Parent information and consent

Effects of infant feeding with goat milk formula or cow milk formula on atopic dermatitis (GIraFFE Study)

Study registration:

NCT04599946 at clinicaltrials.gov

Please read this information carefully. The study staff will answer any questions you may have.

The GIraFFE study was examined by the Ethics Committee and the Data Protection Officer of [your institution's approving committee/person] *and obtained a favourable opinion.*

You will receive a copy of this letter for your records.

PREAMBLE: *Exclusive breastfeeding is the ideal and healthiest way to feed your infant. This study is only offered to families whose children are completely formula-fed or whose parents have decided to provide mixed feeding (breastfeeding combined with formula). If your infant is receiving mixed feeding, but you would like to achieve exclusive breastfeeding, we can offer you support to achieve this, instead of participating in this study.*

Dear Family,

Thank you for your interest in our study that we are conducting together with partners in Spain, Poland and Germany. We want to find out if nutrition in early life affects the onset of atopic dermatitis (also known as eczema and atopic eczema). The study is called the GIraFFE study (**G**oat **I**nfant **F**ormula **F**eeding and **E**czema).

Why are we performing the study?

The increasing number of children with atopic dermatitis and allergies is a major medical problem. We are interested in understanding why some children develop allergies. Atopic dermatitis affects all age groups, but can be a particular concern for infants and small children. In a small study in Australia, infants were fed either a goat milk-based formula or a cow milk-based formula. A difference in the number of infants developing atopic dermatitis in first year of life was found. While goat milk and cow milk formula are both suitable for infant feeding if breastfeeding is not possible, they slightly differ in their composition, types of fat and proteins. These differences in composition might play a role in the development of atopic dermatitis or allergies. Understanding the role of these factors in the development of atopic dermatitis and allergies will help to choose the most suitable formula, and to improve formula composition and guidelines for infant nutrition.

Purpose of study

The aim of the GIraFFE study is to compare if formulas based on goat milk and cow milk have different effects on the development of atopic dermatitis and other related allergic diseases in a larger number of babies. The study formulas have the same composition of the essential nutritional components to support normal growth and

development of infants. Furthermore, we will assess and analyse stool bacteria and bio samples in the participating child as well as exploring other indicators of general health, development and metabolism.

Course of the study (see also Figure 1)

If you agree to participate, your baby will randomly be assigned to receive the cow or the goat milk formula. This randomization is important to exclude that any other factors related to food choice might cause a difference in eczema occurrence. To prevent any potential influence on the study results, neither you nor the study personnel will know which of the formulas your baby receives during the study. You will receive formula free of charge from enrolment until the study visit scheduled around your child's first birthday (age 12 months). After your child's first birthday, the formula supply will end and you will be free to choose what to feed your child, but the study itself will continue with following your child until the 5th birthday (age 60 months). A total of 2296 infants will participate in the GIraFFE study (distributed over 10 study centres in Poland and Spain). The overall study coordinator is Prof. B. Koletzko at the Dr. von Hauner Children's Hospital at the University of Munich, Germany. The local coordination will be done by XXX.

Participation in the GIraFFE study begins during the first three months of life. After the enrolment examination, further appointments for your child are planned here at [your institution] at the age of 4, 6, 12, 24 and 60 months. Every time you visit us, we will examine your child for signs of atopic dermatitis and measure height and weight. We will ask you questions about your child's health and general behaviour. In order to find out about the environment your child grows up in, we will initially ask you about your origin, education and family structure as well as cases of atopic dermatitis and allergic diseases in the family. In order to understand what your child eats and drinks apart from the study formula, we will ask you at each appointment which complementary foods you have already introduced to your child. At the age of 12 months, we also ask a little more about your child's dietary habits. During the first year of life, we also ask about the sleeping habits (BISQ questionnaire) and gastrointestinal comfort (IGSQ questionnaire) of your child. To assess the quality of life of your child, we will ask you to fill a slightly longer questionnaire (ITQOL questionnaire) at 4, 12, 24 and 60 months of age. Most of the questionnaires will be available online, so will be able to fill them online at home and reduce the time needed for each study visit.

If your child shows signs of atopic dermatitis, we record the severity with a standardized tool called SCORAD, when your child comes in for the next scheduled appointment. In addition, the POEM questionnaire is used to record the influence of atopic dermatitis on your child's quality of life.

