NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	A Prospective Active Surveillance Study to Monitor Growth, Development, and Maturation Among Adolescents with Atopic Dermatitis Exposed to Abrocitinib
Protocol number	B7451120
Protocol version identifier	1.0
Date	19 Nov 2024
EU Post Authorization Study (PAS) register number	To be registered before the start of data collection.
Active substance	Abrocitinib, ATC code D11AH08
Medicinal product	Cibinqo®
Product reference	*EU/1/21/1593/001; EU/1/21/1593/002; EU/1/21/1593/003; EU/1/21/1593/004; EU/1/21/1593/005; EU/1/21/1593/006; EU/1/21/1593/007; EU/1/21/1593/008; EU/1/21/1593/009; EU/1/21/1593/010; EU/1/21/1593/011; EU/1/21/1593/012; EU/1/21/1593/013; EU/1/21/1593/014; EU/1/21/1593/015.*
Procedure number	EMEA/H/C/005452
Marketing Authorization Holder(s)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 Brussels 1050 Belgium
Joint PASS	No
Research question and objectives	Is treatment with abrocitinib associated with changes in physical growth and development, sexual maturation, or the incidence of bone fractures among adolescent populations 12-<18 years of age with atopic dermatitis (AD)? The primary objectives are: Among adolescent participants with AD who are treated with abrocitinib and, separately, among adolescent participants with AD unexposed to abrocitinib and receiving advanced systemic treatments, to: • Describe physical growth and development metrics;

	• Describe sexual maturation metrics; • Describe the incidence of bone fractures, stratified by abrocitinib dosage (100 mg and 200 mg QD). Exploratory objectives (sample size permitting) are: Among 1) adolescent participants with AD who are treated with abrocitinib and 2) adolescent participants with AD unexposed to abrocitinib and receiving advanced systemic treatments, to: • Compare physical growth and development metrics; • Compare sexual maturation metrics; • Compare incidence of bone fractures.
Countries of study	United States, Canada, and participating European countries.
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Marketing Authorization Holder(s)

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Atopic dermatitis
ADCT	Atopic Dermatitis Control Tool
AE	Adverse event
aPHV	Age at peak height velocity
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
ClinRO	Clinician-reported outcome
CRF	Case report form
EASI	Eczema Area and Sensitivity Index
EMA	European Medicines Agency
EU	European Union
EUR	Europe
FDA	Food and Drug Agency
HTE	Heterogeneity of treatment effects
IL	Interleukin
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
IR	Incidence rate
IRB	Institutional review board
ITT	Intent to treat
JAK	Janus kinase
NA	North America
NRS	Numerical rating scale
PASS	Post-authorisation safety study
PHQ-4	Patient Health Questionnaire-4
POEM	Patient Oriented Eczema Measure

Abbreviation	Definition
PRO	Patient-reported outcome
PS	Propensity score
PtGA	Patient-reported global assessment
RWD	Real-world data
SAP	Statistical analysis plan
SCORAD	SCORing Atopic Dermatitis
SDS	Standard deviation score
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TAEQ	Targeted adverse event questionnaire
UK	United Kingdom
US	United States
VAS	Visual analogue scale
vIGA-AD	Validated Investigator Global Assessment scale for Atopic Dermatitis

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Title: A Prospective Active Surveillance Study to Monitor Growth, Development, and Maturation Among Adolescents with Atopic Dermatitis Exposed to Abrocitinib

Protocol version: 1.0, 19 Nov 2024

Name and affiliation of main author(s):

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Rationale and background: AD is a common, chronic skin condition characterized by inflammation of the skin and skin barrier defects. Lesions of AD are characterized by erythema, itch, induration/papulation, and oozing/crusting (Hanifin and Reed, 2007; Bieber, 2010). Manifestations of AD typically appear early in life and often precede other allergic diseases such as asthma or allergic rhinitis. The prevalence of AD has been estimated to be 15-30% in children and 2-10% in adults (Oszukowska et al., 2015), presenting a significant burden on health-care resources and patients' quality of life. Abrocitinib (PF-04965842), an orally bioavailable small molecule, is a selective Janus Kinase (JAK) 1 inhibitor. The inhibition of JAK1 modulates multiple cytokines involved in the pathophysiology of AD including interleukin (IL)-4, IL-13, IL-31, IL-22, and interferon gamma. Abrocitinib, available as 50, 100, and 200 mg oral film-coated tablets, was approved by the United States (US) Food and Drug Administration (FDA) for the treatment of moderate-to-severe AD in adults on 14 January 2022 and in adolescents 12 years of age and older on 09 February 2023. It was similarly approved by the European Medicines Agency (EMA) in adults on 9 December 2021 and in adolescents 12 years of age and older on 21 March 2024. As part of the abrocitinib pharmacovigilance plan, a long-term follow-up study is being proposed to actively monitor physical growth and development, sexual maturation, and the incidence of bone fractures in adolescents 12-<18 years of age in the post-approval setting. This study is designated as a post-authorisation safety study (PASS) and is a commitment to the EMA.

Research question and objectives: Is treatment with abrocitinib associated with changes in physical growth and development, sexual maturation, or the incidence of bone fractures among adolescent populations 12-<18 years of age with AD?

The primary objectives are:

Among adolescent participants with AD who are treated with abrocitinib and, separately, among adolescent participants with AD unexposed to abrocitinib and receiving advanced systemic treatments, to:

- Describe physical growth and development metrics;

- Describe sexual maturation metrics;
- Describe the incidence of bone fractures, stratified by abrocitinib dosage (100 mg and 200 mg QD).

Exploratory objectives, if sample size allows, are:

Among 1) adolescent participants with AD who are treated with abrocitinib and 2) adolescent participants with AD unexposed to abrocitinib and receiving advanced systemic treatments, to:

- Compare physical growth and development metrics;
- Compare sexual maturation metrics;
- Compare incidence of bone fractures.

Study design: This is a prospective observational cohort study of adolescents with moderate-to-severe AD who receive abrocitinib or another advanced systemic therapy approved in adolescents for the treatment of moderate-to-severe AD.

Population: This PASS will be conducted as a secondary database study using primary data collected by the CorEvitas International Adolescent AD Registry. This clinical registry enrols 12–<16 -year-olds with moderate-to-severe AD in the US, Canada, and Europe. Participants are followed until they exit the registry or reach 18 years of age (ie, the participant's 18th birthday), whichever comes first. The study period will include registry data collected from 21 March 2024 until 31 December 2035.

Participants who satisfy all the following criteria will be included in analyses for this study:

- Adolescent (12-<16 years of age) enroled in the CorEvitas International Adolescent AD Registry;
- At the time of registry enrolment, or within 6 month prior to registry enrolment:
    - Have newly initiated treatment with abrocitinib; OR
    - Have newly initiated another advanced systemic therapy approved for the treatment of moderate-to-severe AD in adolescents, without previous exposure to abrocitinib;
- Do not have short stature, defined as a height less than the third percentile for their age and sex.

Variables: A range of clinical and patient-reported variables are collected as part of the standard data collection model for the CorEvitas International Adolescent AD Registry. Data collected by this registry will be used to evaluate drug exposure and outcomes of interest for this study. The drug exposure of interest is abrocitinib.

Detailed drug exposure information for medications used to treat AD (eg, drug, dose, frequency, start and stop dates, reasons for stopping and/or starting a drug) are captured for all treatment episodes that occur during a participant's registry participation. Drug information is captured at the time of enrolment, at each subsequent follow-up visit, and on any applicable Targeted Adverse Event Questionnaires (TAEQs) to provide a complete record.

Physical growth and development outcomes will include height standard deviation scores (SDS) and weight SDS. Changes in physical growth will be quantified by the change in height SDS and weight SDS during the study. Sexual maturation will be measured by Tanner staging and age at peak height velocity (aPHV), a measure of timing of somatic maturity. Additionally, the occurrence and characteristics of bone fractures during the study will be collected.

Other variables routinely collected as part of the CorEvitas International Adolescent AD Registry will used to adjust for key participant characteristics in the analysis conducted for this study, as applicable, such as demographics (eg, age, sex, race/ethnicity where collection is permitted under relevant local laws), health behaviour, family medical history, current and prior treatments for AD, comorbidities, and select patient-reported outcomes (PROs). AD characteristics and clinical assessments, as well as laboratory values, where available, are also collected. Additionally, at registry enrolment, participants' height and weight measures from the preceding 5-year period are collected, as well as their biological mother's and father's heights, if known.

Data source: This study will use data collected as part of the CorEvitas International Adolescent AD Registry. Patients can enrol in the registry during a scheduled office visit and parental or guardian informed consent and participant assent are required for registry participation. At registry enrolment, the participant and provider each complete a questionnaire that collects information including participant characteristics, medical history, clinical measures, disease characteristics, and a range of patient- and clinician-reported outcomes (ClinROs).

After registry enrolment, follow-up visits are conducted approximately every 6 months during a regularly scheduled clinical encounter, and/or at the time of AD treatment switch. At each follow-up visit, CorEvitas International Adolescent AD Registry Follow-up Questionnaires are completed to update the participant's health history and health behaviour and to record any changes in disease presentation or treatment that occurred since the prior registry visit. Participants are also assessed by the provider for the occurrence of adverse events and safety events of special interest, as defined by the CorEvitas International Adolescent AD Registry protocol.

Participants may withdraw from the CorEvitas International Adolescent AD Registry at any time at their own will, or they may be removed at the discretion of CorEvitas, or the CorEvitas site investigator, for safety, behavioural, or administrative reasons. Otherwise, participants are followed in the registry until they reach 18 years of age (ie, the participant's 18th birthday). Upon exiting the registry for death, withdrawal, or loss to follow-up, the provider completes a Subject Exit Questionnaire as well as a TAEQ for any associated serious adverse events or Registry protocol-defined safety events of interest, if applicable.

Study size: The proposed primary analyses are descriptive and data on all eligible study participants will be analysed. The study will target the enrolment of approximately 500 participants in the US and Canada (250 abrocitinib, 250 comparators) and 200 participants in Europe (100 abrocitinib, 100 comparators), for a total of approximately 700 participants. Around 250 participants in each cohort from the US and Canada will allow the study to estimate the mean height SDS with a 95% confidence interval (CI) half-width of 0.175, assuming a mean of 0 and a standard deviation of 1.41. The study will also be powered to estimate the mean age at Tanner stage progression with a 95% CI half-width ranging from 2.2 to 3.7 months, depending on sex and Tanner stage, and estimate the incidence rate (IR) of bone fractures with a 95% CI total width of 2.11 bone fractures per 100 person-years.

