the breastfed infant, or the effects on milk production. Abrocitinib (Cibinqo) was secreted in milk of lactating rats. A risk to newborns/infants cannot be excluded and Abrocitinib (Cibinqo) should not be used during breastfeeding.

Fertility

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

4.7   Effects on Ability to Drive and Use Machines

Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 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 Special Warnings and Precautions for Use**).

Tabulated list of adverse reactions

A total of 3582 patients were treated with Abrocitinib (Cibinqo) in clinical studies in atopic dermatitis, among them 2784 patients (representing 3006 patient-years of exposure) were integrated for safety analysis, 1451 patients with at least 48 weeks of exposure. The integrated safety analysis included 1761 patients receiving a constant dose of Abrocitinib 200 mg and 1023 patients receiving 100 mg. 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 Abrocitinib (Cibinqo) in comparison to placebo for up to 16 weeks.

Table 2.   Adverse reactions for Abrocitinib (Cibinqo)

System organ class	Adverse reactions
Infections and infestations	Herpes simplex[a] Herpes zoster[b] Pneumonia
Blood and lymphatic system disorders	Thrombocytopenia Lymphopenia
Metabolism and nutrition disorders	Hyperlipidemia[c]
Nervous system disorders	Headache Dizziness
Vascular disorders	Thrombotic events including pulmonary embolism[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. Hyperlipidemia included dyslipidemia and hypercholesterolemia.
d. Thrombotic events 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 Abrocitinib (Cibinqo) 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.

Among all patients treated with Abrocitinib in the integrated safety analysis, including the long-term extension study, the incidence rate of herpes zoster in patients treated with Abrocitinib 200 mg (4.83 per 100 patient-years) was higher than that of patients treated with 100 mg (2.39 per 100 patient-years). Incidence rates for herpes zoster were also higher for patients 65 years of age and older, patients with a medical history of herpes zoster, patients with severe atopic dermatitis at baseline, and a confirmed ALC $<1.0 \times 10^3/mm^3$ prior to the event of herpes zoster.

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 with Abrocitinib (Cibinqo) in the integrated safety analysis, including the long term extension study, the rate of serious infections was 2.43 per 100 patient-years in the Abrocitinib (Cibinqo) 100 mg group and 2.46 per 100 patient-years in the Abrocitinib (Cibinqo) 200 mg group. The most commonly reported serious infections were herpes simplex, herpes zoster, and pneumonia (see **Section 4.4 Special Warnings and Precautions for Use**).

Opportunistic infections
Most opportunistic infections were cases of multidermatomal cutaneous herpes zoster. Among all patients treated with Abrocitinib (Cibinqo) in the integrated safety analysis, including the long-term extension study, the rate of opportunistic infections was 0.61 per 100 patient- years in the Abrocitinib (Cibinqo) 100 mg group and 1.23 per 100 patient- years in the Abrocitinib (Cibinqo) 200 mg group. Most cases of opportunistic herpes zoster were mild or moderate.

Thrombotic events including pulmonary embolism
Among all patients treated with Abrocitinib (Cibinqo) in the integrated safety analysis, including the long term extension study, the rate of PE was 0.08 per 100 patient-years in the Abrocitinib (Cibinqo) 100 mg group and, 0.17 per 100 patient-years in the Abrocitinib (Cibinqo) 200 mg group. The rate of DVT was 0 per 100 patient-years in the Abrocitinib (Cibinqo) 100 mg group and 0.11 per 100 patient-years Abrocitinib (Cibinqo) 200 mg group (see **Section 4.4 Special Warnings and Precautions for Use**).