In case you agree, we would like to take a small volume of blood (approx. 4-6 ml) from your child by a doctor or trained nurse during visits at 4, 12 and 60 months. We will be happy to share some of the results relevant for the assessment of your child's health such as blood count with you and your paediatrician. For blood sampling we offer applying local anaesthetic cream to the puncture site to avoid inconvenience for your child. At the same time points, we also ask you to collect some stool of your child. A kit for stool collection and instructions will be provided to you.

We will also contact you by phone shortly after enrolment and at 8 and 10 months to ask about the general health of your child, intake of the study formula, to check for signs of atopic dermatitis and, if necessary, go through the questionnaires on severity of atopic dermatitis. Further telephone calls are planned at the age of 18, 36 and 48 months.

You can find further information about the study on our homepage at "www.giraffe-study.com". A description of the study is also available under "www.clinicaltrials.gov/ct2/show/NCT04599946".

The study formulas are manufactured in New Zealand by Dairy Goat Cooperative, which has been producing infant formula for Europe and other parts of the world for more than 30 years. The formulas comply with European directives. Both formulas have the same nutritional composition in terms of total contents of energy, protein, carbohydrates and fat. Both formulas are available as infant milk and follow-on milk. Follow-on formula may be used from the age of 6 months onwards or after the start of complementary feeding (feeding of solids). The follow-on milk has the same energy and macro-nutrient content as infant milk, but vitamins and trace elements are adapted to the advanced age and the concurrent intake of complementary foods.

Child's food and drinks

There are no restrictions on food choices for your child. Just follow the advice of your family doctor and national nutritional recommendations. In general, you should start complementary feeding not before the age of 4 months (17 weeks) and not later than at the age of 6 months. When to start complementary feeding depends on your child's development and differs from child to child. As a guideline you can try to start if your

child can sit upright and hold his head up straight, has the oral motor skills to handle solid foods (no direct pushing out of food with tongue), and is interested in beginning and continuing to eat solids.

If possible do not feed other formula or milk than the provided study formula in the first year of life. Please use the study formula also for other foods usually prepared with milk. This will help to guarantee the success of the study.

Benefits and risks when participating in the study

By participating in this study, your child will have the opportunity to consume high-quality formula milk which has been shown to be safe and well tolerated. In addition, we will provide detailed surveillance of your child's growth, development and health and offer additional advice to you on child care and nutrition. With all infant formulas, a few infants develop intolerances. If in doubt, you can ask study team or your paediatrician or family doctor for advice. Besides the free formula, the provision of the blood count, and small gifts for your child when participating in the study visits, there are no other direct benefits by participating in the study. We will reimburse your travel costs for participating in study visits. Your participation will help to improve infant nutrition for future generations.

The risk of blood collection is negligible. It is possible that a local bruise may form and, in very rare cases, infection and inflammation at the puncture site is possible. For the stool samples, there is a minimal risk of contamination when not appropriately using tubes and storage packs.

If important new findings become known during the course of the study that could affect your decision to continue participating in this study, you will be informed immediately. You may then receive a new parental information and consent to sign if you wish to continue participating in the study. In rare cases it may be required to exclude your child from participation in the study for medical or organizational reasons. In this case, we will inform you, delete all personal contact data and use the study health data collected so far without your personal details (see also below).

Laboratory tests

Blood values provide important information to assess the effects of diet on the body. Laboratory analyses include the full blood count, however most blood results are not intended for the individual use as done in the case of illnesses by your paediatrician. The other blood analyses in the study are performed for scientific evaluations only,

and most are determined in a central laboratory with a longer time interval after blood collection. As many children as possible should participate in the blood collection, so that a sufficient number of samples can be obtained to gain meaningful insights, e.g. in relation to the development of allergies! Therefore, we very much hope that you will agree to a blood sample to be taken from your child. The blood samples are used, in addition to health tests (blood count), to measure substances related to allergies (e.g. immunoglobulins, inflammation) or different nutritional and metabolic effects of the formulas (e.g. lipidome, metabolome) that might be related to health, and genetic markers that influence the development of eczema and allergies. We will inform you about the blood count.

The stool samples are used to assess the development of healthy gut bacteria.