Data analysis: Participant characteristics at baseline, including demographics, clinical and disease characteristics, treatment history, and PROs/ClinROs will be summarized for each exposure cohort. Descriptive summary statistics will be provided for each study outcome. Changes of growth-related measures from baseline to end of follow-up will be provided by exposure cohort, including mean changes in height SDS and weight SDS. The distribution of height percentiles at baseline will be presented, and the proportion of participants whose height percentile decreases by 10% or more will be summarized within each exposure cohort. Median aPHV will be provided by exposure cohort. Tanner staging (a sexual maturity scale) will be provided at enrolment and throughout follow-up. Within each exposure cohort, Tanner staging will be summarized overall, by participant sex, and by sex and age. Average age at Tanner-stage progression for each stage will also be summarized by exposure cohort. The IR of bone fractures (summarised overall and by fracture subcategory) will be presented with associated two-sided 95% CIs by exposure cohort and stratified by abrocitinib dosage (100 mg and 200 mg QD). Relevant characteristics of bone fracture, eg, location, will also be reported. IRs will be expressed as events per 100 person-years of follow-up.

Additional stratified analyses will be performed to assess study outcomes across various demographic attributes (eg, age group, sex), and clinical characteristics (eg, comorbid conditions, prior systemic medications for AD), depending on the availability of relevant data and sample size. Exploratory analyses comparing exposure cohorts will also be conducted for select outcomes depending on the sample size.

Milestones:

- Registration in the HMA-EMA Catalogues of RWD studies: prior to initiating data collection
- Start of data collection (defined as the date from which data extraction starts): 30 September 2025
- Progress report: 28 Feb 2026 and 28 Feb 2028 (2 in total)
- Interim analysis reports: 30 April 2030, 30 April 2032, 30 April 2034 (3 in total)
- End of data collection: 31 January 2036
- Final study report: 31 July 2036

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
Registration in HMA-EMA Catalogues of RWD studies	Pending (prior to the start of data collection)
Start of data collection [a]	30 September 2025
Progress report #1	28 Feb 2026
Progress report #2	28 Feb 2028
Interim report #1	30 April 2030
Interim report #2	30 April 2032
Interim report #3	30 April 2034
End of data collection [b]	31 January 2036
Final study report	31 July 2036

a Given secondary dataset design, start of data collection has been defined as “the date from which data extraction starts” from the registry for the first progress report.

b The planned date on which the analytical dataset will be first completely available; the analytic dataset is the minimum set of data required to perform the statistical analysis for the primary objective(s).

7. RATIONALE AND BACKGROUND

AD is a common, chronic skin condition characterized by inflammation of the skin and skin barrier defects caused by a combination of genetic and environmental factors (Bieber, 2010). Lesions of AD are characterized by erythema, itching, induration/papulation, and oozing/crusting (Hanifin and Reed, 2007; Bieber, 2010). Manifestations of AD typically appear early in life and often precede other allergic diseases such as asthma or allergic rhinitis. The prevalence of AD has been estimated to be 15-30% in children and 2-10% in adults (Oszukowska et al., 2015) presenting a significant burden on health-care resources and patients’ quality of life. The incidence of AD in developed countries has been increasing worldwide (Peters et al., 2010), emphasizing the need for safe and effective therapies.

Treatment for AD can be topical or systemic; approved therapies include corticosteroids and targeted calcineurin, IL, JAK, and phosphodiesterase-4 inhibitors. Abrocitinib (PF-04965842), an orally bioavailable small molecule, is a selective JAK1 inhibitor. The inhibition of JAK1 modulates multiple cytokines involved in the pathophysiology of AD including IL-4, IL-13, IL-31, IL-22, and interferon gamma. Abrocitinib, available as 50, 100, and 200 mg oral film-coated tablets, was approved by the US FDA for the treatment of moderate-to-severe AD in adults on 14 January 2022 and in adolescents 12 years of age and older on 9 February 2023. It was similarly approved by the EMA in adults on 9 December 2021 and in adolescents 12 years of age and older on 21 March 2024. Indication in the US is limited by the FDA to patients whose disease is not adequately controlled with other systemic drug products, while the EMA indicates it can be used in patients for whom treatment applied directly to the skin cannot be used or is not sufficient.

The available clinical and nonclinical data for abrocitinib do not suggest a risk of impaired physical growth and development, impaired sexual maturation, or an increased incidence of bone fractures in patients 12 years of age and older. However, as clinical data are limited, the potential impact of abrocitinib on these outcomes is considered missing information. Therefore, as part of the abrocitinib pharmacovigilance plan, a long-term follow-up study is

being proposed to actively monitor physical growth and development, sexual maturation, and the incidence of bone fractures in adolescents 12-<18 years of age in the post-approval setting.

This noninterventional study is designated as a PASS and is a Category 3 RMP commitment to the EMA.

8. RESEARCH QUESTION AND OBJECTIVES

The purpose of this study is to evaluate, among adolescents (12-<18 years of age) with AD who receive abrocitinib and those unexposed to abrocitinib and receiving advanced systemic treatments for AD, (1) physical growth and development, (2) sexual maturation, and (3) the incidence of bone fractures.

8.1. Primary Objectives

The primary objectives are:

Among adolescent participants with AD who are treated with abrocitinib and, separately, among adolescent participants with AD unexposed to abrocitinib and receiving advanced systemic treatments, to:

- Describe physical growth and development metrics;
- Describe sexual maturation metrics;
- Describe the incidence of bone fractures, stratified by abrocitinib dosage (100 mg and 200 mg QD).

8.2. Exploratory Objectives

The exploratory objectives (sample size permitting) are:

Among 1) adolescent participants with AD who are treated with abrocitinib and 2) adolescent participants with AD unexposed to abrocitinib and receiving advanced systemic treatments, to:

- Compare physical growth and development metrics;
- Compare sexual maturation metrics;
- Compare incidence of bone fractures.

9. RESEARCH METHODS

9.1. Study Design

This will be a prospective observational cohort study of adolescents with moderate-to-severe AD who receive abrocitinib or another advanced systemic therapy approved in adolescents for the treatment of moderate-to-severe AD.

9.2. Setting

This PASS will be conducted as a secondary database study using primary data collected by the CorEvitas International Adolescent AD Registry, a prospective, multicenter,

observational registry that enrols adolescents 12-<16 years of age with moderate-to-severe AD. The registry is modeled after the CorEvitas Adult AD Registry which was launched in 2020 and includes 78 sites in the US and Canada, with 3,928 participants as of 31 March 2024. Dermatological clinics throughout Europe, the US, and Canada, that have a high volume of treated adolescent patients with AD are identified by CorEvitas and asked to participate in the CorEvitas International Adolescent AD Registry.

Data collection occurs via CorEvitas registry questionnaires at the time of enrolment and approximately every 6 months thereafter for the duration of a participant's registry participation. If there is a change in AD treatment, early visit follow-up questionnaires may also be completed. Additionally, the occurrence of adverse events or registry protocol-defined safety events of interest are actively assessed by participating CorEvitas site investigators at each registry visit and recorded in the registry questionnaires. CorEvitas' registry sites are trained by CorEvitas on the registry protocol, data collection, and reporting requirements, including the submission of supporting medical documentation (ie, relevant primary source medical records), for such events at regularly scheduled follow-up visits and when identified between registry visits. Participants are followed until they exit the registry or reach 18 years of age, whichever comes first. Section 9.4 (Data Sources) provides a detailed description of the registry and its participants.

The study population will be drawn from participants enroled in the CorEvitas International Adolescent AD Registry. The study will include participants from Europe, the US, and Canada to maximise sample size and statistical power. The study will include adolescents 12-<16 years of age receiving abrocitinib for the treatment of moderate-to-severe AD as well as adolescents exposed to other approved systemic medications for the treatment of moderate-to-severe AD in adolescents. The study will include registry data collected from 21 March 2024 until 31 December 2035; the recruitment period will be approximately 5 years and participants will be followed until they exit the registry or reach 18 years of age (ie, maximum 6 years follow-up for participants who are enrolled at the age of 12).

9.2.1. Inclusion Criteria

Participants must meet all of the following inclusion criteria to be eligible for the study:

1. Enroled in the CorEvitas International Adolescent AD Registry (12-<16 years of age at the time of enrolment); and
2. At the time of registry enrolment, or within 6 months prior to registry enrolment, newly initiated treatment with abrocitinib or another advanced systemic therapy approved in the US, Canada, or participating European countries for the treatment of moderate-to-severe AD in adolescents.

9.2.2. Exclusion Criteria

Participants meeting any of the following criteria will not be included in the study:

1. Previously used abrocitinib, if more than 6 months prior to registry enrolment; or
2. Have short stature, defined as a height less than the 3rd percentile for age and sex.

9.3. Variables

A range of clinical and participant-related variables are collected as part of the standard data collection model for the CorEvitas International Adolescent AD Registry (Table 1). Data collected by this registry will be used to evaluate drug exposure and outcomes of interest for this study. The drug exposure of interest is abrocitinib use.

Detailed drug exposure information for medications used to treat AD (eg, drug, dose, frequency, start and stop dates, reasons for stopping and/or starting a drug) are captured for all treatment episodes occurring during a participant's registry participation. Drug information is captured at the time of enrolment, at each subsequent registry follow-up visit, and on any applicable TAEQs to provide a complete record.

Physical growth and development outcomes will include height SDS and weight SDS. Changes in physical growth will be quantified by the change in height SDS and weight SDS during the study. Sexual maturation will be measured by Tanner staging and aPHV, a measure of timing of somatic maturity. Additionally, the occurrence of bone fractures during the study and relevant characteristics of the bone fractures will be collected. Registry questionnaires (including Provider Follow-up, TAEQs, and/or Subject Exit questionnaires) will be used to assess incidence of bone fractures. Additional medical records are collected and submitted to the registry to support validation of physician-reported TAEs.

