BMJ Paediatrics Open

Determining the exposure of maternal medicines through breastfeeding: the UmbrelLACT study protocol—a contribution from the ConcePTION project

Martje Van Neste ,[1,2] Nina Nauwelaerts ,[3] Michael Ceulemans ,[1,2,4] Kristel Van Calsteren ,[5,6] An Eerdekens,[7] Pieter Annaert ,[3,8] Karel Allegaert ,[1,2,6,9] Anne Smits [2,6,7]

To cite: Van Neste M, Nauwelaerts N, Ceulemans M, *et al*. Determining the exposure of maternal medicines through breastfeeding: the UmbrelLACT study protocol—a contribution from the ConcePTION project. *BMJ Paediatrics Open* 2024;**8**:e002385. doi:10.1136/bmjpo-2023-002385

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjpo-2023-002385).

KA and AS contributed equally.

MVN and NN are joint first authors.

Received 14 November 2023
Accepted 20 February 2024

Check for updates

© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to
Dr Anne Smits; anne.smits@uzleuven.be

ABSTRACT

Introduction Breastfeeding is beneficial for the health of the mother and child. However, at least 50% of postpartum women need pharmacotherapy, and this number is rising due to the increasing prevalence of chronic diseases and pregnancies at a later age. Making informed decisions on medicine use while breastfeeding is often challenging, considering the extensive information gap on medicine exposure and safety during lactation. This can result in the unnecessary cessation of breastfeeding, the avoidance of pharmacotherapy or the off-label use of medicines. The UmbrelLACT study aims to collect data on human milk transfer of maternal medicines, child exposure and general health outcomes. Additionally, the predictive performance of lactation and paediatric physiologically based pharmacokinetic (PBPK) models, a promising tool to predict medicine exposure in special populations, will be evaluated.

Methods and analysis Each year, we expect to recruit 5–15 breastfeeding mothers using pharmacotherapy via the University Hospitals Leuven, the BELpREG project (pregnancy registry in Belgium) or external health facilities. Each request and compound will be evaluated on relevance (ie, added value to available scientific evidence) and feasibility (including access to analytical assays). Participants will be requested to complete at least one questionnaire on maternal and child's general health and collect human milk samples over 24 hours. Optionally, two maternal and one child's blood samples can be collected. The maternal medicine concentration in human milk will be determined along with the estimation of the medicine intake (eg, daily infant dose and relative infant dose) and systemic exposure of the breastfed child. The predictive performance of PBPK models will be assessed by comparing the observed concentrations in human milk and plasma to the PBPK predictions.

Ethics and dissemination This study has been approved by the Ethics Committee Research UZ/KU Leuven (internal study number S67204). Results will be published in peer-reviewed journals and presented at (inter)national scientific meetings.

Trial registration number NCT06042803.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is still an extensive information gap regarding medicine exposure and safety during breastfeeding. Few case studies on selected medicines have been conducted. However, a diversity of study methods have been used for these investigations.

WHAT THIS STUDY HOPES TO ADD

⇒ This prospective observational study aimed to obtain a generic protocol (umbrella approach) for clinical lactation studies to generate more knowledge on medicine safety during lactation. The presence of ethics and biobank approvals can facilitate rapid patient inclusion and study performance in terms of logistics and feasibility.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The data collected will provide new insights into the transfer of medicines to human milk and support the desired interplay between case reports and physiologically based pharmacokinetic predictions in this research field. Despite centre-specific regulations, the protocol provides a general workflow that can be used as a guide for future clinical lactation studies in and outside our institution.

INTRODUCTION

Breastfeeding is highly recommended by the WHO, more specifically exclusive breastfeeding up to 6 months after birth and continued partially, in combination with complementary feeding, until 2 years of age. This is because breastfeeding has a positive impact on the development and general health of children. Breastfed children are less likely to suffer from childhood infections, at least in part due to antibodies in human milk, and have a lower risk of being overweight.[1] According to Castro *et al*[2] breastfeeding is also related to higher

bmjpo: first published as 10.1136/bmjpo-2023-002385 on 10 April 2024. Downloaded from http://bmjpaedsopen.bmj.com/ on April 26, 2024 by guest. Protected by copyright.

intelligence, with a possible increase up to seven intelligence quotient points and a reduction in child morbidity and mortality.[2] In addition, breastfeeding is also beneficial for maternal health, for example, by reducing the risk of developing breast or ovarian carcinoma.[3]

At least 50% of women need pharmacotherapy in the postpartum period, and this proportion has been rising due to the increasing prevalence of chronic diseases and later-age pregnancies.[4] Meanwhile, an immense information gap regarding the safety of medicines during lactation still exists today, complicating evidence-based decisions on the use and selection of medicines during breastfeeding.[5 6] This often results in unnecessary cessation of breastfeeding or poor adherence to or avoidance of pharmacological treatment.[4 7] Furthermore, the majority of medicines are used off-label during breastfeeding, which may put the child at risk for unknown side effects.[8]

To assess the transfer of medicines in human milk, the relative infant dose (RID) and the milk-to-plasma (M/P) ratio are commonly used as parameters in clinical lactation studies. M/P ratios reported in the literature are often based on single time point assessments. However, as the concentration profiles in human milk and plasma vary individually over time and may not be exactly the same, the M/P ratio may differ significantly depending on the timing of sampling. Ideally, the M/P ratio should be based on the (24-hour) area under the concentration-time curve (AUC) in human milk and plasma.[9] Assuming that only the unbound and unionised medicine fraction will cross the blood–milk barrier, the M/P ratio can be calculated based on the physicochemical properties of a medicine (eg, pH partitioning, protein binding and distribution into milk lipid), for instance, using the non-clinical phase distribution model.[10 11]

Koshimichi *et al*[12] have developed an empirical model to predict the in vivo M/P ratio based on the physicochemical properties of the medicine (ie, polar surface area, molecular weight, lipophilicity as logP and $logD_{7.4}$ and hydrogen bond donors). However, medicines that are dependent on transporters (efflux and uptake) for their active secretion into human milk are not sufficiently well captured by this method.[12] Moreover, an issue with approaches using exposure indexes such as the RID is the arbitrary cut-off point (typically 10%), indicating safe versus non-safe exposure.[9] Importantly, the safety of the child does not only depend on the dosage that the child receives via human milk but also on the toxicity of the medicine and its major metabolites, as well as the absorption, distribution, metabolism and excretion (ADME) profile of the medicine and its metabolites in the child.

Besides the above-mentioned methods to study medicine transfer in human milk, non-clinical (in vitro and in vivo animal) experiments have been developed. Unfortunately, these experiments were often not successful in predicting human milk medicine concentrations due to species-specific differences.[13 14]

Recently, some studies on the prediction of medicine exposure in the child via breastfeeding have been performed using an in silico method, that is, physiologically based pharmacokinetic (PBPK) modelling.[15 16] PBPK modelling allows bottom-up predictions of pharmacokinetics (PK) based on the integration of population-specific physiology data with medicine-specific data on ADME and physicochemistry. These models have been accepted by regulatory authorities and the pharmaceutical industry to predict drug–drug interactions and population-specific PK.[17] Although there are limitations, these models indicate that PBPK modelling is a feasible approach predicting child exposure to maternal medicine via breastfeeding.[18] Lactation and paediatric PBPK models are currently being developed within the Innovative Medicine Initiative (IMI) project ConcePTION[i], a European public–private partnership aiming to establish an ecosystem to generate evidence-based information on the exposure and effects of medicines during pregnancy and lactation.

Breastfeeding women and their breastfed children are often excluded from clinical trials due to ethical and practical reasons, which result in a therapeutic orphan population and a huge knowledge gap.[19] Due to this existing information gap, performing clinical lactation studies is highly needed and can provide valuable information. However, a broad variability in conducting and reporting on clinical lactation studies exists where, for example, essential PK data might be missing, such as dosage or time of medicine intake relative to the sampling time.[20 21] In addition, obtaining ethics approval for samples of each individual woman and each specific compound makes conducting clinical lactation studies time-consuming, while the breastfeeding period is generally limited in time. However, the collection of in vivo human data is essential for the evaluation of lactation PBPK models. These thoroughly evaluated PBPK models will lead to a generic set of breastfeeding-specific population parameters, enabling the construction of structural PBPK frameworks for breastfeeding women and breastfed infants. Such frameworks might subsequently be applied with increasing certainty to similar medicines for which in vivo data are still lacking.

The UmbrelLACT study is a prospective, observational, clinical lactation study to collect data on human milk transfer of maternal medicines and, subsequently, data on child intake and systemic exposure through human milk and the general health outcome of the child. In addition, the results will be used to evaluate the predictive performance of lactation and paediatric PBPK models.

METHODS AND ANALYSIS

Study design

This UmbrelLACT protocol, listing the generic steps of recruitment, sampling, sample storage and data management, has been developed within an interdisciplinary team with the aim of including lactating cases using medicines for which only limited safety information during breastfeeding is available in the literature.

[i]https://www.imi-conception.eu/

bmjpo: first published as 10.1136/bmjpo-2023-002385 on 10 April 2024. Downloaded from http://bmjpaedsopen.bmj.com/ on April 26, 2024 by guest. Protected by copyright.

Distribution of the study awareness and information may occur via different channels, that is, the University Hospitals Leuven, the BELpREG pregnancy registry in Belgium (www.belpreg.be) or external health facilities, so that interested breastfeeding women are able to contact the study team.[22] Each request and compound is evaluated on relevance (ie, added value to available scientific evidence) and feasibility (including timely access to analytical assay). Optionally, available cases in the literature or data from other biobanks with a similar sampling method can be pooled with new data achieved from the current study protocol while respecting all guidelines and regulations in the relevant biobanks to generate more insights from the pooled available observations.

This prospective observational study will evaluate the presence and transfer of medicines in human milk, along with systemic concentrations and health outcomes of the child, without interfering with the maternal pharmacological therapy as previously initiated by the women's treating physician(s). This means lactating women will not be asked by the researchers to initiate or use medicines for research purposes while breastfeeding or expressing milk. In addition, this study does not interfere with the decision to give human milk to the child through breastfeeding or expressed milk.

Due to the umbrella approach, defining a predefined sample size is challenging. We anticipate to enrol about five cases, with a maximum of 15 lactating women, per year, according to feasibility. This will provide evidence of the achievability of implementing the UmbrelLACT protocol in practice.

