

# (Levo)cetirizine Clinical Lactation Study Protocol

## Protocol

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Levocetirizine/cetirizine levels in human milk – an observational, clinical study among breastfeeding women

## IMI2 821520 - ConcePTION

This study is conducted in partnership with ConcePTION; a project where over 50 public and industry partners in Europe and worldwide are co-operating to build an ecosystem for better monitoring and communicating of medication safety in pregnancy and breastfeeding

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## List of Abbreviations

DDD	Defined daily dose
ICF	Informed consent form
MW	Molecular weight
PB	Protein binding
PK	Pharmacokinetics
Pop PK	Population pharmacokinetics
$T_{1/2}$	Half-life
$T_{max}$	The time needed to reach $C_{max}$
$V_d$	Volume of distribution

## 1. PROTOCOL SUMMARY

### 1.1 Synopsis:

**Protocol Title:** Transfer of (levo)cetirizine into human breast milk, and potential adverse effects on nursing infants.

**Short title:** (Levo)cetirizine clinical lactation study

Primary Objectives	Primary Endpoints
Quantifying (levo)cetirizine excretion into human milk	Variability of concentration of (levo)cetirizine in human milk samples
Secondary Objectives	Secondary Endpoints
Monitor the safety of (levo)cetirizine in breastfed infants of mothers using (levo)cetirizine.	Maternal self-reported adverse events among breastfed infants
Detecting the impact of (levo)cetirizine on milk production.	Maternal self-reported perceived changes in milk production

### Overall Design:

<b>Study Phase</b>	Phase IV
<b>Indication</b>	Allergy
<b>Population</b>	Lactating mothers using levocetirizine or cetirizine
<b>Study Type</b>	Observational, non-interventional
<b>Estimated Duration of Study</b>	Three years (2021-2023)

### Number of Participants:

25 to 40 lactating women using levocetirizine or cetirizine will be included in the study.

**Clinical site:** Norway

**Sponsor:** IMI2 821520 – ConcePTION. This study is conducted in partnership with ConcePTION; a project where over 52 public and industry partners in Europe and worldwide are co-operating to build an ecosystem for better monitoring and communicating of medication safety in pregnancy and breastfeeding:

## 2. INTRODUCTION

### 2.1 Background Information

Prospective studies measuring drug concentrations in human milk are necessary to allow an accurate benefit/risk assessment for breastfeeding women in need of medications.

This necessity is clearly stated in the guidelines by the European Medicines Agency “Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations III: Pregnant and breastfeeding women”: *“Once a product is placed on the market, if use in pregnancy and/or during breastfeeding is likely to occur, data collection to obtain a better understanding of risks associated with such use and to identify and characterise risks is important even where no safety concerns have arisen in the pre-authorisation phase.”*

These guidelines also state: *“Increased and adequate data collection and data assessment in a timely manner will enable that patients and prescribers have relevant information to make informed decisions about using medicines during pregnancy or breastfeeding and that they are well-informed about uncertainties”*.<sup>1</sup>

This study is motivated by these guidelines, and precisely, the statement that *“Medicine concentration levels in breast milk samples should be measured and a relative infant dose calculated, to obtain information for supporting the risk assessment and provision of advice on timing of medicine intake relative to breastfeeding where this may be feasible (e.g. for short-term or single dose treatments). Moreover, data on the effect of the medicine on milk production or composition should be collected, if potentially clinically relevant”*.<sup>1</sup>

European regulatory recommendations are in line with those of the US Food and Drug Administration (FDA).<sup>2</sup>

An expert meeting organized by the FDA in 2016 concluded that for the decision about drug treatment during breastfeeding to be evidence-based, needed information includes at a minimum the amount of drug in human milk, the effect of the drug on milk production, and an understanding of the risks of the drug on the breastfed infant based on expected levels of exposure.<sup>3</sup>

In summary, clinical lactation studies quantifying drug excretion to milk are rare, despite the call from regulatory, health care professionals, and researchers alike. There is a need to undertake human lactation studies to determine the transfer of drugs to human milk and facilitate an evidence-based decision about drug use in breastfeeding. Updated information is a prerequisite for optimal treatment of breastfeeding women in need of medications.

### 2.2 Rationale for the study

#### 2.2.1 Allergy in Breastfeeding Women

The benefits of breastfeeding and breast milk for both infants and mothers are established and well known.<sup>4</sup> At the same time, medication use during breastfeeding is common; the exact percentage of women receiving medications during the post-partum period is challenging to define due to the lack of uniform medication use reporting system during breastfeeding.<sup>5</sup>

Approximately 20-30% of women of reproductive age are diagnosed with allergic disorders.<sup>7</sup> Second-generation antihistamines, which have fewer sedative effects than first-generation antihistamines, are the first-line therapy in breastfeeding women.<sup>8</sup> According to the Norwegian Prescription database<sup>6</sup> around 200,000 women aged 15-39 years filled an antihistamine prescription in 2019. The number of women in childbearing who use antihistamines is probably higher since antihistamines are also available over-the-counter (OTC) in Norway.

