PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**CIBINQO®**

Abrocitinib tablets

Tablets, 50 mg, 100 mg and 200 mg abrocitinib, oral

Selective immunosuppressant

Pfizer Canada ULC

17300 Trans-Canada Highway

Kirkland, Quebec H9J 2M5

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS	**06/2023**

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CIBINQO (abrocitinib) is indicated for the treatment of patients 12 years and older with refractory moderate to severe atopic dermatitis, including the relief of pruritus, who have had an inadequate response to other systemic drugs (e.g. steroid or biologic), or for whom these treatments are not advisable.

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

Limitations of Use: Use of CIBINQO in combination with other JAK inhibitors, biologic immunomodulators, or potent immunosuppressants such as methotrexate and cyclosporine has not been studied and is not recommended (see **7 WARNINGS AND PRECAUTIONS, Immune**).

1.1 Pediatrics

Pediatrics (12-17 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of CIBINQO in pediatric patients 12-17 years of age has been established for treatment of moderate to severe atopic dermatitis.

Pediatrics under 12 years of age: The safety and efficacy of CIBINQO in pediatric patients under 12 years of age have not yet been established. Therefore, Health Canada has not authorized an indication for pediatric use in pediatric patients under 12 years of age.

1.2 Geriatrics

Geriatrics ≥65 years of age: Caution should be used when treating geriatric patients with CIBINQO. There are limited data in patients 75 years of age and older. Clinical study results indicated that elderly patients were at increased risk for specific serious adverse events. (see **4.2 Recommended Dose and Dosage Adjustment**, and **7.1.4 Geriatrics**).

2 CONTRAINDICATIONS

CIBINQO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6 Dosage Forms, Strengths, Composition and Packaging**.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **SERIOUS INFECTIONS**
  Patients treated with CIBINQO may be at increased risk for developing serious bacterial, fungal, viral and opportunistic infections that may lead to hospitalization or death; more frequently reported serious infections were predominately viral. *[see 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS]*. If a serious infection develops, interrupt CIBINQO until the infection is controlled. The risks and benefits of treatment with CIBINQO should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with CIBINQO, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see 7 WARNINGS AND PRECAUTIONS]*.

- **MALIGNANCIES**
  Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors used to treat inflammatory conditions. Malignancies were more frequently observed in Rheumatoid Arthritis (RA) patients in a clinical trial with another JAK inhibitor, when compared to the use of TNF inhibitors. *[see 7 WARNINGS AND PRECAUTIONS]*.

- **THROMBOSIS**
  Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with Janus kinase inhibitors used to treat inflammatory conditions. Many of these adverse events were serious and some resulted in death. Consider the risks and benefits prior to treating patients who may be at increased risk. In a clinical trial in RA patients 50 years of age and older, a higher rate of all-cause mortality and thrombosis occurred in patients treated with another JAK inhibitor compared to those treated with TNF inhibitors. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately *[see 7 WARNINGS AND PRECAUTIONS]*.

- **MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)**
  MACE, including non-fatal myocardial infarction, were observed more frequently in RA patients 50 years of age and older in a clinical trial with a different JAK inhibitor compared to TNF inhibitors *[see 7 WARNINGS AND PRECAUTIONS]*.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

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

Treatment with CIBINQO should not be initiated in patients with a platelet count less than $150 \times 10^3/mm^3$, an absolute lymphocyte count (ALC) less than $0.5 \times 10^3/mm^3$, an absolute neutrophil count (ANC) less than $1 \times 10^3/mm^3$ or who have a hemoglobin value less than 8 g/dL. See **7 WARNINGS AND PRECAUTIONS** for additional information on evaluations recommended prior to treatment initiation.

4.2 Recommended Dose and Dosage Adjustment

The recommended starting dose of CIBINQO is 100 mg or 200 mg orally once daily for adolescents and adults under 65 years of age, based on individual goal of therapy and potential risk for adverse reactions. A starting dose of 100 mg once daily is recommended for patients at higher risk of adverse events such as venous thromboembolism (VTE), major adverse cardiovascular event (MACE) and malignancy. If the patient does not respond adequately to 100 mg once daily, the dose can be increased to 200 mg once daily.

A dose of 200 mg once daily may be appropriate for patients who are not at higher risk of VTE, MACE, malignancy, or other potentially serious adverse effects (see **7 WARNINGS AND PRECAUTIONS**), or for patients with an inadequate response to 100 mg once daily. Upon disease control, dose should be decreased to 100 mg once daily. If disease control is not maintained after dose reduction, re-treatment with 200 mg once daily can be considered. Exceeding a daily dosage of 200 mg is not recommended.

The lowest effective dose for maintenance should be considered. Discontinuation of treatment should be considered in patients who show no evidence of therapeutic benefit.

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

Elderly population
The recommended starting dose for patients ≥65 years of age is 100 mg. Some side effects that were more common in elderly patients in clinical trials, including herpes zoster, lymphopenia, and thrombocytopenia, occurred more frequently at the 200 mg daily dosage (see **8.2 Clinical Trial Adverse Reactions**).

Pediatric population
For pediatric patients 12 to < 18 years of age, the starting recommended dose of CIBINQO is 100 mg or 200 mg once daily. Dosage adjustment should be considered based on individual goal of therapy and potential risk for adverse reactions.

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

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) or severe (eGFR <30 mL/min) renal impairment, the recommended dose of CIBINQO is to be reduced by 50% as shown in Table 1.

The use of CIBINQO has not been studied in patients with end-stage renal disease (ESRD) on renal replacement therapy.

Table 1. Dose Adjustments for Renal Impairment

Renal Impairment Stage	Estimated Glomerular Filtration rate (eGFR)	Dose Adjustment	
		Indicated Dose 100 mg Once Daily	Indicated Dose 200 mg Once Daily
Mild	60 to <90 mL/min	None	None
Moderate	30 to <60 mL/min	CIBINQO 50 mg once daily	CIBINQO 100 mg once daily
Severe	<30 mL/min	CIBINQO 50 mg once daily	CIBINQO 100 mg once daily

Hepatic Impairment
No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. The safety of CIBINQO following daily dosing has not been studied in patients with hepatic impairment.

CIBINQO has not been studied in patients with severe hepatic impairment (Child Pugh C).

Concomitant use of CYP2C19 and CYP2C9 inhibitors
The dosage of CIBINQO should be reduced in half when co-administered with strong CYP2C19 and moderate CYP2C9 inhibitors (see **9.4 Drug-Drug Interactions**).

Concomitant use of CYP2C19 and CYP2C9 inducers
Co-administration of CIBINQO with CYP2C19/2C9 inducers is not recommended (see **9.4 Drug-Drug Interactions**).

4.3 Reconstitution

Not applicable

4.4 Administration

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

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

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

4.5 Missed Dose

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, interruption of treatment with CIBINQO until the infection is controlled should be considered (see Section **7 WARNINGS AND PRECAUTIONS**).

Interruption of dosing may be needed for management of laboratory abnormalities as described in Table 3.

5 OVERDOSAGE

There is no experience with overdose of CIBINQO. There is no specific antidote for overdose with 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 dose of 800 mg in healthy volunteers indicate that more than 90% of the administered dose is expected to be eliminated within 48 hours.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 50 mg, 100 mg, 200 mg / abrocitinib	Dibasic calcium phosphate anhydrous, Hypromellose, Iron oxide, Lactose monohydrate, Magnesium stearate, Microcrystalline cellulose, Sodium starch glycolate, Macrogol/PEG, Titanium dioxide and Triacetin

CIBINQO is packaged in bottles or in blisters. Each blister pack contains (7 tablets x 4 blisters) 28 tablets and each bottle contains 30 tablets.