All samples are given a code instead of your child's name. This code is a combination of letters and numbers. The code can be related to all other study health data of your child to facilitate the scientific analysis. The code cannot be directly related to your child and ensures personal contact data protection (see below).

Genetic studies

The causes of atopic dermatitis are manifold. Genetics (inheritance) also plays a major role. Studies have shown that the skin protein Filaggrin plays an important role in the barrier function of the skin. Several changes (loss-of-function mutations) in the Filaggrin gene have been identified in patients with atopic dermatitis and are risk factors for atopic dermatitis.

If you agree to the test of the Filaggrin gene, no additional blood sample needs to be taken. The genetic material (DNA) will be extracted from the blood cells, which are left over from the blood sample taken for the other laboratory tests.

However, the Filaggrin gene is not the only risk factor for a child to develop atopic dermatitis or other allergies. Many other genetic and epigenetic factors are involved. The knowledge is constantly increasing. Until recently it was believed that genetic factors, i.e. genes, were simply present or not present, today we know much more about how genes can be "switched on and off". By examining the whole genetic material in the blood (genome-wide genotyping), we can determine which genetic variants may be relevant for the development of atopic dermatitis, related diseases and the metabolism. Furthermore, switching on or off of specific genes is of relevance can be studied (epigenetic investigation). As we are recruiting a very large number of infants in this study, which is a unique and rare opportunity for scientific

advancement, we also would like to take the opportunity to collect material for these analyses.

If you agree to the examination of the whole genetic material, the genetic material (DNA) is obtained from the blood samples of your child and examined. As for the Filaggrin gene test, no additional blood sample needs to be taken, but DNA would be collected at the ages of 4, 12 and 60 months to detect changes in gene expression.

These genetic tests will only be carried out at a later date when samples are available from as many study participants as possible. The examinations of the hereditary factors are carried out at an external institute under the auspices of the key principal investigator (Prof. B. Koletzko, LMU). Double coding (a continuous laboratory number is assigned to the coded samples before processing) prevents the employees of the external institute from drawing conclusions about personal contact data of study participants. This ensures that this particularly sensitive genetic data is additionally protected. Genetic studies are carried out for research purposes only. It is not possible and not intended to communicate results. The statistical analysis of the genetic data is carried out under the responsibility of Prof. B. Koletzko, without reference to the name of your child.