Limited data exist about the transfer of some of the commonly used second-generation antihistamines into human milk. Only three clinical lactation studies on second-generation antihistamines were identified.<sup>9,10,11</sup> More details about relevant clinical studies are found in section 2.3.1.

The high prevalence of allergic diseases, along with the few clinical studies on the use of antihistamines during breastfeeding, creates a necessity for human lactation studies on antihistamines.

No clinical studies have been done on levocetirizine, the pharmacologically active component in cetirizine. Physiochemical properties for (levo)cetirizine suggest that they are transferred to human milk. The amount excreted and the effects of this exposure on a nursing infant are yet to be studied. The label of (levo)cetirizine products states that cetirizine is excreted into human milk<sup>12</sup> (See Table 1 below for examples). One study has been identified on cetirizine<sup>11</sup>, where only three breastfeeding women were recruited. More details about relevant clinical studies are found in section 2.3.1.

Table 1: Summarizing SmPC text for cetirizine, levocetirizine, and zirtek about breastfeeding ([www.medicines.org.uk/emc/](http://www.medicines.org.uk/emc/)).

Example	SmPC text
Levocetirizine (Xyzal 5mg)	Cetirizine, the racemate of levocetirizine, has been shown to be excreted in human. Therefore, the excretion of levocetirizine in human milk is likely. Adverse reactions associated with levocetirizine may be observed in breastfed infants. Therefore, caution should be exercised when prescribing levocetirizine to lactating women. <sup>12</sup>
Cetirizine (Zirtek 10 mg)	Cetirizine passes into breast milk. A risk of side effects in breastfed infants cannot be excluded. Cetirizine is excreted in human milk at concentrations representing 25% to 90% of those measured in plasma, depending on sampling time after administration. Therefore, caution should be exercised when prescribing cetirizine to lactating women. <sup>13,14</sup>

### 2.2.2 Current Treatment options

Newer antihistamines are preferred in breastfeeding as they generally are thought to have fewer central nervous system adverse effects like drowsiness and fatigue compared to first-generation antihistamines.<sup>15</sup> Studies quantifying second-generation antihistamine excretion in breast milk are limited. Human clinical lactation studies have been conducted for loratadine, terfenadine and its metabolite fexofenadine, and cetirizine; the sample size in these studies was six, four, and three, respectively.<sup>9,10,11</sup> There is thus a lack of evidence-based treatment recommendations for breastfeeding women in need of treatment with antihistamines.

### 2.2.3 Pharmaceutical and Therapeutic Background

Levocetirizine is a non-sedating histamine H<sub>1</sub> receptor antagonist. It is the (R)-enantiomer and the principal pharmacologically active component of the racemic mixture cetirizine. Levocetirizine and cetirizine are indicated for the symptomatic treatment of allergic rhinitis and the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria. Compared to cetirizine, levocetirizine has a higher affinity to H<sub>1</sub> receptors than cetirizine.<sup>16</sup>

Moreover, levocetirizine has fewer sedating activities than other antihistamines.<sup>16</sup> PK parameters for cetirizine and levocetirizine presented in table 1 indicate that they will be excreted into human milk. In this protocol, (levo)cetirizine will be used to refer to cetirizine and levocetirizine.

The low molecular weight, minimum metabolism, and the long plasma half-life of (levo)cetirizine estimate a high excretion into human milk. Nevertheless, the high plasma protein binding of (levo)cetirizine may decrease its transfer to breast milk.

Table 2: PK parameters for cetirizine and levocetirizine.<sup>17</sup>

PK Parameters	Cetirizine	Levocetirizine
T <sub>1/2</sub>	8.3 hours	8 hours
T <sub>max</sub>	0.5-1 hour	1 hour
V <sub>d</sub>	0.4-0.6 l/kg	0.4 l/kg
PB	93%	92%
MW	389 g/mol	389 g/mol
DDD	10 mg	5 mg

## **2.3 Relevant Clinical and Preclinical Studies**

### **2.3.1 Lactation Studies**

To date, no clinical studies have been conducted to quantify levocetirizine excretion into human milk, and potential side effects on nursing infants below one year of age remain unknown. Milk concentrations have been determined only for fexofenadine, loratadine, and its metabolite descarboethoxyloratadine, also known as desloratadine, and only recently for cetirizine.<sup>18</sup> Moreover, the effect of maternal use of (levo)cetirizine on milk production has not been studied.

