NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	CIBINQO™ Pregnancy Registry: An Observational Study of the Safety of Abrocitinib Exposure in Pregnant Women and Their Offspring
Protocol number	B7451095
Protocol version identifier	1.0
Date	06 June 2022
EU Post Authorization Study (PAS) register number	To be registered before the start of data collection
Active substance	Abrocitinib (PF-04965842)
Medicinal product	CIBINQO™
Research question and objectives	The primary objective of the CIBINQO™ Pregnancy Registry is to estimate the crude proportion of maternal, fetal, and infant outcomes of women with moderate-to-severe atopic dermatitis (AD) who are exposed to abrocitinib (CIBINQO) during pregnancy and women with moderate-to-severe AD who are unexposed to CIBINQO during pregnancy. The secondary objective of this study is to compare the proportion of maternal, fetal, and infant outcomes between women with moderate-to-severe AD who are exposed to CIBINQO during pregnancy and women with moderate-to-severe AD who are unexposed to CIBINQO during pregnancy, if sample size permits.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACOG	American College of Obstetricians and Gynecologists
AD	Atopic dermatitis
AE	Adverse event
AEM	Adverse event monitoring
ART	Assisted reproductive technology
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
DOC	Date of conception
DSU	Drug Safety Unit
EDD	Estimated date of delivery
EDP	Exposure during pregnancy
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HCP	Healthcare provider
IEC	Independent ethics committee
IL	Interleukin
INTERGROWTH-21st	International Fetal and Newborn Growth Consortium for the 21st Century
IPTW	Inverse probability of treatment weights
IRB	Institutional review board
JAK	Janus kinase
LMP	Last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	Major congenital malformation
NIS	Non-interventional study
NVSS	National Vital Statistics System
PAS	Post-authorization study
PASS	Post-authorization safety study

Abbreviation	Definition
RR	Relative risk
SAB	Spontaneous abortion
SAC	Scientific advisory committee
SAP	Statistical analysis plan
SESI	Safety events of special interest
SGA	Small for gestational age
SOP	Standard operating procedure
US	United States
VRCC	Virtual research coordination center
WHO	World Health Organization

Note: Abbreviations used only in tables, figures, or an appendix are defined in the table or figure footnotes or the appendix.

3. RESPONSIBLE PARTIES

Principal Investigators of the Protocol

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4. ABSTRACT

Title: CIBINQO™ Pregnancy Registry: An Observational Study of the Safety of Abrocitinib Exposure in Pregnant Women and Their Offspring

Protocol version: 1.0

Authors: Kristin Veley, PPD, part of Thermo Fisher Scientific, Morrisville, NC; Jenny Sun, Pfizer, Inc., New York, NY

Rationale and background:

On 14 January 2022, the United States (US) Food and Drug Administration (FDA) approved abrocitinib (CIBINQO™)—oral, film-coated, 100 or 200 mg tablets—for adults with refractory, moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable (CIBINQO Prescribing Information, 2022). CIBINQO, an orally bioavailable small molecule, is a selective Janus Kinase (JAK) 1 inhibitor.

The available safety data regarding CIBINQO use during pregnancy are limited. Pregnant, breastfeeding women, and women planning to become pregnant or breastfeed, were excluded from clinical trials in the development program of this medicinal product. According to the US drug label, available data from pregnancies reported in clinical trials with CIBINQO are not sufficient to establish a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes (CIBINQO Prescribing Information, 2022). However, CIBINQO exposure during pregnancy may occur, and the available data are insufficient for characterizing risks in pregnant women; therefore, additional data are needed.

The CIBINQO™ Pregnancy Registry will add to the current body of knowledge regarding the safety of CIBINQO exposure during pregnancy. This prospective, registry-based, observational cohort study will be conducted to provide information on maternal, fetal, and infant outcomes following exposure to CIBINQO during pregnancy in the post-approval setting in accordance with the FDA 2019 Guidance for Industry: Postapproval Pregnancy Safety Studies (FDA, 2019).

This non-interventional study is designated as a post-authorization safety study (PASS) and is a postmarketing requirement to the US FDA.

Research question and objectives:

Primary objective:

- To estimate the crude proportion of maternal, fetal, and infant outcomes of women with moderate-to-severe AD who are exposed to CIBINQO during pregnancy and women with moderate-to-severe AD who are unexposed to CIBINQO during pregnancy.

Secondary objective:

- To compare the proportion of maternal, fetal, and infant outcomes between women with moderate-to-severe AD who are exposed to CIBINQO during pregnancy and women with moderate-to-severe AD who are unexposed to CIBINQO during pregnancy, if sample size permits.

The following outcomes will be assessed:

- Major congenital malformations (MCM)
- Minor congenital malformations
- Spontaneous abortions (SAB)
- Stillbirth
- Elective termination
- Preterm birth
- Small for gestational age (SGA)
- Postnatal growth deficiency
- Infant developmental delay

Study design:

The CIBINQO™ Pregnancy Registry Study is a US-based, prospective, observational cohort study designed to evaluate the association between CIBINQO exposure during pregnancy and subsequent maternal, fetal, and infant outcomes. Data will be collected from enrolled pregnant women and the healthcare providers (HCPs) involved in their care or the care of their infants, if applicable. The registry is observational in design; the schedule of office visits and all treatment regimens will be determined by HCPs. Only pertinent data that are documented in participants' medical records during the course of medical care will be collected for the study.

Participants will be followed for 12 months after delivery for live births or until the onset of an adverse pregnancy outcome for fetal losses (SAB, stillbirth, or elective termination). Pregnancy outcomes and exposure information will be assessed throughout pregnancy, with data collection occurring at enrollment, the end of the second trimester, and pregnancy outcome. Infant outcomes will be assessed throughout the infant's first year of life, with active data collection by the registry occurring at 4 and 12 months after delivery. Baseline characteristics will be assessed at enrollment.

Population:

The study population will include pregnant women of any age who meet the following eligibility criteria for inclusion:

- Women of any age who are currently or recently pregnant (recently pregnant defined as enrollment within 1 year of pregnancy outcome)
    - Only prospectively enrolled patients (i.e., women who are currently pregnant at enrollment) will be included in the main analysis population
- Consent to participate in this study and evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study
- Authorization for her HCP(s) to provide data to the registry
- Exposed cohort only: Must receive at least one dose of CIBINQO at any time during pregnancy (from the date of conception [DOC] to pregnancy outcome) or prior to pregnancy (within 1 day prior to the DOC).
- Comparator cohort only: Must have a diagnosis of moderate-to-severe AD at any time prior to pregnancy outcome.

Variables:

The exposed group will include women with moderate-to-severe AD who are exposed to CIBINQO during pregnancy. The primary comparator group will include women with moderate-to-severe AD who are unexposed to CIBINQO during pregnancy. If sample size permits, a secondary comparator group will include the subset of women with moderate-to-severe AD who are exposed to other chronic systemic treatments that are not JAK inhibitors (e.g., dupilumab) during pregnancy.

The outcomes of interest are MCM, minor congenital malformations, SAB, stillbirth, elective termination, SGA, preterm birth, postnatal growth deficiency, and infant developmental delay. Endpoint adjudication will be conducted for occurrences of MCM and minor congenital malformations.

Baseline characteristics collected at enrollment include maternal demographics, maternal pre-pregnancy anthropometrics, maternal obstetrical history, family history of congenital malformations, AD disease information, and baseline pregnancy information.

Data sources:

Data will be collected from enrolled pregnant women and HCPs. A virtual research coordination center (VRCC) will be used for data collection. Therefore, this study does not

involve site investigators (i.e., HCPs are not accountable for consenting and enrolling participants). Participants will be recruited from the US.

Study size:

The registry aims to enroll a minimum of 400 pregnant women (200 abrocitinib-exposed participants, 200 comparator participants) to estimate the proportion of the primary outcome, MCM, with meaningful confidence and precision.

Data analysis:

The analysis population may differ from the population of women enrolled in the registry. The subset of registry participants in the analysis will include women who:

- Have the minimum data required for determining inclusion/exclusion into one of the study cohorts
- Have sufficient data submitted or confirmed by an HCP
- Have a diagnosis of moderate-to-severe AD
- Are prospectively enrolled (i.e., currently pregnant at enrollment)
- Are not exposed to teratogens or investigational medications during pregnancy
- Are not multiple gestation pregnancies for the analyses of preterm birth, SGA, and postnatal growth deficiency

Demographic and baseline characteristics will be summarized with descriptive statistics for each cohort, and balance between cohorts will be assessed using standardized differences. For each continuous variable, the number of observations, median, mean, standard deviation, minimum, and maximum will be reported. For each categorical variable, the frequency and percentage in each category will be reported. Baseline data will be presented before and after applying inverse probability of treatment weights (IPTW) to assess the balance across treatment groups.

The proportion of the outcomes of interest will be calculated and, if sample size permits, compared between the exposed and unexposed cohorts. For each outcome, if the number of events permits, crude and adjusted results will be presented. Relative risks (RR) will be reported along with their 95% confidence intervals. Exact methods will be used to calculate crude (unadjusted) RRs for all outcomes. Adjusted methods will incorporate weights estimated using stabilized IPTW to balance the cohorts with regard to the measured covariates. For each outcome, a weighted generalized linear model using a binomial family and a log (RR) link will be employed to estimate an adjusted RR.

If sample size permits, subgroup analyses will be conducted that consider the timing and extent of exposure, number of systemic therapy exposures during pregnancy, and maternal

age group at conception. Supplementary analyses will be conducted that include participants who were excluded from the analysis population. Sensitivity analyses will also be conducted to examine the extent to which changes in certain methods or assumptions affect the results.

Milestones:

Enrollment of women in the registry is expected to begin in January 2023 and end in March 2026. Data collection will be conducted through December 2027, with the final study report planned for December 2028.

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned date
Final study protocol	31 December 2022
Registration in the EU PAS register	Prior to the start of data collection
Study launch / start of data collection	31 January 2023[1]
End of enrollment	01 March 2026
End of data collection	31 December 2027
Final study report	31 December 2028

1 The registry will launch after FDA and institutional review board approval of the protocol. The actual date may differ.
EU = European Union; PAS = post-authorization study

7. RATIONALE AND BACKGROUND

Abrocitinib (CIBINQO™), an orally bioavailable small molecule, is a selective Janus Kinase (JAK) 1 inhibitor. The inhibition of JAK1 is thought to modulate multiple cytokines involved in the pathophysiology of atopic dermatitis (AD), including interleukin (IL)-4, IL-13, IL-31, IL-22, and interferon gamma. CIBINQO, oral film-coated tablets containing either 100 or 200 mg, was approved in the US on 14 January 2022 and is indicated in the US for the treatment of adults with refractory, moderate-to-severe AD in patients whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable.