Thrombocytopenia
In placebo-controlled studies, for up to 16 weeks, treatment with Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 200 mg, 0 patients treated with Abrocitinib

(Cibinqo) 100 mg or placebo. Among all patients exposed to Abrocitinib (Cibinqo) in the integrated safety analysis, including the long term extension study, the rate of confirmed platelet counts of $<50 \times 10^3/mm^3$ was 0.17 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 Special Warnings and Precautions for Use**). 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 Abrocitinib (Cibinqo) 200 mg and 0 patients treated with Abrocitinib (Cibinqo) 100 mg or placebo. Both cases occurred in the first 4 weeks of exposure. Among all patients exposed to Abrocitinib (Cibinqo) in the integrated safety analysis, including the long term extension, the rate of confirmed ALC $<0.5 \times 10^3/mm^3$ was 0.56 per 100 patient-years for 200 mg and 0 patients per 100 patient-years for100 mg, the highest rate was observed in patients 65 years of age and older (see **Section 4.4 Special Warnings and Precautions for Use**). 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 Abrocitinib (Cibinqo) 100 mg, 0.6% of patients exposed to 200 mg, and 0% of patients exposed to placebo (see **Section 4.4 Special Warnings and Precautions for Use**).

Creatine phosphokinase elevations (CPK)
In placebo-controlled studies, for up to 16 weeks, events of blood CPK increased ($>5 \times$ ULN) were reported in 3.8%of patients treated with 200 mg, 1.8% of patients treated with 100 mg of Abrocitinib (Cibinqo), 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 Abrocitinib (Cibinqo) 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.

Pediatric population

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 851.5 patient-years of

exposure. The safety profile observed in adolescents in atopic dermatitis clinical studies was similar to that of the adult population.

4.9 Overdose and Treatment

Abrocitinib (Cibinqo) was administered in clinical studies up to a single oral dose of 800 mg. There is no experience with overdose of Abrocitinib (Cibinqo). There is no specific antidote for overdose with Abrocitinib (Cibinqo). 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.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of action

Abrocitinib (Cibinqo) 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. Within signaling pathways, 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, Abrocitinib 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 Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 100 mg or 200 mg once daily compared with placebo at Week 12 (see Table 3).

A significantly higher proportion of patients who achieved PP-NRS4 (defined as an improvement of ≥4 points in the severity of PP-NRS) with Abrocitinib (Cibinqo) 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 Abrocitinib

(Cibinqo) 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 Abrocitinib (Cibinqo) monotherapy at Week 12

	MONO-1			MONO-2		
	CBQ			CBQ		
	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)	61.0g (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)
	% 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)

**Table 3.   Efficacy results of Abrocitinib (Cibinqo) monotherapy at Week 12**

	MONO-1			MONO-2		
	CBQ			CBQ		
	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

Abbreviations: CBQ=Cibinqo; 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 Abrocitinib (Cibinqo) 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.
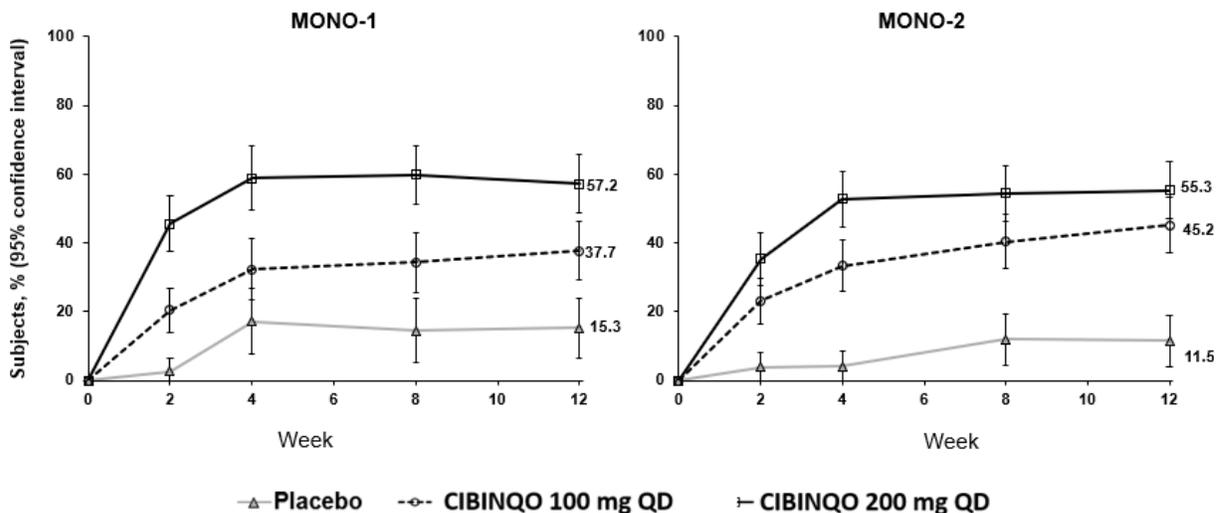