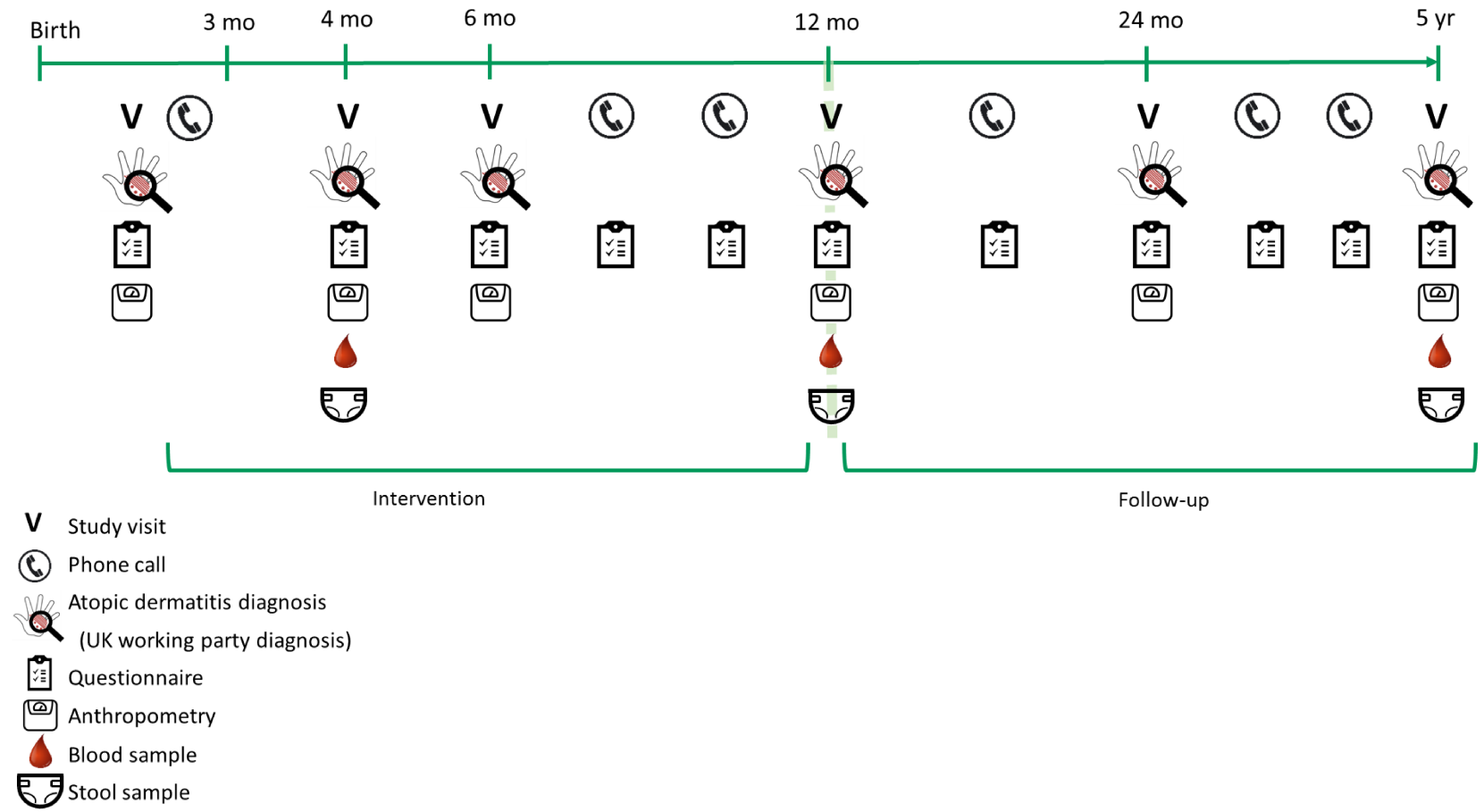
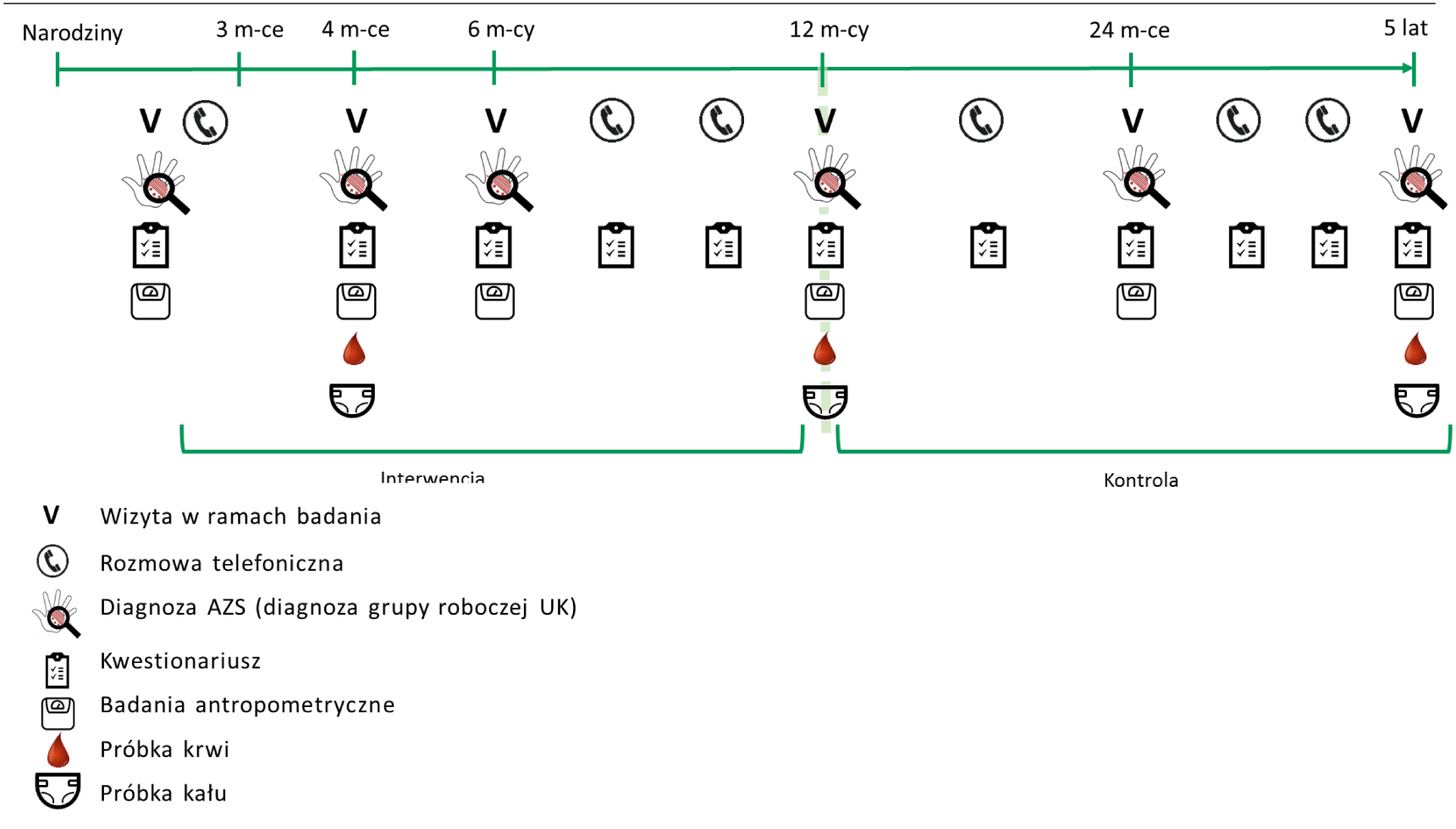