One study estimating loratadine excretion into breast milk was identified.<sup>9</sup> Six breastfeeding women were included in this study. After a single oral dose of 40 mg of loratadine, milk samples were collected. M/P ratio was 1.17. Over 48 hours, the amount of loratadine excreted into milk was 4.2 µg, which was 0.01 of the administered dose, and only 6.0 µg of the active metabolite was transferred to milk. The authors concluded that this dose is unlikely to present infants' hazards.<sup>9</sup>

In another study, milk and blood samples were collected from four lactating mothers after a single administration of 60 mg terfenadine. Samples were collected after reaching steady-state concentration. Terfenadine was not found in milk. However, a low concentration of its active metabolite fexofenadine was transferred to milk. M/P ratio was 0.21. The average milk level of fexofenadine was 41 µg/L, while the average maternal plasma was 309 ng/mL. The study demonstrated that nursing infants are not exposed to more than 0.45% of the recommended maternal weight-adjusted dose. It was concluded that this exposure is unlikely to be associated with untoward effects.<sup>10</sup>

Recently, a study including three breastfeeding women has been conducted in the USA. Milk samples were collected after a single administration of 10 mg cetirizine. Measured AUC was 506.8 ng·hr/mL,  $C_{avg}$  was 21.1 ng/mL,  $C_{max}$  was 49 ng/mL. The calculated Infant dose was 0.0031 mg/kg/day, and RID was 1.77%. According to the authors, this minimal excretion of cetirizine into human milk is unlikely to pose a significant risk to nursing infants.<sup>11</sup>

### **2.3.2 Safety in the pediatric population**

In a double-blinded, placebo-controlled, randomized, multicenter trial of levocetirizine, 5 mg once daily for four weeks was administered to 306 children with allergic rhinitis aged 6 to 12 years.<sup>19</sup> No statistically significant difference in the frequency of adverse events was reported between pediatric patients using levocetirizine and the placebo group.

In another randomized, double-blinded, placebo-controlled trial of 255 children aged 12–24 months who received treatment with (levo)cetirizine, no increase in adverse events frequency has been reported in those treated with levocetirizine than the placebo group. (The frequency was 55.2% in the levocetirizine group compared with 52.6% in the placebo group).<sup>20</sup> The most frequent ADRs were headache, upper respiratory tract infection, and influenza.<sup>20</sup>

Two placebo-controlled studies in 159 pediatric patients aged 6-11 months and aged one year to less than six years exposed to levocetirizine, sleep disorder, somnolence, diarrhea, vomiting, and constipation have been reported.<sup>12</sup>

## 2.4 Benefit/Risk Assessment

This study is observational and will not impact participant's treatment. Therefore, participation in this study will not expose breastfeeding women to additional risks. This study will provide information that can help health care professionals and breastfeeding women make an informed decision about antihistamines in breastfeeding.

### 2.4.1 Summary of the known and potential undesirable effects on human subjects.

Reported undesirable effects in levocetirizine<sup>12</sup> and cetirizine<sup>13</sup> are summarized in table 3.

Table 3: Summary of adverse events as reported in SmPC of levocetirizine and cetirizine

Drug	Age	Reported adverse effects
Levocetirizine	Pediatric patients aged 6-11 months and 1-6 years	Somnolence, sleep disorder, diarrhea, constipation, vomiting
Cetirizine	Children aged from 6 months to 12 years	Somnolence, Rhinitis, Fatigue, Diarrhea

Few colic and irritability cases in infants exposed to antihistamines have been reported.<sup>15</sup>

## 3. OBJECTIVES AND ENDPOINTS

Table 4: Summary of study's objectives and endpoints

Primary Objectives	Primary Endpoints
Quantifying (levo)cetirizine excretion into human milk.	Variability of concentration of (levo)cetirizine in human milk samples.
Assessing the influence of demographics and other co-factors on drug concentrations in human milk.	Variation in mother milk drug levels according to demographics and other co-factors.
Predicting average drug exposure in infants.	Calculation of average and range of simulated relative infant dose (RID).
Secondary Objectives	Secondary Endpoints
Monitor the safety of (levo)cetirizine in breastfed infants of mothers using (levo)cetirizine.	Maternal self-reported adverse events among breastfed infants
Detecting the impact of (levo)cetirizine on milk production.	Maternal self-reported perceived changes in milk production