- Cibinqo 50 mg film-coated tablets: Pink, oval tablet, debossed with “PFE” on one side and “ABR 50” on the other.
- Cibinqo 100 mg film-coated tablets: Pink, round tablet, debossed with “PFE” on one side and “ABR 100” on the other.
- Cibinqo 200 mg film-coated tablets: Pink, oval tablet debossed with “PFE” on one side and “ABR 200” on the other.

7 WARNINGS AND PRECAUTIONS

Please see the **3 SERIOUS WARNINGS AND PRECAUTIONS BOX** at the beginning of Part I: Health Professional Information.

Carcinogenesis and Mutagenesis

Malignancies, including lymphomas, have occurred in patients receiving JAK inhibitors used to treat other inflammatory conditions. In a large, randomized, active-controlled, post-marketing safety study of tofacitinib (another JAK inhibitor) in RA patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of malignancies, particularly lung cancer, lymphoma and non-

melanoma skin cancer (NMSC)) was observed in patients treated with tofacitinib compared to those treated with TNF blockers. CIBINQO is not approved for use in RA.

In patients 65 years of age and older, patients who are long-term current or long-term past smokers, or with other malignancy risk factors (e.g., current malignancy or history of malignancy), abrocitinib should be used with caution.

Non-melanoma skin cancer
NMSCs have been reported in patients receiving abrocitinib. Periodic skin examination is recommended for all patients, particularly those who are at increased risk for skin cancer.

Cardiovascular

Venous thromboembolism (VTE)
Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving Janus kinase (JAK) inhibitors, including CIBINQO.

In a large, randomized, active-controlled postmarketing safety study of tofacitinib (another JAK inhibitor) in RA patients 50 years of age and older with at least one cardiovascular risk factor, a dose-dependent higher rates of VTE including DVT, and PE were observed with tofacitinib compared to those treated with TNF blockers.

CIBINQO should be used with caution in patients at risk for DVT/PE. Risk factors that should be considered in determining the patient's risk for DVT/PE include age ≥65 years, long-term smoking, current malignancy (excluding non-melanoma skin cancer [NMSC]), a medical history of DVT/PE, prothrombotic disorder, use of combined hormonal contraceptives or hormone replacement therapy, patients undergoing major surgery, or prolonged immobilization. Patients should be re-evaluated periodically during abrocitinib treatment to assess for changes in VTE risk.

Promptly evaluate patients with signs and symptoms of VTE and discontinue abrocitinib in patients with suspected VTE, regardless of dose.

Major Adverse Cardiovascular Events (MACE)
Major adverse cardiovascular events were reported in clinical studies of CIBINQO for atopic dermatitis. In a large, randomized, active-controlled, post-marketing safety study of tofacitinib (another JAK inhibitor) in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of MACE defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke was observed with tofacitinib compared to those treated with TNF blockers. CIBINQO 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 CIBINQO. Therefore, in patients 65 years of age and older, patients who are long-term current or long-term past smokers, and patients with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, abrocitinib should be used with caution. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue CIBINQO in patients that have experienced a myocardial infarction or stroke.

Driving and Operating Machinery

Dizziness has been reported in patients receiving CIBINQO, which could influence the ability to drive or operate machines [see **8 ADVERSE REACTIONS**]. Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery. Patients experiencing dizziness should be advised not to drive or operate machines until symptoms abate.

Endocrine and Metabolism

Lipids
Dose-dependent increase in blood lipid parameters were reported in patients treated with CIBINQO. Lipid parameters should be assessed approximately 4 weeks following initiation of CIBINQO 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.

Hematologic

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. Treatment with 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. Platelet count and ALC should be monitored 4 weeks after initiation of therapy with CIBINQO and thereafter according to routine patient management.

Hepatic/Biliary/Pancreatic

CIBINQO is not recommended for use in patients with severe hepatic impairment (see **4.2 Recommended Dose and Dosage Adjustment**, and **10.3 Pharmacokinetics, Special Populations and Conditions**).

Immune

CIBINQO should not be used concomitantly with other potent immunosuppressants. Concomitant use of CIBINQO with other potent immunosuppressants (such as methotrexate and cyclosporine) or other JAK inhibitors has not been evaluated in clinical studies. There is a risk of additive immunosuppression when CIBINQO is co-administered with potent immunosuppressant drugs.

Vaccination
Avoid use of live, attenuated vaccines during or immediately prior to CIBINQO therapy. Prior to initiating 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.

Infections
Serious infections have been reported in patients receiving CIBINQO. The most frequent serious infections in clinical studies were herpes simplex, herpes zoster, and pneumonia. The risks and benefits of treatment with CIBINQO should be carefully considered prior to initiating in patients with active, chronic, or recurrent infections.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with CIBINQO. A patient who develops a new infection during treatment with

CIBINQO should undergo prompt and complete diagnostic testing and appropriate antimicrobial therapy should be initiated. The patient should be closely monitored and CIBINQO 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 CIBINQO therapy and consider yearly screening for patients in highly endemic areas for TB. 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 CIBINQO.

Viral reactivation
Viral reactivation, including herpes virus reactivation (e.g., herpes zoster, herpes simplex), was reported in clinical studies. The rate of herpes zoster infections was higher in patients 65 years of age and older.

Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy and during therapy with CIBINQO. Patients with evidence of active hepatitis B or hepatitis C (positive hepatitis C PCR) infection were excluded from clinical studies. 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 CIBINQO; such patients had HBV DNA monitored. If HBV DNA is detected, a liver specialist should be consulted.

Monitoring and Laboratory Tests

Table 3. Laboratory monitoring guidance

Laboratory measure	**Monitoring guidance**	**Action**
Complete blood count including Platelet Count, Absolute Lymphocyte Count (ALC), Absolute Neutrophil Count (ANC), and Hemoglobin (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 × 103/mm3 and may be restarted once ANC returns above this value.
		Hb: Treatment should be interrupted if Hb < 8 g/dL and may be restarted once Hb returns above this value.
Lipid parameters	Before treatment initiation, 4 weeks after initiation and	Patients should be monitored according to clinical guidelines for hyperlipidemia.

	thereafter according to clinical guidelines for hyperlipidemia.	

Reproductive Health: Female and Male Potential

- **Fertility**

  Based on findings in rats, oral administration of CIBINQO may impair female fertility. Impaired fertility in female rats was reversible 1 month after cessation of abrocitinib oral administration (see **16 NON-CLINICAL TOXICOLOGY**, Reproductive and developmental toxicity).

7.1 Special Populations

7.1.1 Pregnant Women

Women of childbearing potential:
Women of reproductive potential should be advised to use effective contraception during treatment with CIBINQO and for at least 1 month after the last dose. Consider pregnancy planning and prevention for females of reproductive potential.

Pregnancy:
The limited human data on use of CIBINQO in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage. In animal embryo-fetal development studies, oral administration of CIBINQO to pregnant rats during organogenesis resulted in fetotoxicity at exposures equal to approximately 17 times the unbound human AUC at the maximum recommended clinical dose of 200 mg once daily. No fetal malformations were observed. CIBINQO increased the incidence of skeletal variations at equal to or greater than 11 times the unbound human AUC at the maximum recommended clinical dose of 200 mg once daily (see **16 NON-CLINICAL TOXICOLOGY**, **Reproductive and developmental toxicity**).

In a pre- and postnatal development study in pregnant rats, CIBINQO oral administration during gestation and through lactation resulted in lower postnatal survival, lower offspring body weights and/or dystocia with prolonged parturition at exposures equal to or greater than approximately 11 times the unbound human AUC at the maximum recommended clinical dose of 200 mg once daily (see **16 NON-CLINICAL TOXICOLOGY, Reproductive and developmental toxicity**). CIBINQO should not be used during pregnancy unless clearly necessary.

7.1.2 Breast-feeding

There are no data on the presence of CIBINQO in human milk, the effects on the breast-fed infant, or the effects on milk production. CIBINQO was secreted in milk of lactating rats. Women should not breast-feed while treated with CIBINQO. A risk to newborns and infants cannot be excluded and CIBINQO should not be used during breast-feeding.