AD is a common, chronic skin condition characterized by inflammation of the skin and skin barrier defects. AD lesions are characterized by erythema, itching, induration/papulation, and oozing/crusting (Hanifin & Reed, 2007; Bieber, 2012). AD manifestations typically appear early in life and often precede other allergic diseases, such as asthma or allergic rhinitis. The prevalence of AD is estimated to be 15% to 30% in children, and 2% to 10% in adults (Oszukowska et al, 2015)—presenting a significant burden on healthcare resources and patients' quality of life.

AD is the most frequent general skin disease that occurs during pregnancy, as it can be triggered, reactivated, and/or exacerbated by pregnancy (Vestergaard et al, 2019). New onset AD during pregnancy is estimated to be responsible for 60% to 80% of cases among women (Nasca et al, 2020). It is also estimated that 18% to 52% of women with AD will experience worsening of their symptoms during pregnancy (Kemmett & Tidman, 1991; Rakita et al, 2022). Although rare, AD is directly associated with an increased risk of certain complications during pregnancy, including eczema herpeticum, staphylococcus aureus infections, premature rupture of membranes, and staphylococcal neonatal septicemia (Gurvits & Nord, 2011; Hamann et al, 2019). AD is also associated with increased maternal stress and sleep deprivation, which may also indirectly increase the risk for pregnancy complications (Vestergaard et al, 2019).

During pregnancy, topical treatments (including corticosteroids, calcineurin inhibitors, crisaborole, and ultraviolet therapy) tend to be the preferred therapies to treat AD, and are considered to be safe for the fetus (Vestergaard et al, 2019; Heilskov et al, 2020). However, only topical corticosteroids have strong evidence for safety. Systemic therapies (such as corticosteroids, cyclosporin A, and azathioprine) are only recommended with specialist oversight in the event that symptoms do not respond to first-line therapy. However, the evidence for the safety of systemic therapies is considered weak (Vestergaard et al, 2019; Heilskov et al, 2020). Two other systemic therapies (methotrexate and mycophenolate mofetil) are contraindicated during pregnancy, due to strong documented associations with fetal malformations (Heilskov et al, 2020). One of the newest therapies (dupilumab) is not currently recommended during pregnancy, due to an unknown safety profile. However, several recent case studies have reported no adverse pregnancy outcomes associated with dupilumab use (Bosma et al, 2021; Lobo et al, 2021; Akhtar et al, 2022).

The available safety data regarding CIBINQO use during pregnancy are limited. Pregnant and breastfeeding women, and women planning to become pregnant or to breastfeed, were

excluded from clinical trials. According to the US drug label, available data from pregnancies reported in clinical trials with CIBINQO are not sufficient to establish a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Additionally, there are no data on the presence of CIBINQO in human milk, the effects on the breastfed infant, or the effects on milk production, but CIBINQO was secreted in milk of lactating rats. Because of the safety risks in adults, including serious infections, malignancy, and thrombosis, the US drug label advises women not to breastfeed during treatment with CIBINQO and for one day after the last dose (CIBINQO Prescribing Information, 2022). However, CIBINQO exposure during pregnancy is likely to occur, and the available data are insufficient for characterizing the associated risk in pregnant women, and therefore additional data are needed.

The CIBINQO™ Pregnancy Registry will add to the current body of knowledge regarding the safety of CIBINQO exposure during pregnancy. As part of the CIBINQO pharmacovigilance plan, a prospective, registry-based, observational cohort study will be conducted to actively monitor the safety of abrocitinib exposure during pregnancy in the post-approval setting in accordance with the FDA 2019 Guidance for Industry: Postapproval Pregnancy Safety Studies (FDA, 2019). The goal of the registry is to provide information on maternal, fetal, and infant outcomes following exposure to CIBINQO during pregnancy. This registry will be designed to detect and record major and minor congenital malformations, SAB, stillbirths, elective terminations, SGA, preterm birth, postnatal growth deficiency, and infant developmental delay.

This non-interventional study is designated as a PASS and is a commitment (postmarketing requirement) to the US FDA.

8. RESEARCH QUESTION AND OBJECTIVES

The purpose of the CIBINQO™ Pregnancy Registry is to describe and compare the proportion of adverse maternal, fetal, and infant outcomes among women with moderate-to-severe AD who are exposed to CIBINQO during pregnancy and women with moderate-to-severe AD who are unexposed to CIBINQO during pregnancy.

Primary objective:

- To estimate the crude proportion of maternal, fetal, and infant outcomes of women with moderate-to-severe AD who are exposed to CIBINQO during pregnancy and women with moderate-to-severe AD who are unexposed to CIBINQO during pregnancy.

Secondary objective:

- To compare the proportion of maternal, fetal, and infant outcomes between women with moderate-to-severe AD who are exposed to CIBINQO during pregnancy and women with moderate-to-severe AD who are unexposed to CIBINQO during pregnancy, if sample size permits.

The following outcomes will be assessed:

- MCM
- Minor congenital malformations
- SAB
- Stillbirth
- Elective termination
- Preterm birth
- SGA
- Postnatal growth deficiency
- Infant developmental delay

Refer to Section 9.3.2 for the definitions of these outcomes.

9. RESEARCH METHODS

9.1. Study design

The CIBINQO™ Pregnancy Registry is a US-based, prospective, observational cohort study designed to evaluate the association between CIBINQO exposure during pregnancy and subsequent maternal, fetal, and infant outcomes. Participation in the registry is voluntary and participants can withdraw their consent to participate at any time. Data will be collected from enrolled pregnant women and the healthcare providers (HCPs) involved in their care or the care of their infants, if applicable. The registry is observational in design; the schedule of office visits and all treatment regimens will be determined by HCPs. Only data that are typically documented in participants' medical records during the course of medical care will be collected. No additional laboratory tests or HCP assessments will be required as part of this registry. A VRCC will be used for data collection.

All assessments described in this protocol are performed as part of routine clinical practice or standard practice guidelines for the patient population and HCP specialty in the US.

The CIBINQO™ Pregnancy Registry will be launched following protocol endorsement from the FDA and institutional review board (IRB) approval of the protocol. Enrollment of women in the registry is expected to begin in 2023 and end in March 2026. Data collection will be conducted through December 2027. Participants will be followed for 12 months after delivery for live births or until the onset of an adverse pregnancy outcome (SAB, still birth, or elective termination) for non-live births.

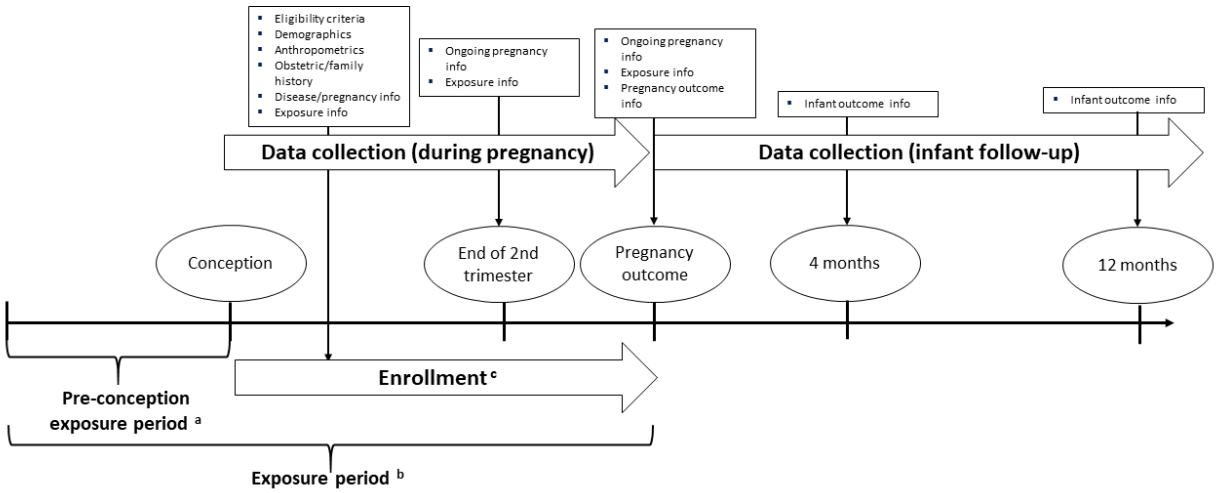
9.2. Setting

The study population will include pregnant women of any age who meet the eligibility criteria for inclusion. The exposed cohort will include women who are exposed to CIBINQO at any time during pregnancy. All pregnant women exposed to CIBINQO will be eligible to participate in the registry, but the analysis population will be limited to women with moderate-to-severe AD. The primary comparator group will include women with moderate-to-severe AD who are unexposed to CIBINQO during pregnancy. If sample size permits, a secondary comparator group will include the subset of women with moderate-to-severe AD who are exposed to other chronic systemic treatments that are not JAK inhibitors (e.g., dupilumab) during pregnancy.

Pregnant women who are interested in participating will self-enroll in the registry through the web-based/mobile application or by calling the VRCC. To enroll, each woman will answer a series of screening questions to assess her eligibility. If eligible, she will be asked to provide informed consent, her primary contact information, alternate contact information for a family member or friend, contact information for HCPs who are/will be involved in her care or the care of her infant, and medical releases to allow these HCPs to provide data to the registry.

Enrolled pregnant women and the HCPs involved in their care or the care of their infants, if applicable, will serve as data reporters to the registry. It is anticipated that the majority of obstetric data will be collected from the pregnant woman's obstetric HCP (e.g., obstetrician, family practitioner, general practitioner who provides care during pregnancy), and that the majority of pediatric data will be collected from the infant's pediatric HCP (e.g., pediatrician, family practitioner, general practitioner who provides pediatric care). After enrollment, the registry may also request data from other HCPs involved in the woman's or infant's care (e.g., prescriber, specialist) or from additional HCPs who were not identified at enrollment (e.g., if a woman does not know who her pediatric HCP will be at the time of enrollment) after appropriate medical release is obtained from the woman.