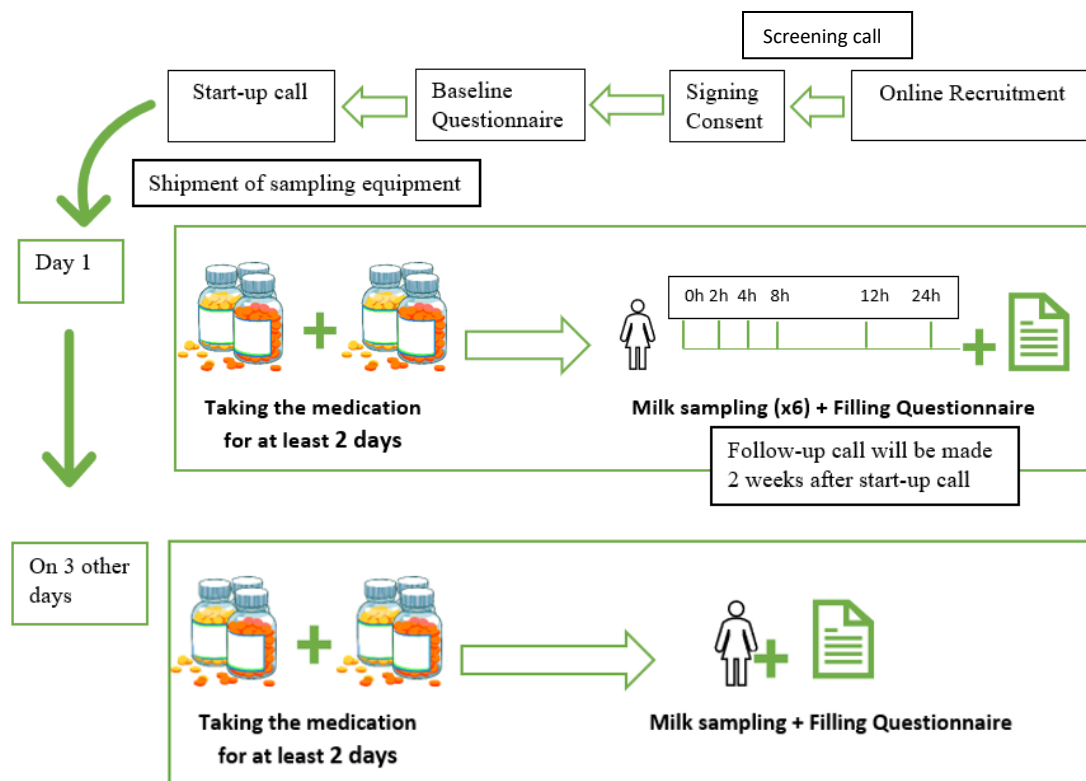


## 4. STUDY DESIGN

### 4.1 Design

This is a phase IV, open-label observational study conducted to detect (levo)cetirizine levels in breastfeeding women and monitor adverse events in nursing infants. No interference with the participants' treatment will be made in this study. In total, 25 to 40 lactating women who meet all inclusion criteria and none of the exclusion criteria will be recruited. The population pharmacokinetics (Pop PK) approach will describe drug concentration in human milk and estimate drug exposure in infants.

**Figure 1a.** Study procedure: Milk sampling regimen and filling out questionnaire



The study procedures in (levo)cetirizine clinical lactation are illustrated in Figure 1a.

First, participants will be asked to answer several questions to determine their eligibility based on the inclusion/exclusion criteria predetermined in the study. Then, after participants submit the eligibility form, a screening call will be made to recheck that the participant meets all of the inclusion criteria and none of the exclusion criteria and explain the consenting process.