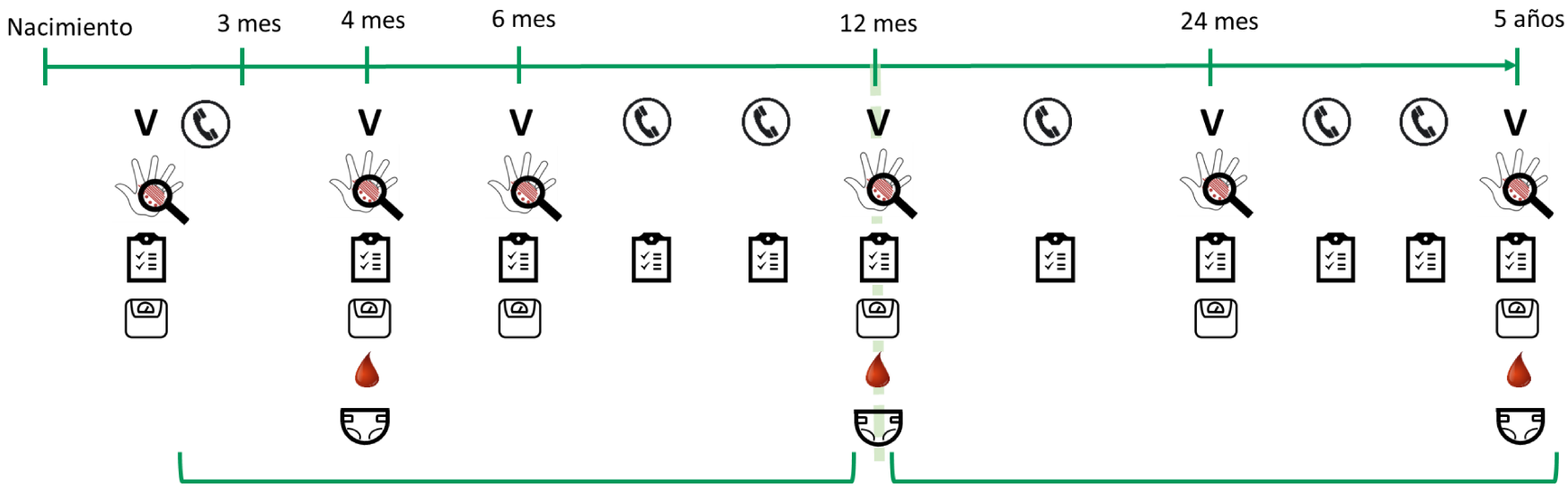