Figure 1. Study Flow Chart



[a] Time to product elimination (5 times terminal half-life); CIBINQO half-life = 5 hours; therefore, time to elimination = 1 day
[b] If a participant is exposed to the product during this time period, she will be considered exposed during pregnancy
[c] Participants may be retrospectively enrolled into the registry up to one year after pregnancy outcome but will not be included in primary analysis.

The data collection process for each participant following routine care will begin at enrollment, and data throughout the pregnancy will be collected at 3 time points: at enrollment, at the end of the second trimester (approximately 26 gestational weeks), and at pregnancy outcome (live birth or fetal loss). For women who enroll after the second trimester, data during pregnancy will be collected at enrollment and at pregnancy outcome. For live-born infants, data from pediatric visits at 4 and 12 months of age will be collected at 2 time points: 4 months and 12 months after delivery. A participant will be considered lost to follow-up if follow-up information is never obtained or is unavailable after the attempts outlined in Section 9.4.1. Pregnant women without pregnancy outcome information will be considered lost to follow-up, and live-born infants without any follow-up data after birth will be considered lost to follow-up.

Data collection efforts will be identical for all enrolled pregnant women regardless of their exposures and study cohort assignment. HCPs who serve as reporters to the registry will be instructed to transcribe data that are readily available in the participants' medical records into the data collection forms. Electronic and paper data collection forms will be used in this study. These data collection forms can be submitted on paper, via email/fax, or via phone.

At enrollment, once consent, registration information (including eligibility criteria), reporter contact information, and medical releases have been provided by the pregnant woman, maternal demographic characteristics and pre-pregnancy anthropometrics will be collected from the pregnant woman. These data will be collected on the ***Registration Form for Participants***. Registration information, including eligibility criteria, will be confirmed by HCP(s), as appropriate. The HCP(s) will additionally provide maternal obstetrical history, family history of congenital malformations, disease information, pregnancy information, and

maternal exposures during pregnancy. All of these data will be collected on the ***Registration Form for Healthcare Providers*** and ***Pregnancy Information Form***. At approximately the end of the second trimester, the HCP(s) will be asked to complete another ***Pregnancy Information Form***, which will collect any updates to pregnancy information and maternal exposures during pregnancy. Around or after the estimated date of delivery (EDD) or after a known pregnancy outcome, the HCP(s) will be asked to complete another ***Pregnancy Information Form*** as well as the ***Pregnancy Outcome Form***, which will collect pregnancy outcome information. For each live-born infant, the pediatric HCP will be asked to complete an ***Infant Outcomes Form***, which will collect infant information, including infant growth and development data, at 2 time points: at approximately 4 and 12 months after delivery. These visits are part of the American Academy of Pediatrics' recommended infant well-child visit schedule (American Academy of Pediatrics, 2021). If a congenital malformation (major or minor) or other event of interest is reported, additional information may be requested from the reporting HCP on the ***Targeted Follow-up Form*** to properly characterize the event. The date each data collection form is completed also will be collected. Additional details on the data collected are available in Section 9.4.

9.2.1. Inclusion criteria

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

- Women of any age who are currently or recently pregnant (recently pregnant defined as enrollment within 1 year of pregnancy outcome)
    - Only prospectively enrolled patients (i.e., women who are currently pregnant at enrollment) will be included in the main analysis population
- Consent to participate in this study and evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study
- Authorization for her HCP(s) to provide data to the registry
- Exposed cohort only: Must receive at least one dose of CIBINQO at any time during pregnancy (from the DOC to pregnancy outcome) or prior to pregnancy (within 1 day prior to the DOC).
- Comparator cohort only: Must have a diagnosis of moderate-to-severe AD at any time prior to pregnancy outcome.

9.2.2. Exclusion criteria

Participants will be excluded from the registry if they do not meet the inclusion criteria listed above.

Some participants included in the registry may be excluded from the statistical analysis (details in Section 9.7).

9.2.3. Participant recruitment and retention

9.2.3.1. Participant recruitment

An active, targeted, multi-pronged recruitment campaign will be employed to recruit participants for the registry. The campaign will focus on pregnant women, patients with moderate-to-severe AD, patients using CIBINQO or other products for the treatment of moderate-to-severe AD, obstetric HCPs, HCPs who are likely to treat patients with moderate-to-severe AD, and HCPs who are likely to prescribe CIBINQO. Obstetric HCPs and HCPs who are likely to treat patients with moderate-to-severe AD may be identified via HCP directories and/or professional associations. Pregnant women, patients with moderate-to-severe AD, and patients using CIBINQO may be identified through patient support groups and external data sources, such as pharmacy/medical claims or electronic medical records. The sponsor's existing infrastructure for distributing CIBINQO and supporting stakeholders (e.g., Pfizer Med Info and the patient assistance program) may be leveraged to identify HCPs who are known to prescribe CIBINQO or a comparator medication and pregnant women who are using CIBINQO or a comparator medication.

A multi-modal approach will be used to deliver registry education and recruitment materials to targeted HCPs and patients. This approach involves direct-to-HCP outreach as well as online and print advertising directed to both HCPs and patients. In addition, stakeholders may be identified and provided with information regarding the registry via telephone through the Medical Information Contact Center and the patient assistance program.

Direct-to-HCP outreach will be achieved by delivering recruitment materials to targeted HCPs via email, fax, and/or hardcopy mail. HCPs can use any approach to identify potentially eligible participants. In addition, the Sponsor's representatives may provide registry education and recruitment materials to HCPs in person. HCPs will be asked to identify potential registry participants and encourage their participation by informing them about the registry and providing them with the patient-directed registry recruitment materials. The VRCC will be available to answer questions from those who are potentially interested in participating in the registry.

Information regarding the registry and the registry recruitment materials will also be available online. A registry-specific website will be developed at http://cibinqopregnancyregistry.com/, where all recruitment materials will be available for download. This website will be accessible through the CIBINQO product website and discoverable in any internet browser by performing a search related to pregnancy and CIBINQO, abrocitinib, and/or moderate-to-severe AD. Information regarding the registry and/or a link to the registry website will be available on websites that aim to provide medical information to pregnant women, including but not limited to the following websites:

- FDA listing of pregnancy registries on www.fda.gov, www.clinicaltrials.gov
- Society for Maternal-Fetal Medicine listing of registries
- PPD website

A web-based interface compatible with both computers and mobile devices will also be developed to improve information accessibility and enable broader participation. The web-based interface will comply to the standards outlined by the Americans with Disabilities Act. As deemed necessary, online advertisements on social media sites or other relevant websites (e.g., professional association websites or websites commonly visited by pregnant women) or applications may be used to inform potential participants of the registry.

Various print materials will also be used to provide information related to the registry and to facilitate recruitment. The CIBINQO prescribing information provides registry information including contact information. Information related to the registry may also be directed to HCPs via announcements/publications in relevant professional journals/newsletters or presentations/exhibits at relevant professional meetings. As deemed necessary, print advertisements in newspapers or magazines with targeted patients among their readership may be used to direct potential participants to the registry, and recruitment materials may be distributed to locations commonly frequented by targeted patients (e.g., ultrasound clinics, gynecologic surgery centers).

In addition to the registry information in the product label, educational materials designed to elicit interest in registry participation will be developed. All messaging will be aligned with the product label. Materials may include:

- An information sheet and/or brochure that will briefly describe the registry purpose and procedures, including the incentives for participation
- Information on how to access the registry web-based/mobile application
- Registration form and sample participant consent form
- Prescribing information
- Participant consent-to-contact card (this card enables the VRCC to contact the potential participant and provide additional information about the registry)

Additional details on study recruitment, such as the specific virtual recruitment initiatives (i.e., Everyday Health), will be described in a separate Recruitment Plan.

9.2.3.2. Retention strategy

A retention strategy, facilitated by engaging both the participant and HCP, will seek to minimize the reporting burden on these groups to the extent possible.

The registry staff will serve as the first and single point of communication for both registry participants and HCPs. The specialized staff, many of whom are obstetric nurses, have experience collecting data for observational studies from both patients and research-naive HCPs. They are experts at developing a rapport with HCPs and participants to facilitate data collection and build one-on-one relationships that will promote retention and reduce overall loss to follow-up. To promote HCP engagement, status updates may be shared with HCPs through various means (i.e., email, newsletters, and the registry website). Materials provided

will emphasize the mission of the registry to promote participant engagement and point participants to the website.

The registry will use streamlined data collection processes and simple, concise data collection forms that focus on endpoints of interest to reduce the burden of reporting. The registry will provide multiple options for communication and data submission (e.g., phone, fax, mail, email [PPD encrypts all incoming and outgoing emails], website, web-based/mobile application) and a flexible follow-up schedule to enhance retention and maximize data reporting. At enrollment, the registry will also ask the participant to provide contact information of family members or friends in case the participant cannot be reached, which can further promote retention.

Finally, the registry will provide an honorarium to participants and their HCPs who serve as data reporters to the registry. Compensation will be sent to HCPs involved in pregnant women's care once pregnancy outcome data have been collected. Compensation will be sent to participants once pregnancy outcome data have been collected if fetal loss occurs or once 12-month infant outcome data have been collected if live birth occurs. Compensation will be sent to pediatric HCPs once 12-month infant outcome data have been collected.

9.2.3.3. Assessment of recruitment and retention

To maximize recruitment and retention, the registry's recruitment and retention strategies will be flexible and will be continuously assessed. The registry will assess recruitment and retention by collecting information from reporters (i.e., HCPs and participating women) on the sources from which they received information about the registry (recruitment) and the reasons for which they ceased participation or were lost to follow-up (retention). Based on these assessments, the registry's recruitment and retention strategies will be adjusted to maximize registry participation.

The scientific advisory committee (SAC) will also be consulted regarding recruitment and retention strategies. The SAC will be an independent group of recognized experts (not associated with the Sponsor) in the fields of teratology, epidemiology, maternal and fetal medicine, and therapeutic areas from academia and private practice. The SAC is responsible for overseeing the scientific affairs of the registry, including its ongoing monitoring. The responsibilities of the SAC will be described in a charter to which each SAC member will agree.

9.3. Variables

9.3.1. Exposure

Exposure to CIBINQO is a condition for inclusion into the exposed cohort. Exposure is defined as bodily uptake of any CIBINQO at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (within a specified time period based on the product's half-life). Due to the half-life of CIBINQO (5 hours), participants will be considered exposed during pregnancy if a dose is taken up to 5 half-lives (approximately 1 day) prior to the DOC.