Figure 1.   Proportion of patients who achieved EASI-90 over time in MONO-1 and MONO-2
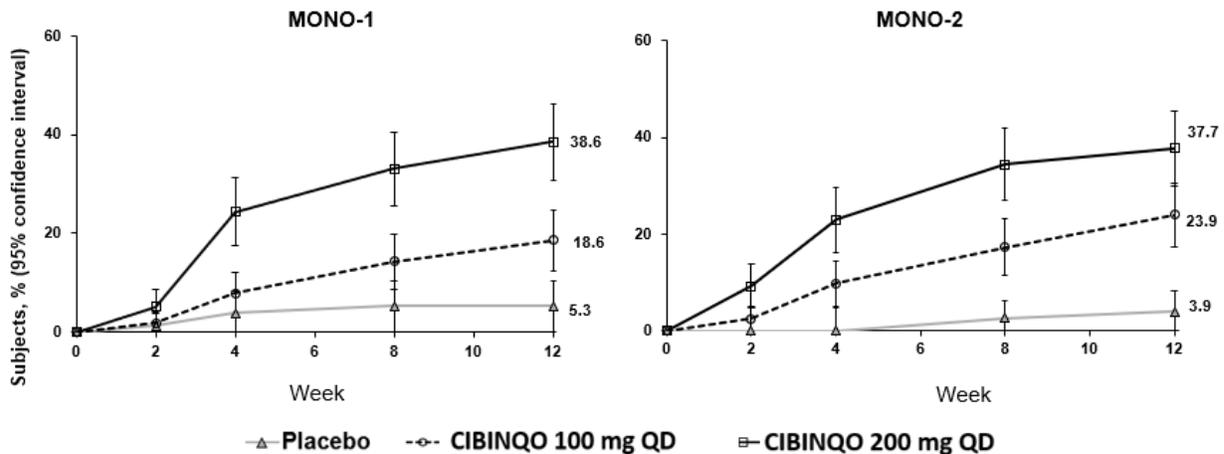
Abbreviations: EASI=Eczema Area and Severity Index; QD=once daily.
PP-NRS4 responders were patients with ≥4-point improvement in Peak Pruritis Numerical Rating Scale (PP-NRS) from baseline.

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 Abrocitinib (Cibinqo) 100 mg or 200 mg once daily compared with placebo at Week 12 (see Table 4).

The proportions of patients achieving PP-NRS4 with Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) doses at Week 2 and Week 16.

The proportion of patients achieving PP-NRS4 with Abrocitinib (Cibinqo) 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 abrocitinib (Cibinqo) 100 mg once daily and dupilumab at Week 2.

Table 4. Efficacy results of Abrocitinib (Cibinqo) with concomitant topical therapy