Inclusion and exclusion criteria

Breastfeeding women can be included when they are at least 18 years old and are exclusively or partially breastfeeding (or expressing milk) at the time of milk sampling. Eligible cases are using medicines, for any indication, for at least five half-lives of the medicine (ie, to be at a steady-state concentration of the medicine) and are willing to express and collect human milk during at least 24 hours. Mothers of twins are excluded. Their breastfed neonate (from birth up to 28 days postnatal age), infant (1 month–23 months) or preschool child (2–6 years) can be included if the gestational age is at least 24 weeks and if written informed parental consent is obtained.

Study visits

Screening visit

Study information and contact details of the study team are distributed to individual, eligible mothers in the University Hospitals Leuven via the BELpREG initiative or external health facilities.[22] Interested breastfeeding women can contact the study team. Subsequently, a screening visit (by phone, video call or at an already planned real-life consultation for medical follow-up) will be planned to explain the study and discuss informed consent in case of interest for participation (see online supplemental file 1) (table 1).

Characteristics from the mother and child and the maternal pharmacotherapy, such as listing medicine intake during the 3 days prior to sampling, will be collected via a self-reported questionnaire, according to the Food and Drug Administration (FDA) guidelines on clinical lactation studies and PBPK analyses.[23 24] This includes medical data to interpret maternal medicine exposure (eg, confounding factors such as smoking, alcohol and renal function), child exposure (eg, maturational factors, medicine, etc) and to adequately evaluate the PBPK models (eg, maternal biometry, renal and liver function). The medical data to be collected can be found in the online supplemental file 2.

Sampling day

After inclusion, a sampling day is planned at least 2 weeks postpartum (non-colostrum phase). Steady-state intake of the medicine and the possibility of milk expression over 24 hours are requested. If the participant gives consent for additional sampling days, the interval should be at least 1 week and preferably 2–3 months for chronic treatment (see table 1). Human milk sampling is performed at the patient's home or during hospitalisation for medical reasons, with self-directed sampling instructions provided (see online supplemental file 3). A member of the study team is generally present during the first human milk sample collection to assist with the procedure and is afterwards available during the 24-hour collection period. Blood sampling is performed at the patient's home or outpatient clinic at the University Hospitals Leuven by a trained member of the study team.

Human milk

The total available milk volume of one feed is collected from both breasts by using an electric pump each time the woman would normally breastfeed her child. For each sampling moment, the total volume of milk (determined using a measurement cup) and sampling time are noted to simulate the child's milk intake of a feeding session. Subsequently, 5–10 mL is transferred in a test tube for analysis (maximum 10% of the collected volume of each feed). The participant decides how the remainder of the collected milk is used.

Maternal blood

Blood collection (6–10 mL EDTA or another tube, depending on the compound) will be performed within a 1-hour interval from the first feeding (expressing) after medicine intake and 24 hours after medicine intake (preferably with milk collection within 1 hour of blood sampling).

Children's blood

Blood collection from the child will be performed on the same day as maternal sampling if parental consent is obtained. A maximum of 5% of the total blood volume of the child[25] will be collected in an EDTA or another tube, depending on the type of compounds.

bmjpo: first published as 10.1136/bmjpo-2023-002385 on 10 April 2024. Downloaded from http://bmjpaedsopen.bmj.com/ on April 26, 2024 by guest. Protected by copyright.

Table 1 Overview of the timing of the study visits and investigations of included patients.

	Screening visit	Sampling day 1	Sampling day 2 (optional*)	Sampling day 3 (optional*)	Follow-up children †
Signed informed consent from mother with parental informed consent for child	X				
Collecting medical data of the mother and child	X	X	(X)	(X)	
Collecting medicine list with last intake and medicine data during 3 days prior to the sampling day	X	X	(X)	(X)	
Collecting medicine-specific information (formulation, timing, dose and confounders)		X	(X)	(X)	
Collecting 24-hour human milk samples, starting at the time of medicine intake		X	(X)	(X)	
Collecting two maternal blood samples: one at the time of the first milk pumping session after medicine intake and one at the last pumping session of the 24-hour period		(X)	(X)	(X)	
Collecting a single child's blood sample within the 24-hour period of milk collection, if approval of the parent(s) is obtained		(X)	(X)	(X)	
Questionnaire-1 about the general health of the child until the day of sampling (see online supplemental file)		X	(X)	(X)	
Questionnaire-2 about the general health of the child (see online supplemental file)					X

Investigations, which are optional, are mentioned between brackets.
*In the case of multiple sampling days, a minimum lag time of 1 week between sampling days will be maintained. For chronic treatment, second or third sampling can be performed with a lag time of 2 months.
†Two weeks after the last sampling day in the case of an acute treatment; and 2 months after the last sampling day in the case of a chronic treatment. In the case of a combination of acute and chronic treatment, the questionnaire will be sent 2 weeks and 2 months after the last sampling day.

Milk samples will be stored in the fridge (4°C) at the patient's home for a maximum of 24 hours, transported on ice, together with the optional blood samples, and finally stored at −80°C until bioanalysis. Blood samples will be centrifuged (10 min, 3000×g and 4°C) and the plasma (supernatant) will be frozen at −80°C until bioanalysis. Specific additional sample handling can be added, depending on the compound(s) of interest. If the participant is taking a second compound of interest, the samples can be analysed for that compound as well.

Variables related to the general health of the child, such as growth, hospital admissions and medicine intake, will be questioned. The first questionnaire will be given to the parents on the sampling day and the second will be given 2 weeks (in the case of short-term treatment) or 2 months (in the case of chronic treatment) after the milk and/or blood collection (see online supplemental files 4,5). If an acute and chronic treatment is combined, the participants will be asked to complete the questionnaire at 2 weeks and 2 months after the last sampling day.

Biochemical analysis

For the quantification of the concentration of medicines in the milk and blood samples, liquid chromatography with tandem mass spectrometry (LC-MS/MS) will mainly be used, or a different method depending on the compound(s), at a facility where the requested assay(s) is/are or will easily become available for human milk or another matrix. The exploration of the required method of bioanalysis and its availability is part of the feasibility assessment. If a sensitive LC-MS/MS method, or a different method depending on the compound(s), needs to be developed, the recovery, specificity, linearity, precision and accuracy of this method will be determined prior to determining the human milk and plasma concentrations of the milk samples.[21]

Healthy volunteers

Milk (100–300 mL) and plasma samples (15–20 mL) of healthy volunteers, breastfeeding women without pharmacotherapy for an underlying medical condition, are required for method development of new milk and plasma assays, validation of the analytical methods and development of improved PBPK models. According to the European Medicines Agency (EMA) guidelines on bioanalytical method validation, initial donations from six healthy volunteers are required, and for each new assay development, subsequent donations are needed.[26] Besides an informed consent form, a questionnaire will be used to identify the exposure of healthy volunteers to,

bmjpo: first published as 10.1136/bmjpo-2023-002385 on 10 April 2024. Downloaded from http://bmjpaedsopen.bmj.com/ on April 26, 2024 by guest. Protected by copyright.

for example, nicotine, caffeine and alcohol at the time of sampling (see online supplemental files 6,7).

Biobank

All milk and blood samples collected from patients and healthy volunteers will be handled, transported and stored according to the developed standard operating procedures. Storage of the samples will occur at UZ/KU Leuven (biobank approval received on 25 November 2022). After bioanalysis, the leftover samples will be stored for 10 years at UZ/KU Leuven.

Outcomes

Outcomes will be reported by performing descriptive statistics using Microsoft Excel, R and Rstudio (R Foundation for Statistical Computing). Since this is an exploratory clinical study, results should be interpreted with caution. If feasible, we aim to collect several cases per compound.

Primary outcome

The primary outcome of the included cases will be the quantification of the concentration of medicines in human milk. Subsequently, the 24-hour AUC-based M/P ratio will be determined, if at least two paired plasma and milk concentrations are available or if the AUC in plasma can be extracted from the literature (Equation 1).

$$\text{M/P ratio} = \frac{\text{AUC}_{\text{human milk}}}{\text{AUC}_{\text{plasma}}} \quad (1)$$

However, the M/P ratio for a single time point will be calculated using the paired milk and plasma samples. Furthermore, milk and plasma PK parameters of medicines and relevant metabolites will be estimated, such as the area under the milk concentration–time curve, the average concentrations (Cave, ie, AUC divided by collection and/or dosing interval), mean milk concentration, peak and trough milk concentration and time to reach peak milk concentration (if available, depending on dosing and lactation regimen). The plasma PK parameters, such as AUC, (time to) peak plasma concentration, plasma clearance (CL) or apparent oral CL, apparent volume of distribution and terminal half-life, will be compared with scientific literature results, if available.

Secondary outcomes

First, an estimation of the child's exposure to maternal medicine via human milk will be calculated using the daily infant dosage (DID, mg/kg/day) for the mother–child pair (Equation 2).

For the mother–child pair:

$$DID\left(\frac{\frac{mg}{kg}}{day}\right) = \sum_{i=1}^{n}\left(\frac{Milk\ Concentration_i\left(\frac{mg}{L}\right) * Milk\ Volume_i\ (L)}{Infant\ weight\ (kg)}\right) \quad (2)$$

Furthermore, the DID (mg/kg/day) will be calculated for an exclusively breastfed child with a milk intake of 150 mL/kg/day and, to estimate the child's risk, of 200 mL/kg/day (Equation 3), as well as the RID (%) (Equation 4).[24]

For an exclusively breastfed child:

$$DID\left(\frac{\frac{mg}{kg}}{day}\right) = Average\ Steady-State\ Milk\ Concentration\left(\frac{mg}{L}\right) \times Infant\ Milk\ Intake\left(\frac{\frac{L}{kg}}{day}\right) \quad (3)$$

$$\text{RID}\ (\%) = \frac{DID\left(\frac{\frac{mg}{kg}}{day}\right)}{Daily\ Maternal\ Dose\left(\frac{mg}{day}\right)/Maternal\ Weight\ (kg)} \times 100 \quad (4)$$

The estimated DID via human milk will further be compared with, and divided by, the approved therapeutic dose in children, resulting in the relative infant therapeutic dose ($\text{RID}_{\text{therapeutic}}$) (Equation 5).

$$\text{RID}_{therapeutic}\ (\%) = \frac{DID\left(\frac{\frac{mg}{kg}}{day}\right)}{Daily\ Therapeutic\ Infant\ Dosage\left(\frac{\frac{mg}{kg}}{day}\right)} \times 100 \quad (5)$$

Moreover, the average infant medicine plasma concentration at steady state (Css, ave) will be estimated (Equation 6).

$$Average\ Infant\ Medicine\ Plasma\ Concentration\left(\frac{mg}{L}\right) = \frac{DID\left(\frac{\frac{mg}{kg}}{day}\right)}{Apparent\ Oral\ Clearance_{Infants}\left(\frac{\frac{L}{h}}{kg}\right) \times 24h} \quad (6)$$

The relative infant exposure via breastfeeding will be determined by calculating the child/maternal plasma ratio based on the paired mother–child plasma sample, upon availability of the child's plasma.