Detailed information on dose, route, frequency, dates/duration of exposure, and indication/reason for use will be collected, and exposure will be further categorized by earliest trimester of exposure. Exposure information will be updated at each pregnancy follow-up, and changing exposures will be accounted for in the analysis.

9.3.2. Outcomes

Table 1 presents the definitions of the outcomes of interest. For outcomes not reported by the HCP, additional information on outcome ascertainment is provided. Safety events of special interest (SESI), such as major and minor congenital malformation events, will be adjudicated. Additional details on the adjudication process will be available in a separate Adjudication Charter.

Table 1. Outcome Definitions and Ascertainment

Outcome	Definition	Ascertainment
Major congenital malformation (MCM)	An abnormality of body structure or function that is present at birth, is of prenatal origin (i.e., birth defect), has significant medical, social, or cosmetic consequences for the affected individual, and typically requires medical intervention (CDC, 2020)	The registry defines and codes MCMs with criteria specified by the CDC MACDP (CDC, 2021). a) Exclusion criteria for analyses: To avoid misattribution of the malformation to the medication, MCMs not associated with medication exposure, such as chromosomal abnormalities, genetic syndromes, prematurity-related conditions in infants born at <36 gestational weeks (e.g., patent ductus arteriosus, patent foramen ovale, inguinal hernias, or undescended testes), and positional effects (e.g., hip dislocation due to breech position or abnormal skull shape due to crowding by multiple fetuses), will not be considered MCMs in the statistical analyses (Holmes & Westgate, 2011). b) Adjudication process: A panel of 2 independent experts in clinical genetics and neonatology, blinded to exposure, will review all MCMs reported to the registry and classify them using the CDC's MACDP system. Additionally, the birth defect evaluators will provide their opinions regarding the timing of the development of observed defects. If additional information is needed to aid in classification, the birth defect evaluators will request additional information using the targeted follow-up process outlined in Section 9.4.1. These assessments will be recorded in the database. If there is a discrepancy, a third expert will independently review and code the case serving as tie breaker. These reviews will occur soon after the MCM is reported. Additional reviews will occur if new information is received for the case, as well as the possible temporal association between exposure (to CIBINQO or comparator product) and the development of observed defects. Additionally, the SAC will review all MCM cases reported to the registry and reach consensus on the coding of each case. The Sponsor will not be involved in any activities related to case review or adjudication.
Minor congenital malformation	An anomaly or abnormality of body structure that is present at birth, is of prenatal origin (i.e., birth defect), poses no significant health problem in the neonatal period, and tends to have limited social or cosmetic consequences for the affected individual (CDC, 2020)	The registry defines and codes minor congenital malformations with criteria specified as defined by CDC (CDC, 2019). The same process for adjudicating MCMs will be used to adjudicate minor congenital malformations.
Spontaneous abortion (SAB)	An involuntary fetal loss or the expulsion of the products of conception occurring at <20 gestational weeks	Section 9.3.3 provides information on the methods used to calculate gestational age.

Table 1. Outcome Definitions and Ascertainment

Outcome	Definition	Ascertainment
Stillbirth	As defined by the ACOG, an involuntary fetal loss occurring at ≥20 gestational weeks or, if gestational age is unknown, a fetus weighing ≥350 g (ACOG, 2020)	Section 9.3.3 provides information on the methods used to calculate gestational age.
Elective termination	A voluntary fetal loss or interruption of pregnancy that occurs for any reason, including but not limited to for the preservation of maternal health or due to fetal abnormalities	-
Preterm birth	A live birth occurring at <37 gestational weeks	Section 9.3.3 provides information on the methods used to calculate gestational age.
Small for gestational age (SGA)	Birthweight <10th percentile for sex and gestational age using standard growth charts for full and preterm live-born infants (Battaglia & Lubchenco, 1967)	For the determination of SGA, the registry will utilize the sex-specific international growth reference standards from the INTERGROWTH-21st for those born between $24^{0/7}$ and $42^{6/7}$ gestational weeks (Villar et al, 2014; Villar et al, 2016). The INTERGROWTH-21st standards are the latest available global reference standards, representing contemporary information from an international, multiethnic, diverse population, and have been specifically developed for modern research.
Postnatal growth deficiency	Weight, length, or head circumference in $<10^{th}$ percentile for sex and chronological age using standard growth charts	Postnatal growth deficiency, as part of routine care, will be evaluated at 4 and 12 months of infant age; deficiencies in weight, length, and head circumference will be evaluated separately. For the determination of postnatal growth deficiency, the registry will utilize the sex-specific international growth reference standards from the WHO for children ages 0 to 59 months. The WHO growth standards are recommended for use in the US for infants and children 0 to 2 years of age (CDC, 2010).
Infant developmental delay	Failure to achieve the developmental milestones for chronological age, as defined by the CDC (CDC, 2022)	Infant developmental delay, as part of routine care, will be evaluated at 4 and 12 months of infant age for each CDC-defined category (social/emotional, language/communication, cognitive, and movement/physical development), separately.

ACOG = American College of Obstetricians and Gynecologists; CDC = Centers for Disease Control and Prevention; INTERGROWTH-21st = International Fetal and Newborn Growth Consortium for the 21st Century; MACDP = Metropolitan Atlanta Congenital Defects Program; MCM = major congenital malformation; SAB = spontaneous abortion; SAC = scientific advisory committee; SGA = small for gestational age; US = United States; WHO = World Health Organization.

9.3.3. Pregnancy dating

The registry will conform to the American College of Obstetricians and Gynecologists (ACOG) recommendations for determining the "best" EDD, then EDD will be used to calculate gestational age. Per ACOG, gestational age and the EDD should be determined by the obstetric HCP as soon as data are obtained regarding the last menstrual period (LMP), first accurate ultrasound, or both. ACOG considers ultrasound measurement of the embryo or fetus in the first trimester (up to and including $13^{6/7}$ gestational weeks) the most accurate method to establish or confirm gestational age and discourages against changing the EDD based on subsequent ultrasounds. Any pregnancy without an ultrasound before $22^{0/7}$ gestational weeks to confirm or revise the EDD should be considered suboptimally dated. If the pregnancy resulted from assisted reproductive technology (ART), the obstetric HCP should use ART-derived gestational age (e.g., based on age of embryo and date of transfer) to determine EDD. ACOG further recommends that the best estimate of EDD by the obstetric HCP, rather than estimates based on LMP alone, be used for research purposes (ACOG, 2017).

Based on ACOG's recommendations, the registry will collect the EDD from the obstetric HCP, and the HCP will report whether the EDD was calculated based on LMP, ultrasound, or ART data. If ultrasound-based, whether the ultrasound was performed at $<14^{0/7}$, $14^{0/7}$ to $21^{6/7}$, or $\geq 22^{0/7}$ gestational weeks will also be recorded. EDD data will be collected on each data collection form throughout pregnancy. If the HCP reports a corrected EDD on subsequent forms that is different from the EDD initially reported, the registry will evaluate whether a correction is appropriate, based on the timing of the correction and the methods used to determine the corrected EDD, and follow-up with the HCP, if needed. Based on EDD, the following information will be calculated:

- First day of LMP, defined as $0^{0/7}$ gestational week, will be calculated as EDD minus 280 days (40 weeks)
- Gestational age will be calculated as the number of weeks elapsed since the first day of LMP
  - Gestational weeks $0^{0/7}$ to $13^{6/7}$ will be considered the first trimester
  - Gestational weeks $14^{0/7}$ to $27^{6/7}$ will be considered the second trimester
  - Gestational weeks $28^{0/7}$ to pregnancy outcome will be considered the third trimester
- DOC, defined as $2^{0/7}$ gestational weeks, will be calculated as first day of LMP plus 14 days (2 weeks)

If EDD is not reported by the HCP but LMP data are available, the registry will use first day of LMP to calculate EDD, gestational age, and DOC.

Women will be considered exposed during pregnancy if the exposure occurs any time from 1 day prior to the DOC to the pregnancy outcome. For the analysis of MCM, first trimester exposure will be defined as exposure from 1 days prior to the DOC to $13^{6/7}$ gestational weeks.

9.3.4. Other variables

A diagnosis of moderate-to-severe AD is a condition for inclusion into the unexposed cohort. For this registry, moderate-to-severe AD will be defined as an HCP-confirmed diagnosis of AD and the use of a chronic systemic treatment for AD within 1 year prior to DOC. Disease information, including date of diagnosis, previous and current use of chronic systemic treatments for AD, and AD severity will be collected from HCPs.

A comprehensive list of data collected are summarized in Section 9.4.

9.4. Data sources

All data will be collected via data collection forms. Table 2 provides a summary of the data collection process, including the forms that will be used to collect the data, the timing for completion of each form, the potential reporters or sources of the data, and the types of data that will be collected.

Table 2. Summary of Data Collection Process

Data Collection Form	Data Sources/Reporters	Timing of Completion	Data Collected
Registration Form for Participants	Participant	Enrollment	• Registration information, including eligibility criteria • Maternal demographic characteristics • Maternal pre-pregnancy anthropometrics
Registration Form for HCPs	Obstetric HCP and prescriber, if needed	Enrollment	• Registration information, including eligibility criteria • Maternal obstetrical history • Family history of congenital malformations • AD disease information • Baseline pregnancy information

Table 2. Summary of Data Collection Process

Data Collection Form	Data Sources/Reporters	Timing of Completion	Data Collected
Pregnancy Information Form	Obstetric HCP and prescriber, if needed	Enrollment, end of 2nd trimester[a], and EDD/pregnancy outcome[a]	• Ongoing pregnancy information • Maternal exposures during pregnancy
Pregnancy Outcome Form	Obstetric HCP and pediatric HCP, if needed	EDD/pregnancy outcome	• Pregnancy outcome information • AD disease information
Infant Outcomes Form	Pediatric HCP	4 and 12 months after delivery	• Infant outcome information at 4 and 12 months
Targeted Follow-up Form	Obstetric, pediatric, or other HCP	Any time after pregnancy outcome	• Targeted follow-up information

AD = atopic dermatitis; EDD = estimated date of delivery; HCP = healthcare provider.
a Obtain updated information since the previous contact.