	Week 2				Week 12				Week 16			
	CBQ				CBQ				CBQ			
	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: CBQ=Cibinqo; 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
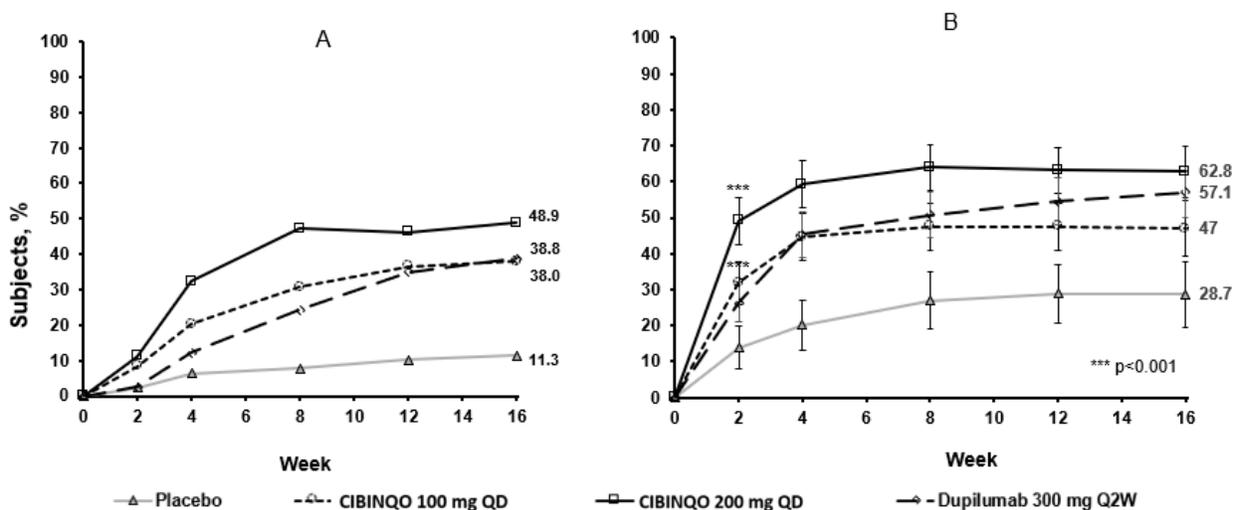
Abbreviations: EASI=Eczema Area and Severity Index; PP-NRS=Peak Pruritus Numerical Rating Scale; QD=once daily; Q2W=every 2 weeks.
EASI-90 was based on EASI ≥90% improvement from baseline.
PP-NRS4 response was based on achieving at least 4 points improvement in the severity of Peak Pruritus Numerical Rating Scale (PP-NRS).

Patients who received dupilumab and subsequently enrolled in EXTEND were randomized to either Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) [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 Abrocitinib (Cibinqo) [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 Abrocitinib (Cibinqo) treatment for at least 92 weeks or until availability of commercial product in their country. In EXTEND, patients received Abrocitinib (Cibinqo) with or without background medicated topical therapy. Patients who were previously randomized to Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) in a

qualifying parent study were randomized to either Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) treatment and entered EXTEND, 14% and 22% of patients continuing Abrocitinib (Cibinqo) 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 27% of patients continuing Abrocitinib (Cibinqo) 200 mg once daily achieved IGA response by Week 16 and Week 24, respectively. Among patients who did not achieve EASI-75 after 12 weeks of Abrocitinib (Cibinqo) treatment and entered EXTEND, 32% and 45% of patients continuing Abrocitinib (Cibinqo) 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 34% and 54% of patients continuing Abrocitinib (Cibinqo) 200 mg once daily achieved EASI-75 response by Week 16 and Week 24, 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 48 of cumulative Abrocitinib (Cibinqo) treatment for both doses of Abrocitinib (Cibinqo) [53% and 57% for IGA (0 or 1) response, 69% and 71% for EASI-75, and 52% and 69% for PP-NRS4 with 100 mg once daily and 200 mg once daily, respectively].

Health related outcomes

Treatment with either dose of Abrocitinib (Cibinqo) as monotherapy resulted in significantly improved patient-reported outcomes at 12 weeks compared with placebo (see Table 5). A significantly larger proportion of the Abrocitinib (Cibinqo) 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. Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) groups compared with placebo at 12 weeks.

Table 5. Additional endpoint results with Abrocitinib (Cibinqo) monotherapy at Week 12

	MONO-1			MONO-2		
	CBQ			**CBQ**		
	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)
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 (95% CI)	-2.1[b] (-2.5, -1.6)	-1.6 (-2.0, -1.1)	-1.0 (-1.7, -0.4)	-1.7[a] (-2.2, -1.2)	-1.6[a] (-2.1, -1.1)	-0.6 (-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 (95% CI)	-1.8[d] (-2.2, -1.4)	-1.4[b] (-1.8, -0.9)	-0.2 (-0.8, 0.4)	-1.4[d] (-1.8, -1.0)	-1.0[c] (-1.5, -0.6)	0.3 (-0.3, 0.9)

Table 5. Additional endpoint results with Abrocitinib (Cibinqo) monotherapy at Week 12

	MONO-1			MONO-2		
	CBQ			CBQ		
	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

Abbreviations: CBQ=Cibinqo; 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 Abrocitinib (Cibinqo) 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). Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) groups compared with placebo at 12 weeks.