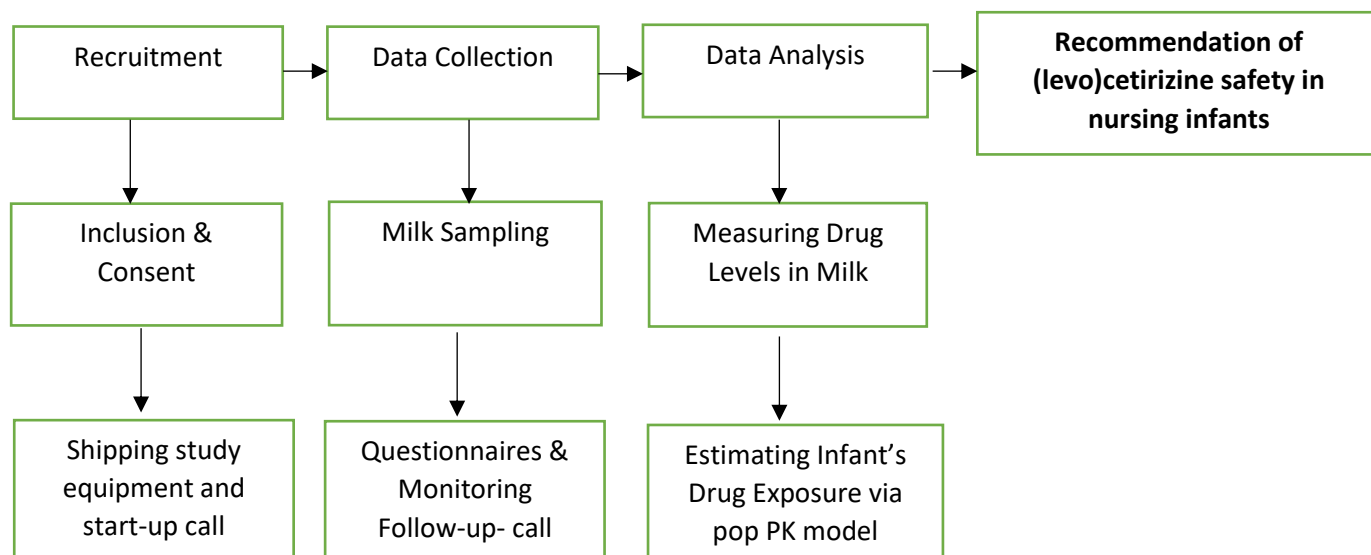
Participants will then be asked to answer the baseline questionnaire. Thereafter, a start-up call with the participants will be scheduled to provide support and information on the practical procedures, including milk sampling and the shipment.

The follow-up questionnaires will be answered on day one, where (6 milk samples) will be provided, and at each consecutive milk sampling day 2, 3, and 4, where one milk sample will be delivered.

Two to three weeks after the start-up call, a follow-up call will be made to answer any potential questions that might have arisen along the process. More details about milk sampling are found in section 6.4.1.

## 4.2 Study process

The study process is depicted in Figure 1b.



**Figure 1b.** Study Process

## 4.3 Scientific Rationale for Study Design

### 4.3.1 Milk Only Study

FDA recommends milk-only studies unless there is a reason to conduct another type of clinical lactation study (Guidance Document-Clinical Lactation Studies: Considerations for Study Design).<sup>2</sup>

Pharmacokinetics of (levo)cetirizine in adults is well established, and therefore blood samples from breastfeeding mothers are not needed. FDA recommends a mother-infant pair study when there is evidence that the drug accumulates in human milk.

No lactation studies have been conducted on levocetirizine. The clinical study conducted on cetirizine, the racemic mixture of levocetirizine, showed no accumulation of the drug in human milk.<sup>11</sup> Therefore, a mother-infant pair study is probably not required.

### 4.3.2 Population Pharmacokinetics

Population pharmacokinetics (pop PK) is a method used to describe a given drug's concentration-time profiles within a given population using the measured calculation in individuals' biological fluids.<sup>21</sup> Pop PK approach is based on non-linear mixed effect modeling techniques that allow estimating both fixed (i.e., invariant) population parameters and random effects (i.e., inter-individual and residual variability).<sup>21</sup>

In clinical lactation studies, the pop PK approach can be used to estimate infants' exposure to drugs in breast milk. The high clinical value of pop PK is due to integrating individual covariates in the model that conventional PK studies may neglect. Therefore, pop PK gives better estimates of pharmacokinetic parameters of real-life patients.<sup>21</sup>

FDA recommends that milk sampling should avoid disruption of the breastfeeding routine. Intensive milk sampling is both inconvenient to breastfeeding mothers and can be a concern in lactation studies. Unlike conventional PK studies where richly sampled data is required, several samples collected from a heterogeneous population are sufficient to build the pop PK model.<sup>21</sup>

Pop PK analysis will be performed by team experts on these analyses.

### 4.4 Study Duration

The study recruitment period will be one year. Recruitment will start in the allergy season, if possible. Participation in the study will start when the first study informed consent is signed, and end when the follow-up call of the last participant is completed, or six months after the last participant is recruited, whichever comes last.

The study will be completed by the end of the IMI ConcePTION project period in 2024.

### 4.5 Beginning and End of Study Definition

The study begins when the first participant signs the informed consent form. The study recruitment period ends when the last participant delivers the milk sample(s), withdraws from the study, or is lost to follow-up.

### 4.6 Criteria for the termination of the study

The study recruitment will be stopped when 25 participants providing 9 milk samples each have fully participated in the study. Additionally, recruitment may be stopped due to procedure related problems or if the number of discontinuations for administrative reasons is too high.