The following data will be collected:

Registration Information (reported by the participant)

- Date of first contact with registry
- Date of consent (enrollment)
- Recruitment source(s)
- Minimum data for assignment to a study cohort, including:
  - Pregnancy status
  - Diagnosis (AD) information
  - Exposure information
  - Prior enrollment (in this registry) status
- Minimum data for assignment to a study cohort (reported by HCP), including:
  - Pregnancy status
  - Diagnosis information
  - Exposure information

Maternal Demographic Characteristics (reported by the participant)

- Date of birth
- Ethnicity
- Race
- Education

Maternal Pre-Pregnancy Anthropometrics (reported by the participant)

- Pre-pregnancy anthropometrics (weight and height)

Maternal Obstetrical History (reported by the obstetric HCP)

- Number of previous pregnancies, including multiple gestations
- Outcomes of previous pregnancies (SAB, stillbirth, elective termination, live birth)
- Complications of previous pregnancies (e.g., pregnancy-induced hypertension, pre-eclampsia, eclampsia, gestational diabetes, preterm labor, placenta previa, placental abruption, incompetent cervix, ectopic pregnancy, molar pregnancy)
- Characteristics of previous live births (preterm, SGA, postnatal growth deficiency, infant developmental delay)
- Number of previous fetuses/infants with congenital malformations (major and minor) and contributing factors

Family History of Congenital Malformations (reported by the obstetric HCP)

- Maternal and paternal family history of congenital malformations (major and minor), including specific malformation and relation of family member to mother or father

Disease Information (reported by the obstetric and/or prescribing HCP)

- Maternal history of moderate-to-severe AD, including date of diagnosis
- Characteristics of moderate-to-severe AD, including disease severity
- Prescription for chronic systemic treatments for AD within 1 year prior to DOC
- Previous and current use of chronic systemic treatments for AD, including dose, route, frequency, and dates/duration of exposure, if available

Baseline Pregnancy Information (reported by the obstetric HCP)

- Timing of first prenatal office visit
- First day of LMP
- Method of conception

Ongoing Pregnancy Information (reported by the obstetric HCP)

- Number of fetuses
- EDD and method of determination (i.e., LMP, ultrasound, or ART data); if ultrasound-determined, timing of ultrasound ($<14^{0/7}$, $\geq 14^{0/7}$ and $\leq 21^{6/7}$, $22^{0/7}$, or $\geq 22^{0/7}$ gestational weeks)
- Prenatal tests (e.g., ultrasound, amniocentesis, maternal serum alpha-fetoprotein, chorionic villus sampling) performed, including type of test (diagnostic or screening), date of test, and results/findings (e.g., congenital malformations)
- Relevant maternal medical conditions, including, but not limited to
    - Thyroid abnormalities
    - Infectious diseases
    - Asthma
    - Diabetes
    - Hypertension
    - Seizure disorder
    - Autoimmune diseases
    - Anemia
    - Depression and other psychiatric disorders
    - Hepatitis
    - Sexually transmitted diseases
    - Uterine or cervical abnormalities, including congenital uterine abnormalities
    - Cancer

- Concurrent pregnancy-related maternal medical conditions or pregnancy complications, including
    - Pregnancy-induced hypertension
    - Pre-eclampsia
    - Eclampsia
    - Gestational diabetes
    - Preterm labor
    - Placenta previa
    - Placental abruption
    - Incompetent cervix
    - Ectopic pregnancy
    - Molar pregnancy

Maternal Exposures During Pregnancy (reported by the obstetric and/or prescribing HCP)

- Exposure to CIBINQO, including indication/reason for use (FDA-approved or off-label), dose, route, frequency, and dates/duration of exposure, if available
- Exposure to other drugs or biological products (including prescription and non-prescription drugs, dietary supplements, vaccines, known teratogens, and investigational medications), including indication/reason for use, dose, route, frequency, and dates/duration of exposure, if available
- Exposure to tobacco, alcohol, marijuana, or recreational or illicit drugs, including timing of exposure, if available

Pregnancy Outcome Information (reported by the obstetric and/or pediatric HCP)

- Pregnancy outcome (for each fetus, classified in one of the following mutually exclusive categories: SAB, stillbirth, elective termination, and live birth)
- Date of pregnancy outcome
- Gestational age at pregnancy outcome
- Fetal/infant sex
- Fetal/infant weight, length, and head circumference at pregnancy outcome

- Route of delivery (i.e., spontaneous vaginal delivery, assisted vaginal delivery, or cesarean delivery)
- 5-minute Apgar score
- Congenital malformations (major and minor) and assessment of potential contributing factors
- For a non-induced fetal loss (SAB, stillbirth), factors that may have had an impact on the fetal loss and attribution
- For elective termination, reason (e.g., finding on prenatal test, risk to mother's health, undesired pregnancy)
- Maternal weight at (just prior to) pregnancy outcome

Infant Outcome Information (reported by the pediatric HCP)

- Infant weight, length, and head circumference at birth (if not provided at pregnancy outcome) and at 4 and 12 months of age
- Achievement of the developmental milestones in each Centers for Disease Control and Prevention (CDC)-defined category (social/emotional, language/communication, cognitive, and movement/physical development) at 4 and 12 months of age
- Congenital malformations (major and minor) and assessment of potential contributing factors
- Infant death, including date and cause of death
- Breastfeeding information, including breastfeeding start/stop dates and maternal medicinal and recreational exposures during breastfeeding

Targeted Follow-up Information (reported by the obstetric, pediatric, and/or other HCP)

- Details of congenital malformations (major or minor) or other conditions of interest
- Etiology
- Outcome attribution
- Specific questions requested by the sponsor and/or the birth defect evaluator

9.4.1. Attempts to obtain follow-up information

In the month that the follow-up is due, the HCP will be contacted and asked to provide follow-up information. If needed, 3 subsequent attempts will be made approximately every

2 weeks via various modes of communication (e.g., phone, fax, email, hardcopy mail). If no response is received from the HCP, additional attempts may occur at the next planned data collection time point. When appropriate, the participant will be asked to encourage her HCP to provide the missing data. After the 3 subsequent attempts, a final communication to obtain follow-up data will be sent to the HCP via certified mail indicating that the participant will be considered lost to follow-up if no further data are received. If, at any point in the follow-up process, the participant withdraws consent or the HCP indicates that the participant is lost to follow-up, no further attempts will be made. The reason the participant was lost to follow-up (e.g., no response from HCP, no response from participant, or participant withdrawal of consent) will be documented.

9.4.2. Follow-up process for clarification of information

For critical data points (e.g., EDD, exposure, and outcome data), if there are outstanding questions, discrepancies between forms or missing data, the appropriate HCP will be contacted for clarification. If needed, 3 subsequent attempts will be made at intervals of approximately 2 weeks. If no further information is obtained, qualified registry staff or the principal investigator will make a logical determination on discrepant information based on the available data. All clarifications and/or changes will be documented and traceable.

9.5. Study size

9.5.1. Assessment of study feasibility

To assess the feasibility of this study, data-driven assumptions regarding the prevalence of moderate-to-severe AD, pregnancy, and CIBINQO uptake were made to estimate the number of women who will potentially be exposed to CIBINQO during pregnancy. The prevalence of AD overall among women of childbearing age was assumed to be 5.5%, with 50% having moderate-to-severe AD (Barbarot et al, 2018; Fuxench et al, 2019; Chidwick et al, 2020); the proportion receiving pharmacotherapy was assumed to be 70% (Beck et al, 2014; Boguniewicz et al, 2017; Napolitano et al, 2021). It was further assumed that 3% of those receiving pharmacotherapy would be treated with CIBINQO (Pfizer internal projections). These assumptions were applied to the population of women of childbearing potential in the US (approximately 74.5 million; US Census Bureau, 2020), which yielded an estimated 43,038 women of childbearing potential who will potentially receive CIBINQO each year. After application of the general fertility estimates in the US (56.0 pregnancies per 1,000 women aged 15 to 44 years; Osterman et al, 2022) and the proportion of pharmacotherapy discontinuation during pregnancy among women with moderate-to-severe AD (10% assumed percentage of discontinuation due to severity of symptoms and risk during pregnancy), it was estimated that 6,507 women may potentially be exposed to CIBINQO during pregnancy over the course of 3 years. Given a 3% MCM prevalence among live births (CDC, 2008) in the US general population, these CIBINQO-exposed pregnancies can be expected to result in approximately 195 live births with MCM.

If the registry were to capture one fourth of these births, a total of 49 lives births with MCM may be enrolled.

9.5.2. Sample size

Sample size calculations were performed with SAS® statistical software (version 9.4 or higher, SAS Institute, Cary, NC) and PASS 2021 Power Analysis and Sample Size software (version 21.0.3, CSS, LLC, Kaysville, Utah, USA) for the outcomes of interest. For the calculations, general population prevalence estimates were obtained for most (but not all) of the outcomes of interest from various sources, including the Metropolitan Atlanta Congenital Defects Program (MACDP), the National Vital Statistics System (NVSS), the National Institute for Child Health and Human Development's Consecutive Pregnancies Study and Consortium on Safe Labor Study, and published literature.

The registry will aim to enroll 728 pregnant women, 364 in each cohort. This sample size will afford the study the ability to achieve its primary and secondary objectives. Sample size calculations are based on the primary outcome, MCM, which is also the outcome with the most restrictive denominators and one of the lowest estimates in the general population. For the primary objective (to estimate crude proportions of outcomes), a sample size of 200 participants per cohort will be targeted to estimate the prevalence of MCM with ±3% precision; for the secondary objective (to compare proportions of outcomes between cohorts), a sample size of 364 participants per cohort will be targeted to detect a 3-fold increase in the risk of MCM. Regardless of the sample size achieved, the study will be able to fulfill the primary objective and estimate the crude proportion of the study outcomes with varying precision.

For the primary objective, calculations were performed to determine the achievable precision of outcome prevalence estimates for a range of sample sizes. Table 3 presents by outcome the sample size (number of live births or pregnant women, depending on the outcome) required in each cohort to detect a range of precisions, from 1% to 5%. Precision is calculated as the half-width of the two-sided 95% confidence interval using the Wilson (score) method for binomial proportions, and the prevalence of the outcomes of interest observed in the registry was assumed to be equivalent to that of the general population. As shown in Table 3, 145 live births in the analysis population of each cohort are needed to estimate the prevalence of MCM with ±3% precision.