Table 6. Additional endpoint results with Abrocitinib (Cibinqo) in combination with medicated topical therapies at Week 12

	COMPARE		
	CBQ		
	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)
LSM POEM			
Baseline mean (SD)	21.5 (5.3)	20.9 (5.5)	20.4 (6.1)

Table 6. Additional endpoint results with Abrocitinib (Cibinqo) in combination with medicated topical therapies at Week 12

	COMPARE		
	CBQ		
	200 mg QD + Topical N=226	100 mg QD + Topical N=238	Placebo + Topical N=131
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: CBQ=Cibinqo; 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.

Open label induction, randomized withdrawal study (REGIMEN)
A total of 1,233 patients received open label Abrocitinib (Cibinqo). 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 Abrocitinib (Cibinqo) in combination with topical therapy.

Table 7. Efficacy results of Abrocitinib (Cibinqo) in REGIMEN

	CBQ 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] % responders (95% CI)	68.3 (65.3, 71.3)

Abbreviations: CBQ=Cibinqo; 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 ³2 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
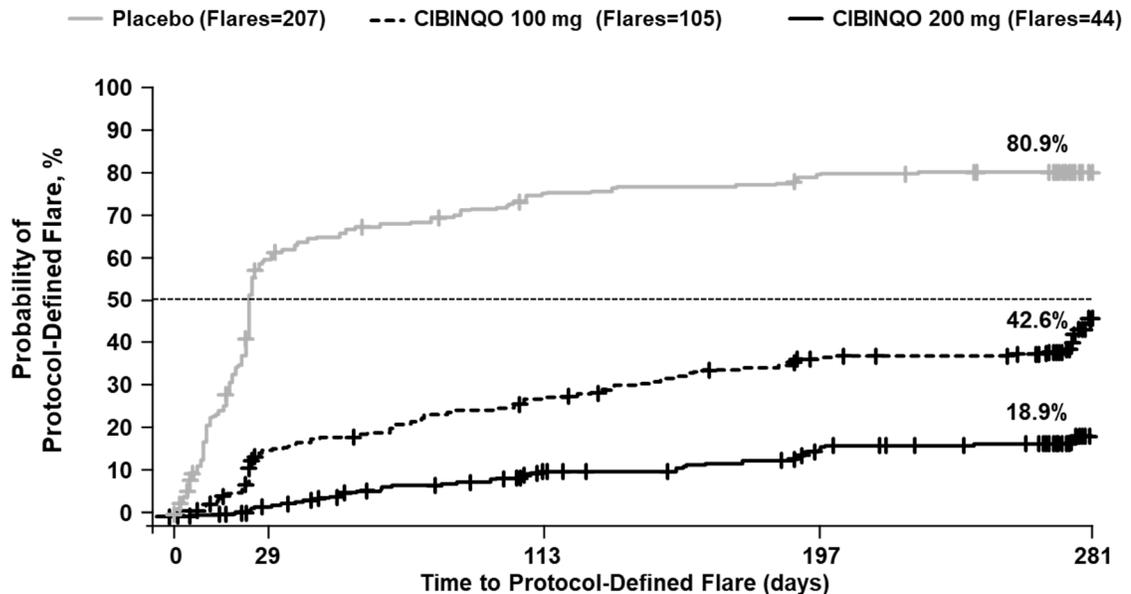
Abrocitinib (Cibinqo) used in monotherapy
Protocol-defined flare=A loss of at least 50% of the EASI response at Week 12 and an IGA score of 2 or higher.
Multiplicity-controlled p <0.0001 200 mg versus placebo; 100 mg versus placebo; 200 mg versus 100 mg.

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.

Pediatric population
The efficacy and safety of Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) in TEEN

| | TEEN[d] | | |
| | CBQ | | PBO |
	200 mg QD N=94	100 mg QD 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: CBQ=Cibinqo; 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. Cibinqo used in combination with medicated topical therapy.
e. Statistically significant with adjustment for multiplicity versus placebo.