## 5. STUDY POPULATION

### 5.1 Inclusion Criteria

The participant will be eligible for inclusion in the study if the participant:

- I. Mother > 18 years, with well-established breastfeeding, and their infant is at least eight weeks old.
- II. Is using (levo)cetirizine during breastfeeding, and is at a steady-state, i.e., has used the drug daily for at least two days before sampling.
- III. Provides written informed consent for the study and can sign with an electronic ID.

## 5.2 Exclusion Criteria

The participant will be excluded from the study if the participant:

1. Mothers <18 years
2. Mother's with preterm infants (gestational age < 34 weeks)
3. Mothers to twins
4. Mothers to infants with malformations or severe illness
5. Inability to communicate due to language barriers for the mother.

## 5.3 Sample Size

A total of 20 to 25 breastfeeding women is considered sufficient to quantify the transfer of (levo)cetirizine excretion into human milk (2). This is also bearing in mind that levocetirizine/cetirizine is expected to show relatively little variability between participants due to its pharmacological and pharmacokinetic properties (standard dosing regimen, no active metabolites, no genetic polymorphism, similar bioavailability between administration forms, no food interactions). Therefore, we will aim for up to 40 participants to allow for a few dropouts.

## 5.4 Rationale for Study Population

Lactating women who are at least 18 years of age treated with (levo)cetirizine. Infants  $\geq 8$  weeks will be included in the study. Lactation studies should favorably be initiated six weeks after delivery. This period will give the mother time to rest after delivery and breastfeeding to be well established. Additionally, Infants under two months of age are most vulnerable to adverse drug reactions.<sup>22</sup>

The FDA recommends that milk sampling occurs after mature milk development (approximately ten days post-partum). Colostrum or transitional milk collection may overestimate drug transfer in mature milk. Leaky gap-junctions between the mammary alveolar cells in early post-partum may allow for increased drug passage into milk. These junctions close by the second week of lactation.<sup>23</sup>

## 5.5 Recruitment Strategy

Several patient organizations will be used to advertise for this clinical study. Examples are The Norwegian Asthma and Allergy Association, Tryggmammamedisin, Ammehjelpen, and The Norwegian Women's Public Health Association. Social media websites like Facebook will also be used to recruit potential participants.

Advertisements and an informative video will be distributed through appropriate channels.

All online recruitment methods will direct participants to the study website to register by signing an online consent form with an electronic ID. Prior to consenting, each participant will be asked to confirm their eligibility to participate in the study electronically (electronic confirmation on the study website). Participants will then be asked to fill an online baseline questionnaire before being enrolled in the study.

Study participants will be contacted for a start-up call where detailed information about the study procedures will be provided. Moreover, instructions will be sent to the participants along with the study equipment.

## **5.6 Discontinuation of Study Drug and Participant Withdrawal**

### **5.6.1 Participant Withdrawal from Study**

A participant is withdrawn from the study if the participant withdraws consent from the study. Participants can withdraw from the study at any time without specifying a reason. All dropouts will be adequately recorded.

The participant's data will be used in analyses that are in progress at the time of the withdrawal request, or that have been performed before the request being received by the sponsor. The participant's data will not be used in any new analyses started after the request is received.

Participants who withdraw should be encouraged to continue to be followed for reporting potential adverse events, and when possible, deliver a final milk sample.

Study personnel contact details to be used if participants want to withdraw from the study will be provided in the consent form.

### **5.6.2 Lost to Follow Up**

If a participant/potential participant is not reachable, three attempts will be made to contact the participants. A participant is considered lost to follow-up if the participant is non-responsive after three attempts from the last established contact.

## **STUDY ASSESSMENTS AND PROCEDURES**

### **6.1 Analysis of Drug Levels**

Measurement of levocetirizine and cetirizine levels in milk will be carried out using a validated method consisting of liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). The method will be developed and validated prior to the analysis by the Department of Pharmacy, Drug Delivery, Uppsala University (UPPS), Sweden.

The samples will be analysed by team members at the Department of Pharmacy, Drug Delivery, Uppsala University (UPPS), Sweden.

### **6.2 Pharmacokinetics Assessments**

Measured milk drug concentrations will be analyzed using the pop PK approach and summarized to obtain a mean concentration-time profile. The pop PK model then allows retrieving individual pharmacokinetic parameters, and thus the most probable concentration-time profile for each patient included in the population.

Pharmacokinetic characterization of each participant will be carried out using population PK/PD parameter estimation programs such as NONMEN.

Pop PK will then be used to define the main pharmacokinetic parameters of the selected drugs along with their variability in milk, and to study the influence of co-factors on drug disposition in lactating mothers.