Other variables routinely collected as part of the CorEvitas International Adolescent AD Registry will be available for this study for potential use to adjust for key participant characteristics, as applicable, such as demographics (eg, age, sex, race/ethnicity where collection is permitted under relevant local laws), health behaviour, family medical history, current and prior treatments for AD, comorbidities, and select PROs (detailed in Section 9.3.3). AD characteristics and clinical assessments, as well as laboratory values, where available, are also collected. Additionally, at registry enrolment, participants' height and weight measures from the preceding 5-year period are collected, as well as their biological mother's and father's heights, if known.

Table 1. CorEvitas International Adolescent AD Registry key variables

Variable	Role	Data Source(s)	Operational Definition
AD Diagnosis Date	Clinical features, duration of disease	Provider-reported (Enrolment)	Month/Year of AD Diagnosis
Age at AD Onset	Clinical features	Provider Reported (Enrolment)	Age at time of AD diagnosis (in years)
Height and weight (historical measures)	Clinical features	Provider-reported (Enrolment)	History of pediatrician-measured height and weight and calculated height and weight percentiles

Table 1. CorEvitas International Adolescent AD Registry key variables

Variable	Role	Data Source(s)	Operational Definition
Height	Clinical features	Provider-reported (Enrolment, Follow-up)	Measured height at time of visit (inches or centimetres)
Weight	Clinical features	Provider-reported (Enrolment, Follow-up)	Measured weight at time of visit (pounds or kilograms)
Medical History	Clinical features	Provider-reported, (Enrolment, Follow-up)	Presence or absence of medical conditions or history of events of interest (at time of enrolment), with onset date
Comorbidities, adverse events, and drug toxicities	Clinical features	Provider-reported (Enrolment, Follow-up)	Presence or absence of new onset medical conditions or AEs of special interest with onset date
History of infections	Clinical features	Provider-reported (Enrolment, Follow-up)	Presence or absence of (current, prior) serious or nonserious infections with onset date and infection type
New Adverse Events, Comorbidities, Drug Toxicities, and Infections	Adverse events	Provider-reported (assessed at Follow-up)	Presence or absence of AEs or new onset comorbidities occurring after enrolment
Physician Global Assessment	Disease activity instruments	Provider-reported (assessed at Enrolment, Follow-up)	Physician Global Assessment of disease activity at time of visit
Biologic and non-biologic systemic medications for AD	AD treatments	Provider-reported (Enrolment, Follow-up)	Presence or absence of specific current/prior biologics, non-biologics, small molecules, corticosteroids, other systemic medications (Note: at enrolment this includes treatment history since AD diagnosis)
Dose	AD treatments	Provider-reported (Enrolment, Follow-up)	Prescribed dose in medication-appropriate units (eg, g, mg, mg/kg)

Table 1. CorEvitas International Adolescent AD Registry key variables

Variable	Role	Data Source(s)	Operational Definition
Frequency of administration	AD treatments	Provider-reported (Enrolment, Follow-up)	Prescribed frequency of administration
Start date	AD treatments	Provider-reported (Enrolment, Follow-up)	Date of drug initiation (confirmed start date) for specified AD therapy(ies)
Discontinuation date (or ongoing)	AD treatments	Provider-reported (Enrolment, Follow-up)	Date of drug discontinuation or confirmation of ongoing status for specified AD therapy(ies)
Drug planned decided at visit (ie, the current registry visit)	AD treatments	Provider-reported (Enrolment, Follow-up)	Prescribed (pending) changes to AD treatment are captured at each registry follow-up visit, including drug stop, start, or dose change. Actual confirmed 'Start date' for new drugs or dose changes is captured at the next registry visit following the prescribed change.
Health insurance	Demographics	Provider-reported (Enrolment, Follow-up)	Presence or absence of health insurance and type (as applicable)
Year of birth	Demographics	Patient-reported (Enrolment)	Participant's year of birth
Sex	Demographics	Patient-reported (Enrolment)	Participant's self-reported sex
Race	Demographics	Patient-reported (Enrolment)	Participant's self-reported race
Ethnicity	Demographics	Patient-reported (Enrolment)	Participant's ethnicity (Hispanic or non-Hispanic)
Pregnancy	Patient characteristics	Patient-reported (Enrolment, Follow-up)	Pregnancy (current pregnancy, pregnancy since prior visit)
Smoking, other tobacco, or alcohol use	Lifestyle factors	Patient-reported (Enrolment, Follow-up)	Use of cigarettes, tobacco/nicotine products (including e-cigarettes) or alcohol reported at or after enrolment

Table 1. CorEvitas International Adolescent AD Registry key variables

Variable	Role	Data Source(s)	Operational Definition
Patient Global Assessment	Patient-reported outcomes	Patient-reported (Enrolment, Follow-up)	Measured at registry enrolment and follow-up visits
Patient Oriented Eczema Measure (POEM)	Patient-reported outcomes	Patient-reported (Enrolment, Follow-up)	Measured at registry enrolment and follow-up visits
Sleeplessness Numerical Rating Scale (NRS)	Patient-reported outcomes	Patient-reported (Enrolment, Follow-up)	Measured at registry enrolment and follow-up visits
Average Pruritus NRS	Patient-reported outcomes	Patient-reported (Enrolment, Follow-up)	Measured at registry enrolment and follow-up visits
Peak Pruritus NRS	Patient-reported outcomes	Patient-reported (Enrolment, Follow-up)	Measured at registry enrolment and follow-up visits
Skin Pain NRS	Patient-reported outcomes	Patient-reported (Enrolment, Follow-up)	Measured at registry enrolment and follow-up visits
Fatigue NRS	Patient-reported outcomes	Patient-reported (Enrolment, Follow-up)	Measured at registry enrolment and follow-up visits
Registry-defined Targeted Adverse Events	Adverse event of special interest	TAEQ (Malignancy, Major Adverse Cardiovascular Events (MACE), Serious Infection, Venous thromboembolism, Serious Hepatic, Ocular AE, and other Serious Adverse Events)	Structured capture for reporting and characterization of registry-defined targeted adverse events occurring during the study period
Fracture Events	Adverse event of special interest	Provider Follow-up, Bone Fracture TAEQ[a]	Structured capture for identification of serious and nonserious fracture events; Detailed characterization of serious fracture events via TAEQ

Table 1. CorEvitas International Adolescent AD Registry key variables

Variable	Role	Data Source(s)	Operational Definition
Pregnancy Event		Patient-reported (Enrolment, Follow-up), Pregnancy Event Questionnaire[a]	Structured capture for identification and characterization of pregnancy through outcome including maternal details, infant status, pregnancy risks, complications, outcome
Reason for exit	Study discontinuation	Exit Questionnaire	Reason for registry exit (withdrew consent, moved, lost to follow-up [unknown vital status], administrative, or death)
Exit due to death	Death[a]	Exit Questionnaire	Report of death as reason for registry exit
Date of death	Death[a]	Exit Questionnaire	Reported date of death
Primary cause of death (TAE)	Death[a]	Exit Questionnaire	Primary cause(s) of death, TAE details as available
Associated with death (TAE)	Death[a]	Exit Questionnaire	Any other AEs associated with death, if applicable

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; cm = centimeters; CV = cardiovascular; DILI = drug-induced liver injury; eg = example; g = grams; GI = gastrointestinal; Hg = mercury; HZ = herpes zoster; IV = intravenous; kg = kilograms; LFTs = liver function tests; mg = milligrams; mm = millimeters; SAE = serious adverse event; TAEQ = Targeted Adverse Event Questionnaire

a. Medical records are requested to support central review and verification of reported TAE events.

9.3.1. Exposure

Abrocitinib is the exposure of interest. Two exposure cohorts will be created for this study for primary and exploratory analyses (as applicable): namely an abrocitinib-exposed cohort and a comparator cohort. The comparator cohort will comprise advanced systemic therapies that are approved in adolescents for moderate-to-severe AD, including dupilumab, baricitinib, lebrikizumab, tralokinumab, and upadacitinib, noting that the final list of products will be finalized in the statistical analysis plan (SAP). The exposure for the comparator cohort will include biologic or other non-biologic advanced systemic medications approved for the treatment of moderate-to-severe AD in adolescents in the EU at the time of registry enrolment. If new systemic therapies are approved for the treatment of moderate-to-severe AD in adolescents during the study period, subsequent exposures to the new approved systemic therapies will also be included in the comparator cohort. Drug exposure is reported by the treating healthcare provider at enrolment into the registry, and any changes to exposure are reported at follow-up visits.

All participants included in this study are candidates for systemic therapies for moderate-to-severe AD and are expected to be comparable in terms of disease activity and baseline risk. The Registry collects additional data that will be used to further characterize the populations represented by each exposure cohort, such as demographics, comorbidities, treatment history, and disease severity. This data can be used to assess for significant differences between the abrocitinib and comparator cohorts and can be used in a propensity score (PS) model to help mitigate any confounding, should it exist.

9.3.1.1. Drug Exposure Classification

A hierarchical exposure definition will be used for all analyses so that once exposure to abrocitinib occurs, time may not be attributed to the comparator cohort (Figure 1). This constitutes the most inclusive definition of abrocitinib exposure and allows the comparator cohort to be free of any prior or subsequent abrocitinib use.