To estimate the number of pregnant women who will need to be enrolled to result in 145 live births, several factors were considered, including the expected proportion of live births in the registry, the proportion of enrolled women expected to be exposed to CIBINQO in the first trimester, and the proportion of enrolled women expected to be excluded from the analysis population. It was assumed that 90% of enrolled women would be exposed in the first trimester, 90% of enrolled pregnancies would result in a live birth (Covington et al, 2010; Veley et al, 2020), and 10% of enrolled women would be excluded from the analysis population due to not having a diagnosis of moderate-to-severe AD, occurrence of pregnancy outcome prior to enrollment (retrospectively enrolled participants), exposure to a known teratogen or an investigational medication during pregnancy (teratogen/investigational medication-exposed participants), or lack of pregnancy outcome data (participants lost to follow-up). Given these assumptions, to attain 145 live births per cohort, 200 pregnant women would need to be enrolled in each of the 2 cohorts of the study population, and a minimum of 400 women would need to be enrolled in the registry. This sample size will

afford the study the ability to estimate the prevalence of MCM in each cohort with ±3% precision with 95% confidence interval.

Table 3. Sample Size Calculations for the Primary Objective

Outcome	Reference Prevalence	Reference	Denominator	Sample Size Needed per Cohort to Estimate Prevalence with Specified Precision								
				1%	1.5%	2%	2.5%	3%	3.5%	4%	4.5%	5%
MCM	3.0%	CDC, 2008	Live births	1,143	521	303	201	145	111	89	73	61
SAB	11.8%	Wu et al, 2019	Pregnant women	4,000	1,779	1,002	642	446	328	252	199	162
Stillbirth	0.596%	MacDorman & Gregory, 2015	Live births and stillbirths	333	184	124	93	74	61	52	45	39
Elective termination	18.6%	Jatlaoui et al, 2019	Live births	5,815	2,584	1,453	930	645	474	363	286	232
Preterm birth	8.47%	Martin et al, 2021	Singleton live births	2,983	1,329	750	482	336	248	191	152	124
SGA	10.0%	By definition	Singleton live births	3,461	1,540	868	557	388	286	219	174	141
Postnatal growth deficiency	10.0%	By definition	Singleton live births	3,461	1,540	868	557	388	286	219	174	141

CDC = Centers for Disease Control; MCM = major congenital malformation; reference prevalence = prevalence of outcome in general population for pregnant women of any age; SAB = spontaneous abortion; SGA = small for gestational age.
The outcome infant developmental delay is not listed in the table because a published reference rate is not available.
Sample size calculations were performed in the PASS software for the outcomes of interest; precision is calculated as the half-width of the two-sided 95% confidence interval using the Wilson (score) method for binomial proportions.

For the secondary objective, calculations were performed to determine the achievable detectable relative risk for each outcome and a range of sample sizes. Table 4 presents by outcome the sample size (number of live births or pregnant women, depending on the outcome) required in each cohort to detect a range of RR, from 1.5 to 5.5. Sample size calculations were performed using the Fisher's exact conditional test with Walters normal approximation method, and assuming a power of 80%, a 2-sided α level of 0.05, an equal number of women in each cohort (although other sampling ratios were considered), and observed prevalence of the outcomes of interest in the unexposed cohort equivalent to reference comparator prevalence in the general population. As shown in Table 4, 265 live births in the analysis population of each cohort are needed to detect a 3-fold increase in the prevalence of MCM between cohorts, or a relative risk of 3.

Applying the same assumptions previously mentioned, to attain 265 live births per cohort, 364 pregnant women would need to be enrolled in each of the 2 cohorts of the study population, and a minimum of 728 women would need to be enrolled in the registry. This sample size will afford the study the ability to detect a 3-fold increase in the risk of the primary outcome, MCM, for the secondary analysis. Additionally, Table 5 shows that without any adjustments for multiple comparisons, this sample size will offer the study >80% power to detect a 3-fold increase in all other outcomes except stillbirth (for which the study will have 21.4% power to detect a 3-fold increase).

Table 4. Sample Size Calculations for the Secondary Objective

Outcome	Reference Prevalence in Non-exposed Group	Reference	Denominator	Sampling Ratio (Exposed: Unexposed)	Sample Size Needed per Cohort to Detect Specific RR (Exposed: Unexposed)								
					RR= 1.5	RR= 2.0	RR= 2.5	RR= 3.0	RR= 3.5	RR= 4.0	RR= 4.5	RR= 5.0	RR= 5.5
MCM	3.0%	CDC, 2008	Live births	1:1	2,627	796	413	265	190	146	117	97	82
SAB	11.8%	Wu et al, 2019	Pregnant women	1:1	596	177	90	57	40	30	24	19	16
Stillbirth	0.596%	MacDorman & Gregory, 2015	Live births and stillbirths	1:1	13610	4142	2159	1389	999	769	619	516	440
Elective termination	18.6%	Jatlaoui et al, 2019	Live births	1:1	343	100	50	31	21	15	12	9	NA[1]
Preterm birth	8.47%	Martin et al, 2021	Singleton live births	1:1	868	260	134	85	60	46	36	30	25
SGA	10.0%	By definition	Singleton live births	1:1	721	215	110	70	49	37	29	24	20
Postnatal growth deficiency	10.0%	By definition	Singleton live births	1:1	721	215	110	70	49	37	29	24	20

CDC = Centers for Disease Control; MCM = major congenital malformation; NA = not available; reference prevalence = prevalence of outcome in general population for pregnant women of any age; RR = relative risk; SAB = spontaneous abortion; SGA = small for gestational age.
The outcome infant developmental delay is not listed in the table because a published reference rate is not available.
Sample size calculations were performed in SAS (version 9.4) for the outcomes of interest using Fisher's exact conditional test with Walters normal approximation method, and assuming a power of 80% and a 2-sided α level of 0.05.
1 For elective termination, a relative risk of 5.5 with a reference prevalence of 18.6% in the unexposed cohort would result in an estimate above 100% in the exposed cohort.

Table 5. Power Calculations

Outcomes	Power Estimate
MCM	80%
SAB	>80%
Stillbirth	21.4%
Elective termination	>80%
Preterm birth	>80%
SGA	>80%
Postnatal growth deficiency	>80%

MCM = major congenital malformation; SAB = spontaneous abortion; SGA = small for gestational age.
The outcome infant developmental delay is not listed in the table because a published reference rate is not available.
Power calculations were performed in SAS (version 9.4) for the outcomes of interest using Fisher's exact conditional test with Walters normal approximation method, and assuming a sample size of 265 per cohort, a relative risk of 3.0 and a 2-sided α level of 0.05.

9.6. Data management

9.6.1. Data collection forms

As used in this protocol, the term data collection form should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A completed data collection form is required for each included patient. The completed original data collection forms are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. PPD shall ensure that the data collection forms are securely stored in SharePoint folders in encrypted electronic form and will be password protected to prevent access by unauthorized third parties. Paper forms are destroyed/shredded immediately after database entry.

PPD has ultimate responsibility for the collection and reporting of all data entered on the data collection forms and any other data collection forms as required and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The data collection form serves as the source document. Any corrections to entries made in the data collection forms must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

9.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, PPD agrees to keep all study-related records. The records should be retained by PPD according to

local regulations or as specified in the vendor contract, whichever is longer. PPD must ensure that the records continue to be stored securely for so long as they are retained.

If PPD becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless PPD and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Records must be retained for longer than 15 years if required by applicable local regulations.

PPD must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data analysis

9.7.1. Analysis population

To provide valid effect estimates, the analysis population may differ from the population of women enrolled in the registry. The subset of registry participants included in the analysis will include women who:

- Have the minimum data required for determining inclusion/exclusion into one of the study cohorts
- Have sufficient data either submitted or confirmed by an HCP (i.e., an HCP must submit or confirm the data used to define the eligibility criteria)
- Have a diagnosis of moderate-to-severe AD
- Are prospectively enrolled (i.e., currently pregnant at enrollment)
- Are not exposed to teratogens or investigational medications during pregnancy
- Are not multiple gestation pregnancies for the analyses of preterm birth, SGA, and postnatal growth deficiency

Within each cohort, the baseline characteristics of those included in the analysis population will be compared with those excluded from the analysis population to evaluate potential differences between the population enrolled in the registry to the analysis population.

9.7.2. Primary analysis: Crude outcome proportions

Demographic and baseline characteristics will be summarized with descriptive statistics for each cohort. For each continuous variable, the number of observations, median, mean, standard deviation, minimum, and maximum for each cohort will be reported. For each categorical variable, the frequency and percentage in each category by cohort will be reported.

For each exposure group, the proportion of participants with the outcomes of interest will be calculated. The proportion with the outcomes of interest will be calculated as described in Table 6.

In the analysis of MCMs, participants will be classified into exposure groups (CIBINQO exposed or comparator group) based on exposure during the first trimester (i.e., the etiologically relevant window). For all other outcomes, exposure groups will be defined based on exposure at any point during pregnancy. The exposed group will consist of women exposed to CIBINQO during pregnancy. The unexposed comparator group (i.e., primary comparator group) will consist of women not exposed to CIBINQO during pregnancy.

Table 6. Calculation of Outcome Proportion

Outcome	Numerator	Denominator
Primary Outcome – Major Congenital Malformation (MCM)		
Primary analysis: among live births	Live births with confirmed (i.e., adjudicated) MCMs (excluding MCMs not associated with medication exposure) among women with pregnancy outcome data and, based on exposure classifications measured during the first trimester	Live births among women with pregnancy outcome data and, if applicable based on cohort, exposure during 1st trimester
Sensitivity analysis: among all pregnancy outcomes	Live births and fetal losses with confirmed MCMs (excluding MCMs not associated with medication exposure) among women with pregnancy outcome data and, if applicable based on cohort, exposure during first trimester	Live births and fetal losses among women with pregnancy outcome data and, if applicable based on cohort, exposure during 1st trimester
Secondary Outcomes		
Minor congenital malformations	Live births with minor congenital malformations among women with pregnancy outcome data	Live births among women with pregnancy outcome data
Spontaneous abortion (SAB)	SABs among women with pregnancy outcome data who are enrolled (and exposed, if applicable based on cohort) prior to 20 gestational weeks	Women with pregnancy outcome data who are enrolled (and exposed, if applicable based on cohort) prior to 20 gestational weeks
Stillbirth	Stillbirths among women with pregnancy outcome data	Women with pregnancy outcome data
Elective termination	Elective terminations among women with pregnancy outcome data	Women with pregnancy outcome data
Preterm birth	Singleton preterm live births without MCMs among women with pregnancy outcome data who are enrolled (and exposed, if applicable based on cohort) prior to 37 gestational weeks	Singleton live births without MCMs among women with pregnancy outcome data who are enrolled (and exposed, if applicable based on cohort) prior to 37 gestational weeks

Table 6. Calculation of Outcome Proportion

Outcome	Numerator	Denominator
Small for gestational age (SGA)	Singleton live births without MCMs who are SGA among women with pregnancy outcome data	Singleton live births without MCMs with weight data among women with pregnancy outcome data
Postnatal growth deficiency (at 4 and 12 months)	Singleton infants without MCMs who were not born preterm or SGA with postnatal growth deficiency based on weight/length/head circumference among infants with weight/length/head circumference data at the time point	Singleton infants without MCMs who were not born preterm or SGA with weight/length/head circumference data at the time point
Infant developmental delay (at 4 and 12 months)	Infants without MCMs who were not born preterm with developmental deficiency in a particular category among infants with developmental milestone data for the category at the time point	Infants without MCMs who were not born preterm with developmental milestone data for the category at the time point

MCM = major congenital malformation; SAB = spontaneous abortion; SGA = small for gestational age.