7.1.3 Pediatrics

Pediatrics (12-17 years of age):
Based on the data submitted and reviewed by Health Canada, the safety and efficacy of CIBINQO in pediatric patients 12-17 years of age has been established for treatment of moderate to severe atopic dermatitis.

Of the 2856 patients with atopic dermatitis exposed to CIBINQO, a total of 364 adolescents (12 to less than 18 years of age) were enrolled in CIBINQO studies. The safety profile observed in adolescents in atopic dermatitis clinical studies was similar to that of the adult population. There were no adolescent patients who developed platelet counts $<75 \times 10^3/mm^3$ or ALC $<0.5 \times 10^3/mm^3$.

Pediatrics under 12 years of age:
The safety and efficacy of CIBINQO in pediatric patients under 12 years of age have not yet been established. Therefore, Health Canada has not authorized an indication for pediatric use in pediatric patients under 12 years of age.

7.1.4 Geriatrics

A total of 176 patients 65 years of age and older were treated with abrocitinib in clinical studies in atopic dermatitis. The safety profile observed in elderly patients was generally 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 CIBINQO, 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 CIBINQO (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 that of patients younger than 18 years of age (2.12 per 100 patient-years). There are limited data in patients above 75 years of age. (see **10 CLINICAL PHARMACOLOGY, Special Populations and Conditions**)

Use in patients 65 years of age and older

Considering the increased risk of MACE, malignancies, serious infections, and all-cause mortality in patients 65 years of age and older, as observed in a large randomized study of tofacitinib (another JAK inhibitor), abrocitinib should be used with caution in these patients.

For more information on the CIBINQO Education Program (Prescriber Brochure and Patient Card), please visit the CIBINQO website (www.cibinqo.ca).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most commonly reported dose-related adverse reactions (ARs) occurring in ≥2% of patients treated with 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 were infections.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

A total of 3802 patients were treated with Cibinqo in clinical studies in atopic dermatitis; among them 3004 patients (representing 3680 patient-years of exposure) were integrated for safety analysis, 1549 patients with at least 48 weeks of exposure.

Four placebo-controlled studies were integrated (608 patients on 100 mg once daily, 590 patients on 200 mg once daily and 342 patients on placebo) to evaluate the safety of CIBINQO in comparison to placebo for up to 16 weeks. Table 4 presents dose-related ADRs from these studies by Preferred term (PT) for CIBINQO listed by decreasing medical seriousness.

Table 4. Adverse Reactions Reported in ≥1% of Patients with CIBINQO up to 16 weeks

	Number (%[a]) of Patients		
	Placebo N = 342	**CIBINQO 100 mg N = 608**	**CIBINQO 200 mg N = 590**
Nasopharyngitis	27 (7.9)	75 (12.4)	51 (8.7)
Nausea, n (%)	7 (2.1)	37 (6.0)	86 (14.5)
Vomiting, n (%)	3 (0.9)	9 (1.5)	19 (3.2)
Abdominal pain upper (%)	0	4 (0.6)	11 (1.9%)
Abdominal discomfort	1 (0.3)	3 (0.5)	7 (1.2)
Herpes simplex*	6 (1.8)	20 (3.3)	25 (4.2)
Headache	12 (3.5)	36 (6.0)	46 (7.8)
Dizziness	3 (0.9)	11 (1.8)	17 (2.9)
Acne	0 (0.0)	10 (1.6)	28 (4.7)
Blood CPK increased	5 (1.5)	14 (2.3)	17 (2.9)
Urinary tract infection	4 (1.2)	10 (1.7)	13 (2.2)
Fatigue	2 (0.5)	10 (1.6)	8 (1.3)
Impetigo	1 (0.3)	9 (1.5)	3 (0.5)
Oropharyngeal pain	2 (0.6)	8 (1.4)	6 (1.0)
Hypertension	2 (0.7)	7 (1.2)	5 (0.8)
Influenza	0 (0.0)	7 (1.2)	6 (1.1)
Gastroenteritis	2 (0.6)	7 (1.1)	8 (1.3)
Dermatitis contact	1 (0.3)	6 (1.1)	3 (0.5)
Herpes zoster	0 (0.0)	2 (0.3)	7 (1.2)
Thrombocytopenia	0 (0.0)	0 (0.0)	9 (1.5)

[a] Study size adjusted percentages
* Herpes simplex includes oral herpes, ophthalmic herpes simplex, genital herpes, and herpes dermatitis.

Overall 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 CIBINQO 100 mg and 200 mg, respectively. Most infections were mild or moderate.

Serious Infections:
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 Cibinqo 100 mg or 200 mg, including the long-term extension study, the rate of serious infections was 2.20 per 100 patient-years in the Cibinqo 100 mg group and 2.69 per 100 patient-years in the Cibinqo 200 mg group. The most commonly reported serious infections were herpes simplex, herpes zoster and pneumonia.

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 Cibinqo 100 mg or 200 mg, including the long-term extension study, the rate of opportunistic infections was 0.58 per 100 patient-years in the Cibinqo 100 mg group and 1.17 per 100 patient-years in the Cibinqo 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 Cibinqo 100 mg or 200 mg, including the long-term extension study, the rate of PE was 0.06 per 100 patient-years in the Cibinqo 100 mg group and 0.13 per 100 patient-years in the Cibinqo 200 mg group. The rate of DVT was 0.13 per 100 patient-years in the Cibinqo 100 mg group and 0.09 per 100 patient-years in the Cibinqo 200 mg group.

Thrombocytopenia:
In placebo-controlled studies, for up to 16 weeks, treatment with 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 Cibinqo 200 mg, 0 patients treated with Cibinqo 100 mg or placebo. Among all patients treated in clinical studies with consistent dosing regimens of either Cibinqo 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 $<75 \times 10^3/mm^3$. 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 Cibinqo 200 mg and 0 patients treated with Cibinqo 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 Cibinqo 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 $<0.5 \times 10^3/mm^3$.

Nausea:
Nausea was most frequent in the first week of 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 adolescents (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. There were no adolescent patients who developed platelet counts < 75 x 10^3/mm^3 or ALC < 0.5 x 10^3/mm^3.

Elderly:
A total of 176 patients 65 years of age and older were treated with abrocitinib in clinical studies in atopic dermatitis. 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 CIBINQO, including the long-term extension study, confirmed ALC <0.5 × 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 × 10^3/mm^3. The incidence rate of herpes zoster in patients 65 years of age and older treated with CIBINQO (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 are limited data in patients above 75 years of age.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

In the All Exposure Pool (which included subjects from 5 clinical studies plus a long-term extension study), adolescent subjects were more likely to have any Adverse Event (AE) relative to the 18 - <65-year-old subgroup. The results of an additional study conducted in adolescents using a combination therapy of CIBINQO with medicated topical treatments were consistent with this finding. There was no clustering of AEs driving the difference and, as such, the overall AE profile was similar.

In the All Exposure Pool, there were no meaningful differences in the proportions of adolescent subjects having serious infection relative to the other age groups. The IR for all herpes zoster infections was lowest in the adolescent subgroup relative to the other age groups. No adolescent subject had hematology laboratory values meeting pre-specified discontinuation criteria. In the Primary Pool, a similar proportion of adolescent subjects in the placebo and abrocitinib groups had shifts above 130 mg/dL in LDL.

8.3 Less Common Clinical Trial Adverse Reactions

Blood and lymphatic system disorders: Thrombocytopenia, Lymphopenia
Metabolism and nutrition disorders: Hyperlipidemia (dyslipidemia and hypercholesterolemia)
Vascular disorders: Venous thromboembolism (includes pulmonary embolism and deep vein thrombosis)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

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 Cibinqo 100 mg, 0.6% of patients exposed to 200 mg, and 0% of patients exposed to placebo.