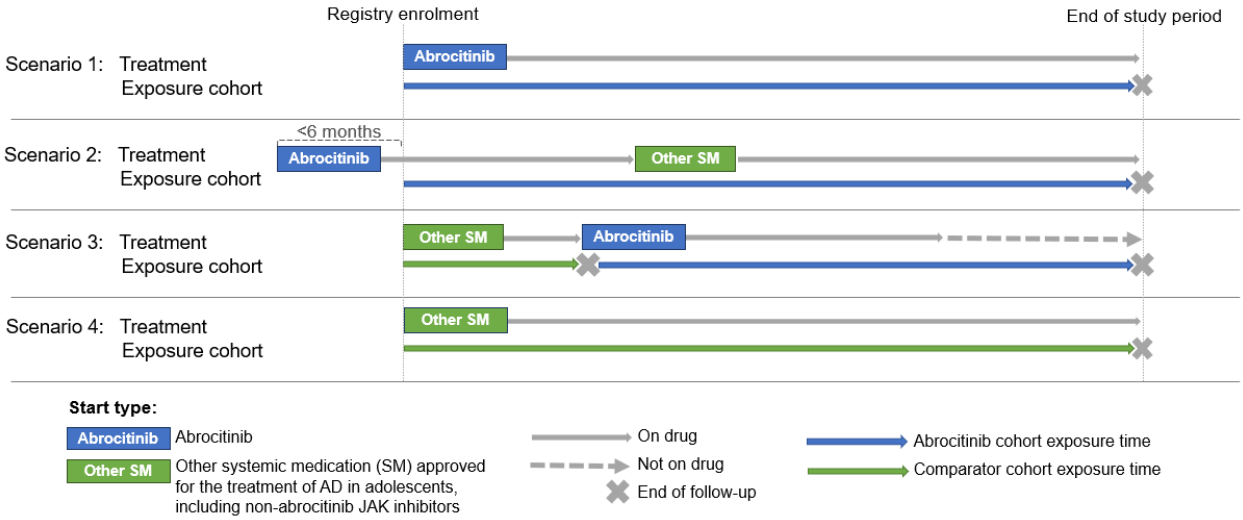
Using this definition, participants will be assigned to the abrocitinib exposure cohort at the initiation of abrocitinib. For participants who initiate abrocitinib within 6 months prior to registry enrolment, the index date will be defined as the registry enrolment date; these will be considered prevalent users. For participants who initiate abrocitinib at the time of registry enrolment or any time during follow-up, the index date will be defined as the date of treatment initiation; these will be considered incident users. Participants will then remain in the abrocitinib cohort regardless of any subsequent treatment changes during follow-up. Abrocitinib cohort exposure episode time will start at the assigned index date and continue until the end of the study, death, or exit from the registry.

Participants without previous exposure to abrocitinib who initiate another advanced systemic medication for the treatment of moderate-to-severe AD, at the time of registry enrolment or within 6 months prior to enrolment, will be assigned to the comparator cohort. If initiation occurs within the 6 months prior to registry enrolment, the index date will be defined as the registry enrolment date (prevalent users). If initiation occurs at the time of registry enrolment, the index date will be defined as the date of treatment initiation (incident users). Comparator cohort exposure time will start at the assigned index date and continue until the initiation of abrocitinib, the end of the study, death, or exit from the registry.

Under the hierarchical definition, participants who initiate abrocitinib within the 6 months prior to, or at the time of, registry enrolment can only contribute one exposure episode (to the abrocitinib cohort). Participants assigned to the comparator cohort at registry enrolment and who are never exposed to abrocitinib (ie, do not subsequently initiate abrocitinib) can similarly only contribute one exposure episode (to the comparator cohort). However, if a participant's abrocitinib exposure follows a qualifying comparator exposure episode, that participant can contribute a maximum of two exposure episodes, one to the comparator cohort and one to the abrocitinib cohort.

Participants' treatment patterns during follow-up will be summarized in the study results. If warranted, additional sensitivity analyses will be explored to evaluate alternative exposure classifications.

Figure 1. Examples of hierarchical exposure cohort classification



9.3.2. Outcomes

Primary study outcomes are described below.

9.3.2.1. Physical Growth and Development

Physical growth and development outcomes will include mean change from baseline to end of follow-up in participant's height SDS and weight SDS measures. Other descriptive measures of growth will also be reported including standing height, height percentiles, weight, weight percentiles, body mass index (BMI), BMI percentiles, and BMI SDS. The proportion of participants whose height percentile decreases 10% or more will be reported.

Measurements of body weight and height are collected in the office of the dermatologist or qualified dermatology practitioner. BMI will be derived using body weight in kilograms (kg) divided by height in metres (m) squared (kg/m^2). Height, weight, and BMI percentiles will be calculated based on the US Centers for Disease Control and Prevention (CDC) clinical growth chart sex-specific reference values for children and adolescents 2-20 years of age using the Lambda Mu and Sigma (LMS) method (CDC, 2023; Flegal and Cole, 2013).

SDS, also known as z-scores, are used to quantify a measurement's distance from the mean and are widely used in anthropometry. Height, weight, and BMI measures will be converted to height, weight, and BMI SDS, respectively, using the aforementioned CDC LMS method. For example, a participant of average height for their age and sex will have an SDS value of 0. A smaller absolute SDS represents measurements closer to the mean, while a larger absolute SDS represents measurements farther from the mean. A participant with a shorter height than the average for their age and sex will have a negative SDS, while a participant taller than average will have a positive SDS.

9.3.2.2. Sexual Maturation

Sexual maturation will be measured by (1) Tanner staging and (2) aPHV (a measure of timing of somatic maturity).

9.3.2.2.1. Tanner Staging

Pubertal development will be evaluated by participant self-assessment using Tanner staging, also known as Sexual Maturity Rating. Tanner staging is an objective classification system that tracks the development and sequence of secondary sex characteristics of children during puberty. The staging ranges from Tanner stage 1 (pre-pubertal form) to Tanner stage 5 (final adult form). Tanner stage 2 marks the onset of puberty and typically begins between 8 to 13 and 9 to 14 years of age for females and males, respectively (Emmanuel, 2022). The physical markers of pubertal progression used in Tanner staging include a pubic hair and breast development scale for females and a pubic hair and external genitalia scale for males. Participants are provided a sex-specific diagram and asked to self-assess their Tanner stage at enrolment and at each follow-up visit until progression to stage 5 or the end of follow-up, (ie, reaching 18 years of age or exit from the registry) whichever comes first.

Age at progression to each Tanner stage will be determined by the participant's age at the time of follow-up when they first self-report the next sequential Tanner stage. Delayed onset of puberty is considered if Tanner stage 2 is not reached by age <13 (ie, by 13th birthday) for females or by age <14 (ie, by 14th birthday) for males (Emmanuel, 2022).

For sites and participants willing to participate in clinical Tanner staging assessment, the dermatologist, site investigator, or trained clinical staff designee will also assess Tanner staging at enrolment and during each registry follow-up visit. Due to privacy concerns of the participant and comfort level of the provider, clinical Tanner staging may not be feasible in this study for all participants, but the subset with both self-reported and provider-assessed staging will enable validation of self-reported Tanner staging.

9.3.2.2.2. Age at PHV

Age at PHV, known as aPHV, is an important somatic maturation milestone. aPHV can vary greatly between individuals suggesting that it is part of a dynamic process that can occur at various stages of puberty as measured by Tanner staging (Granados, 2015). aPHV is defined as the age at maximal height velocity after 8 years of age for females, and after 10 years of age for males (Aksglaede et al., 2008). Height velocity (cm/year) will be calculated based on measurements obtained at registry visits and using the historical height measurements collected at enrolment from the preceding 5-year period. Of note, a minimum of 3 height measurements are required to estimate this outcome and a participant's aPHV can only be determined if their height velocity increases then decreases in the collected registry data.

9.3.2.3. Bone Fractures

The occurrence of bone fractures during study follow-up with be assessed. A bone fracture occurs when there is a partial or complete break in the continuity of a bone. Bone fracture events that occur during the registry follow-up period are documented on a dedicated Bone Fracture TAEQ. The TAEQ is completed at the follow-up visit in which the fracture was

reported, or should the site become aware of a fracture between follow-up visits, within 24 hours of awareness. Information collected on the Bone Fracture TAEQ includes the date of the event, fracture characterization (eg, closed, open, displaced, nondisplaced), type (eg, traverse, oblique, spiral, linear, etc.), and location. The cause of the fracture (injury or pathological) is documented and additional information is collected to evaluate for potential pathological or fragility fractures not associated with trauma, including any known risk factors (eg, underlying medical conditions) that may weaken bones (eg, osteoporosis, chronic corticosteroid use, renal or hepatic disease, genetic conditions). While cause of bone fractures will not be analysed in this study, cause information is collected in the registry data to support description/characterization of bone fracture events. Supporting redacted medical records documenting the bone fracture event are also submitted, where available.

9.3.3. Other Variables

Other key variables are collected on provider enrolment and follow-up questionnaires, including AD characteristics and clinical features (eg, location of AD involvement, history of relevant allergies and related conditions), details pertaining to any AD treatment change since the prior registry visit, if applicable, comorbidities, and laboratory measures collected per standard-of-care, if available. The following ClinROs are also collected at each visit:

- Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD)™
- Assessment of nail changes due to AD (visual analog scale, VAS)
- AD body surface area
- Eczema Area and Severity Index (EASI)
- SCORing AD (SCORAD)

Similarly, participant-reported data collected at each visit include questions about alcohol and substance use, exposure to secondhand smoke, and the following PROs:

- Patient Global Assessment (PtGA) AD Disease Control and Severity
- Patient Oriented Eczema Measure (POEM)
- Children's Dermatology Life Quality Index (CDLQI)
- Patient Health Questionnaire (PHQ-4)
- AD Control Tool (ADCT)
- SCORAD Average Pruritus – past 3 days (VAS)
- SCORAD Sleeplessness – past 3 days (VAS)
- Average Pruritus – past 7 days (numerical rating scale, NRS)
- Peak Pruritus – past 24 hours (NRS)
- Skin Pain – past 24 hours (NRS)
- Fatigue – past 7 days (NRS)

Additionally, Subject Exit Questionnaires collect information related to the date and reason for exit from the registry. When exit is reported to be due to death, data on cause and date of death, and relevant source documents are collected. TAEQs are completed for any associated targeted adverse events.

9.4. Data Sources

This study will use real world data collected in the context of routine clinical care from the CorEvitas International Adolescent AD Registry. The registry is a prospective, multicentre, observational registry initiated to evaluate treatment outcomes in adolescents with moderate-to-severe AD. Dermatology clinics from select European countries, the US, and Canada are recruited to participate.

Enrolment in the registry is voluntary. To be eligible to participate in the registry, a patient must meet all of the following criteria:

- Have been diagnosed with moderate-to-severe AD by a dermatologist or qualified dermatology practitioner;
- Be 12-<16 years of age at the time of enrolment;
- At the time of registry enrolment, or within 6 months prior to registry enrolment, have been prescribed a new commercially available advanced therapy and/or conventional systemic therapy for the treatment of moderate-to-severe AD in adolescents in the context of routine clinical care that is consistent with local prescribing guidelines and/or regulations for the country where the site is located;
- Provide parental or guardian consent and participant assent for registry participation; to include evidence of institutional review board (IRB)/Ethics committee-approved informed assent documentation indicating that the patient (or a legally acceptable representative) agrees to participate and has been informed of all pertinent aspects of participation in the CorEvitas International Adolescent AD Registry.