9.7.3. Secondary analysis: Comparative analysis

If sample size permits, the proportion of outcomes will be compared between treatment groups. Demographic and baseline characteristics will be summarized with descriptive statistics for each cohort, and balance between cohorts before and after applying IPTW will be assessed using standardized differences.

For each outcome, if the number of events permits, unadjusted and adjusted RR will be reported along with their 95% confidence intervals. Exact methods will be used to calculate crude (unadjusted) RR and 95% confidence intervals for all outcomes.

Adjusted RR for the association of CIBINQO and each outcome of interest will be estimated using generalized linear models weighted by IPTW. First, IPTW will be used to balance the treatment groups with respect to the measured covariates (i.e., adjust for baseline confounding). Stabilized treatment weights will be estimated as the marginal probability of treatment divided by the probability of treatment conditional on measured baseline covariates (Chesnaye et al, 2021). Then for each outcome, a generalized linear model weighted by IPTW using a binomial family and a log (RR) link will be employed to estimate an adjusted relative risk (Robins et al, 1994; Robins et al, 1995; Scharfstein et al, 1999). The Clopper-Pearson method will be used to derive 95% confidence intervals.

The potential baseline covariates and confounders included in the treatment weights may vary for each outcome. The potential covariates may include, but are not limited to, maternal age at conception, calendar year at conception, maternal race and ethnicity, maternal pre-pregnancy body mass index, AD disease characteristics, maternal comorbidities, maternal concomitant medications, maternal lifestyle characteristics (e.g., exposure to smoking, alcohol, marijuana, etc.), number of previous pregnancies, and outcomes and complications of previous pregnancies.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (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.

9.7.4. Subgroup and sensitivity analyses

If sample size permits, subgroup analyses will be conducted that consider the timing of exposure (earliest trimester of exposure), extent of exposure (cumulative dose during pregnancy or relevant exposure window), number of systemic therapy exposures during pregnancy (1 or ≥1), and maternal age group at conception (<18, 18 to <35, 35 to <45, and ≥45 years). The analysis of MCM will be stratified by earliest trimester of exposure, with a primary focus on exposure during the first trimester.

Sensitivity analyses will also be conducted to examine the extent to which changes in certain methods or assumptions affect the results. The sensitivity analyses may include, but are not limited to:

- Applying a stricter definition of prospective enrollment to the analysis of MCM. For this analysis, women who enroll or make initial contact with the registry prior to diagnostic prenatal testing will be considered prospectively enrolled, and women who enroll or make initial contact with the registry after diagnostic prenatal testing, regardless of the results, will be considered retrospectively enrolled.

- Accounting for the correlation between previous and subsequent pregnancies in the same woman and multiple gestation pregnancies using mixed models in the analysis of the outcome.

- Including the propensity score and a variable for treatment in an unweighted generalized linear model using a binomial family and a log (RR) link to test the robustness of IPTW.

- Applying inverse probability of censoring weights to account for potential informative censoring due to differential loss to follow up.

9.7.5. Missing data

For critical data points, missing values are expected to be minimal, thereby negating the need for imputation. The frequency and percentage of participants with missing data for each data point will be presented. If there is a high degree of missing covariate data, further imputation may be considered to minimize the loss of observations in the analysis.

For start and end dates of medical conditions or exposures, if the month and year are known but the day is missing, then the day will be imputed for analyses: missing start dates will be set to the first day of the month, and missing end dates will be set to the last day of the month. Listings will continue to present the day as missing. If the year is known but the month is missing, missing start dates would be set to the first day and first month of the year

and missing end dates will be set to the last day and last month of the year. Listings will continue to present the month as missing.

9.8. Quality control

PPD will ensure that the data obtained and delivered to the sponsor are of high quality will be an ongoing, multistep process involving programming of edit checks for critical data variables in the electronic data capture system and visual review for completeness, logic, consistency, and accuracy. As is recommended in regulatory guidance documents, data collection forms have been carefully designed to ensure data quality and integrity. Participant-reported data may be verified by the appropriate HCP. PPD will follow their standard operating procedures (SOPs) as they relate to training of personnel, data handling, and processing, complying with 21 Code of Federal Regulations (CFR) Part II and Good Pharmacoepidemiology Practice (GPP).

9.9. Strengths and limitations of the research methods

Prospectively pregnancy registries offer several advantages over retrospective primary data collection studies and secondary database studies. The prospective design mitigates the potential for recall bias, a bias that may be introduced in retrospective primary data collection studies. Additionally, this prospective registry offers the potential to capture rich patient information that would not be captured in secondary databases. Critical data are provided directly from the HCPs and participants, including information that may not be routinely captured in medical records. This direct capture of data can minimize the potential for exposure, outcome, and covariate misclassification.

The general limitations of pregnancy registries with voluntary participation are well known, and these will apply to this study as well. One key limitation of the study is the limited size of the population of pregnant women expected to be exposed to CIBINQO during pregnancy. To maximize recruitment and retention, a multi-modal approach will be used to deliver registry education and recruitment materials to targeted HCPs and patients. The registry's recruitment and retention strategies will be flexible and will be continuously assessed. Based on these assessments and feedback form the SAC, the registry's recruitment and retention strategies will be adjusted as needed to maximize registry participation.

Another key limitation of the registry, due to the voluntary nature of participation, relates to representativeness. Since participation in the registry is voluntary, the pregnant women who voluntarily enroll in the registry may not be representative of the overall target population of pregnant women with moderate-to-severe AD in the US. This could introduce selection bias and affect the generalizability of the results. To minimize the potential for selection bias, a multi-faceted recruitment strategy will be employed.

As the registry will enroll women only after recognition of pregnancy and in some cases may be much later in pregnancy, there will be left truncation of the enrolled population. That is, the enrolled population of pregnant women will include women with a shortened period at risk of the outcomes of interest and exclude women who have already had certain outcomes (e.g., SAB, elective termination). To minimize the impact of this potential bias, statistical

methods may be used to address left truncation, and the registry's recruitment strategy will encourage recruitment of participants as early in pregnancy as possible.

Additionally, women in the exposed cohort may differ from those in the comparator cohort in important factors that could impact pregnancy outcomes. For example, patients who seek and receive CIBINQO for moderate-to-severe AD may have more severe disease than the comparator patients, so confounding by indication will need to be carefully considered for the comparison. Furthermore, there may be misclassification of disease severity, particularly in the comparator cohort, as use of chronic systemic therapies for AD will be used as a proxy for moderate-to-severe disease. Standardized methods for assessing AD severity are not available and severity is not routinely documented in medical records.

To minimize the impact of potential confounders, the registry will record the characteristics of women in both cohorts and use statistical methods to examine and account for any differences between cohorts in the analysis. The registry will employ identical data collection and follow-up procedures across the registry cohorts to minimize any potential recording/detection bias. Although statistical methods will be used to account for confounding, it may not be possible to control for all variables (e.g., unknown) that could influence the results of the study. Therefore, residual confounding remains a possibility.

Outcome misclassification is possible, especially with regard to minor congenital malformations that may be overlooked or unreported. Although some MCMs may not be easily visible at birth, most will be apparent by 12 months of age, so misclassification of these outcomes is expected to be minimal in this registry.

Also, it is possible that outcomes among pregnant women and infants lost to follow-up could differ from those with documented outcomes. Inverse probability of censoring weights may be considered to address potential biases due to informative censoring.

Finally, the presence or absence of MCMs will not be known for pregnancies that resulted in fetal losses (stillbirths, SABs, and elective terminations). The data collection form attempts to obtain information on MCMs detected at the time of the fetal loss. However, the reporting physician may not know the condition of the lost fetus, which would increase the potential for outcome misclassification for MCMs.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

All parties will comply with all applicable laws and regulations, including those regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures—except where required by applicable law.

Patient personal data will be stored at PPD in encrypted electronic form, and will be password-protected to ensure that only authorized study staff have access. PPD will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of a disaster. In the event of a potential personal data breach, PPD shall be responsible for determining whether one has in fact occurred; and if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to processing personal data, when study data are compiled for transfer to Pfizer and/or other authorized parties, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. PPD will maintain a confidential list of study participants, linking each patient's numerical code to their actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data, consistent with the vendor contract and applicable privacy laws.

10.2. Patient consent

Informed consent will be obtained for each registry participant. Electronic consent will be available through the registry's web-based/mobile application. Should participants prefer to enroll via phone, this registry qualifies for a waiver of documentation of informed consent. Adult participants will be given the option to provide verbal consent under the waiver of documentation of informed consent, or signed informed consent through the web-based/mobile application or via courier. Adults are defined as individuals who have attained the legal age for consenting to treatments, procedures, or clinical investigations under applicable law in various states within the US.

Minors are defined as individuals who have not attained the legal age for consenting to treatments, procedures, or clinical investigations under applicable law in various states within the US. The definitions of a minor and an emancipated minor vary by state within the US. This registry will follow applicable laws for the participant's resident state. If a minor requests participation in the registry and all eligibility criteria are met, the registry will obtain assent from the minor and signed written consent from a parent or guardian through the web-based/mobile application or via courier. Written consent from both parent(s) or both guardian(s) will be obtained in the US states whose local laws and regulations require this.