Creatine Phosphokinase Elevations (CPK):
In placebo-controlled studies, for up to 16 weeks, events of blood CPK increased were reported in 1.8% of patients treated with placebo, 1.8% and 3.8% of patients treated with 100 mg and 200 mg of CIBINQO, respectively. Most elevations were transient, and none led to discontinuation. In the clinical studies, there were no reported events of rhabdomyolysis.

8.5 Post-Market Adverse Reactions

Not applicable.

9 DRUG INTERACTIONS

9.1 Drug Interactions Overview

When recommended dose is 100 mg or 200 mg CIBINQO dose should be reduced by half to 50 mg or 100 mg once daily respectively in patients receiving strong inhibitors of cytochrome P450 (CYP) 2C19 (e.g., fluconazole, fluvoxamine, fluoxetine) and in patients receiving one or more concomitant medicinal products that result in both moderate inhibition of CYP2C9 (e.g., amiodarone, fluconazole) as well as strong inhibition of CYP2C19. The use of CIBINQO is not recommended concomitantly with strong inducers of CYP enzymes (e.g., rifampin).

9.4 Drug-Drug Interactions

The drugs listed in table 5 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Potential for Other Drugs to Affect Pharmacokinetics of Abrocitinib:
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 below.

Table 5 - Established or Potential Drug-Drug Interactions

<Proper/Common name>	Source of Evidence	Effect	Clinical comment
Fluvoxamine Fluconazole	CT	When 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.	Caution should be exercised when administering CIBINQO with dual strong CYP2C19~~/~~ and moderate CYP2C9 inhibitors, or strong CYP2C19 inhibitors alone. Dosage reduction of CIBINQO is recommended *[see 4.2 Recommended Dose and Dosage Adjustment, 10 ACTION AND CLINICAL PHARMACOLOGY]*
Rifampin	CT	Administration of 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%.	Coadministration of CIBINQO with strong or moderate *CYP2C19/CYP2C9 inducers* is not recommended *[see 10 ACTION AND CLINICAL PHARMACOLOGY]*
Probenecid	CT	When 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.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Potential for Abrocitinib to Affect Pharmacokinetics of Other Drugs:

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 and its metabolites M1, M2 and M4 at unbound steady-state plasma Cmax of 1.3, 0.36, 0.35 and 0.95 µM, respectively, at the maximum clinical dose of 200 mg once daily, 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.

No clinically significant effects of 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 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 AUCinf and Cmax 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).

9.5 Drug-Food Interactions

CIBINQO was administered without regard to food.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been evaluated.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been evaluated.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Abrocitinib is a highly selective 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. Abrocitinib modulates the signaling pathway at the point of JAK1, preventing the phosphorylation and activation of STATs.

Abrocitinib reversibly and selectively inhibits JAK1 by blocking the adenosine triphosphate (ATP) binding site. In a cell-free isolated enzyme assay, abrocitinib has biochemical selectivity for JAK1 over the other 3 JAK isoforms JAK2 (28-fold), JAK3 (>340-fold) and tyrosine kinase (TYK) 2 (43-fold), and even higher selectivity over the broader kinome. In cellular settings, where JAK enzymes transmit signals in pairs (i.e., JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/JAK2, JAK2/TYK2), abrocitinib preferentially inhibits cytokine-induced STAT phosphorylation mediated by receptors utilizing JAK1 relative to receptors utilizing JAK2 only or JAK2/TYK2 pairs. The relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known. Both the parent compound and the active metabolites (M1 and M2) inhibit cytokine signaling with similar levels of selectivity.

10.2 Pharmacodynamics

Treatment with 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.

10.3 Pharmacokinetics

Table 6 - Summary of Abrocitinib and its Active Metabolites Pharmacokinetic Parameters after Single Oral Administration* of Abrocitinib in Healthy Participants**

	C_{max} (ng/mL)[a]	T_{max} (h)[b]	$t_{½}$ (h)[c]	$AUC_{0-\infty}$ (ng·h/mL)[a]	CL/F (L/h)[a]	Vz/F (L)[a]
100 mg						
Abrocitinib	420.2	1	4.3	1578	63.41	323.3
M1	49.0	1	4.3	565.6	N/A	N/A
M2	95.8	1	2.9	532.9	N/A	N/A
200 mg						
Abrocitinib	756.5	1	5.9	3902	51.24	375.2
M1	210.2	1	4.2	998.5	N/A	N/A
M2	162.1	2	3.9	1197	N/A	N/A

* Steady-state C_{max} of the unbound active moiety (abrocitinib + M1 + M2) was approximately 1.37-fold higher relative to the single-dose.

** C_{max} and AUC values of abrocitinib in AD patients are ~30% higher at steady-state relative to healthy volunteers, based on population PK analysis.

[a] Geometric mean

[b] Median

[c] Arithmetic mean

(M1 and M2 metabolites)

Absorption

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 over the recommended daily dosage range. Coadministration of 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, CIBINQO was administered without regard to food.

Distribution:

After intravenous administration, the volume of distribution of 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 bind predominantly to albumin. 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 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.

Elimination

The elimination half-life of abrocitinib is about 5 hours. CIBINQO 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 and Conditions

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

  Pediatric (under 12 years of age):
  The pharmacokinetics of CIBINQO in pediatric patients under 12 years of age have not yet been established.

- **Geriatrics** After considering hepatic or renal impairment effects related to increasing age in the elderly, age ≥65 years does not have a clinically significant effect on exposures of abrocitinib or active moiety.

- **Sex** Body weight, gender, CYP2C19/2C9 genotype, race, and age did not have a clinically meaningful effect on CIBINQO exposure.

- **Pregnancy and Breast-feeding** Women of reproductive potential should be advised to use effective contraception during treatment and for 1 month following the final dose of CIBINQO. The limited human data on use of CIBINQO in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage.

  In a pre- and postnatal development study in pregnant rats, CIBINQO oral administration during gestation and through lactation resulted in lower postnatal survival and lower offspring body weights at exposures equal to or greater than approximately 11 times the unbound human AUC the maximum recommended clinical dose of 200 mg once. CIBINQO should not be used during pregnancy unless clearly necessary.

- **Hepatic Insufficiency** Patients with mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment had approximately 4% decrease and 15% increase in active moiety AUCinf, 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. In clinical studies, 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.

- **Renal Insufficiency** 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 AUCinf, respectively, compared to patients with normal renal function (eGFR ≥90 mL/min). 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.

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

11 STORAGE, STABILITY AND DISPOSAL

Store CIBINQO at room temperature, 15°C - 30°C in original package.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

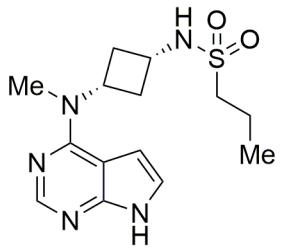
Drug Substance

Proper name: abrocitinib

Chemical name: N-((1s,3s)-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide

Molecular formula and molecular mass: $C_{14}H_{21}N_5O_2S$ and 323.42 Daltons

Structural formula:



Physicochemical properties:

Appearance: Abrocitinib is a white to pale-colored powder.

Aqueous Solubility: The solubility of abrocitinib in water is 0.04 mg/mL at 25ºC. When pH values are less than 4.0, the compound demonstrates the characteristics of a high solubility compound, dissolving rapidly. At pH values greater than 4.0, the compound demonstrates the characteristics of a low solubility compound and thus dissolves more slowly.