Patients are ineligible to be enroled in the CorEvitas International Adolescent AD Registry if any of the following conditions are true:

- They are participating or planning to participate in a blinded clinical trial for an AD drug;
- They are unable or unwilling to provide standing height measurements;
- They are unable or unwilling to provide parental/guardian consent and/or their own assent to participate in the registry.

Registry sites are trained on the eligibility criteria, processes for data collection, and evaluation and documentation of adverse events and Registry protocol-defined safety events of interest. Registry data are collected approximately every 6 months, or at the time of AD treatment change, in the context of routine care. Data are collected through detailed provider and participant questionnaires and source documents are submitted by participating providers. Adolescents who meet the inclusion criteria are enroled into the registry after having provided assent and parental consent. Participants can withdraw from the registry at any time at their own request, without giving any reason and without consequences for their future treatment.

9.4.1. Enrolment Visits

Participants are enroled in the CorEvitas International Adolescent AD Registry during a scheduled office visit. At enrolment, the participant and provider each complete a questionnaire that collects information including participant characteristics, medical history, clinical measures, disease characteristics, and a range of PROs and ClinROs.

9.4.2. Follow-up Visits

After the enrolment visit, follow-up visits are conducted during regularly scheduled clinical encounters, approximately every 6 months, and/or at the time of AD treatment switch. At each follow-up visit, participants are assessed for the occurrence of adverse events or Registry protocol-defined safety events of interest. Serious adverse events and Registry protocol-defined safety events of interest, per the CorEvitas International Adolescent AD Registry protocol, are reported via TAEQs. Additionally, detailed clinical assessments, PROs, ClinROs, and any changes to the participant's health history, health behaviour, or changes in disease presentation or treatment are collected on participant and provider follow-up questionnaires. Participants may withdraw from the CorEvitas International Adolescent AD Registry at any time at their own will, or they may be removed at the discretion of CorEvitas, or the CorEvitas site investigator for safety, behavioural, or administrative reasons. Otherwise, participants are followed in the registry until 18 years of age (ie, the participant's 18th birthday) or other date of registry exit. Upon exiting the registry (eg, for death, withdrawal, loss to follow-up, or turning 18 years of age), the provider completes a Subject Exit Questionnaire as well as a TAEQ for any associated Registry protocol-defined safety event of interest, if applicable.

The CorEvitas International Adolescent AD Registry questionnaires enable structured capture of validated disease activity and severity measures, and detailed safety and comorbidity information directly from the participants and their dermatology provider(s). Detailed information pertaining to serious and non-serious Registry protocol-defined safety events of interest are collected during routine clinical care on customised TAEQs, including bone fractures. Sites are trained to complete and submit TAEQs within 1 business day of awareness (including TAEs they are informed of between registry visits), and to collect appropriate medical records to support medical review and confirmation of TAEs reported to CorEvitas. Submitted TAEs and source documentation undergo standard quality control and central verification by the CorEvitas Pharmacovigilance Department.

9.5. Study Size

The primary analyses are descriptive and data on all eligible participants will be analysed, unless otherwise noted. The study will target the enrolment of approximately 700 participants, comprised of 500 participants in the US and Canada (250 abrocitinib, 250 comparators) and 200 participants in Europe (EUR; 100 abrocitinib, 100 comparators). Study enrolment will occur for approximately 5 years with up to an additional 6 years of follow-up to assess study outcomes between the ages of 12 and <18. For participants residing in North America (NA), approximately 250 participants in each cohort will allow the study to estimate the mean change in height SDS with a 95% CI half-width of 0.175, assuming a mean of 0 and a standard deviation of 1.41 (Table 2). The study will also be powered to estimate the mean age at Tanner stage progression with a 95% CI half-width ranging from 2.2 to 3.7 months, depending on sex and Tanner stage (Table 3), and estimate the IR of bone fractures, including multiple bone fractures per participant, with a total 95% CI width of 2.11 fractures per 100 person-years (Table 4).

Table 2. Estimated 95% CI half-widths for estimating mean change in height SDS

Region	N per cohort	Reference values	CI half-width
EUR only	100	Mean=0, SD=1.41	0.276
NA only	250		0.175
EUR + NA pooled	350		0.148

Table 3. Estimated 95% CI half-widths (months) for estimating age at Tanner stage progression

Region	N per cohort	N per sex, per cohort*	Reference SD range	Range of CI half-width (months), depending on Tanner stage	
				Females	Males
EUR only	100	50	Females[1]: 1.06-1.74 Males[2]: 1.02-1.10	3.6 - 5.9	3.5 - 3.8
NA only	250	125		2.3 - 3.7	2.2 - 2.3
EUR + NA pooled	350	175		1.9 - 3.1	1.8 - 2.0

* Assuming equal enrolment between females and males
1 Marshall, 1969; 2 Marshall, 1970

Table 4. Estimated 95% CIs for estimating bone fracture IR

Region	N per cohort	Reference value	95% CI[1]	CI total width
EUR only	100	3.0/100 person-years	(1.63, 5.07)	3.44
NA only	250		(2.08, 4.19)	2.11
EUR + NA pooled	350		(2.21, 3.98)	1.77

1 Ulm, 1990

For the exploratory comparative analyses, to evaluate physical growth and development, the difference between the two exposure cohorts in mean change in height SDS is proposed. A sample size of 250 participants enroled in each exposure cohort in NA will give the study the ability to detect a minimum difference of 0.4 between the two cohorts in the mean change in height SDS from baseline to the end of follow-up with 80% power and a 2-sided significance level of 0.05, using an assumed standard deviation of 1.41 (Table 5).

Table 5. Minimum detectable difference for mean change in height SDS

Region	N per cohort	Reference values	Detectable different (SDS)	Conversion (cm)	
				Females	Males
EUR only	100	Mean=0, SD=1.41	0.6	3.61	4.14
NA only	250		0.4	2.41	2.76
EUR + NA pooled	350		0.3	1.81	2.07

To compare the incidence of bone fractures, assuming an average of 4.5 years of follow-up, 250 NA participants enroled in each exposure cohort will give the study the ability to detect a rate ratio of 1.85 (Table 6).

Table 6. Detectable rate ratio for bone fracture incidence

Region	N per cohort	Reference value	Detectable rate ratio
EUR only	100	3.0/100 person years	2.51
NA only	250		1.85
EUR + NA pooled	350		1.69

Participant enrolment will be continuously monitored. If it appears the sample accrual will not meet the set targets, expanding to other sites/regions will be explored, as necessary.

9.6. Data Management

The study will be conducted using data collected in the CorEvitas International Adolescent AD Registry. Data are collected through detailed questionnaires completed at routine clinical care visits and source documents are collected and submitted by participating health care providers.

The clinical database is designed and maintained according to CorEvitas' standard data management procedures. Data extraction and data transfer protocols used to prepare the clinical data sets for analytical use are executed by CorEvitas according to standard, validated procedures at an established frequency.

For this study, statistical analyses conducted by CorEvitas will be performed using R Statistical Software (R Core Team 2023) or STATA (StataCorp, LP, College Station, TX), using the latest version(s) available at the time of analyses. All analyses will be carried out under the direction of the Vice President of Biostatistics for CorEvitas.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

The population of participants in this study will be characterised with respect to demographics, clinical and disease characteristics, and treatment history using descriptive statistics by exposure cohort as defined in Section 9.3.1. All pre-defined adverse events/reactions collected in the registry (Appendix Table A) will be tabulated as counts and rates for each exposure cohort in the interim safety analysis and in the final study report. Follow-up time per exposure episode and baseline participant characteristics, including the key variables listed in Section 9.3.3, will be presented by exposure cohort. Continuous variables will be summarised using descriptive statistics including mean, median, standard deviation, interquartile range (IQR), minimum, and maximum. Categorical variables will be summarised using frequency and percent. Standardised differences will be used to compare baseline characteristics between cohorts. An absolute standardised value greater than 0.1 would indicate a notable difference between participants who receive abrocitinib versus those in the comparator cohort (Austin, 2009).

The primary and exploratory analyses described below will be performed separately by region, among participants who reside in NA and among participants who reside in EUR. The exploratory analysis will be conducted separately by region if sample size allows.

9.7.1. Primary Analyses

For the primary analyses, descriptive statistics for each outcome of interest will be computed separately by exposure cohort.

For physical growth and development metrics, mean and SD will be presented for continuous measures related to height, weight, and BMI, including change from baseline to end of follow-up in height SDS, weight SDS, and BMI SDS. The baseline distribution of height percentiles will be presented, and the proportion of participants whose height percentile decreases by 10% or more will be reported. In addition to descriptive statistics, figures will be created to depict participant's growth trajectories over time.

Sexual maturation outcomes will be described by Tanner Staging and aPHV. Due to expected data availability and completeness, participants' self-assessed Tanner staging will be used for all analyses. Within each cohort, Tanner staging will be presented using counts and percentages overall, and by sex and age. Mean and SD will be used to report the age at Tanner stage progression for each stage. The proportion of participants who experience delayed puberty using Tanner stages (as defined in Section 9.3.2.2.1) will be also presented. Among participants where aPHV can be determined (as defined in Section 9.3.2.2.2), the median and IQR will be reported.

Where available, results from the clinical assessment of Tanner staging will be used to validate the reliability of participants' self-assessments. Among visits where both participant- and provider-assessed Tanner staging is available, concordance will be calculated as the percentage of visits where the participant and provider report the same Tanner stage. Interrater reliability will also be calculated using a weighted kappa, where kappa ≥0.6 represents adequate agreement (Fleiss et al., 2003).

The IR of bone fractures, overall and by fracture type, will be estimated within each exposure cohort. For the abrocitinib exposure cohort, IR will be stratified by abrocitinib dosage (100 mg and 200 mg QD). Abrocitinib exposures will be categorized into dose level categories of 100 mg or 200 mg QD, taking into consideration the starting dose and the

duration of treatment with 100 mg or 200 mg QD. Details of the dose level categorization used in the main analysis of the IR of bone fracture, including consideration for dose switching during the exposure period, will be pre-specified in the SAP. Both event-level and participant-level IRs will be presented. The event-level IR is defined as the total number of events (including first and any subsequent bone fractures per participant) per 100 person-years of total follow-up. The participant-level IR is calculated using follow-up time to first bone fracture event and is defined as the number of participants with at least one bone fracture per 100 person-years. Each IR will be reported with an associated 95% CI, calculated using the exact Poisson method. Any relevant exclusions from incidence estimations due to prior medical history, if necessary, will be described in detail in the SAP. Given events prior to registry enrolment will not have been captured among prevalent users, a sensitivity analysis will restrict to incident users (Section 9.7.3.6).