At the initial screening with potential participants, the registry web-based/mobile application or registry associate will obtain consent to collect basic information about the individual, such as age and state of residence, to determine whether the individual is a minor and to ensure that applicable local laws and regulations are followed.

10.2.1. Additional safeguards for children in clinical investigations

Although this registry involves the collection of information on infants after birth, the registry protocol will be conducted in full consideration of 21 CFR Part 50, Subpart D, Additional Safeguards for Children in Clinical Investigations (for FDA-regulated human subjects research) (FDA, 2022). This registry will ascertain maternal and infant information

only via maternal and pediatric HCPs, and no clinical specimens will be collected from the infants. Therefore, data collected regarding the infants of women in this pregnancy registry will involve no greater than minimal risk to the infants. Although the infants will be too young to provide assent, the registry protocol will require permission from the mothers, and they will be asked to provide authorization for release of medical information from their infants' HCPs.

10.2.2. Electronic informed consent process

The website will contain information about the registry, and will provide access to the study's web-based/mobile application. Via this application, the participant will register through their computer or mobile device using credentials such as name, email address, and/or password. At any time during the registration and consent process, the participant may contact the VRCC via the registry phone number, which will be prominently displayed on the study's web-based/mobile application.

Once the participant has registered, the application will automatically start the consent process. The application will present the contents of the consent in a scrollable window. The participant will review the document, and the application will present the following options: "Hold," "Disagree," and "Sign and Publish."

If the participant has questions during the consent process, they will be encouraged to stop the consenting process on the application via the "Hold" button and call the VRCC, where study specialists will assist with any questions. The participant can resume/complete the consent process at any time. If the participant does not wish to provide consent, they will be directed to choose the "Disagree" option, and the process will stop. If the participant wishes to provide consent, they will be directed to choose "Sign and Publish."

The application will provide an option for the participant to view or email their completed consent form(s).

After the informed consent, the participant will complete the medical release form(s) and answer some basic medical information questions.

10.2.3. Waiver of documentation of informed consent

The following US regulations indicate that the waiver of documentation of informed consent is appropriate for this registry.

As is stated in US CFR, 21 CFR 56.109 [and additionally in 45 CFR 46.117(c)(2)]:

> (c) An IRB shall require documentation of informed consent in accordance with 50.27 of this chapter, except as follows:
>
> > (1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of

harm to subjects and involves no procedures for which written consent is normally required outside the research context

(d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require PPD to provide subjects with a written statement regarding the research.

The research involves no more than minimal risk to participants. This is an observational study that involves no experimental intervention and poses no possibility of physical harm. The only potential risk is a breach of confidentiality, and the registry has well-established procedures in place to prevent any such breach. Extensive safeguards are in place to ensure that participants' privacy is protected:

1. An adequate plan is provided to protect the identifiers from improper use and disclosure (Section 10.1).

2. An adequate plan is provided to remove the identifiers at the earliest opportunity.

3. Adequate assurances are provided that the protected health information will not be reused or disclosed to any other person or entity.

The research involves no procedures for which written consent is normally required outside the research context. Enrollment in this observational study will be strictly voluntary, and participants can withdraw their consent to participate at any time. The schedule of patient visits and all treatment regimens will be at the discretion of the treating HCP. Data submitted to the registry will be limited to data routinely collected and documented in the patient's medical record.

10.3. Patient withdrawal

Enrollment in this observational study will be strictly voluntary, and participants can withdraw their consent to participate at any time.

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the PPD for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if applicable. PPD would inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. PPD may retain and continue to use any data collected before such withdrawal of consent.

10.4. Institutional review board/Independent ethics committee

It is the responsibility of PPD to have prospective approval of the study protocol, protocol amendments, materials describing the consent process (e.g., statement regarding agreement

to participate), and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/independent ethics committee (IEC). All correspondence with the IRB/IEC should be retained by PPD. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The protocol will be submitted to the applicable regulatory authority and central IRB for approval prior to registry implementation. The protocol, waiver of documentation of informed consent, and waiver of informed consent will be reviewed and approved by an IRB before study implementation. A signed and dated statement that the protocol and waivers have been approved by the IRB will be given to the sponsor before study initiation. Prior to study start, the PPD principal investigator will sign a protocol signature page confirming their agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol. If an inspection of the VRCC is requested by a regulatory authority, the VRCC must inform the sponsor immediately of this request.

10.5. 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, following generally accepted research practices described in the following guidances:

- FDA Guidance for Industry: Postapproval Pregnancy Safety Studies (FDA, 2019)
- European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices (GVP) Product- or Population-Specific Considerations III: Pregnant and Breastfeeding Women (EMA, 2019)
- GPP issued by the International Society for Pharmacoepidemiology (GPP, 2015)
- International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS) (CIOMS, 2009)
- EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP, 2021)
- FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (FDA, 2005)
- The International Ethical Guidelines for Health-related Research Involving Humans issued by the CIOMS in collaboration with the World Health Organization (WHO) (CIOMS, 2016).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The table below summarizes the requirements for recording safety events on the data collection form and for reporting safety events on the Non-interventional Study (NIS)

Adverse Event Monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (AE); (2) non-serious adverse events (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section "Definitions of safety events."

Safety Event	**Recorded on the Data Collection Forms**	**Reported on the NIS AEM Report Form to Pfizer Safety within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during breast feeding medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE/ SAE) Note: Any associated AE is reported together with the exposure scenario.
Scenarios involving exposure to a drug during pregnancy	All (regardless of whether associated with an AE)	Only when associated with an AE/ SAE

AE = adverse event; AEM = adverse event monitoring; NIS = non-interventional study; SAE = serious adverse event

For each AE, the Evidera/PPD VRCC must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (refer to section "Serious Adverse Events" below).

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the Evidera/PPD VRCC **regardless of whether the event is determined by the Evidera/PPD VRCC to be related to CIBINQO**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the Evidera/PPD VRCC does not become immediately aware of the occurrence of a safety event, the Evidera/PPD VRCC must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far-right column of the table above that are reportable to Pfizer within 24 hours of awareness, the Evidera/PPD VRCC is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an Evidera/PPD VRCC may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the data collection forms. In general, this

will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

This protocol will use an external Endpoint Adjudication Committee wherein, to maintain scientific integrity, adjudication of clinical endpoints (i.e., MCM, minor congenital malformations) defined in the study objectives will be performed. The Endpoint Committee is responsible for ongoing analysis of AEs and of their adjudication as endpoints. Any AE that is not adjudicated as an endpoint by the Endpoint Committee is reportable and is forwarded to the Drug Safety Unit (DSU). In addition, when the HCP has judged an AE to have a causal relationship with CIBINQO or other medications used to treat AD in this patient population, the Evidera/PPD VRCC must still report the event to Pfizer, even if that event is a component of the endpoint.

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of CIBINQO or other medications used to treat AD in this patient population or the time of the patient's informed consent if s/he is being treated with CIBINQO or other medications used to treat AD in this patient population at study start, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study or other medications used to treat AD in this patient population on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (e.g., patient changes his/her mind about participation, failed screening criteria), the reporting period ends on the date of the decision to not enroll the patient.

If the Evidera/PPD VRCC becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to CIBINQO or other medications used to treat AD in this patient population, the SAE also must be reported to Pfizer Safety.

Causality assessment

The Evidera/PPD VRCC is required to request and record the causal relationship determined by the HCP. For AEs with a causal relationship to CIBINQO or other medications used to treat AD in this patient population, follow-up by the Evidera/PPD VRCC is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the Evidera/PPD VRCC, and Pfizer concurs with that assessment.

An HCP's causality assessment is the determination of whether there exists a reasonable possibility that CIBINQO or other medications used to treat AD in this patient population caused or contributed to an AE. If the HCP's final determination of causality is "unknown" and s/he cannot determine whether CIBINQO or other medications used to treat AD in this patient population caused the event, the safety event must be reported within 24 hours.

If the HCP cannot determine the etiology of the event but s/he determines that CIBINQO or other medications used to treat AD in this patient population did not cause the event, this should be clearly documented on the data collection forms and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE);
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;

- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the HCP or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Serious adverse events

A SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute AEs);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (eg., for procedure required by the study protocol)

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) CIBINQO, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to CIBINQO (maternal exposure).

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to CIBINQO prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

For exposure during pregnancy in studies of pregnant women, data on the exposure to CIBINQO during pregnancy are not reportable unless associated with serious or non-serious AEs.

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed, with the exception of those studies conducted in pregnant women (as described in above), for which data on the exposure are not reportable unless associated with serious or non-serious adverse events.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with CIBINQO, this information must be submitted to Pfizer, irrespective of whether an AE has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to CIBINQO in a pregnant woman (e.g., a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy

outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, SAB, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the HCP assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

For non-interventional studies conducted in pregnant women, data on the pregnancy outcome and non-serious AEs are expected to be collected and analyzed in the study database. In such instances, only EDPs associated with a SAE are to be reported.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the healthcare professional, patient, or consumer. Such events may be

related to professional practice, healthcare products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer)

- Confusion with regard to invented name (e.g., trade name, brand name)

The Evidera/PPD VRCC must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/ SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE

- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

    - An identifiable reporter

    - A suspect product

    - The event medication error

Overdose, misuse, extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the Evidera/PPD VRCC, irrespective of the presence of an associated AE/ SAE.

Lack of efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the Evidera/PPD VRCC, irrespective of the presence of an associated AE/ SAE or the indication for use of the Pfizer product.

Occupational exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the Evidera/PPD VRCC, irrespective of the presence of an associated AE/ SAE.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if PPD is aware of any new information that might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, PPD will inform Pfizer immediately of any urgent safety measures taken by PPD to protect the study patients against any immediate hazard, and of any serious breaches of this non-interventional study protocol of which the investigator becomes aware of.

The registry will produce a final comprehensive study report that will be submitted to the appropriate regulatory authorities. The report will include a presentation of the registry design, methodology, results to date, and an interpretive discussion of the biostatistical analysis results. Additionally, this study will be disclosed and registered in the European Union (EU) Post-authorization Study (PAS) Register.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

MACDP Birth Defects Code List

https://cioms.ch/publications/product/international-ethical-guidelines-for-health-related-research-involving-humans/

CDC List of Minor Congenital Anomalies

https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/appendices/appendix-b.html