Figure 1. Study plan


Narodziny
3 m-ce
4 m-ce
6 m-cy
12 m-cy
24 m-ce
5 lat
Interwencja
Kontrola
V Wizyta w ramach badania
Rozmowa telefoniczna
Diagnoza AZS (diagnoza grupy roboczej UK)
Kwestionariusz
Badania antropometryczne
Próbka krwi
Próbka kału



V Visita de estudio

Llamada telefónica

Diagnóstico de dermatitis atópica (DA)
(Diagnóstico *UK working party*)

Cuestionario

Antropometría

Muestra de sangre

Muestra de heces

Study evaluation

The data and samples are used exclusively for scientific purposes. The study evaluation is carried out by Prof. Koletzko and his co-workers at the Children's Hospital of the University of Munich, Germany. The data interpretation and publication of study results is carried out by the scientists and medical doctors involved in the study.

Data collected in this study may be used for joint analyses with other studies (meta-analyses), which may include sharing of data with third parties. Double coding of the data as in the genetic analysis described above prevents the employees of the external institute from drawing conclusions about personal contact data of study participants.

After the last follow-up time point of the last subject, we will keep blood samples for up to 5 years to perform all planned analysis. As new insights are constantly obtained in research, we ask you to allow us to keep any excess blood samples during this period, so that blood is not wasted and is still available for possible future, innovative analyses in the context of the study.

In case any excess biomaterials (blood and/or stool) are available after this 5 year period, these will be transferred to a registered biobank (Hauner Biobank, Dr. von Hauner Children's Hospital, LMU, Germany) if you approve. Before transfer to the biobank all data that directly identify you (personal contact data) will be deleted. Your donated biomaterials and the study health data will be made available exclusively for medical research purposes. In order to realize the largest possible public benefit they can be used for a wide range of medical research. The biomaterials and the study health data are intended to be stored and made available for medical research for an undetermined period of time.

All use of data that goes beyond the context of the study will be approved by the ethical committee of the evaluation site.

Study funding

The study is sponsored by Dairy Goat Co-operative (N.Z.) Ltd (18 Gallagher Drive, Hamilton, New Zealand; www.dgc.co.nz; DGC) owned by the farmers who supply goat milk. DGC and the New Zealand Ministry for Primary Industries funded this work as part of the Caprine Innovations NZ (CAPRINZ) Sustainable Food & Fibre Futures Partnership programme. Funding covers the necessary study staff and equipment, all planned aspects of the study, laboratory tests and provision of study formula. Any future

scientific investigations will be carried out with further industrial funding or state support.

Insurance

Although no complications are expected, all study participants are covered by a study insurance. The insurance covers all damage to health that occurs as a result of the measures applied in connection with the study up to a maximum amount of € XXXX.

In case of damage, you can contact the insurer directly (xxx, tel.: xxx; policy number: xxx) and assert your claims. To ensure the insurance cover is not jeopardized, you must tell us all medical treatments that your child undergoes during the study phase (exceptions are preventive examinations and vaccinations). This also applies to the use of new medications. If you or your child have any damage to your health that may have occurred as a result of participating in the study, please inform the relevant study staff and the above-mentioned insurance company.

Voluntariness / Withdrawal Clause

Participation in the study is voluntary. With your signature on the "Consent Declaration" you give your consent to your child's participation in this study. You have the right to stop participating in the study at any time without giving reasons and without disadvantages.

Compensation

For participation in the study you will be compensated for expenses.

If you have further questions about this study or if you think you or your child have suffered a study-related health impairment, we are at your disposal; Tel.: xxx E-mail: GIraFFE.Studie@xxx.xx

Data protection:

The following data protection rules apply as part of the study.

Data protection: This study complies with the rules on medical confidentiality and data protection in accordance with the European and [your countries] directives and the Helsinki Declaration. Your contact details will be stored in a database (MedSciNet, Stockholm, Sweden, http://medscinet.com/). This database only stores personal contact data, but no medical data. In order to deliver the study formula, your contact details are passed on to an external logistics company (xxx). The company is prohibited from using this data for purposes other than the delivery of the study formula. The company is subject to [XXX] statutory data protection regulations.

All other data - i.e. "study health data" - which are not used for contact organisation are stored in separate database (MedSciNet, Stockholm, Sweden, http://medscinet.com/ as well as in the hospital of the University of Munich). Personal contact data such as name or address is not collected in this database. The assignment to your child's name can only be done using a code, which can only be assigned to a name with the active help of the staff at the study center. Thus, all collected data and findings of your child are pseudonymized.

You have the right to receive information about your stored personal contact data at any time, to correct it or, if necessary, to have it deleted.