In addition to exposure cohort, the outcomes of interest may be presented by other demographic attributes (eg, age group, sex) or clinical characteristics (eg, comorbid conditions, prior systemic medications for AD), where appropriate, depending on the availability of relevant data and sample size. More details will be provided in the SAP.

The primary analyses are descriptive with no a priori hypotheses.

9.7.2. Exploratory Analyses

Physical growth and development outcomes, sexual maturation, and the incidence of bone fractures will be compared across exposure cohorts as exploratory analyses, if sample size allows. This study will use observational data, thus inherent baseline differences may exist between the exposure cohorts. To adjust for these differences and preserve sample size, inverse probability of treatment weighting (IPTW) will be used. IPTW methods will help mitigate channeling bias by balancing potential confounders between the abrocitinib and comparator cohorts. More details, including specific variables, risk factors, and key covariates, determined a priori, that will be used to balance disease severity and other relevant participant characteristics between exposure cohorts, will be provided in the SAP. After applying IPTW, conventional linear regression models will be fit for continuous outcomes, including mean change in height SDS, mean change in weight SDS, aPHV, and age at Tanner stage progression (eg, for age at progression to stage 2, the milestone for determining delayed puberty). To compare bone fractures, generalized linear regression models will be used. A robust sandwich variance estimator will be used in all models and point estimates; rate ratios will be calculated, along with 95% CIs, to describe the relationship between each outcome in the abrocitinib cohort relative to the comparator cohort. Any covariate that does not balance (absolute value of the standardised difference >0.1) across the exposure cohorts after applying IPTW will be included as a covariate in the regression models. Details regarding sufficient sample sizes required to perform the comparative analyses will be provided in the SAP.

9.7.3. Sensitivity Analyses

9.7.3.1. Pooled North American and European Sensitivity Analyses

As sensitivity analyses, the primary and exploratory analyses are proposed to be performed on a pooled sample of NA- and EUR-residing participants to increase sample size and statistical power. The pooled exploratory analysis will be conducted if sample size allows. However, prior to performing such analyses, the feasibility of pooling will be investigated using a 2-step process.

First, whether there is a complete or quasi-complete covariate separation by region will be assessed. This check will determine whether there are inherent differences in risk profiles (observed covariates) by region that would make pooling the NA- and EUR-residing populations inappropriate (ie, very little to no overlap observed in the risk-profiles of participants by region). To assess for complete or quasi-complete separation, a logistic regression model to predict region (NA vs. EUR) will be fit. Any variable not in balance, determined via standardised differences, in the comparison between the NA- and EUR-residing populations will be included as a covariate. Results from this model will indicate whether any of the covariates, or a combination of covariates, are perfectly predictive of a participant's geographical location (meaning, one of the predictor variables, or a combination thereof, perfectly separates the regional cohorts completely or nearly completely). A separation of covariates by region will not be a totally limiting factor in conducting a pooled analysis, but it will inform which covariates may be influential in any differential effects by region in the outcomes of interest. This will be relevant for the second pooling feasibility step, assessing the heterogeneity of treatment effects (HTE) across regions. HTE is the non-random variability in the direction and magnitude of a covariate's effect on an outcome by some subgroup. This check will determine if there are systematic differences in the outcomes by region and by drug exposure (ie, whether the effect of treatment varies across participant populations). To test for HTE, the statistical interaction between drug treatment and region will be evaluated using conventional regression approaches. Specifically, for each outcome, a multivariable regression model will be fit to include all observable covariates at baseline (X), exposure cohort indicator (abrocitinib vs. comparator; X1), region indicator (NA vs. EUR; X2), and the interaction between cohort and region (X1X2). That is:

$$\hat{y} = b_0 + bX + b_1x_1 + b_2x_2 + b_3X_1X_2$$

If a complete separation of covariates by region is found in step 1, the working definition (eg, weight categorisation) of the given covariate for the HTE investigation (X) will be redefined to prevent region from being a linear combination of any subset of covariates. The statistical significance of b_3 will indicate whether there is a differential impact of treatment by region.

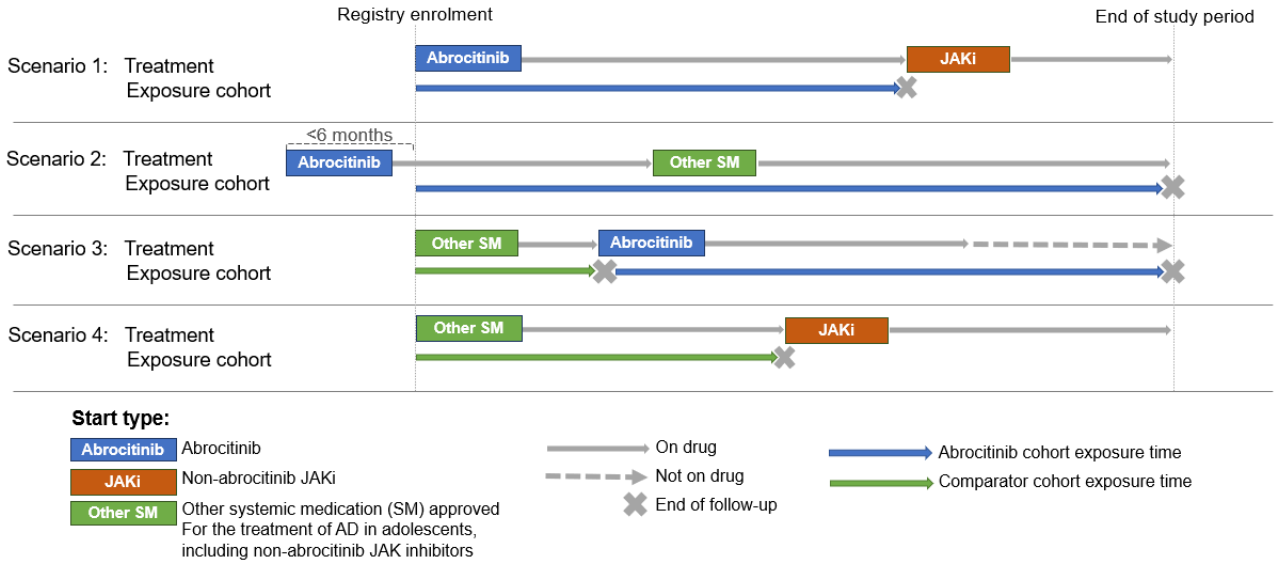
For outcomes where there is no observable HTE by region (ie, the interaction is not statistically significant), the analytic approaches described, including both descriptive and comparative analyses, will be performed as a sensitivity analysis using pooled exposure cohorts (NA + EUR).

9.7.3.2. Hierarchical Exposure Cohort Classification Excluding Other JAK Inhibitors Sensitivity Analyses

To allow for isolation of the impact of abrocitinib vs. detection of potential pharmacological class effects, should any exist, the primary and exploratory analyses using the hierarchical exposure classification definition will be repeated among NA-residing participants excluding non-abrocitinib JAK inhibitor use (if the sample size for the exploratory analysis allows). Under this definition, non-abrocitinib JAK inhibitors are not considered qualifying initiations for the comparator cohort and any participant with non-abrocitinib JAK inhibitor use within the 6 months prior to or at the time of registry enrolment will be excluded from analyses. Exposure episodes will be defined as they are in the main analysis, but follow-up time will be censored upon the start of a non-abrocitinib JAK inhibitor by a participant in either exposure cohort (Figure 2). That is, exposure time for the abrocitinib cohort will start at the assigned index date and continue until initiation of a non-abrocitinib JAK inhibitor, the end of the

study, death, or exit from the registry. Exposure time in the comparator cohort will start at the assigned index date and continue until the initiation of abrocitinib, initiation of a non-abrocitinib JAK inhibitor, the end of the study, death, or exit from the registry.

Figure 2. Examples of hierarchical exposure cohort classification, excluding other JAK inhibitors



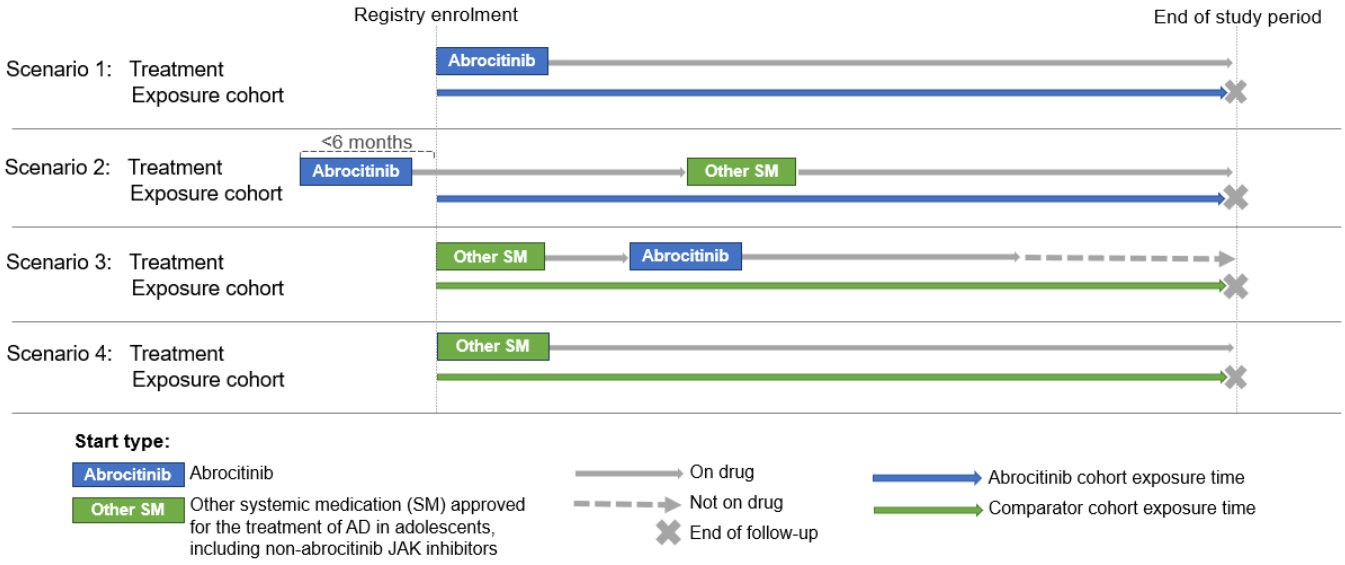
9.7.3.3. Intent to Treat Exposure Cohort Classification Sensitivity Analysis

Among the NA-residing participants only, primary and exploratory analyses will be repeated (if sample size allows, for the exploratory analysis) using an “intent-to-treat” (ITT) exposure definition as a sensitivity analysis given that outcomes include the evaluation of changes in measurements from baseline through the end of follow-up.