Polymorphism: Only one crystalline anhydrous form (Form 1) of abrocitinib has been identified.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Table 7 - Summary of patient demographics for clinical trials in Atopic Dermatitis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range) (years) And Gender	Efficacy endpoints
MONO-1 **B7451012**	Phase 3 randomized, double-blind, placebo-controlled, parallel group, multi-center study.	Abrocitinib 100 mg QD Abrocitinib 200 mg QD Placebo. Treatment duration was 12 weeks (randomized period).	Randomized: 387 100 mg: 156 200 mg: 154 Placebo: 77	Mean age: 29 years (Range: 12 - 65 years) Female: 43.2% Male: 56.8%	Co-primary • IGA response[a] at Week 12 • EASI-75[b] at Week 12 Key secondary • PP-NRS4 at Weeks 2, 4, and 12 • Change from baseline in PSAAD at Week 12
MONO-2 **B7451013**	Phase 3 randomized, double-blind, placebo-controlled, parallel group, multi-center study.	Abrocitinib: 100 mg QD Abrocitinib 200 mg QD Placebo Treatment duration was 12 weeks (randomized period).	Randomized: 391 (randomized 2:2:1) 100 mg: 158 200 mg: 155 Placebo: 78	Mean age: 35.1 (Range: 12 - 65 years) Female: 41.4% Male: 58.5%	

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range) (years) And Gender	Efficacy endpoints
REGIMEN B7451014	Phase 3 randomized withdrawal, double-blind, placebo-controlled, multi-center study.	12-weeks of 200 mg QD open label. Responders were then randomized to 200 mg QD, 100 mg QD or matching placebo up to 52 weeks.	Randomized: 798 (controlled phase) (randomized 1:1:1) 100 mg: 265 200 mg: 266 Placebo: 267	Female and Male Mean age: (Range: 12 years and Older)	**Primary Endpoint:** Loss of response requiring rescue treatment was compared among groups during the blinded treatment period. Loss of response was defined as a loss of at least 50% of the EASI response at Week 12 and an IGA score of 2 or higher. **Key Secondary Endpoint:** Loss of response based on an IGA score of 2 or higher.
EXTEND B7451015	Phase 3 multi-center, LTE study in subjects at least 12 years of age with moderate-to- severe atopic dermatitis.	Subjects previously randomized to abrocitinib 200 mg or 100 mg QD in the qualifying Phase 3 study will be allocated to the same dose.	Planned: 3000	Female and Male Mean age: (Range: 12 years and Older)	Primary Long-term safety (Incidence of clinical abnormalities and change from baseline in clinical laboratory values, ECG measurements, and vital signs.)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range) (years) And Gender	Efficacy endpoints
COMPARE B7451029	Randomized, double-blind, placebo-controlled, double-dummy, parallel group, multi-center study to investigate the efficacy and safety of abrocitinib and dupilumab in comparison with placebo in adults on background topical therapy who have moderate-to-severe atopic dermatitis.	Abrocitinib: 200 mg or 100 mg QD taken orally. Dupilumab: 300 mg administered subcutaneously every other week (with a loading dose of 600 mg at baseline). Matching placebo will be administered accordingly. The total treatment period is 20 weeks.	Total randomized: 838 (randomized 2:2:2:1) Abrocitinib 200 mg: 226 Abrocitinib 100 mg: 238 Dupilumab 300 mg: 243 Placebo: 131	Mean age; 37.7 (Range: 18 years and Older) 93.5% ≥65 years of age 6.5% Female: 51.1% Male: 48.9%	Co-primary • IGA response at Week 12 • EASI-75 at Week 12 Key secondary • PP-NRS4 at Week 2 • IGA response at Week 16 • EASI-75 at Week 16

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range) (years) And Gender	Efficacy endpoints
TEEN B7451036	Phase 3, randomized, double-blind, placebo-controlled, multi-center study investigating the efficacy and safety of abrocitinib co-administered with background medicated topical therapy in adolescent participants 12 to <18 years of age with moderate-to-severe atopic dermatitis	Abrocitinib 100 mg QD Abrocitinib 200 mg QD Placebo Treatment duration = 12 weeks	Randomized: 297 (randomized 1:1:1) 100 mg: 95 200 mg: 96 Placebo: 96	Mean age: 14.9 (Range: 12 to <18 years of age) Female: 49.1% Male: 50.1%	**Primary Endpoints:** Response based on the IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≤2 points at Week 12 Response based on the EASI-75 response at Week 12 **Key Secondary Endpoints**: Response based on at least 4 points improvement in the PP-NRS from baseline at Weeks 2, 4, and 12; Change from baseline in PSAAD total score at Week 12.

Abbreviations: ABR=abrocitinib; CI=confidence interval; EASI=Eczema Area and Severity Index; LSM=least squares mean; IGA=Investigator Global Assessment; LTE = long term extension, N=number of patients randomized; PP-NRS=Peak Pruritus Numerical Rating Scale; PSAAD=Pruritus and Symptoms Assessment for 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 at week 12.
b. EASI-75 responders were patients with ≥75% improvement in EASI, from baseline at week 12.
c. PP-NRS4 responders were patients with ≥4-point improvement in PP-NRS from baseline.

The efficacy and safety of CIBINQO as monotherapy and in combination with background medicated topical therapies were evaluated in 3 pivotal randomized, double-blind, placebo-controlled studies [MONO-1, MONO-2, and COMPARE] in 1616 patients 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 in these studies were those who had inadequate response to previous topical medication, or were patients for whom topical treatments were medically inadvisable, or who had received systemic therapies, including dupilumab. In each of the pivotal studies, over 40% of patients had prior exposure to systemic therapy. In MONO-1 and MONO-2, 6% of the patients had received dupilumab, whereas prior use of dupilumab was not allowed in COMPARE.

Eligible patients from qualifying parent studies were able to enroll in the long-term extension study EXTEND, e.g., if they completed the full treatment period of the any of the pivotal qualifying parent studies.

MONO-1, MONO-2, and COMPARE assessed the co-primary endpoints of IGA and EASI-75 responses at Week 12. Key secondary endpoints in MONO-1 and MONO-2 included improvement of ≥4 points in the severity of PP-NRS (PP-NRS4) at Week 12 and change from baseline to Week 12 for the Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD). The PSAAD is an 11-item, self-reported instrument using a 24-hour recall period, designed to assess the severity of key symptoms and signs of atopic dermatitis including itching, pain, dryness, flaking, cracking, bumps, redness, discoloration, bleeding, fluid, and swelling. Key secondary endpoints in COMPARE were PP-NRS4 at Week 2 in addition to IGA response and EASI-75 at Week 16. The designs of the pivotal and long-term extension studies are summarized in Table 7.

Study Results

Treatment with 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 CIBINQO 100 mg or 200 mg once daily compared with placebo at Week 12 (see Table 8). Higher proportion of patients also achieved EASI-90 with CIBINQO 100 mg or 200 mg once daily compared with placebo at Week 12 (18.6% and 38.6% vs. 5.3% in MONO-1; 23.9% and 37.7% vs. 3.9% in MONO-2).

A significantly higher proportion of patients who achieved PP-NRS4 (defined as an improvement of ≥4 points in the severity of PP-NRS) with CIBINQO 100 mg or 200 mg once daily compared with placebo was observed as soon as Week 2 and persisting through Week 12 (see Table 8). Higher proportions of patients achieved PP-NRS4 with CIBINQO 100 mg or 200 mg once daily compared with placebo by Day 6 and Day 3 (2 days after the first dose), respectively. Higher proportion of patients also achieved PP-NRS

(0 or 1) with CIBINQO 100 mg or 200 mg once daily compared with placebo at Week 12 (21.1% and 35.4% vs. 3.2% in MONO-1; 21.3% and 32.4% vs. 5.5% in MONO-2).

Table 8. Efficacy Results of CIBINQO Monotherapy at Week 12

	MONO-1			MONO-2		
	ABR			ABR		
	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-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)
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)
	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: ABR=abrocitinib; 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.

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. The proportion of PP-NRS4 responders was also significantly higher with CIBINQO 200 mg and 100 mg once daily than placebo at Week 2 and Week 4 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.

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 CIBINQO 100 mg or 200 mg once daily compared with placebo at Week 12 (see Table 89). Higher proportion of patients also achieved EASI-90 with CIBINQO 100 mg or 200 mg once daily compared with placebo at Week 16 (38.0% and 48.9% vs. 11.3%).