Third, maternal questionnaires will be used as an instrument to investigate the health outcome of the exposed children up to a maximum of 2 months after the last sampling day and will provide valuable, although limited, information on the potential side effects of maternal medicines' use in the breastfed child.

Finally, PBPK modelling according to Jones *et al*[27] will be explored.[27 28] Maternal PBPK models allow for predicting the concentration–time profile of the medicines in plasma and human milk and to predict PK parameters (eg, AUC and C_{max} in plasma and human milk, M/P ratio, DID and RID).[29] In addition, paediatric PBPK models can be used to predict the child's systemic exposure (eg, plasma concentration-time profile, AUC and C_{max}). The data acquired from this study could be used to evaluate and validate the predictive performance of the developed PBPK models by comparing the observed data to the predicted concentration and parameters (such as M/P ratio), as adequate evaluation of PBPK models can be achieved with relatively few data and cases. Consequently, the child's systemic exposure and the exposure-related child risks, such as the relative exposure, will be predicted by using this bottom-up approach and will be evaluated if data is available. This is done in accordance with the 'Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation' from EMA and 'Physiologically Based Pharmacokinetic Analyses—Format and Content' from the FDA.[23 30]

bmjpo: first published as 10.1136/bmjpo-2023-002385 on 10 April 2024. Downloaded from http://bmjpaedsopen.bmj.com/ on April 26, 2024 by guest. Protected by copyright.

Research experiences

A screening and enrollment log will be used while conducting this UmbrelLACT study. Based on this screening log, we will be able to report on the experiences of the patients, such as reasons for not participating in this study or the feasibility of data and sample collection.

Patient and public involvement

This UmbrelLACT study protocol was created as part of the IMI ConcePTION project and finds its origin in the advice requests the (clinical) research team receives regarding medicine safety during breastfeeding. Furthermore, the feasibility of the 24-hour human milk collection period was successfully executed in a recently published case report of our group.[31] The project is compliant with the WHO breastfeeding recommendations.[1]

Ethics and dissemination

This study has been approved by the Ethics Committee Research UZ/KU Leuven (internal study number S67204; 20/01/2023). Patient data and samples will be pseudonymised.

To recruit participants, the UmbrelLACT study has been shared through the website (www.belpreg.be/borstvoeding/) and the social media accounts of the BELpREG initiative. Furthermore, this study has been shared with healthcare providers, such as paediatricians, obstetricians, midwives and lactation consultants.

Study results will be published in peer-reviewed journals and will be presented at (inter)national scientific meetings.

Author affiliations
[1]Clinical Pharmacology and Pharmacotherapy, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium
[2]L-C&Y, KU Leuven Child & Youth Institute, Leuven, Belgium
[3]Drug Delivery and Disposition, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium
[4]Department for Health Evidence, Radboud University Medical Center, Nijmegen, Netherlands
[5]Gynaecology and Obstetrics, University Hospitals Leuven, Leuven, Belgium
[6]Department of Development and Regeneration, KU Leuven, Leuven, Belgium
[7]Neonatal Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium
[8]BioNotus GCV, Niel, Belgium
[9]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, Netherlands

Acknowledgements The research leading to these results was conducted as part of the ConcePTION consortium. This paper only reflects the personal views of the stated authors. The authors are grateful to KU Leuven, YouReCa and the Flemish Government for supporting the IdeaLab project 'MomsMed', in which most of the authors were involved and which boosted the interdisciplinary collaboration on clinical lactation research within our institute. Furthermore, we would like to thank Dr Neel Deferm, Dr Ruben Heremans and Dr Dries Ceulemans for their help in conceiving this project. This research was also presented as an abstract at the ESDPPP meeting of 2023.

Contributors MVN, NN, KA and AS conceived this project. MVN, NN, MC, KA and AS participated in the trial design. The first draft of the manuscript was written by MVN and NN and revised by MC, KVC, AE, PA, KA and AS. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding The ConcePTION project 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 programme and EFPIA. NN also received a PhD scholarship from Research-Foundation-Flanders (1S50721N). The research activities of AS are supported by a Senior Clinical Investigatorship of the Research Foundation, Flanders (FWO) (18E2H24N). The research activities of MC are supported by the Internal Funds KU Leuven (PDMt1/23/020).

Competing interests K.A. is deputy editor in chief and A.S. an Editorial board member of the journal BMJ PO. P.A. is co-owner of the company BioNotus GCV. The remaining authors declare no conflict of interest.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethics Committee Research UZ/KU Leuven (internal study number S67204; 20/01/2023). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Martje Van Neste http://orcid.org/0000-0002-0424-450X
Nina Nauwelaerts http://orcid.org/0000-0001-5301-6813
Michael Ceulemans http://orcid.org/0000-0002-4130-5869
Kristel Van Calsteren http://orcid.org/0000-0002-2438-6783
Pieter Annaert http://orcid.org/0000-0003-3525-7351
Karel Allegaert http://orcid.org/0000-0001-9921-5105
Anne Smits http://orcid.org/0000-0002-0710-6698

REFERENCES

1 WHO. Breastfeeding, Available: https://www.who.int/health-topics/breastfeeding#tab=tab_1 [Accessed 29 Nov 2021].
2 Amiel Castro R, Glover V, Ehlert U, *et al*. Breastfeeding, Prenatal depression and children's IQ and behaviour: a test of a moderation model. *BMC Pregnancy Childbirth* 2021;21:62.
3 Del Ciampo LA, Del Ciampo IRL. Breastfeeding and the benefits of Lactation for women's health. *Rev Bras Ginecol Obstet* 2018;40:354–9.
4 Saha MR, Ryan K, Amir LH. Postpartum women's use of medicines and Breastfeeding practices: A systematic review. *Int Breastfeed J* 2015;10:28.
5 De Hondt L, Gorsen SL, Verburgh P, *et al*. Health care providers' perspective and knowledge about peri-surgical medication and practices in Breastfeeding women. *Int J Environ Res Public Health* 2023;20:3379.
6 Fomina YY, Byrne JJ, Spong CY. Evaluating strength of recommendations for commonly administered medications in lactating women. *J Matern Fetal Neonatal Med* 2023;36:2163626.
7 Odom EC, Li R, Scanlon KS, *et al*. Reasons for earlier than desired cessation of Breastfeeding. *Pediatrics* 2013;131:e726–32.
8 Ren Z, Bremer AA, Pawlyk AC. Drug development research in pregnant and lactating women. *Am J Obstet Gynecol* 2021;225:33–42.
9 Anderson PO, Sauberan JB. Modeling drug passage into human milk. *Clin Pharmacol Ther* 2016;100:42–52.
10 Atkinson HC, Begg EJ. Prediction of drug distribution into human milk from Physicochemical characteristics. *Clin Pharmacokinet* 1990;18:151–67.

bmjpo: first published as 10.1136/bmjpo-2023-002385 on 10 April 2024. Downloaded from http://bmjpaedsopen.bmj.com/ on April 26, 2024 by guest. Protected by copyright.

11 Fleishaker JC, Desai N, McNamara PJ. Factors affecting the milk-to-plasma drug concentration ratio in lactating women: physical interactions with protein and fat. *J Pharm Sci* 1987;76:189–93.
12 Koshimichi H, Ito K, Hisaka A, *et al*. Analysis and prediction of drug transfer into human milk taking into consideration secretion and reuptake clearances across the Mammary Epithelia. *Drug Metab Dispos* 2011;39:2370–80.
13 Kimura S, Morimoto K, Okamoto H, *et al*. Development of a human Mammary epithelial cell culture model for evaluation of drug transfer into milk. *Arch Pharm Res* 2006;29:424–9.
14 McNamara PJ, Burgio D, Yoo SD. Pharmacokinetics of cimetidine during Lactation: species differences in cimetidine transport into rat and Rabbit milk. *J Pharmacol Exp Ther* 1992;261:918–23.
15 Garessus EDG, Mielke H, Gundert-Remy U. Exposure of infants to isoniazid via breast milk after maternal drug intake of recommended doses is clinically insignificant irrespective of Metaboliser status. A Physiologically-based pharmacokinetic (PBPK) Modelling approach to estimate drug exposure of infants via breast-feeding. *Front Pharmacol* 2019;10:5.
16 Abduljalil K, Pansari A, Ning J, *et al*. Prediction of drug concentrations in milk during Breastfeeding, integrating predictive Algorithms within a Physiologically-based pharmacokinetic model. *CPT Pharmacometrics Syst Pharmacol* 2021;10:878–89.
17 Maharaj AR, Edginton AN. Physiologically based pharmacokinetic modeling and simulation in pediatric drug development. *CPT Pharmacometrics Syst Pharmacol* 2014;3:e150.
18 Anderson PO, Momper JD. Clinical Lactation studies and the role of pharmacokinetic modeling and simulation in predicting drug exposures in Breastfed infants. *J Pharmacokinet Pharmacodyn* 2020;47:295–304.
19 Byrne JJ, Spong CY. Is it Safe?"-The many unanswered questions about medications and breast-feeding. *N Engl J Med* 2019;380:1296–7.
20 Wang J, Johnson T, Sahin L, *et al*. Evaluation of the safety of drugs and biological products used during Lactation: workshop summary. *Clin Pharma and Therapeutics* 2017;101:736–44.
21 Anderson PO. Guidelines for reporting cases of medication use during Lactation. *Breastfeeding Medicine* 2022;17:93–7.
22 Ceulemans M, Van Calsteren K, Allegaert K, *et al*. Information needs and counseling preferences among potential users of the future Teratology information service in Belgium: A cross-sectional study involving the public and healthcare professionals. *Int J Environ Res Public Health* 2022;19:8605:14:.
23 FDA. Physiologically based pharmacokinetic analyses — format and content: guidance for industry FDA-2016-D-3969. 2018.
24 FDA. Clinical Lactation studies: considerations for study design Guidance for Industry Draft Guidance FDA-2018-D-4525. 2019.
25 FDA. General clinical pharmacology considerations for neonatal studies for drugs and biological products guidance for industry. FDA-2019-D-3132. 2022.
26 European Medicines Agency: Committee for medicinal products for human use (CHMP). *Guideline on Bioanalytical Method Validation* 2011.
27 Jones HM, Mayawala K, Poulin P. Dose selection based on Physiologically based pharmacokinetic (PBPK) approaches. *AAPS J* 2013;15:377–87.
28 Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development - part 2: introduction to pharmacokinetic modeling methods. *CPT Pharmacometrics Syst Pharmacol* 2013;2:e38.
29 Nauwelaerts N, Macente J, Deferm N, *et al*. Generic Workflow to predict medicine concentrations in human milk using Physiologically-based pharmacokinetic (PBPK) Modelling—A contribution from the conception project. *Pharmaceutics* 2023;15:1469.
30 European Medicines Agency: Committee for medicinal products for human use (CHMP) guideline on the reporting of Physiologically based pharmacokinetic (PBPK) Modelling and simulation. 2018.
31 Nauwelaerts N, Ceulemans M, Deferm N, *et al*. Case report: Bosentan and Sildenafil exposure in human milk - A contribution from the conception project. *Front Pharmacol* 2022;13:881084.

bmjpo: first published as 10.1136/bmjpo-2023-002385 on 10 April 2024. Downloaded from http://bmjpaedsopen.bmj.com/ on April 26, 2024 by guest. Protected by copyright.