The obtained concentration-time profiles will be used to estimate the infant's exposure to the drug by simulating drug levels in milk under various conditions that encompass variability among mothers, as well as parameters linked to milk consumption.

The existing equilibrium between plasma and milk concentrations will allow estimating drug disposition in plasma, and the fraction of passage in the milk from the collected milk samples.<sup>24</sup>

Therefore, the built model will estimate drug passage to human milk and retrieve the expected milk concentration-time profiles under the appropriate dosage regimen. The pharmacokinetic modeling procedure will be as follows:

First, a population pharmacokinetic model will be created from the data collected in milk. Several single and multi-compartment models will be compared to depict the drug while identifying the parameters responsible for the observed variations in the population of interest (i.e., statistical models).

The covariates will then be sequentially incorporated into the base model (i.e., structural plus error models) and retained in the model only if they reach statistical significance. The latter factors will then be combined, and only the most significant ones included to obtain the final covariate model.

The model will be validated using standard statistical techniques in pop PK and the results compared to the literature to detect and quantify the differences in drug disposition between lactating women and the general adult population.

Finally, concentration-time profiles of drugs in milk will be simulated according to different dosage regimens.

Milk concentration will be used to estimate the amount of the drug ingested by nursing infants according to the following equation<sup>24</sup>:

<sup>a</sup>**Note:** Dosing units [e.g., mcg, units, grams] may be changed as appropriate in the following equations:

**Estimated daily infant dose via breast milk (mg/kg/day) = drug concentration in breast milk (mg/mL) x volume breast milk ingested (mL/kg/day)<sup>a</sup>**

<sup>a</sup>When the actual volume of milk ingested by the infant is not known, 150 mL/kg/day will be used in the calculation (the amount assumed to be ingested by an exclusively breastfed infant)

Besides, the two following variables will be calculated:

Infant dose relative to the weight-adjusted maternal dose:

**Relative infant dose (%) = estimated daily infant dose via breast milk (mg/kg/day) / maternal dose (mg/kg<sup>b</sup>/day) x 100**

<sup>b</sup>**Note:** Calculation uses maternal dose per kg, not fixed dose; if maternal weight is unknown, 70 kg is being used in the calculations.

Infant dose relative to the used therapeutically for an infant of the same age (Hale, T. W., 2012):  
**Relative infant dose (%) = estimated daily infant dose via breast milk (mg/kg/day) / infant therapeutic dose (mg/kg/day) x 100**

## **6.3 Study Assessments**

### **6.3.1 Adverse Events Reporting**

Potential adverse events in breastfed infants will be collected retrospectively by the mother once during the four days of milk sampling. The mother will specifically be asked close-ended questions about the following symptoms in the breastfed child the last three days: Drowsiness, sedation, poor feeding or refusal of the breast, rash, bruising or bleeding, constipation, diarrhea, stools with blood or abnormal color, fever.

## **6.4 Study Related Procedures**

### **6.4.1 Milk Sampling**

Milk sampling will be carried out at the study participant's home by the breastfeeding woman herself. Each participant will be asked to provide milk samples on four different days (Figure 1a). On day 1, participants will be asked to donate 6 milk samples at the following time points: 0t, 2t, 4t, 8t, 12t, 24t. Participants will also be asked to donate 1 milk sample on 3 other different days. It is up to each participant when the 3 other milk samples are taken, as long as the drug is taken for 2 consecutive days prior to milk sampling, and the whole process doesn't exceed 3 months due to study logistic reasons.

Each milk sample will be 20 ml collected in appropriate containers. It is required that the participant has been using the cetirizine/levocetirizine for at least two consecutive days before milk sampling to ensure steady-state. Although it is preferential that participants provide all requested milk samples, it is not a requirement. Delivering the first 6 milk samples from day 1 is sufficient for participants to be included in the study.

The participant will be provided with the milk collection kit and all the necessary equipment for the collection. Electric pumps of the same brand will be used for all participants. Sampling can be made irrespective of the time of drug intake for (levo)cetirizine.

### **6.4.2 Processing and Shipments of Milk Samples**

Milk samples will be stored in a plastic container in the woman's freezer until all samples have been collected, then shipped in ice packs to the Uppsala Biobank, Uppsala, Sweden



(Registration number 827 at the Swedish Health and Social Care Inspectorate). Sample preparation and storage will be done at the Uppsala Biobank.

## **6.5 Administrative and General Procedures**

### **6.5.1 Informed Consents**

Informed consent will be obtained from each potential participant prior to participation in this clinical study. Informed consent forms (ICF) will be signed using an electronic ID. All ICFs and any other written patient material will be approved by the Regional Committees for Medical Research Ethics (REC) in advance of use. Three consent forms will be used in this study, one for the main study, which will be signed by the mother, one for the collection of health information about infants where both parents will sign on, and the third one is for storage of milk samples in the Uppsala Biobank for future biomedical research where the mother will sign on.