The exposure cohort for participants who are prescribed abrocitinib or another systemic medication for the treatment of moderate-to-severe AD in adolescents will be determined by the earliest qualifying treatment initiation. For participants who are prescribed a new treatment at the time of registry enrolment, the index date will be defined as the date of treatment initiation. For participants who initiate treatment within 6 months prior to registry enrolment, the index date will be defined as the registry enrolment date. If the first qualifying initiation is abrocitinib, participants will contribute to the abrocitinib cohort for analysis. If the first qualifying initiation is another advanced systemic medication prescribed for the treatment of moderate-to-severe AD in adolescents, including non-abrocitinib JAK inhibitors, participants will contribute to the comparator cohort.

Under the ITT definition, participants will only contribute to their original exposure cohort, regardless of treatment changes during follow-up (Figure 3). A participant can only have one exposure episode for the duration of their enrolment. Exposure time will start at the assigned index date and continue until the end of the study, death, or exit from the registry.

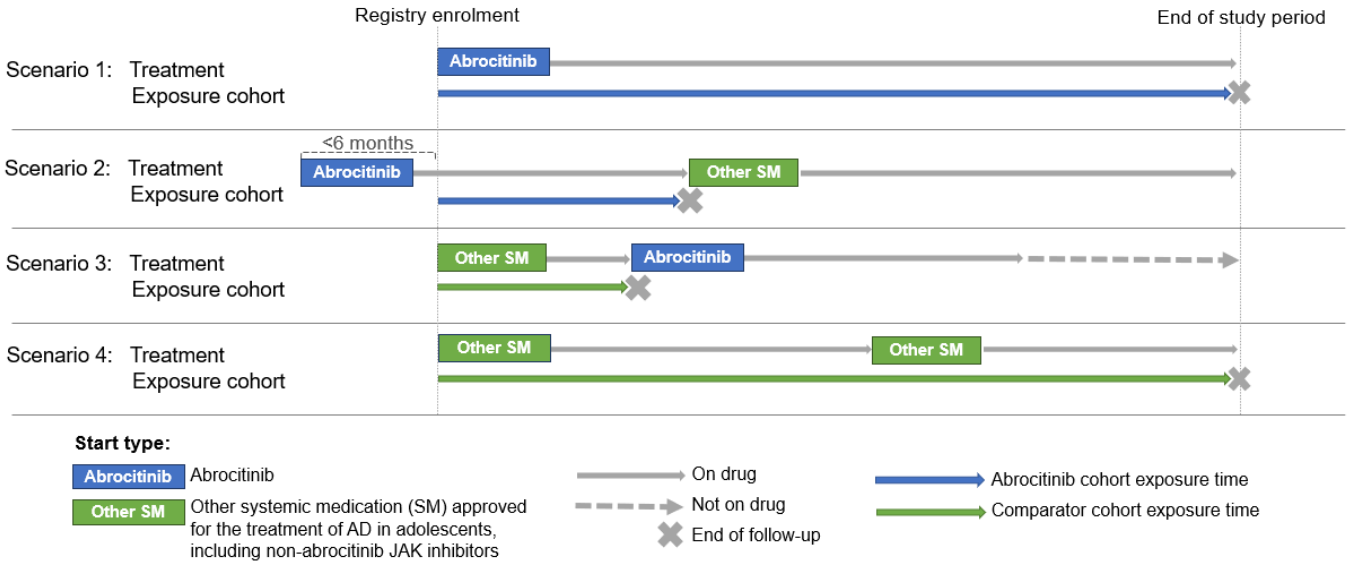
Figure 3. Examples of ITT exposure cohort classification



9.7.3.4. Per Protocol Exposure Cohort Classification Sensitivity Analysis

Since this is an observational study with treatment decisions made in real-world clinical practice, post-index treatment changes may be common, and these treatment changes may confound the association between index treatment and outcomes. Therefore, among the NA-residing participants only, primary and exploratory analyses will be repeated using a per protocol cohort classification as a sensitivity analysis for the primary hierarchical approach to define exposure time (if sample size allows, for the exploratory analysis). Under this classification, the first qualifying initiation will determine a participant's exposure cohort for analysis (as in the ITT approach), however follow-up time can be censored due to certain treatment changes during follow-up. For participants in the abrocitinib cohort, follow-up time will be censored if abrocitinib is discontinued or at the start of another systemic medication. For participants in the comparator cohort who initiate a non-abrocitinib advanced systemic medication, including other JAK inhibitors, follow-up time will be censored if they discontinue approved systemic treatments for AD or start abrocitinib. Employing this censoring restricts follow-up time to only include exposure to the original treatment plan used to determine a participant's exposure cohort for analysis (Figure 4).

Figure 4. Examples of per protocol exposure cohort classification



9.7.3.5. Propensity Score Matched Analysis

The exploratory analyses will be repeated (if sample size allows) using PS-matching methods as a sensitivity analysis to IPTW. While the sample size of a PS-matched analysis can be lower than that using IPTW, possible truncation of extreme weights using IPTW can increase residual bias, so this sensitivity analysis will provide the opportunity to evaluate the robustness of the findings from the IPTW analyses. More details on matching algorithms and calipers will be provided in the SAP.

9.7.3.6. Restriction to Incident Users

The main analyses include incident and prevalent users (Section 9.3.1.1). If sample size permits, all analyses will be repeated as a sensitivity restricting to incident users only to minimize any time-related biases introduced by the inclusion of prevalent users. For example, depletion of susceptibles may occur for acute-onset safety outcomes.

9.8. Quality Control

This study will use data collected by the CorEvitas International Adolescent AD Registry.

Data storage, management, and analyses will be conducted according to the Registry's standard procedures. Registry sites are trained on the International Adolescent AD Registry protocol prior to site initiation, including required clinical assessments, medication exposure details, and safety reporting requirements. TAE reporting guidelines are made available for site reference and include case definitions for outcomes of interest in the registry population and supporting documentation requirements by event type. Sites are also trained on registry data collection, including questionnaire completion and data entry requirements. The electronic data capture system utilizes automated edit or logic checks to facilitate completeness and data accuracy. Automatic system queries and automatic feedback or help instructions are programmed to reinforce data collection requirements.

Sites that contribute to the CorEvitas International Adolescent AD Registry are subject to periodic, risk-based onsite and remote monitoring visits by CorEvitas monitors to ensure that the CorEvitas International Adolescent AD Registry protocol, data collection requirements, and applicable research regulations are being followed. In accordance with the CorEvitas Registry Monitoring Plan, the monitors may review source documents (ie, original medical records) to confirm that the data recorded on questionnaires and case report forms (CRFs)/data collection tools (DCTs) are accurate (except for pre-identified source data directly recorded on the questionnaires or CRF/DCT). The CorEvitas Registry Investigator and institution allow CorEvitas monitors and appropriate regulatory authorities to have direct access to source data to perform this verification. These personnel, bound by patient privacy laws, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

The CorEvitas Registry site may also be subject to review by the IRB, and/or to quality assurance audits performed by CorEvitas, or companies working with or on behalf of CorEvitas, and/or to inspection by appropriate regulatory authorities.

9.9. Limitations of the Research Methods

This study has several limitations. One of the limitations is that this study is a real-world observational study and hence random allocation of participants to the abrocitinib or comparator cohort cannot be performed. Thus, the potential for confounding by indication cannot be avoided.

The inclusion of non-abrocitinib JAK inhibitors in the comparator cohort for the main analysis has the potential to limit the ability to detect a potential signal between the abrocitinib and comparator cohorts. The proposed hierarchical sensitivity analysis excluding non-abrocitinib JAK inhibitor use will help to mitigate this potential bias, should it exist.

Consistent with most observational studies, the possibility of channeling biases, misclassification of outcomes of interest, and generalisability are potential limitations when evaluating event rates (Lobo et al., 2006). As abrocitinib is a new systemic therapy for the treatment of moderate-to-severe AD, it is possible that participants treated with abrocitinib will represent those with refractory or more difficult to treat disease, longer disease duration, history of multiple failed AD therapies, and/or comorbidities that may increase the risk for outcomes of interest. Biases resulting from channeling may present as increased rates of adverse outcomes of interest in the early phases of the study. Comparison to contemporaneous internal comparators may illuminate such expected channeling. Adjustment for key indicators of disease severity, participant characteristics, and past therapies will be performed during analyses. Although most of the biases resulting from channeling may be accounted for using registry and study eligibility criteria aligned with diagnosis of moderate-to-severe AD and IPTW methods, some bias may still present as increased rates of adverse outcomes of interest in the study, particularly soon after a product's approval, as providers gain experience with the newly approved medication and may be more or less likely to prescribe for patients with certain characteristics (eg, disease severity, treatment history, certain types of comorbidities, or past medical history). CorEvitas requires the collection and submission of anonymised medical records to support confirmation of the classification details reported by the registry site, for serious adverse events and Registry protocol-defined safety events of interest, thus minimising potential for biases due to misclassification.

Similarly, several confounding factors may affect adolescents' growth, development, and maturation. The study will attempt to mitigate confounding by indication by employing IPTW methods, where appropriate, to account for measured confounders. However, some confounding factors may not be feasible to capture in this study such as environmental and nutritional factors, exercise, and sleep habits.