Questionnaire of medical and medicine data

Medicine history

Please note in the table below your medicine list or the medicine you use regularly with the date of your latest intake/administration. By medicine, we also mean freely available medicine, vitamin supplements and herbal mixtures.

Name of medicine, vitamin, herbal mixtures, … (commercial and generic)	Date of latest intake/administration	Dosage strength (eg 50 mg) and number of doses (eg 3 tablets/dag)	Start of intake of medicine, as specific as possible (eg 01/01/2020, 3 months ago, >5 year,…)

Please note in the table below the medicine you have taken **during the 3 days before the sampling day**. It is important to give an honest overview of all the medicine you have taken and/or have forgotten. This might clarify possible strange observations we find during analysing the samples. By medicine, we mean medicine that you use daily, but also the medicine you use occasionally, ranging from prescripted medicine to over-the-counter, vitamin supplements and herbal mixtures.

Date	Time of intake/administration (also report if the medicine has not been taken)	Name of medicine, vitamin, herbal mixtures, … (commercial and generic)	Dosage strength (eg 50 mg) and number if dose units (eg 2 tablets) and/or forgotten doses	Intake before/after/not in combination with a meal

Medicine on the sampling day

Please note all information relating to the **medicine you have taken on the sampling day** in the table below. This means both the medicine that will be studied in this study and other medicine you have taken. By all medicine, we mean prescription medicine but also freely available medicine, vitamin supplements or herbal mixtures.

Time of intake (also report if you have forgotten to take prescription medicine)	**Name of medicine** (commercial and generic, e.g. lipitor and atorvastatin), **form of medicine** (e.g. film-coated tablet) and **time** since the medicine has been taken	**Reason of use/intake** (reason why the medicine was prescribed and if possible the date of the diagnosis, and the date when the medicine was started)	**amount, dose and frequence of intake/administration** (e.g. twice a day 1 tablet of 1 mg or three times/day one capsule)	**Side effects** (report what side effects you possibly experienced from this medicine)	Intake before/after/not in **combination with a meal**

Maternal data

Please fill in the information below regarding yourself.

Age: Click or tap here to enter text.

Weight (in kg): Click or tap here to enter text.

Height (in cm): Click or tap here to enter text.

What is your ethnicity? Click or tap here to enter text.

☐ Caucasian

☐ North-African

☐ Black or sub-saharan

☐ Middle-Eastern

☐ Asian

☐ Latinx or Hispanic

Are you following a particular diet or feeding regime (e.g. vegetarian, vegan, lactose intolerance, gluten free, halal, keto diet, intermittent fasting, …)? If yes, specify :

☐ Yes: Click or tap here to enter text.

☐ No

Please fill in the information below regarding your most recent delivery.

How many weeks were you pregnant at the moment of delivery: Click or tap here to enter text.

How many days/weeks after the delivery took the sampling day plase: Click or tap here to enter text.

Are you breastfeeding exclusively?

☐ Yes, my child is exclusively breastfed

☐ No, my child is partially breastfed, in combination with other types of feeding.

To what extent does your child receive other types of feeding? Click or tap here to enter text.

☐ No, breastfeeding was stopped on following date because of: Click or tap to enter a date.

How many times per day do you breastfeed: Click or tap here to enter text.

How is breastfeeding going? Do you experience problems? Click or tap here to enter text.

Please fill in the information below regarding your medical history.

Do you have kidney problems?

☐ Yes: Click or tap here to enter text.

☐ No

Do you have liver problems?

☐ Yes: Click or tap here to enter text.

☐ No

Do you have other medical problems? If yes, specify

☐ Yes: Click or tap here to enter text.

☐ No

Did you have any previous pregnancies?

- **If yes, when and how did they go?**

  eg: 2015, no problems, sponaneous delivery at 38 weeks, son, healthy

eg: 2017, miscarriage at 7 weeks gestational age

☐ Yes: Click or tap here to enter text.

☐ No

- **If yes, did you breastfeed before?**

☐ Yes: Click or tap here to enter text.

☐ No

Please fill in the information below regarding your use of stimulants.

Are you smoking currently? If yes, How many?

☐ Yes: Click or tap here to enter text.

☐ No

Do you use drugs currently (e.g., cannabis, cocaine…)? If yes, what and how many?

☐ Yes: Click or tap here to enter text.

☐ No

How often do you use alcohol during the period you are breastfeeding?

☐ Daily

☐ Weekly

☐ Monthly

☐ Less than once per month

☐ Never

Data of the child

Please fill in the information below regarding the child you are breastfeeding

Sex of the child: Click or tap here to enter text.

Postnatal age (in days): Click or tap here to enter text.

Birtweight (in grams): Click or tap here to enter text.

Birthheight (in cm): Click or tap here to enter text.

Apgar score (if known): Click or tap here to enter text.

Ethnicity?

☐ Caucasian
☐ North-African
☐ Black or sub-saharan
☐ Middle-Eastern
☐ Asian
☐ Latinx or Hispanic

Was your child hospitalised during the period between birth and sampling day?

☐Yes ☐ No

If yes, period (describe how many days your child has stayed in the hospital)	Reason (describe the symptoms or condition why your child has been hospitalised eg. Prematurity, an accident, planned hospitalisation, disease, fever)

Did your child experience other (serious) health problems during the period between birth and today?

☐ Yes: Click or tap here to enter text.

☐ No

Biometrics:

The growth of your child (weight, length and head circumference) gives us an idea of his/her health and development. Please fill in the table below with all available measurements from birth until the sampling day (also see 'Kindboekje' of Kind & Gezin, if possible)

Date	Age	Weight	Length	Head circumference

Other remarks relating to the health of your child: Click or tap here to enter text.

Instructions on sampling and storage

We hereby provide you with practical instructions for obtaining a correct breast milk sample. One of the researchers will go over this with you and assist you with the first sampling. Do not hesitate to ask additional questions or contact us if anything is unclear.

Breast milk samples

Please express all breast milk during a **period of 24 hours, starting from the time of medicine intake**. The milk expressions occur with an electric pumping device.

STEP 1. From each expression, you should note the **total volume of milk** from both breasts together. You can write this volume down together with the date and the time of expression in the table below.

STEP 2. From each expression, you should transfer **5 to 10 ml** of the total volume into a Falcon tube (Figure 1) (max 10% of the total expressed volume of that expression). This means up to the indication with number 10. Wash your hands thoroughly first. Use a syringe (Figure 2) to draw up the milk and transfer it to the tube. The tubes you have received are labelled. Please use a new, clean syringe and the next tube for each expression.

STEP 3. Please note down the **correct label nummer** in the table for the correct expression. You should also note the time and dosage of the last medicine intake.

STEP 4. The sample of 10 ml should be stored immediately after collection in the refrigerator (4°C) for a maximum period of 24h. The sample will be collected within 24h by 1 of the investigators.

Figure 1: Falcon tube

Figure 2: Syringe

Blood sample collection

You can also agree to donate 2 blood sample. The first blood sample will be drawn within a 1-hour interval of the first expression after medicine intake we are studying. The second blood sample will be drawn 24 hours after medicine intake. Preferably also within 1 hour of an expression. It is important to collect the blood and milk samples within a short period of time in relation to each other. This way we get an accurate idea of the extent to which your medicine ends up in the milk. Please note the information of each blood sample in the table below.

If a blood sample from your child will also be drawn, then please also note the information of this sample in the table below.

Please add in the table below how the samples were stored.

The samples may be stored in the refrigerator (4°C) for a maximum of 24h.

Summary table of sample collection

Collection of samples					**Storage of samples**		
Date and time of sample collection	**Type of sample** (Milk, blood from mother of blood from child)	**In case of milk sample: total of expressed volume**	**Sample label**	**Sample volume**	Time when sample was put in the refrigerator	Temperature (if possible, note the exact temperature)	When were the samples transferred to KU Leuven?

Questionnaire-1 general health of the child

Date of sampling day: Click or tap here to enter text.

Date of completing questionnaire: Click or tap here to enter text.

Current weight (in kg): Click or tap here to enter text.

Current height (in cm): Click or tap here to enter text.

Describe the current feeding behaviour of your child (exclusive breastfeeding, combined breast –and formula feeding, breastfeeding + gruel, …): Click or tap here to enter text.

Was your child hospitalised during the period between birth and sampling day?

☐Yes

Period (describe how many days your child has stayed in the hospital)	Reason (describe the symptoms or condition why your child has been hospitalised eg. Prematurity, an accident, planned hospitalisation, disease, fever)

☐ No

Did your child experience other (serious) health problems during the period between birth and sampling day?

☐ Yes: Click or tap here to enter text.

☐ No

Did your child receive medicine, vitamins, food supplements, … that has been <u>prescribed by a doctor</u> in the last 7 days?