The proportions of patients achieving PP-NRS4 with 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 CIBINQO doses at Week 2 (Figure 1). Higher proportion of patients also achieved PP-NRS (0 or 1) with CIBINQO 100 mg or 200 mg once daily compared with placebo at Week 16 (24.7% and 32.0% vs. 11.7%).

Abrocitinib 200 mg QD had more rapid onset of relief of pruritus than dupilumab. The proportion of patients achieving PP-NRS4 with 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 CIBINQO 100 mg once daily and dupilumab at Week 2.

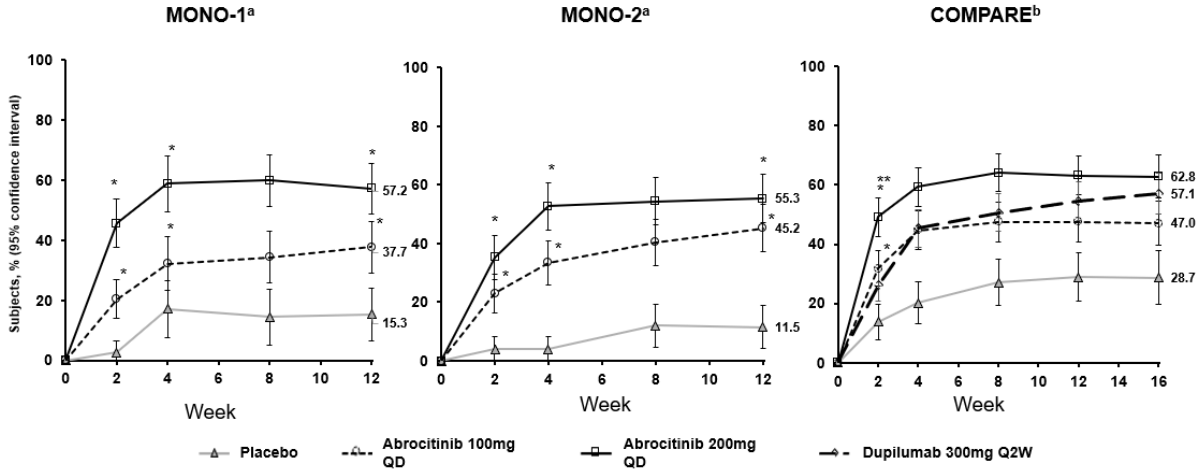
Table 9. Efficacy Results of CIBINQO with Concomitant Topical Therapy

	Week 2				Week 12				Week 16			
	ABR				ABR				ABR			
	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	15.2	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-75[b]	30.0	25.4	10.9	14.0	70.3[e]	58.7[e]	27.1	58.1	71.0[e]	60.3[e]	30.6	65.5
PP-NRS4[c]	49.1[e,f]	31.8[d]	13.8	26.4	63.1	47.5	28.9	54.5	62.8	47.0	28.7	57.1

Abbreviations: ABR=abrocitinib; DUP=dupilumab; EASI=Eczema Area and Severity Index; N=number of patients randomized; PBO=placebo; 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, 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.

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



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

a. Abrocitinib used as monotherapy.
b. Abrocitinib used in combination with medicated topical therapy.
* Statistically significant with adjustment for multiplicity versus placebo.
** Statistically significant with adjustment for multiplicity versus dupilumab.

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.

Early onset of treatment effect, prior to the time-points selected for formal efficacy assessments, was observed for both doses of abrocitinib for the proportion of subjects who achieved IGA response, EASI-75, or PP-NRS4 response in all studies, and for change in PSAAD from baseline in the monotherapy studies.

Abrocitinib 200 mg QD had more rapid onset of relief of pruritus than dupilumab. Starting at Day 2 through Week 16, abrocitinib 200 mg QD had higher PP-NRS4 responder proportion than dupilumab, whereas abrocitinib 100 mg was similar to dupilumab over time.

The totality of data demonstrates that both abrocitinib doses relieved the signs and symptoms of moderate-to-severe AD, including skin clearance, itch relief and improvement of quality of life, either as monotherapy or in combination with background medicated topical therapy in adults and adolescents.

Switch from Dupilumab to Abrocitinib:
Patients who received dupilumab and subsequently enrolled in EXTEND were randomized to either CIBINQO 100 mg or 200 mg once daily upon entering EXTEND. Among responders to dupilumab in COMPARE, the majority did not show evidence of a loss of response 12 weeks after switching to CIBINQO. Some non-responders to dupilumab in COMPARE also demonstrated an IGA and EASI-75 response after switching to CIBINQO, though response rates relative to a comparator were not determined.

Long-term Efficacy:
The majority of patients who achieved a response at Week 12 of a qualifying study and entered EXTEND did not show evidence of a loss of the treatment response at Week 48 [60% and 70% for IGA (0 or 1) response, 79% and 87% for EASI-75, and 62% and 83% for PP-NRS4 with 100 mg once daily and 200 mg once daily, respectively].

Secondary endpoints on quality of life PRO:
There was improvement in different indexes of symptoms and quality of life in adults and adolescents with AD, consistent with the changes observed in the main efficacy parameters.

Treatment with either dose of CIBINQO as monotherapy resulted in improved patient-reported outcomes at 12 weeks compared with placebo. A larger proportion of the 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. Both CIBINQO 100 mg and 200 mg groups also had a 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).

Improved patient-reported atopic dermatitis symptoms and sleep disruption as measured by the Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD), Patient Oriented Eczema Measure (POEM), Night Time Itch Scale (NTIS), and SCORing Atopic Dermatitis (SCORAD) sleep loss subscale were observed in both groups. In addition, anxiety and depression symptoms as measured by the Hospital

Anxiety and Depression Scale (HADS) total score were reduced in the CIBINQO 100 mg and 200 mg groups compared with placebo at 12 weeks.

In COMPARE, a larger proportion both of the CIBINQO 100 mg and 200 mg groups had clinically meaningful reductions in DLQI total scores (defined as a 4-point improvement) from baseline to Week 12 compared with placebo. CIBINQO groups also had a 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).

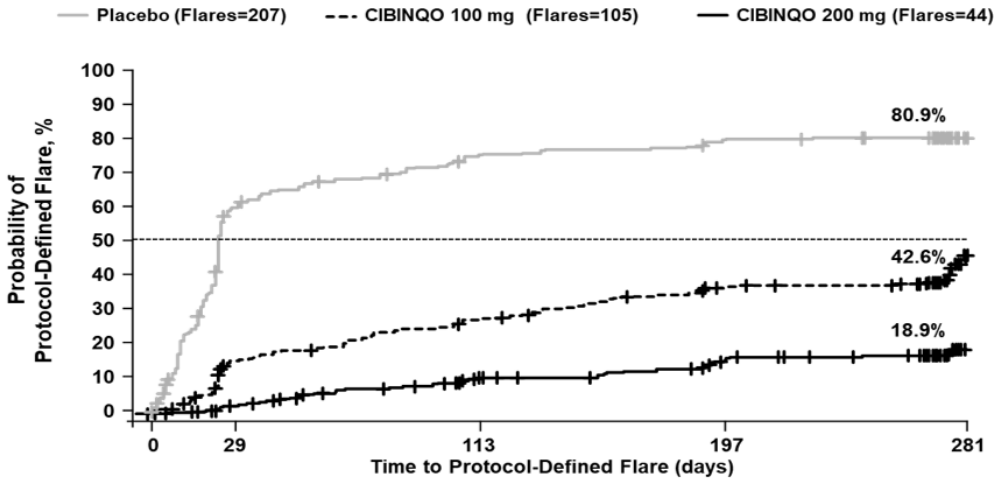
Both CIBINQO 100 mg and 200 mg improved patient-reported atopic dermatitis symptoms and sleep disruption as measured by the POEM and SCORAD sleep loss subscale, respectively. In addition, anxiety and depression symptoms as measured by the HADS total score were reduced in both the CIBINQO 100 mg and 200 mg groups compared with placebo at 12 weeks.