Responsible for data processing is Prof. [local PI].

Contact details of the data protection officers:

In the event of a complaint, you have the right to contact the respective data protection supervisory authority. For [your institution] this is:

Data Protection Officer

[XXX contact information of local data protection officer]

The higher authority for [your institution] is:

[contact information of a federal or similar higher level data protection officer]

Data access:

Access to personal database with name, contact details, contact information, and ID codes (connecting study health data to personal contact data) is limited to persons involved in the study under supervision of Prof. [local PI]. For organizational reasons and to monitor the study, also personal under the supervision of Prof. B. Koletzko (LMU) will have access to the personal database. Dairy Goat Co-operative Ltd. can commission monitoring of the quality of the study. The monitor (currently Uta Clausen) is committed to data protection and has access to personal and study health data on site. Decoding of individual study participants is only carried out for safety reasons ("medical reasons"). The monitoring company is subject to the local, statutory data protection regulations. All persons with access to the data are listed in a log file and have a personal, traceable login.

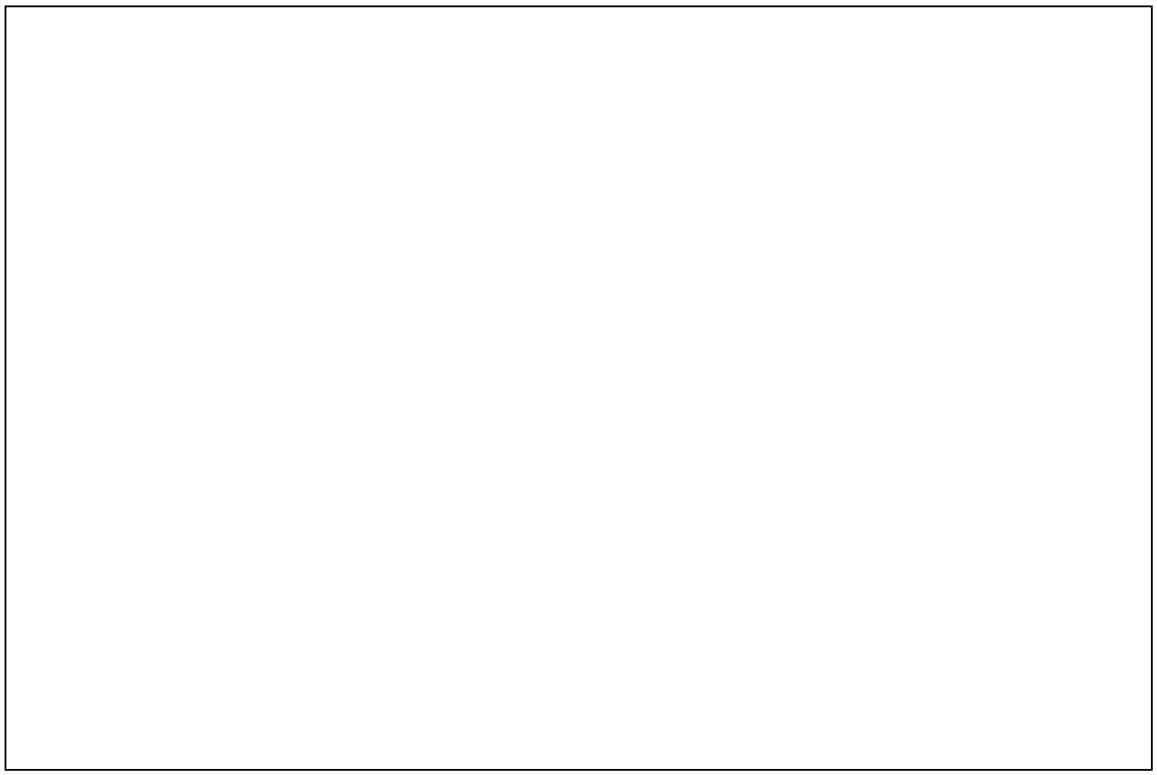
Dairy Goat Co-operative Ltd, LMU and the study centres/sites have access to study health data. Dairy Goat Co-operative Ltd. has never access to personal contact data. Study centers only have access to the personal contact data of participants at their site(s). Use of a code will protect your identity and ensure the confidentiality of your data. As data controller, LMU will apply contractual, organizational and security measures ensuring the maintenance of an adequate protection level required by the European and [study site's country] statutory data protection regulations. During those procedures, you and your child identity will not be disclosed.