☐ Yes

Name medicine, vitamin, food supplement…	Indication (reason why the medicine was prescribed)	Dosage strength (eg 50 mg) and number of dose units (eg 2 tablets) and/or forgotten doses	Period (when and how long was the medicine taken)

☐ No

Dit your child receive medicine, vitamins, food supplements, … <u>without a prescription</u> in the last 7 days

☐ Yes

Name medicine	Indication (reason why the medicine was prescribed)	Dosage strength (eg 50 mg) and number of doses (eg 2 tablets) and/or forgotten doses	Period (when and how long was the medicine taken)

☐ No

Other remarks relating to the general health of your child: Click or tap here to enter text.

Questionnaire-2 general health of the child

Date of sampling day: Click or tap here to enter text.

Date of completing questionnaire: Click or tap here to enter text.

Current weight (in kg): Click or tap here to enter text.

Current height (in cm): Click or tap here to enter text.

Describe the current feeding behaviour of your child (exclusive breastfeeding, combined breast –and formula feeding, breastfeeding + gruel, …): Click or tap here to enter text.

Was your child hospitalised during the period between the sampling/study day and today?

☐Yes

Period (describe how many days your child has stayed in the hospital)	Reason (describe the symptoms or condition why your child has been hospitalised eg. Prematurity, an accident, planned hospitalisation, disease, fever)

☐ No

Did your child experience other (serious) health problems during the period between the sampling/study day and today?

☐ Yes: Click or tap here to enter text.

☐ No

Did your child receive medicine, vitamins, food supplements, … that has been <u>prescribed by a doctor</u> in the last 7 days?

☐ Yes

Name medicine, vitamin, food supplement…	Indication (reason why the medicine was prescribed)	Dosage strength (eg 50 mg) and number of doses (eg 2 tablets) and/or forgotten doses	Period (when and how long was the medicine taken)

☐ No

Dit your child receive medicine, vitamins, food supplements, … <u>without a prescription</u> in the last 7 days

☐ Yes

Name medicine	Indication (reason why the medicine was prescribed)	Dosage strength (eg 50 mg) and number of doses (eg 2 tablets) and/or forgotten doses	Period (when and how long was the medicine taken)

☐ No

Other remarks relating to the general health of your child: Click or tap here to enter text.

Title of the study: **Clinical lactation study on the exposure to medicines via human milk: an umbrella study protocol (UmbrelLACT)**

Sponsor of the study: *UZ Leuven*

Research organisation*: UZ Leuven, Herestraat 49, 3000 Leuven*

Medical Ethics Committee: *Ethische Commissie onderzoek UZ / KU Leuven*

Local investigators:

Local research-physicians UZ Leuven:

- Prof. Dr. Anne Smits, neonatology department
- Prof. Dr. Kristel Van Calsteren, gynaecology-obstetrics department
- Dr. An Eerdekens, neonatology department

Researchers of the department of Pharmaceutical and pharmacological sciences, KU Leuven
- Prof. Pieter Annaert
- Prof. Dr. Karel Allegaert
- Dr. Michael Ceulemans
- Nina Nauwelaerts
- Dr. Martje Van Neste

Researchers of the department of Development and regeneration, KU Leuven
- Dr. Ruben Heremans
- Dr. Dries Ceulemans

I. Information vital to your decision to take part

Introduction

You are participating in a clinical study to examine the transfer of medicine via breast milk. Participating in this study does not change your medical follow-up or treatment in any way, and you will not receive therapeutical advice from our investigational team. You take the medication that has been prescribed by your doctor and you have decided to breastfeed or express human milk, independent from this study. You indicate that you are willing to donate human milk samples for analysis. For this study, we ask your consent to use:

- Bodily samples (human breast milk samples and optionally blood samples)
- Data from your medical records that are relevant for this study
- Data from questionnaires regarding your and your child's health, that we ask you to fill out

Before you agree to take part in this study, we invite you to take note of its implications in terms of organisation, possible risks and benefits, to allow you to make a decision with full awareness of the implications. This is known as giving "informed consent".

Please read these few pages of information carefully and ask any questions you want to the investigator or his/her representative. There are 3 parts to this document: the information essential to your decision, your written consent and supplementary information (appendices) detailing certain aspects of the basic information.

If you take part in this clinical study, you should be aware that:

- The treatment offered to you by your doctor in accordance with current recommendations will not be altered if you take part in the study.
- This clinical study is being conducted after having been reviewed by the ethics committee Research UZ/KU Leuven.
- Your participation is voluntary and must remain free from any coercion. It requires the signature of a document expressing your consent. Even after having signed this document, you can stop taking part by informing the investigator. Your decision not to take part or to stop taking part in the study will have no impact on the quality of your care or on your relationship with the investigator.
- The data collected on this occasion are confidential and your anonymity is guaranteed during publication of the results.

- Insurance has been taken out in case you should suffer any damage in connection with your participation in this clinical study.
- You will not incur any charges for the visits/consultations, examinations or treatments specific to this study.
- You may contact the investigator or a member of his/her team at any time should you need any additional information.

Further information about your “Rights as a participant in a clinical study” can be found in appendix 2.

Objectives and description of the study protocol

You participate in a clinical study involving the exposure of medicine via breast milk. This is an exploratory study. This means that results of this study have to be interpreted with caution and will not with certainty result in therapeutic advice. There will be around 5 to 15 patients per year included.

This clinical study investigates if and how much of medicine, that is taken by the mother, reaches the breast milk. Moreover, we will examine if this medicine is absorbed by your child through your breast milk. Data of transfer of medicine through human breast milk is limited for different medicines, such as atorvastatin, venlafaxine, topiramate, pregabalin and the medicine you have been prescribed. The goal or this study is to collect this data to provide clear information to mothers and health care workers in the future about medicine in combination with breast feeding.

When you participate, at the earliest 2 weeks after the birth, human milk samples will be collected during a period of 24 hours. This happens at home or at the hospital if you are hospitalised for medical reasons. On the day that we collect the human milk samples, we can also optionally collect 2 blood samples from you, more specific 1 at the time of the first milk expression after medication intake and 1 at the last milk expression during the 24h period. If you give consent, we can collect 1 blood sample from your child to measure the amount of medicine in its body. Finally, medical data of you and your child, of medication intake, of the samples and of your general health will be collected. The obtained data will be used to evaluate the predictive ability of computer models. These computer models aim to predict the exposure to medicines via human milk and consequently the exposure of the child.

You are taking medication with limited available data on transfer via human milk. Furthermore, to participate in this study, you are a lactating mother (≥18 years) who has taken daily medication for a while and is willing to collect human milk (and optionally blood samples). You cannot have participated in a clinical study with an experimental medicine in the last three months.

Course of the study

Your participation in the study will last around 2 weeks, in case of an acute treatment, and 2 months, in case of a chronic treatment and involve minimally 2 (house) visits.

The (house) visits and examinations that we will describe, are part of the study. Participating in this study does not change your medical follow-up or the treatment you receive, which is in accordance with the current recommendations and independent of your possible participation in this study. Some additional procedures will be required in context of the study and are explained below (with more information in appendix 1).

The following moments will be scheduled for this study:

1. Screening moment, online or physical,
    a. During the screening, **information** of this study will be discussed with you. If you decide to participate, a signed informed consent is required. In case of an online screening moment, you will be asked to sign the informed consent form and to send the signed informed consent form back to the study team.
    b. Thereafter, we ask you during this screening to register medical data of you and your child:
        i. All necessary data and information for this study, such as age, weight, length, gestational age at delivery, breastfeeding pattern and medical diagnosis. Also information regarding smoking, alcohol intake, origin, diet, (other) medication intake, kidney- and liver function. For this purpose, a questionnaire will be used, and data from your medical file.

ii. All necessary data and information of your child for this study, such as age, birthweight, current weight, Apgar score, sex, known medical conditions, medication use, origin, exclusive breastfeeding (if not, the volume of the taken food has to be specified), kidney- and liver function, and data on the general health of your child. For this purpose, a questionnaire will be used, and data from the medical file of your child.

2. day of sample collection, where we will collect the following samples
    a. **Human milk:** You are asked to collect milk samples from every expressing session during a period of 24 hours starting after medication intake. Every expressing session the total volume will be recorded and a sample of human milk (5 to 10 ml, maximum 10% of the total expressed volume from that session) will be taken.
    b. *Optionally* 2 **blood samples**: The first blood sample (maximum 10 ml) will be drawn at the time of the first expressing session after medication intake. The second blood sample (maximum 10 ml) will be drawn at the time of the last expressing session (after 24h). The blood samples and the milk samples allow us to investigate to what extent the taken medication passes into breast milk.
    c. *Optionally* 1 **blood sample from your child**: If consent is obtained, a blood sample (1-5% of the total blood volume of your child, according to current recommendations) will be drawn from your child by a doctor or a study team member with experience in neonatal blood collection.
    d. A **questionnaire**: to register the general health of your child, a questionnaire will be presented on the sampling day. This questionnaire has to be filled in and sent back in one week. Completing the questionnaire takes approximately 5 minutes of your time. Your contact information can be used to send you this questionnaire.
3. *Optionally*, other sampling days can be planned. In case of multiple sampling days, an interval of minimally 1 week will be taken into account. In case of a chronic treatment, an interval of 2 to 3 months will be preferred.
4. Follow-up of the child
    a. A **questionnaire** to register the general health of your child, will be send to you after 2 weeks (acute treatment) or after 2 months (chronic treatment). This questionnaire has to be filled in and sent back in one week. Completing the questionnaire takes approximately 5 minutes of your time. Your contact information can be used to send you this questionnaire.

Description of the risks

Your participation in this study means that there will be optional blood samples. This might (in rare circumstances) cause pain, bleeding, hematomas, or a local infection at the area of blood collection. Some participants can feel light-headed or faint during the blood collection. The study members performing the blood collection will do all they can to minimise these inconveniences.

Benefits

Your participation in this study will not yield any personal benefits. Participation in this study will result in our better understanding of transfer of medicine via breast milk and, subsequently, we can recommend better treatment to breastfeeding mothers in the future. We want to emphasise that data collected from 1 person will not be sufficient to produce therapeutical advice (both for you and for others). However, the data can help us develop and improve computer models that predict the transfer of medicine via breast milk. This data, together with potential prospective data (including data of other medicine), can help us refine the computer models.

Withdrawal from the study

Your participation is voluntary. You are entitled to withdraw from the study for any reason, and without having to justify your decision.

You have the right to withdraw your consent to the study for any reason and without having to justify your decision. If you withdraw your consent to take part in the study, to guarantee the validity of the research, the data and samples encoded up to the point at which you withdraw, will be retained. From

the moment you withdraw your consent, no new data or samples may be collected or may be sent to the sponsor.