Since adolescents may enter exposure cohorts at different ages, their growth may vary. Further, assessments are only ascertained at approximate 6-month intervals, limiting the accuracy of observed timing of Tanner stage progression and aPHV. Regression and smoothing methods may be employed to interpolate such milestones. However, maximal outcomes, such as PHV, are limited to the participant's data collected in the registry and may only reflect a local, rather than the global, maximum of a participant's development, especially when follow-up time is short. Additionally, while aPHV can occur after 8 and 10 years of age for females and males, respectively, participants must already be 12-<16 years of age at enrolment, so early occurrence of aPHV may not be observed. However, historical height collection at enrolment is intended to diminish this limitation. Further, since it is not feasible to centrally acquire participants' height and weight at each visit, these measures are subject to random measurement error. To mitigate this limitation, instructions will be provided to all registry sites to standardise height and weight data collection methods as much as possible (eg, obtain a standing height with the participant barefoot).

This study includes analysis of the IR of bone fractures by abrocitinib dose level (200 mg and. 100 mg QD), as requested by CHMP and proposed in response to 1st CHMP Day 90 Other Concern 5 during the evaluation of the Type II Variation for adolescents (Procedure No. EMEA/H/C/005452/II/0010). A potential limitation to this analysis is that dose may change in some participants during the study period, since patients in real-world clinical practice may increase or decrease their abrocitinib dosage according to achievement of efficacy or individual tolerability. To analyze bone fracture IR by abrocitinib dose level, abrocitinib exposures who will be included in this analysis will be categorized into dose level categories of 100 mg or 200 mg QD, taking into consideration the starting dose and the duration of treatment with 100 mg or 200 mg QD. Details of the dose level categorization for the main analysis of bone fractures, including consideration for dose switching, will be pre-specified in the SAP. The SAP will be submitted to the EMA with the first progress report (scheduled for 30 April 2026).

Lastly, due to the sensitive nature of the Tanner assessment, some adolescents may be unwilling to provide responses, resulting in incomplete registry data. Further, pubertal progression will not be assessable for adolescents enroled after attaining full pubertal development (Tanner stage 5), thus hindering the study's power for this outcome. Also of note, the limitations related to accuracy of self-reported Tanner staging have been previously reported (Desmangles et al., 2006). Analyses, such as concordance and interrater reliability, are planned to assess self-reported Tanner staging in this study and should be considered when evaluating Tanner stage related outcomes.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

10.2. Patient Consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

This study will utilise pre-processed data being collected via the prospective CorEvitas International Adolescent AD Registry. The CorEvitas International AD Registry protocol is reviewed and approved by designated central and local IRBs, including IntegReview IRB, prior to initiation of research activities by registry sites. The CorEvitas International Adolescent AD Registry investigator sites that contribute to the registry are responsible for obtaining approval to participate in the registry study by the designated Central IRB, or through local or academic IRBs (where institutionally required).

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/ECs. All correspondence with the IRB/EC must be retained.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in the European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP, 2023), US Food and Drug Administration's (FDA) industry guidance, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (FDA, 2005), the International Society for Pharmacoepidemiology's (ISPE's) Guidelines for Good Pharmacoepidemiology Practices (ISPE Guidelines, 2016), STROBE guidelines (von Elm et al., 2008), and the principles of the Declaration of Helsinki (World Medical Association, 2013). Per Pfizer's subscription to the CorEvitas database, analyses may be conducted by authorised third parties and in accordance with CorEvitas' scientific review and publications policies.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study will involve data that exist as structured data by the time of study start. In these data sources, individual participant data will not be retrieved or validated by Pfizer, and it is not possible for Pfizer to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (ie, identifiable participant, identifiable reporter, a suspect product, and event) cannot be met.

Adverse events collected in the registry during the study period will be summarized in the interim and final reports as counts and rates in each study cohort, as described in Section 9.7.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This study will be registered in the HMA-EMA Catalogues of RWD studies. Two progress reports and three interim reports will be completed. Additionally, a final study report, reflecting cumulative data from the full study period, will be submitted to the EMA by Pfizer communicating the study results. Some or all data from this study may be developed into abstracts for presentation at scientific conferences, and/or developed into manuscripts for external publication purposes.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participants is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: A Prospective Active Surveillance Study to Monitor Growth, Development, and Maturation Among Adolescents with Atopic Dermatitis Exposed to Abrocitinib

EU PAS Register® number: To be registered before the start of data collection
Study reference number (if applicable): N/A

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7, 8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8.1, 8.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.7.1

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.1, 9.7.2
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.1, 9.7.2
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9.3.2, 9.4.2

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	6, 9.2
	4.2.2 Age and sex	☒	☐	☐	9.2, 9.5
	4.2.3 Country of origin	☒	☐	☐	9.2, 9.5
	4.2.4 Disease/indication	☒	☐	☐	9.2
	4.2.5 Duration of follow-up	☒	☐	☐	9.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1, 9.2.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.8
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.3.1.1
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.3.1.1

Comments:

IR analyses will be stratified by abrocitinib dose (as noted in the objectives and Section 9.7.1)

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.8
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.7.2, 9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
	9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4	Are stratified analyses included?	☒	☐	☐	9.7
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.2
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7	Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	9.7.3

Comments:

Methods for handling missing data will be discussion in the Statistical Analysis Plan.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.4
13.3 Have data protection requirements been described?	☒	☐	☐	9.8, 10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Heather Ward

Date: 06/Aug/2024

Signature:

ANNEX 3. ADDITIONAL INFORMATION

Appendix Table A. CorEvitas International Adolescent AD Registry AEs, TAEs*, and targeted events

Body system/Event type	Event/Condition
Anaphylaxis/hypersensitivity	Non-serious hypersensitivity reaction
	Severe hypersensitivity reaction or anaphylaxis*
Cardiovascular	Non-serious cardiac arrhythmia
	Non-serious congestive heart failure
	Serious congestive heart failure*
	Coronary angioplasty with or without cardiac stent*
	Coronary artery bypass graft*
	Non-serious coronary artery disease
	Myocardial infarction*
	Stable peripheral arterial disease
	Peripheral arterial thromboembolic event*
	Peripheral ischemia or gangrene (necrosis)*
	Stroke*
	Transient ischemic attack*
	Unstable angina*
	Urgent peripheral arterial revascularization*
	Other arterial thromboembolism event*
	Other non-serious cardiac condition
	Other serious cardiac condition*
	Other non-serious vascular condition
	Other serious vascular condition*

Body system/Event type	Event/Condition
Hepatic/Gastrointestinal	Crohn's disease
	Eosinophilic esophagitis
	Fatty liver disease/Nonalcoholic steatohepatitis
	Gastroesophageal reflux disease/acid reflux
	Hepatic event with liver function tests >3x upper limit of normal
	Hepatotoxicity: drug-induced liver injury*
	Hepatotoxicity: other hepatotoxicity*
	Ulcerative colitis
	Other non-serious gastrointestinal disorder
	Other non-serious hepatic event
	Other serious hepatic event or event requiring biopsy*
Malignancy	Breast cancer*
	Cervical cancer*
	Colon cancer*
	Leukemia*
	Lung cancer*
	Lymphoma*
	Melanoma skin cancer*
	Non-melanoma skin cancer basal cell*
	Non-melanoma skin cancer squamous cell*
	Pre-malignancy
	Prostate cancer*
	Uterine cancer*
	Other malignancy*
Musculoskeletal	Serious fracture*
	Non-serious fracture*
Ophthalmologic/Ocular	Blepharitis*
	Cataract
	Conjunctivitis[1]*
	Glaucoma
	Herpetic eye disease (H. simplex or H. zoster)*
	Keratitis*
	Keratoconus
	Ocular ulcer (e.g., corneal ulcer, ulcerative blepharitis, ulcerative conjunctivitis)*
	Retinal detachment*
	Other ocular event (new onset or worsening)*
Venous thromboembolism	Deep vein thrombosis*
	Pulmonary embolism*

Body system/Event type	Event/Condition
	Other venous thromboembolism*
Other event or condition	Anxiety
	Non-serious asthma
	Serious asthma*
	Attention-deficit/hyperactivity disorder
	Autism spectrum disorder
	Non-serious chronic obstructive pulmonary disease
	Serious chronic obstructive pulmonary disease exacerbation*
	Depression
	Diabetes mellitus (Type I or Type II)
	Eosinophilia
	Fibromyalgia
	Hyperlipidemia
	Hypertension
	Insomnia
	Interstitial lung disease/pulmonary fibrosis
	Surgery/medical procedure
	Other non-serious medical condition
	Other serious medical condition*
	Other non-serious metabolic condition
	Other musculoskeletal condition
	Other non-serious neurological disorder
	Other non-serious psychiatric disorder
	Other non-serious respiratory condition
	Death*
Infection	Progressive multifocal leukoencephalopathy*
	Active tuberculosis*
	Serious COVID-19 (confirmed or suspected)*
	Other infection (Any infection listed below that is deemed serious[2] is considered a TAE)
	Bronchitis
	Candidiasis (cutaneous, genital/vulvovaginal, oropharyngeal)
	Cellulitis or erysipelas
	Cold sores (herpes labialis)
	Diverticulitis
	Eczema herpeticum
	Furuncles (boils)
	Gastroenteritis

Body system/Event type	Event/Condition
	Herpes zoster (shingles, ear or eye involvement, or other)
	Human immunodeficiency virus/AIDS
	Meningitis/Encephalitis
	Molluscum contagiosum
	Osteomyelitis
	Otitis (ear infection)
	Pneumonia
	Sepsis
	Sinusitis
	Superficial skin infection (e.g., impetigo pustules)
	Upper respiratory infection
	Urinary tract infection
	Viral hepatitis
	Warts (cutaneous)
	Other infection
	Other skin infection
Pregnancy[3]	Pregnancy events occurring on or after registry enrollment
Death[4]	Unknown cause of death
	Accident resulting in death

Note: TAEs are denoted by an asterisk
* TAEs require the submission of appropriate medical records and completion of a TAEQ to support medical review and event confirmation.
1 Including allergic, drug-induced, infectious (bacterial, viral, or unknown pathogen), non-allergic non-infectious (e.g., atopic conjunctivitis), vernal, and conjunctivitis of unknown etiology.
2 A serious infection is one that requires IV antibiotics, requires or prolongs hospitalization, is life threatening, or causes death, disability, permanent damage, a congenital abnormality, or is otherwise serious in the opinion of the site investigator (i.e., may jeopardize the patient and require intervention to prevent one of the other serious outcomes).
3 Pregnancy is a targeted event but is not considered an AE.
4 Death terms captured via Exit form, in addition to all pre-specified adverse event terms available with ability to select outcome of death and/or assign as a primary cause of death via the Exit form.

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