5.2 Pharmacokinetic Properties

<u>Absorption</u>

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 Abrocitinib (Cibinqo) 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, Abrocitinib (Cibinqo) was administered without regard to food (see **Section 4.2 Dosage and Method of Administration**).

Distribution

After intravenous administration, the volume of distribution of Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 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 (Cibinqo) 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. Abrocitinib 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 Abrocitinib exposure (see **Section 4.2 Dosage and Method of Administration**).

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

Pediatric (under 12 years of age)
The pharmacokinetics of Abrocitinib in pediatric patients under 12 years of age have not yet been established (see **Section 4.2 Dosage and Method of Administration**).

<u>Renal impairment</u>

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 Dosage and Method of Administration**). 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.

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

<u>Hepatic impairment</u>

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 Dosage and Method of Administration**). In clinical studies, Abrocitinib (Cibinqo) 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

<u>Genotoxicity</u>

Abrocitinib (Cibinqo) is not mutagenic in the bacterial mutagenicity assay (Ames assay). Although Abrocitinib (Cibinqo) is aneugenic in the in vitro TK6 micronucleus assay,

Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 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, Abrocitinib (Cibinqo) resulted in a 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 Abrocitinib (Cibinqo) related tumorigenicity was observed following oral Abrocitinib (Cibinqo) 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

Abrocitinib (Cibinqo) 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. Abrocitinib (Cibinqo) 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 reversed 1 month after cessation of Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 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. Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) during organogenesis at exposures equal to 11 times the unbound human AUC at the MRHD of 200 mg. Abrocitinib (Cibinqo) 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 Abrocitinib (Cibinqo) 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 (comparable to a 3 month old human) resulted in macroscopic and microscopic bone findings. When dosing was initiated at postnatal Day 10 (at exposures greater than or equal to 0.8 times the unbound human AUC at the MRHD of 200 mg), macroscopic bone findings (malrotated and/or impaired use of forelimbs or hindlimbs or paws, fractures, and/or femoral head abnormalities) were noted. Only the microscopic bone dystrophy finding (similar to that observed in rat general toxicity studies of up to 1 month) was fully reversible after cessation of treatment.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-Life

Please see outer package for the expiry date.

6.2 Storage Condition (s)

Store at temperatures not exceeding 30°C.

6.3 Availability

Abrocitinib (Cibinqo) 50 mg Film-Coated Tablet: PVC/PVDC/Aluminum Foil Blister Pack of 7's (Box of 14's)

Abrocitinib (Cibinqo) 100 mg Film-Coated Tablet: PVC/PVDC/Aluminum Foil Blister Pack of 7's (Box of 14's)

Abrocitinib (Cibinqo) 200 mg Film-Coated Tablet: PVC/PVDC/Aluminum Foil Blister Pack of 7's (Box of 14's)

6.4 Incompatibilities

Not applicable.

7.0 FDA REGISTRATION NUMBER

Abrocitinib (Cibinqo) 50 mg Film-Coated Tablet: DR-XY48381
Abrocitinib (Cibinqo) 100 mg Film-Coated Tablet: DR-XY48137

Abrocitinib (Cibinqo) 200 mg Film-Coated Tablet: DR-XY48139

8.0 DATE OF FIRST AUTHORIZATION /RENEWAL OF THE AUTHORIZATION

Abrocitinib (Cibinqo) 50 mg Film-Coated Tablet: 30 September 2022
Abrocitinib (Cibinqo) 100 mg Film-Coated Tablet: 27 June 2022
Abrocitinib (Cibinqo) 200 mg Film-Coated Tablet: 27 June 2022

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by:
Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg, Mooswaldallee 1
79090 Freiburg, Germany

Marketing Authorization Holder:
Pfizer, Inc.
19F-20F 8 Rockwell Building, Hidalgo Drive,
Rockwell Center, Poblacion, Makati City 1210,
Metro Manila, Philippines

Revision No.: 1.2 Revision Date: 23 May 2023 Reference: CDS version 3.0, 4.0/CPR details of 50 mg/BoH comments on Contraindication Reference Date: 15 March 2022, 26 July 2022/30 September 2022/23 May 2023