Samples of biological material collected during the study

The sponsor of the study undertakes that the samples will only be used within the context defined in the section “Progress of clinical research” and its appendices.

Samples collected for the analyses described for the study in this document

Since technical progress in this area is constant, if you agree, we would like to retain the surplus of your samples of biological material for 10 years for future studies in the context of the present clinical research, namely a better understanding of the transfer of medicine via breast milk. Any research outside the context described in this document may only be conducted with the approval of an ethics committee.

If you take part in this clinical study, we ask you:

- To cooperate fully in the smooth running of this study.
- Not to conceal any information relating to your state of health, the medication you are taking or the symptoms you are experiencing.
- To inform your investigator if you have been approached to participate in another clinical study while taking part in this study, in order to discuss if you can participate in the investigational study and if you have to stop your participation to this study.

You should also be aware that:

- for your safety, it is advisable for your GP, if you have one, or other specialists in charge of your health to be informed of your participation in this study. We will ask you to confirm your agreement but will respect your wish not to inform them where applicable.

Contact

If you need further information, but also if you have problems or concerns, you can contact the investigator (prof. Dr. A. Smits) on the following telephone number +32 16 34 35.

If you have any questions relating to your rights as a participant in a clinical study, you can contact the ombudsman of your institution on this telephone number: +32 16 34 48 18. If necessary, he/she can put you in contact with the ethics committee.

Title of the study: Clinical lactation study on the exposure to medicines via human milk: an umbrella study protocol (UmbrelLACT)

II. Informed consent

Participant

- I declare that I have been informed of the nature of the study, its purpose, its duration, any risks and benefits and what is expected of me. I have taken note of the information document and the appendices to this document.
- I have no personal benefit of participation. I understand that data measured on my collected milk samples (of 1 person) are not sufficient to produce therapeutical advice.
- I have had sufficient time to think about it and discuss it with a person of my choice, such as my GP or a member of my family.
- I have had the opportunity to ask any questions that came to mind and have obtained a satisfactory response to my questions.
- I understand that my participation in this study is voluntary and that I am free to end my participation in this study without this affecting my relationship with the therapeutic team in charge of my health.
- I take medication that has been prescribed by my treating doctor and the combination with breastfeeding is my own decision. This is not happening on request of the investigational team of this study.
- I understand that data about me will be collected throughout my participation in this study and that the investigator and the sponsor of the study will guarantee the confidentiality of these data in accordance with applicable European and Belgian legislation.
- I agree to my personal data being processed as described in the section dealing with confidentiality guarantees (appendix 2).
- I understand that milk samples will be collected during my participation in the study.
- I agree/do not agree (**delete as appropriate**) that 2 blood samples will be collected during my participation in the study.
- I agree/do not agree (**delete as appropriate**) to the sponsor retaining samples of biological material collected during the study for 10 years for subsequent research purposes but limited to the context of the present study.
- I agree/do not agree (**delete as appropriate**) that I can be contacted in the future for consent if researchers want to use the data and samples collected for the present study outside of the context of the present study.
- I agree that my GP and other specialist concerned with my health, can be contacted to ask for additional information about my health or the health of my child, If necessary.

I have received a copy of the information to the participant and the informed consent form.

Surname, first name, date and signature of the participant.

Parents / guardian

Name and first name of your child: ….…….....

I agree/do not agree (delete as appropriate) that 1 blood sample will be collected from my child.

Name parent / guardian: …….. Date: ……...

Signature parent / guardian: ……..…….....

Name parent / guardian: …….. Date: ……...

Signature parent / guardian: ……..…….....

Witness/Interpreter

I was present during the entire process of informing the patient and I confirm that the information on the objectives and procedures of the study was adequately provided, that the participant (or his/her legal representative) apparently understood the study and that consent to participate in the study was freely given.

Surname, first name and qualification of the witness/interpreter:

Date and signature of the witness/interpreter.

Investigator

I, the undersigned ……, confirm that I have verbally provided the necessary information about the study and have given the participant a copy of the information document.

I confirm that no pressure was applied to persuade the patient to agree to take part in the study and that I am willing to answer any additional questions if required.

I confirm that I operate in accordance with the ethical principles set out in the latest version of the "Helsinki Declaration", the "Good Clinical Practices" and the Belgian Law of 7 May 2004 related to experiments on humans.

Surname, first name, date and signature of the investigator's representative

Surname, first name, date and signature of the investigator

Title of the study: Clinical lactation study on the exposure to medicines via human milk: an umbrella study protocol (UmbrelLACT)

III. Supplementary information

1: Supplementary information on the organisation of the study

Participation in the study

The investigator or the investigator's representative will provide you the informed consent and necessary information for you and your child. As soon as you decide to take part in the study, some medical data about you and your child will be collected. Together, a time will be determined when the blood and breast milk collection can take place. You will be asked to keep a record of the medication you and your child are taking 3 days prior to the day of sample collection. It is important for the accuracy of our study that you register this information as correctly as possible.

Sample Collection

In mutual agreement, one (or more) day(s) will be determined on which breast milk (and optionally blood) samples will be collected. In case of multiple sampling days, an interval of minimally 1 week will be taken into account.
You will be asked to express your breast milk at the moment of a feeding session over a period of 24 hours. You are asked to register the total volume of the milk and the moment of sampling, and then bring 5 to 10 mL of the milk in a delivered 'Falcon-tube' for this research. Afterwards, you can decide for yourself how to use the remaining breast milk.
In addition to breast milk, optionally 2 blood samples (each maximum 10 ml) will be drawn. These blood samples will be drawn during the first hour after the first and last expressing session.

If consent has been given for a blood sample from your child, we will schedule this blood collection on the day of your sample collection. On this day, one blood sample will be drawn from your child (1-5% ot the total blood volume of your child, according to the current recommendations). This blood sample will be drawn by a doctor or researcher experienced in neonatal blood collection.

Blood samples and breast milk will be transported to a facility with the necessary equipment (e.g. BioNotus), where they will be analysed.

Finally, you will also receive a first questionnaire regarding the general health of your child. You will have 1 week to complete this questionnaire. This will take about 10 minutes of your time. Your contact information can be used to send you this questionnaire.

Follow-up of your child

After 2 weeks, in the case of acute treatment, or 2 months, in the case of chronic treatment, you will receive again a questionnaire about your child's general health. You will then again have 1 week to complete this questionnaire. This will take about 10 minutes of your time. Your contact information can be used to send you this questionnaire.

2: Supplementary information on the protection and the rights of the participant in a clinical study

Ethics Committee

This study has been reviewed by an independent Ethics Committee, namely the Ethics Committee of Research UZ/KU Leuven, which has issued a favourable opinion. It is the task of the Ethics Committee of Research UZ/KU Leuven to protect people who take part in a clinical trial. They make sure that your rights as a patient and as a participant in a clinical study are respected, that based on current knowledge, the risks to which participants will be exposed have been correctly evaluated and will be reasonably controlled..
You should not under any circumstances take the favourable opinion of the Ethics Committee of Research UZ/KU Leuven as an incentive to take part in this study.

Voluntary participation

Before signing, do not hesitate to ask any questions you feel are appropriate. Take the time to discuss matters with a trusted person if you so wish.

Your participation in the study is voluntary and must remain free of any coercion: this means that you have the right not to take part in the study or to withdraw without giving a reason, even if you previously agreed to take part. Your decision will not affect your relationship with the investigator or the quality of your future therapeutic care.

However, it is advisable for your safety to inform the investigator if you have decided to stop taking part in the study.

If you agree to take part, you will sign the informed consent form. The investigator will also sign this form to confirm that he/she has provided you with the necessary information about the study. You will receive a copy of the form.

Costs associated with your participation

If you decide to take part in this study, all the examinations or procedures necessary for the study will be paid for by the sponsor.

If you decide to participate in this study, there will not be any additional costs for you or your insurance company.

Since this is a non-sponsored study, you will not receive a compensation for participating.

Guarantee of confidentiality

Your participation in the study means that you agree to the investigator collecting data about you and your child and to the study sponsor using these data for research purposes and in connection with scientific and medical publications.

Your data will be processed in accordance with the European General Data Protection Regulation (GDPR) and with the Belgian legislation on the protection of natural persons with regard to the processing of personal data. UZ Leuven shall act as data controller for your data. You are entitled to ask the investigator what data are being collected about you and your child and what is their use in connection with the study. This data concerns your current clinical situation but also some of your background, the results of examinations carried out within the context of care of your health in accordance with the current standards and obviously the results of examinations required by the protocol. You have the right to inspect these data and correct them if they are incorrect[1].

The investigator has a duty of confidentiality vis-à-vis the data collected.

This means that he/she undertakes not only never to reveal your or your childs name in the context of a publication or conference but also that he/she will encode (your and your childs identity will be replaced by an ID code in the study) your and your childs data.

The investigator and his/her team will therefore be the only ones to be able to establish a link between the data transmitted throughout the study and your and your childs medical records[2].

[1] These rights are guaranteed by the European Data Protection Regulation (GDPR), by the Belgian legislation on the protection of natural persons with regard to the processing of personal data and by the Law of 22 August 2002 on patient rights.

[2] For clinical trials, the law requires this link with your records to be retained for 20 years. In the case of a advanced therapy medicinal product using human biological material, this period will be a minimum of 30 years and a maximum of 50 years in accordance with the Belgian Law of 19 December 2008 on the use of human biological material and the applicable royal decrees.

The personal data transmitted will not contain any combination of elements that might allow you or your child to be identified[3].

For the study data manager designated by the sponsor, the data transmitted will not allow you or your child to be identified. The latter is responsible for collecting the data gathered by all investigators taking part in the study, processing them and protecting them in accordance with the requirements of the Belgian law on the protection of privacy.

To verify the quality of the study, it is possible that your medical records will be examined by persons subject to professional secrecy and designated by the Ethics Committee of Research UZ/KU Leuven, the sponsor of the study or an independent audit body. In any event, this examination of your and your child's medical records may only take place under the responsibility of the investigator and under the supervision of one of the collaborators designated by him/her.

The (encoded) study data will be able to be sent to Belgian or other regulatory authorities, to the relevant ethics committee and/or to organisations working in collaboration with the sponsor.

Your consent to take part in this study therefore also implies your consent to the use of your encoded medical data for the purposes described in this information form and to their transmission to the aforementioned people and authorities.

The sponsor will use the data collected within the context of the study in which you are taking part, but would also like to be able to use them in connection with other research concerning the same condition as yours. Any use of your data outside the context described in this document is only possible with the approval of the ethics committee.