### **6.5.2 Collection of Health-Related Information**

Participants will be asked to provide background and health-related information needed to develop the Pop PK model and calculate the RID.

Sociodemographic characteristics, breastfeeding practices, medical history, information about (levo)cetirizine intake, concomitant medication use, and infant's health information will be collected via the baseline questionnaire. The baseline questionnaire will be filled after the participant has consented to participate in the study.

General information about the drug's impact on the nursing infant and milk production will be collected via a follow-up questionnaire. The baseline questionnaire and the follow-up questionnaires will include the participants' full identity and represent the study's primary source document.

The collected health related information is in accordance to the FDA recommendation on the design of clinical lactation studies (2). FDA recommends collecting data about several groups of variables. Those variables can be classified into maternal factors (maternal weight, age, gestational age at delivery, stage of lactation, length of time postpartum, smoking, alcohol intake, concomitant drugs, ethnicity, race, and existing medical conditions), infant factors (age, weight, history of prematurity, drugs, existing medical conditions, ethnicity, and race), the exclusivity of breastfeeding, timing of milk sample in relation to the dose and days postpartum.<sup>2</sup> Moreover, two new assessments were recently recommended to be included in clinical lactation studies, collecting drug's effect on milk production and safety information in the nursing infants.

Collected data will be stored securely in the study database; Services for sensitive data (TSD) allow further analyses. TSD is a platform used by researchers at UiO. The database records will be identified only with the patient study number and initials.



## **7. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATION**

### **7.1 Code of Conduct**

This clinical study will be conducted in compliance with local and national regulations, the International Council for Harmonization Good Clinical Practice (ICH-GCP), and the ethical principles in the Declaration of Helsinki.

Prior to starting the study, approval from the Regional Ethics Committee and Data Protection Officer at the University of Oslo (UiO) will be obtained. A Data Protection Impact Assessment (DPIA) will be performed by UIO/study PI.

As confirmed by The Norwegian Medicines Agency (NoMA), the study is exempted from submission to NoMA, as no invasive interventional procedures will be performed in the study.

### **7.2 Direct Access to Source Data/Documents**

The primary investigator will permit audits, REC review, and regulatory inspections, providing direct access to source data/documents.

### **7.3 Data Handling and Record-Keeping**

Data collected will be processed, stored, and utilized in compliance with the EU general data protection regulation (GDPR)<sup>25</sup>. Participants will be assigned a unique study ID. Personal information that can make participants identifiable will be stored at TSD, UIOs server for sensitive data. Only anonymous data will be shared with researched outside UIO.

Participants will be informed that the sponsor (ConcePTION) will use personal study-related data in accordance with local data protection law. Participants will also be oriented that collected data can be subject to audits and inspection from regulatory authorities, as needed.

Records and documents, including ICF will be retained for five years after study completion.

All data collected through the questionnaires will be stored at TSD, UIOs server for sensitive data.

Anonymous information from the analysis of (levo)cetirizine in breast milk will be stored at the bioanalytical center in Uppsala, and shared with the pop PK expert group in ConcePTION for pop PK analysis. Information that can make participants identifiable will not be shared the researched outside UiO. Processed anonymous, aggregated data, i.e., bioanalysis results, PopPK modeling, will be stored at the central ConcePTION database in Utrecht.

Breast milk samples will not be used for other purposes than stated in this study without agreement with UIO, approval from the ethics committee, and informed consent from the patients.

### **7.4 Source Documents**

Source documents in this study are the electronic questionnaires that will be stored at TSD, UIOs server for sensitive data.

Source documents should be contemporaneous, original, accurate, and complete. Changes to source data should be traceable.

### **7.5. Insurances**

All patients in Norway are entitled to compensation for patient injury in accordance with the Patient Injuries Act.

## **8. PUBLICATION POLICY**

The Sponsor commits to publishing the study's results according to the pre-specified plans for data analysis.

The study will be registered in the Clinical Trials Register prior to its start (clinicaltrials.gov.) The results of the study will be published as scientific papers in peer-reviewed journals. Preparation of such manuscripts will be prepared independently by the investigators and in accordance with International Council for Harmonization Good Clinical Practice (ICH-GCP), and the ethical principles in the Declaration of Helsinki.

The following funding disclosure will be used:

"Publication from this project is part of the activities within the ConcePTION project. It has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 821520. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and EFPIA." ‘

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