Open label induction, randomized withdrawal study (REGIMEN):

A total of 1,233 patients received open label Cibinqo at a dosage of 200 mg/day. 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 Cibinqo in combination with topical therapy.

Figure 2. Time to protocol-defined flare



Number at Risk					
200 mg → Placebo	267	122	63	48	20
200 mg → 100 mg	265	225	179	151	58
200 mg → 200 mg	266	255	220	201	69

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.

Pediatric data results

Data from the Phase 3 monotherapy studies indicate that the treatment with both abrocitinib doses resulted in clinically meaningful efficacy in adults and adolescents, with demonstration of dose-dependent increase in treatment effect. The efficacy and safety were also evaluated in open label induction, randomised 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.

In adolescents, abrocitinib 100 mg QD and 200 mg QD achieved higher IGA responder proportions than placebo at Week 12 in both Phase 3 monotherapy studies. The treatment effect (IGA responder proportion corrected for placebo) was clinically meaningful for both abrocitinib doses (13.5% and 22.5% for 100 mg QD and 200 mg QD, respectively).

In adolescents, abrocitinib 100 mg QD and 200 mg QD achieved higher EASI-75 responder proportions than placebo at Week 12 in both Phase 3 monotherapy studies. The 95% confidence intervals for placebo-corrected responder proportions for both doses of abrocitinib excluded zero in the monotherapy pool, suggesting true treatment effects. The treatment effect was clinically meaningful for both abrocitinib doses (35.4% and 47.6% for 100 mg QD and 200 mg QD, respectively, in the monotherapy pool), with evidence of dose-dependency.

The efficacy and safety of Cibinqo in combination with background medicated topical therapy was evaluated in the Phase 3 randomised, 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-NRS4 at the baseline visit prior to randomisation. 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 10. Adolescent efficacy results of 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 who received at least one dose of study treatment; 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.

Comparative Bioavailability Studies

This Phase 1 randomized, open-label, single-dose, crossover study in healthy participants was to estimate the rBA of single 200 mg doses of the commercial tablet formulation of PF-04965842 and a variant formulation with a slower dissolution rate, compared to the Phase 3 tablet formulation. The effect of food on the BA of the commercial tablet formulation was also evaluated.

15 MICROBIOLOGY

Not applicable

16 NON-CLINICAL TOXICOLOGY

Rats (Wistar Han or Sprague Dawley) and cynomolgus monkeys were chosen as the nonclinical test systems for general toxicology studies because all the nonclinical studies of the marketed JAK1/3 inhibitor, tofacitinib (Xeljanz), were conducted in these species, and they have shown sensitivity to the pharmacological inhibition of JAK.

Genotoxicity

CIBINQO is not mutagenic in the bacterial mutagenicity assay *(Ames assay).* Although CIBINQO is aneugenic in the in vitro TK6 micronucleus assay, 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 Tg.rasH2 mice administered CIBINQO for 6 months 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, 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 CIBINQO -related tumorigenicity was observed following oral 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

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. 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 post implantation loss in rats 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 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 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. CIBINQO resulted in an 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 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 CIBINQO during organogenesis at exposures equal to 11 times the unbound human AUC at the MRHD of 200 mg. 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 rat pre- and postnatal development study in pregnant rats, oral administration of 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.

Juvenile Toxicity
Administration of abrocitinib to juvenile rats (comparable to a 3-month old human infant) resulted in adverse macroscopic and microscopic bone findings. When dosing was initiated at postnatal Day 10 (at exposures ≥ 0.8 times the unbound human AUC at the MRHD of 200 mg), macroscopic bone findings included malrotated paws, fractures, and/or femoral head abnormalities. The microscopic bone dystrophy finding was fully reversible after cessation of treatment.

17 SUPPORTING PRODUCT MONOGRAPHS

Not applicable

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]CIBINQO®

abrocitinib tablets

Read this carefully before you start taking **CIBINQO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CIBINQO**.

Serious Warnings and Precautions

CIBINQO may cause serious side effects, including:

- **Serious infections**: CIBINQO is a medicine that affects your immune system. CIBINQO can lower the ability of your immune system to fight infections. This can cause serious infections that can lead to hospitalization or death. The most common types of infections were caused by viruses. Before you take CIBINQO tell your healthcare professional if you have an infection or get infections that often come back. Your healthcare professional will assess the risks before you begin treatment with CIBINQO if you have a chronic and reoccurring infection. They will closely monitor you for symptoms of an infection during and after your treatment with CIBINQO. This includes monitoring you for symptoms of tuberculosis. Your healthcare professional may suspend your treatment if you develop a serious infection.
- **Cancer**: CIBINQO may increase your risk of getting cancer, by changing the way your immune system works. Before you take CIBINQO, tell your healthcare professional if you have ever had cancer. People taking a medicine in the class of medicines called Janus kinase (JAK) inhibitors may have a higher risk of certain cancers including lymphoma.
- **Blood clots**: CIBINQO may increase your risk of getting blood clots in the veins of your legs (**deep vein thrombosis**), lungs (**pulmonary embolism**, or arteries (**arterial thrombosis**). These blood clots can be serious or life threatening. Your healthcare professional will assess your risk of getting blood clots and tell you if it is safe to take CIBINQO. Blood clots in the veins of the legs and lungs have happened more often in people who are taking JAK inhibitors.
- **Heart problems, Stroke and Death**: JAK inhibitors may increase your risk of heart problems including heart attack or your risk of stroke. These can lead to death.

See section "**Other warnings you should know about**" for more information on these serious side effects.

What is CIBINQO used for?

CIBINQO is used to treat patients 12 years of age and older with:

- Moderate to severe atopic dermatitis (a type of eczema).
- It includes relief of skin itching in these patients.

CIBINQO is only used in patients who:

- Have not responded sufficiently to other non-topical medicines
- Cannot take other non-topical medicines for this condition.

CIBINQO should be used with caution in elderly patients 65 years of age and over.

How does CIBINQO work?
CIBINQO interferes with an enzyme called Janus Kinase (JAK). It is a medicine known as a JAK inhibitor. Normally JAK enzymes help turn on your immune system when you need it. However, when it is too active this can also lead to inflammation that could result in swelling, redness and pain. CIBINQO works by attaching to the JAK enzyme to lower its activity.

What are the ingredients in CIBINQO?
Medicinal ingredients: abrocitinib
Non-medicinal ingredients: dibasic calcium phosphate anhydrous, hypromellose, iron oxide red, lactose monohydrate, Macrogol/PEG, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, titanium dioxide and triacetin.

CIBINQO comes in the following dosage forms:
Film-coated tablets: 50 mg, 100 mg and 200 mg.

Do not use CIBINQO if:

- you are allergic to abrocitinib or to any of the other ingredients in CIBINQO. If you are not sure, talk to your healthcare professional before taking CIBINQO.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CIBINQO. Talk about any health conditions or problems you may have, including if you:

- are taking other immunosuppressant medicines such as methotrexate and cyclosporine or other JAK inhibitor medicines.
- have an infection or get infections that often come back.
- have hepatitis virus B or C infection.
- have liver problems.
- have kidney problems.
- have a low platelet count or white blood cell count.
- have or have had cancer.
- are 65 years of age or older.
- are a long-term current or past smoker.
- have a history of heart problems.

Other warnings you should know about:

CIBINQO may cause serious side effects, including:

- **Serious Infections:** Tell your healthcare professional if you have an infection or get infections that often come back. Taking CIBINQO increases your risk of developing serious infections such as herpes simplex, shingles (herpes zoster) and pneumonia. CIBINQO may also make infections such as shingles and herpes simplex come back. Your healthcare professional will closely monitor you for infection during and after your treatment. They may put you on antimicrobial therapy if you develop a new infection during treatment. They might also stop your treatment with CIBINQO. They will also screen you for the following infections before and during treatment with CIBINQO:

- **Tuberculosis (TB):** You should not take CIBINQO if you have an active TB infection. Your healthcare professional may put you on preventative medication before beginning treatment with CIBINQO. You will be given this if you are newly diagnosed with inactive TB or had an untreated previous diagnosis of inactive TB.