If you withdraw your consent to take part in the study, to guarantee the validity of the research, the data encoded up to the point at which you withdraw will be retained. No new data may be sent to the sponsor.
If you have any questions relating to how your data are being processed, you may contact the investigator. The data protection officer in your hospital can be contacted as well: DPO - UZ Leuven, Herestraat 49, 3000 Leuven, e-mail dpo@uzleuven.be.

Finally, if you have a complaint concerning the processing of your data, you can contact the Belgian supervisory authority who ensures that privacy is respected when personal data are processed.

The Belgian supervisory authority is called:
Data Protection Authority (DPA)
Drukpersstraat 35,
1000 Brussels
Tel. +32 2 274 48 00
e-mail: contact@apd-gba.be
Website: https://www.dataprotectionauthority.be

Future of your sample(s) collected during the study

The sample encoding procedure is the same as that used for your medical data. Samples sent to the sponsor will therefore only include your study ID code.

The manager of these samples Biobank UZ/KU Leuven undertakes to use them within the context of clinical research and to destroy them at the end of the scheduled storage period.

The sample of biological material taken is deemed to be a "donation" and you should be aware that, in principle, you will not receive any financial benefit (royalties) associated with the development of new therapies derived from the use of your donation of biological material and which may be of commercial value.

If you withdraw your consent to take part in the study, you may contact the investigator and have those of your samples that have not yet been used destroyed. The results obtained from your samples before you withdraw your consent remain the property of the study sponsor.

Insurance

Any participation in a clinical study involves a risk, however small it is. Even if there is no fault, the sponsor accepts responsibility for damage caused to the participant (or in the event of death, his/her

[3] The database containing the results of the study will therefore not contain any combination of elements such as your initials, your gender and your full date of birth (dd/mm/yyyy).

dependants) and directly or indirectly linked to his/her participation in the study. The sponsor has taken out insurance for this responsibility[4].

If the investigator believes that a link with the study is possible (the insurance does not cover the natural progression of your disease or the known side effects of your normal treatment), he/she will inform the study sponsor, which will initiate the declaration procedure to the insurance company. The latter will appoint an expert - if it considers it necessary - to assess whether there is a link between your new health problems and the study.

In the event of disagreement either with the investigator or with the expert appointed by the insurance company and also whenever you feel it is appropriate, you or - in case of death - your dependants may bring proceedings against the insurer directly in Belgium (name of insurance company, policy number, contact).

The law provides that the insurer may be summoned to appear either before the judge of the location where the event giving rise to the damage occurred, or before the judge of your domicile, or before the judge of the insurer's registered offices.

[4] In accordance with Article 29 of the Belgian Law related to experiments on humans (7 May 2004)

Translation of the informed consent for healthy volunteers

Title of the study: Clinical lactation study on the exposure to medicines via human milk: an umbrella study protocol (UmbrelLACT)

Informed consent for the healthy volunteer

Sponsor of the study: *UZ Leuven*

Research organisation*: UZ Leuven, Herestraat 49, 3000 Leuven*

Medical Ethics Committee: *Ethische Commissie onderzoek UZ / KU Leuven*

Local research-physicians University Hospitals Leuven:
- Prof. Dr. Anne Smits, neonatology department
- Prof. Dr. Kristel Van Calsteren, gynaecology-obstetrics department
- Dr. An Eerdekens, neonatology department

Researchers of the department of Pharmaceutical and pharmacological sciences, KU Leuven
- Prof. Pieter Annaert
- Prof. Dr. Karel Allegaert
- Dr. Michael Ceulemans
- Nina Nauwelaerts
- Dr. Martje Van Neste

Researchers of the department of Development and regeneration, KU Leuven
- Dr. Ruben Heremans
- Dr. Dries Ceulemans

I. Information vital to your decision to take part

Introduction

This clinical study investigates transfer of medicine via human milk. To develop reliable measurement techniques to determine medicines in human milk and blood samples, we also need human milk and blood samples from healthy volunteers for verification. You are participating in the study as a healthy volunteer to donate these control human milk and blood samples. You have decided to breastfeed or express human milk, independent of this study. You indicate your willingness to provide human milk samples (and optionally blood samples) for the development of measurement techniques to investigate medicines. For this study, we ask your consent to use:

- Bodily samples (human milk samples and optionally blood samples)
- Data from questionnaires regarding your health

Before you agree to take part in this study, we invite you to take note of its implications in terms of organisation, possible risks and benefits, to allow you to make a decision with full awareness of the implications. This is known as giving “informed consent”.

Please read these few pages of information carefully and ask any questions you want to the investigator or his/her representative. There are 3 parts to this document: the information essential to your decision, your written consent and supplementary information (appendices) detailing certain aspects of the basic information.

If you take part in this clinical study, you should be aware that:

- This clinical study is being conducted after having been reviewed by the ethics committee Research UZ/KU Leuven.
- Your participation is voluntary and must remain free from any coercion. It requires the signature of a document expressing your consent. Even after having signed this document, you can stop taking part by informing the investigator. Your decision not to take part or to stop taking part in the study will have no impact on the quality of your care or on your relationship with the investigator.
- The data collected on this occasion are confidential and your anonymity is guaranteed during publication of the results.

- Insurance has been taken out in case you should suffer any damage in connection with your participation in this clinical study.
- You will not incur any charges for the visits/consultations, examinations or treatments specific to this study.
- You may contact the investigator or a member of his/her team at any time should you need any additional information.

Further information about your "Rights as a participant in a clinical study" can be found in appendix 2.

Objectives and description of the study protocol

You are donating samples as part of a clinical study involving the exposure of medicine via human milk. This is an exploratory study. This means that results from this study should be interpreted with considerable caution and will not necessarily lead to therapeutic advice.

This clinical study investigates if and how much of medicine, that is taken by the mother, reaches the human milk. Moreover, we will examine if this medicine is absorbed by your child through your human milk. To (further) develop our analytic methods for this study, we need human milk and blood samples from healthy women. On participation, we ask you to collect human milk samples (total 100-300 ml) no earlier than 2 weeks after delivery. This can happen at home or in the hospital, e.g. if your child is hospitalised for medical reasons. If samples are collected at your home, the samples can be collected by someone from the study team after agreement. On the day of human milk sample collection, we also ask you to optionally donate one blood sample (20 ml).

The results of the analytical methods will further be used to improve the predictive performance of computer models. These computer models aim to predict the exposure of medicine through human milk, and consequently the exposure in the child.

To participate in this study, you have to be a lactating mother (≥18 years), who is healthy to the best of your knowledge and willing to collect human milk (and optionally blood) samples. You cannot have participated in a clinical study with an experimental medicine in the last three months.

Course of the study

Your participation in the study will last approximately 1 hour.

The examinations that we will describe, are part of the study. Participating in this study does not change the medical follow-up you receive, which is in accordance with the current recommendations and independent of your possible participation in this study. Some additional procedures will be required in context of the study and are explained below (with more information in appendix 1).

The following moments will be scheduled for this study:

1. Screening moment, online or physical
    a. During the screening, **information** of this study will be discussed with you. If you decide to participate, a signed informed consent is required. In case of an online screening moment, you will be asked to sign the informed consent form and to send the signed informed consent form back to the study team.
    b. Thereafter, we ask you during this screening to register exposure:
        i. Data such as gestational age at delivery, breastfeeding pattern and general health. Also information regarding exposure to smoking, alcohol, medication, contact with contrast medium and diet.
2. day of sample collection, where we will collect the following samples:
    a. **Human milk**: You are asked to donate 100 to 300 ml of human milk during one or multiple expression session(s).
    b. **Blood sample**: The blood sample will comprise a maximum of 20 ml.

Description of the risks

Your participation in this study means that there will be optional blood samples. This might (in rare circumstances) cause pain, bleeding, hematomas, or a local infection at the area of blood collection.

Some participants can feel light-headed or faint during the blood collection. The study members performing the blood collection will do all they can to minimise these inconveniences.

Benefits

Your participation in this study will not yield any personal benefits. Participation in this study will allow us to develop analytical methods to better understand the transfer of medicines into human milk. The results of the analyses may additionally help to develop and improve computer models that predict the transfer of medicines into human milk.

Withdrawal from the study

Your participation is voluntary. You are entitled to withdraw from the study for any reason, and without having to justify your decision.

You have the right to withdraw your consent to the study for any reason and without having to justify your decision. If you withdraw your consent to take part in the study, to guarantee the validity of the research, the data and samples encoded up to the point at which you withdraw, will be retained. From the moment you withdraw your consent, no new data or samples may be collected or may be sent to the sponsor.

Samples of biological material collected during the study

The sponsor of the study undertakes that the samples will only be used within the context defined in the section “Progress of clinical research” and its appendices.

Samples collected for the analyses described for the study in this document

Since technical progress in this area is constant, if you agree, we would like to retain the surplus of your samples of biological material for 10 years for future studies in the context of the present clinical research, namely developing analytical methods. Any research outside the context described in this document may only be conducted with the approval of an ethics committee.

If you take part in this clinical study, we ask you:

- To cooperate fully in the smooth running of this study.
- Not to conceal any information relating to your state of health, the medication you are taking or have missed, or the symptoms you are experiencing.
- To inform your investigator if you have been approached to participate in another clinical study while taking part in this study, in order to discuss if you can participate in the investigational study and if you have to stop your participation to this study.

Contact

If you need further information, but also if you have problems or concerns, you can contact the investigator (prof. Dr. A. Smits) on the following telephone number +32 16 34 35.

If you have any questions relating to your rights as a participant in a clinical study, you can contact the ombudsman of your institution on this telephone number: +32 16 34 48 18. If necessary, he/she can put you in contact with the ethics committee.