For the laboratory analyses, the blood samples are only passed on with a code and do not allow any conclusions to be drawn about an individual study participant. The storage of the samples and some laboratory analyses are carried out in laboratories of the hospital of the University of Munich. Genetic analyses and some further examinations are carried out at external institutes. For the genetic analyses, a 2nd encryption by the employees of the external institute is carried out. This double coding ensures that the genetic data is additionally protected. Unblinding is only possible through the study center, but not through the external institute.

In case of withdrawal of consent, the name and your personal contact details will be deleted from our database. Your child's data stored until then will now be used anonymously. In addition, the name and personal contact details of all study participants will be deleted within one month of completion of the study (including analysis of bio-samples). The written documents, including this declaration of consent, will be kept in the study center until the end of the study and in a suitable warehouse until the end of the statutory retention period (12 years after the end of the study).

In the case of publication of the study results, the confidentiality of your child's personal contact data is also guaranteed, as the data is reproduced, if at all, in an anonymized form. On request, we will inform you about general study results. In the event of additional investigations or data collection that go beyond the above-mentioned course of study, we will

Before you enter the study, you have the opportunity to write down specific questions, which should be discussed in more detail with you.



Consent & Privacy Policy for the participation of my/our child in the GIraFFE study

Effects of infant feeding with goat milk formula or cow milk formula on atopic dermatitis

(GIraFFE study)

Surname, first name of the child	Birth date

The study conditions have been fully explained to me and all questions have been clarified to my satisfaction. I have received the form with the study information. I have had plenty of time to read this form and ask questions. Possible risks and disadvantages for my child were explained to me. I know that I can ask any question about this study and the investigations now and in the future. I know that I/my child can withdraw from the study at any time without having to give reasons or that I or my child would suffer any disadvantages. I hereby consent to my child's participation in the study:

Date	Surname, First name 1. parent or legal guardian	Signature 1. parent or legal guardian

I have sole custody: ☐ Yes ☐ No

Date	Name, Forename 2. parent or legal guardian	Signature 2. parent or legal guardian

Date	Name, Forename Study personnel	Signature

I have taken note of the data protection information within the scope of the participant information. I hereby consent to the collection and use of my child's personal contact data in accordance with these conditions.

Date	Surname, First name 1. parent or legal guardian	Signature 1. parent or legal guardian

Date	Name, Forename	Signature
	2. parent or legal guardian	2. parent or legal guardian

Date	Name, Forename	Signature
	Study personnel	Study personnel

Consent & Privacy Policy for the genetic examination of my/our child in the GIraFFE study and for biobanking

Effects of infant feeding with goat milk formula or cow milk formula on atopic dermatitis

(GIraFFE study)

Surname, First name of the child	Birth date

☐ I hereby agree that genetic material may be extracted, stored and examined from my child's blood. Genotyping in the GIraFFE study is used to identify a possible genetic cause of a **modified skin protein (filaggrin)** that may be related to the appearance of atopic dermatitis (eczema). Participation in the examination does not involve any further health risks beyond the blood collection.

☐ I hereby agree that genetic material may be extracted, stored and examined from my child's blood. The **genome-wide genotyping and epigenetic investigations** serve to uncover the genetic causes of diseases and causes of allergies and metabolic changes within the GIraFFE study. Participation in the examination does not involve any further health risks beyond the blood collection.

☐ I hereby agree that any excess bio-samples are transferred together with anonymized study health data to a registered biobank as described in the study information.

The data and results will be used exclusively as outlined in the subject information. Only authorized employees of the study can access the encrypted data. Data will not be passed on to unauthorized third parties. The genetic data obtained in the course of this study shall be retained for up to 10 years after completion of the scientific study or until revocation has been made.

I know that I can ask further questions now and in the future about this study. I know that I can withdraw from voluntary participation in the study at any time without having to give reasons. I voluntarily consent to the collection, processing and use of personal contact data in accordance with the information sheet of the study.

Date	Surname, First name 1. parent or legal guardian	Signature 1. parent or legal guardian

Date	Surname, First name	Signature
	2. parent or legal guardian	2. parent or legal guardian

Date	Surname, First name	Signature
	Study personnel	Study personnel