- **Viral hepatitis:** Tell your healthcare professional if you have hepatitis virus B or C infection. They will also screen you these infections before you start treatment with CIBINQO.

Talk to your healthcare professional if you get any symptoms of an infection including, shingles, herpes simplex, pneumonia or other infection while you are taking CIBINQO.

- **Cancer:** Before you take CIBINQO, tell your healthcare professional if you have or have had cancer. CIBINQO may increase your risk of getting certain cancers. If you smoke, this might further increase your risk of getting certain cancers while taking CIBINQO. Your healthcare professional may want to examine your skin regularly for any sign of cancer.

- **Blood Clots:** CIBINQO may increase your risk of getting blood clots in the veins of your legs or lungs. Your healthcare professional will assess your risk of getting blood clots and tell you if it is safe to take CIBINQO. While you are taking CIBINQO, your healthcare professional will continue to assess your risk of getting blood clots. You are more likely to get blood clots while taking CIBINQO if you:

  - Are immobile for a long time.
  - Have major surgery.
  - Are 65 years of age or older.
  - Have had blood clots in the veins of your legs or lungs in the past.
  - Have an inherited blood clothing disorder.
  - Take hormone therapy or birth control pills.
  - Are a long-term current or past smoker.
  - Have certain kinds of cancer.

  Stop taking CIBINQO and talk to your healthcare professional right away if you get any symptoms of blood clots in the veins of your legs (**deep vein thrombosis**) or lungs (**pulmonary embolism**) while you are taking CIBINQO.

- **Heart problems, Stroke and Death:** CIBINQO may increase your risk of heart attacks and stroke. You may be more likely to get these if you are 65 years of age or older, are or were a long-term smoker, or have a history of heart problems. Talk to your healthcare professional about these risk factors.

  Stop taking CIBINQO and get immediate medical help if you develop any symptoms of a heart attack during treatment with CIBINQO.

See the "**Serious side effects and what to do about them**" table for more information on these and other serious side effects.

Vaccinations:

You should not receive live or attenuated vaccines while receiving CIBINQO or immediately before you start treatment. Your immunizations should be up to date before taking CIBINQO. This includes vaccines for shingles. Talk to your healthcare professional before taking CIBINQO if you are planning to receive a vaccine.

Pregnancy:

Before taking CIBINQO, tell your healthcare professional if you are pregnant, think you might be pregnant or are planning to become pregnant. You should avoid becoming pregnant while you are taking CIBINQO and for at least 1 month after stopping treatment. This is because CIBINQO may harm your unborn baby. Use effective birth control during treatment and for at least 1 month after your last dose of CIBINQO. Talk to your healthcare professional about effective birth control methods. Tell your healthcare professional right away if you become pregnant or think you may be pregnant while taking CIBINQO.

Breastfeeding:

Before you take CIBINQO, tell your healthcare professional if you are breastfeeding or plan to breastfeed. You should not breastfeed while you are taking CIBINQO. This is because it may pass into your breastmilk and harm your baby. Talk to your healthcare professional about the best way to feed your baby if you are taking CIBINQO.

Monitoring and tests:

Your healthcare professional should do blood tests before you start taking CIBINQO and also while you are taking CIBINQO. You should not take CIBINQO if your white blood cell count or platelet count is too low. Your healthcare professional may stop or interrupt your treatment for a period of time depending on your blood test results. Your healthcare professional will also monitor your blood lipid levels while you are taking CIBINQO.

Driving and using machines:

CIBINQO may cause dizziness, which can affect how well you drive or use machines. Do NOT drive or use dangerous machines until you know how CIBINQO affects you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CIBINQO:

- Fluconazole, used to treat fungal or yeast infections.
- Fluvoxamine, used for the treatment of some psychiatric disorders.
- Amiodarone, used to treat heart rhythm problems.
- Fluoxetine, used for the treatment of some psychiatric disorders.
- Miconazole, used to treat fungal or yeast infections.
- Rifampicin, used to treat tuberculosis (TB) and other infections.

- Probenecid, used to treat gout and renal problems.

How to take CIBINQO:

- Take CIBINQO exactly as your healthcare professional has told you to.
- Check with your healthcare professional if you are not sure.
- You can take CIBINQO with or without food. However, if you experience nausea taking CIBINQO with food might make your nausea better.
- Take CIBINQO at about the same time each day.
- Swallow tablets whole with water. Do not split, crush, or chew the tablets.
- CIBINQO can be used with or without prescribed topical medications for atopic dermatitis. Topical medications are lotions, creams, or ointments applied to your skin.
- If you have kidney problems, talk to your healthcare professional. You may need to take a lower dose.
- Your healthcare professional might also give you a lower dose if you are taking certain other medicines.

Usual dose:

Adolescents (between 12 and 18 years of age) and adults: The recommended starting dose is 100 mg or 200 mg once a day. Your healthcare professional will prescribe the dose that is right for you. They may change your dose depending on your condition and the risk of side effects.

Taking more than 200 mg in a day is not recommended.

Patients over 65 years of age should start with 100 mg in a day.

Overdose:

If you think you, or a person you are caring for, have taken too much CIBINQO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember. But if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Go back to the regular dosing schedule. Never take two doses at the same time.

What are possible side effects from using CIBINQO?

These are not all the possible side effects you may have when taking CIBINQO. If you experience any side effects not listed here, tell your healthcare professional.

Side effects with CIBINQO may include:

- acne
- cold sores (also known as oral herpes simplex)
- dizziness
- headache
- nausea

- abdominal pain
- vomiting
- urinary tract infection
- nose or throat infection, pain in the nose or throat, runny or stuffy nose
- feeling tired
- red sores or blisters, often around the nose and mouth

CIBINQO can cause abnormal blood test results. Your healthcare professional may do blood tests before you start CIBINQO and while you take it. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Herpes simplex (infection of the genitals, eyes or skin caused by the herpes simplex virus): tingling, pain or itching in genital area, small red blisters or sores on penis, scrotum or vaginal area, redness, pain or swelling around the eye, blurred vision, watery eyes, tingling, pain or itching in genital area, small red blisters or sores on any skin area.		√	
Infections: fever, chills, muscle aches, flu-like symptoms, cough, sore throat, diarrhea or stomach pain, feeling tired.		√	
UNCOMMON			
Blood clots: • **Deep vein thrombosis** (blood clot in legs): swelling, pain, leg may be warm to the touch and may appear red. • **Pulmonary embolism** (blood clot in lungs): chest pain that may increase with deep breathing, cough, coughing up bloody sputum, shortness of breath.			√ √
Cancer including skin cancer. Symptoms may be variable		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat			√
Lymphopenia (low white blood cells): get infections more easily.		√	
Pneumonia: (lung infection): chest pain when you breath or cough, confusion, cough which may produce phlegm, fatigue, fever, sweating and shaking, chills, nausea, vomiting or diarrhea, shortness of breath.		√	
Shingles, also known as herpes zoster (skin infection): a painful skin rash of fluid-filled blisters, blisters appear along a strip of skin, itching or tingling of the skin.		√	
Thrombocytopenia (low blood platelets): bruising or bleeding		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store CIBINQO at room temperature between 15°C - 30°C.
- Store CIBINQO in the original package.
- Keep out of reach and sight of children.

If you want more information about CIBINQO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.pfizer.ca) or by calling 1-800-463-6001.
- For more information on the CIBINQO Education Program (Prescriber Brochure and Patient Card), please visit the CIBINQO website (www.cibinqo.ca).

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