Title of the study**: Clinical lactation study on the exposure to medicines via human milk: an umbrella study protocol (UmbrelLACT)**

II. Informed consent

Participant

- I declare that I have been informed of the nature of the study, its purpose, its duration, any risks and benefits and what is expected of me. I have taken note of the information document and the appendices to this document.
- I understand that I do not gain personal benefit of participation.
- I have had sufficient time to think about it and discuss it with a person of my choice, such as my GP or a member of my family.
- I have had the opportunity to ask any questions that came to mind and have obtained a satisfactory response to my questions.
- I understand that my participation in this study is voluntary and that I am free to end my participation in this study without this affecting my relationship with the therapeutic team in charge of my health.
- I understand that data about me will be collected throughout my participation in this study and that the investigator and the sponsor of the study will guarantee the confidentiality of these data in accordance with applicable European and Belgian legislation.
- I agree to my personal data being processed as described in the section dealing with confidentiality guarantees (appendix 2).
- I understand that milk samples will be collected during my participation in the study.
- I agree/do not agree (**delete as appropriate**) that one blood sample will be collected during my participation in the study.
- I agree/do not agree (**delete as appropriate**) to the sponsor retaining samples of biological material collected during the study for 10 years for subsequent research purposes but limited to the context of the present study.
- I agree/do not agree (**delete as appropriate**) that I can be contacted in the future for consent if researchers want to use the data and samples collected for the present study outside of the context of the present study.
- I have received a copy of the information to the participant and the informed consent form.

Surname, first name, date and signature of the participant

Witness/Interpreter

I was present during the entire process of informing the patient and I confirm that the information on the objectives and procedures of the study was adequately provided, that the participant (or his/her legal representative) apparently understood the study and that consent to participate in the study was freely given.

Surname, first name and qualification of the witness/interpreter:

Date and signature of the witness/interpreter.

Investigator

I, the undersigned ……, confirm that I have verbally provided the necessary information about the study and have given the participant a copy of the information document.

I confirm that no pressure was applied to persuade the patient to agree to take part in the study and that I am willing to answer any additional questions if required.

I confirm that I operate in accordance with the ethical principles set out in the latest version of the "Helsinki Declaration", the "Good Clinical Practices" and the Belgian Law of 7 May 2004 related to experiments on humans.

Surname, first name, date and signature of the investigator's representative	Surname, first name, date and signature of the investigator

Title of the study**: Clinical lactation study on the exposure to medicines via human milk: an umbrella study protocol (UmbrelLACT)**

III. Supplementary information

1 : Supplementary information on the organisation of the study

Participation in the study

The investigator or the investigator's representative will provide you the informed consent and necessary information for you. As soon as you decide to take part in the study, some medical data about you will be collected. Together, a time will be determined when the blood and breast milk collection can take place.

Sample collection

In mutual agreement, a day will be determined on which human milk (and optionally blood) samples will be collected.
You will be asked to express your human milk and to donate 100 to 300 ml. This amount may be expressed in multiple expression sessions. Afterwards, you can decide for yourself how to use the remaining breast milk.
In addition to human milk, optionally a blood sample will be drawn.

Blood and human milk samples will be used to develop and validate analytical methods.

2 : Supplementary information on the protection and the rights of the participant in a clinical study

Ethics Committee

This study has been reviewed by an independent Ethics Committee, namely the Ethics Committee of Research UZ/KU Leuven, which has issued a favourable opinion. It is the task of the Ethics Committee of Research UZ/KU Leuven to protect people who take part in a clinical trial. They make sure that your rights as a patient and as a participant in a clinical study are respected, that based on current knowledge, the risks to which participants will be exposed have been correctly evaluated and will be reasonably controlled..
You should not under any circumstances take the favourable opinion of the Ethics Committee of Research UZ/KU Leuven as an incentive to take part in this study.

Voluntary participation

Before signing, do not hesitate to ask any questions you feel are appropriate. Take the time to discuss matters with a trusted person if you so wish.

Your participation in the study is voluntary and must remain free of any coercion: this means that you have the right not to take part in the study or to withdraw without giving a reason, even if you previously agreed to take part. Your decision will not affect your relationship with the investigator or the quality of your future therapeutic care.

However, it is advisable for your safety to inform the investigator if you have decided to stop taking part in the study.

If you agree to take part, you will sign the informed consent form. The investigator will also sign this form to confirm that he/she has provided you with the necessary information about the study. You will receive a copy of the form.

Costs associated with your participation

If you decide to take part in this study, all the examinations or procedures necessary for the study will be paid for by the sponsor.

If you decide to participate in this study, there will not be any additional costs for you or your insurance company.

Since this is a non-sponsored study, you will not receive a compensation for participating.

Guarantee of confidentiality

Your participation in the study means that you agree to the investigator collecting your data and to the study sponsor using these data for research purposes and in connection with scientific and medical publications.

Your data will be processed in accordance with the European General Data Protection Regulation (GDPR) and with the Belgian legislation on the protection of natural persons with regard to the processing of personal data. UZ Leuven shall act as data controller for your data. You are entitled to ask the investigator what data are being collected about you and what is their use in connection with the study. This data concerns your current clinical situation but also some of your background, the results of examinations carried out within the context of care of your health in accordance with the current standards and obviously the results of examinations required by the protocol. You have the right to inspect these data and correct them if they are incorrect[1].

The investigator has a duty of confidentiality vis-à-vis the data collected.

This means that he/she undertakes not only never to reveal your name in the context of a publication or conference but also that he/she will encode (your identity will be replaced by an ID code in the study) your data.

The investigator and his/her team will therefore be the only ones to be able to establish a link between the data transmitted throughout the study and your medical records[2].

[1] These rights are guaranteed by the European Data Protection Regulation (GDPR), by the Belgian legislation on the protection of natural persons with regard to the processing of personal data and by the Law of 22 August 2002 on patient rights.

[2] For clinical trials, the law requires this link with your records to be retained for 20 years. In the case of a advanced therapy medicinal product using human biological material, this period will be a minimum of 30 years and a maximum of 50 years in accordance with the Belgian Law of 19 December 2008 on the use of human biological material and the applicable royal decrees.

The personal data transmitted will not contain any combination of elements that might allow you to be identified[3].

For the study data manager designated by the sponsor, the data transmitted will not allow you to be identified. The latter is responsible for collecting the data gathered by all investigators taking part in the study, processing them and protecting them in accordance with the requirements of the Belgian law on the protection of privacy.

To verify the quality of the study, it is possible that your medical records will be examined by persons subject to professional secrecy and designated by the Ethics Committee of Research UZ/KU Leuven, the sponsor of the study or an independent audit body. In any event, this examination of your medical records may only take place under the responsibility of the investigator and under the supervision of one of the collaborators designated by him/her.

The (encoded) study data will be able to be sent to Belgian or other regulatory authorities, to the relevant ethics committee and/or to organisations working in collaboration with the sponsor.

Your consent to take part in this study therefore also implies your consent to the use of your encoded medical data for the purposes described in this information form and to their transmission to the aforementioned people and authorities.

The sponsor will use the data collected within the context of the study in which you are taking part, but would also like to be able to use them in connection with other research concerning the same condition as yours. Any use of your data outside the context described in this document is only possible with the approval of the ethics committee.

If you withdraw your consent to take part in the study, to guarantee the validity of the research, the data encoded up to the point at which you withdraw will be retained. No new data may be sent to the sponsor.
If you have any questions relating to how your data are being processed, you may contact the investigator. The data protection officer in your hospital can be contacted as well: DPO - UZ Leuven, Herestraat 49, 3000 Leuven, e-mail dpo@uzleuven.be.

Finally, if you have a complaint concerning the processing of your data, you can contact the Belgian supervisory authority who ensures that privacy is respected when personal data are processed.

The Belgian supervisory authority is called:
Data Protection Authority (DPA)
Drukpersstraat 35,
1000 Brussels
Tel. +32 2 274 48 00
e-mail: contact@apd-gba.be
Website: https://www.dataprotectionauthority.be

Future of your sample(s) collected during the study

The sample encoding procedure is the same as that used for your medical data. Samples sent to the sponsor will therefore only include your study ID code.

The manager of these samples Biobank UZ/KU Leuven undertakes to use them within the context of clinical research and to destroy them at the end of the scheduled storage period.

The sample of biological material taken is deemed to be a “donation” and you should be aware that, in principle, you will not receive any financial benefit (royalties) associated with the development of new therapies derived from the use of your donation of biological material and which may be of commercial value.

If you withdraw your consent to take part in the study, you may contact the investigator and have those of your samples that have not yet been used destroyed. The results obtained from your samples before you withdraw your consent remain the property of the study sponsor.

Insurance

Any participation in a clinical study involves a risk, however small it is. Even if there is no fault, the sponsor accepts responsibility for damage caused to the participant (or in the event of death, his/her

[3] The database containing the results of the study will therefore not contain any combination of elements such as your initials, your gender and your full date of birth (dd/mm/yyyy).

dependants) and directly or indirectly linked to his/her participation in the study. The sponsor has taken out insurance for this responsibility[4].

If the investigator believes that a link with the study is possible (the insurance does not cover the natural progression of your disease or the known side effects of your normal treatment), he/she will inform the study sponsor, which will initiate the declaration procedure to the insurance company. The latter will appoint an expert - if it considers it necessary - to assess whether there is a link between your new health problems and the study.

In the event of disagreement either with the investigator or with the expert appointed by the insurance company and also whenever you feel it is appropriate, you or - in case of death - your dependants may bring proceedings against the insurer directly in Belgium (name of insurance company, policy number, contact).

The law provides that the insurer may be summoned to appear either before the judge of the location where the event giving rise to the damage occurred, or before the judge of your domicile, or before the judge of the insurer's registered offices.

[4] In accordance with Article 29 of the Belgian Law related to experiments on humans (7 May 2004)

KU LEUVEN

Translation of the Dutch questionnaire for donor milk

Questionnaire for voluntarily donation of human milk samples

We kindly ask you to read this data thoroughly. We ask you to answer in all honesty. The answers you give us will of course be treated confidentially.

1. How many weeks were you pregnant at the time of delivery: ……

2. Do you smoke? YES NO
   Are there any smokers in your home? YES NO
   If YES, do they smoke indoors? YES NO

3. Do you suffer from one or more specific health conditions? YES NO
   If YES, which health condition(s)?
   ……
   ……

4. Do you suffer from one or more chronic infections? YES NO
   If YES, which infection(s)?
   ……
   ……

5. Are you currently taking any medication? YES NO
   If YES, which and how much?
   ……
   ……
   ……

6. Are you following a specific diet? YES NO
   If YES, what does this diet consist of?
   ……
   ……

7. Do you drink coffee, tea or energy drinks? YES NO
   If YES, which and how much?
   ……
   ……

   Do you drink alcoholic beverages (beer, wine, aperitif ...)?
   ☐ Never
   ☐ Less than once a week
   ☐ Several times a week: numbers of glasses per week: ……

8. Have you undergone any investigations requiring contrast medium? YES NO
   If YES, which ones and on which date?
   ……
   ……

Optional additional information:
……

2
Fout! Verwijzingsbron niet gevonden.

……
……
……