

INFORMATION FOR PARENTS

Dear Parents,

Your child, with your consent, takes part in the study entitled: „An assessment of the effectiveness and safety of the 4-step milk ladder compared to 6-step milk ladder in children with IgE-mediated cow's milk protein allergy: an open randomized study”. During this study, children with IgE-mediated cow’s milk allergy will have gradually introduced cow’s milk proteins to their diet according the appropriate milk ladder.

What is the milk ladder?

Baked cow's milk proteins combined with wheat proteins are characterized by lower allergenicity – which means that their consuming is associated with lower possibility of causing an allergic reaction compared to raw milk. The milk ladder involves the gradual introduction of increasing amounts of cow’s milk proteins, starting from a small amount of baked milk and working up to subsequently greater amounts of less processed products containing cow’s milk proteins, ending with raw cow’s milk. This method seems to be effective and, at the same time, is at lower risk of adverse events after reintroduction of cow’s milk protein to the child’s diet.

There are many recipes and designs for milk ladders. In this study, we will use a 6-step and 4-step food ladder (Table 1). Your child will be randomly assigned to one of two interventions. Currently, we do not know which of the proposed food ladders allows for faster tolerance acquisition and whether both are equally safe.

INTERVENTION GROUP	CONTROL GROUP
<b>Step 1. Muffin</b>	<b>Step 1. Cookie</b>
4-week administration of the tolerated amount of cow’s milk in the diet in a previously tested form	4-week administration of the tolerated amount of cow’s milk in the diet in a previously tested form
<b>Step 2. Pancake</b>	<b>Step 2. Muffin</b>
4-week administration of the tolerated amount of cow’s milk in the diet in a previously tested form	4-week administration of the tolerated amount of cow’s milk in the diet in a previously tested form
<b>Step 3. Baked hard cheese</b>	<b>Step 3. Pancake</b>
4-week administration of the tolerated amount of cow’s milk in the	4-week administration of the tolerated amount of cow’s milk in the diet in a

diet in a previously tested form	previously tested form
<b>Step 4. Yoghurt/ Pasteurised cow milk or modified cow milk</b>	<b>Step 4. Baked hard cheese</b>
	4 weeks administration of the tolerated amount in the diet in a previously tested form
	<b>Step 5. Yoghurt</b>
	4-week administration of the tolerated amount of cow's milk in the diet in a previously tested form
	<b>Step 6. Pasteurised cow milk or modified cow milk</b>

**How will we introduce the first and subsequent steps of the milk ladder?**

The first and each subsequent step of the ladder will be conducted using oral food challenge (OFC) with various forms of the milk (including cookie, muffin, pancake, cheese, yoghurt and raw milk), in a tested amount adapted to the child's age, in hospital setting under medical supervision according to the instructions you will receive.

Before the first OFC, you will receive recipes according to which you will be asked to prepare the food for the first and each subsequent OFC.

**What is an oral food challenge (OFC)?**

An oral food challenge is the introducing of a product form the first and each subsequent step of the ladder in hospital setting, under medical supervision, according to the specific protocol tailored to yours child needs and safety.

**How to prepare the child for the OFC?**

The child should be healthy on the day of the OFC. If a child has another allergic disease, it should be well controlled. Optimally, all antihistamines should be discontinued if the child takes them permanently, but this decision must be discussed with the physician.

In the morning on the day of the planned OFC, the child can eat his standard breakfast – a half of the usual portion to limit his/her hunger before and during OFC.

Be prepared that after completing the OFC, the child will remain in the hospital for another 4-6 hours for observation.

Don't forget to take with you a prepared meal with cow's milk proteins that your child will be challenged with.

### **How to further introduce products with cow's milk proteins at home?**

After a negative OFC (OFC without any adverse effects), during the next 4-weeks, you will be instructed to give your child the tolerated amount of cow's milk protein at home.

*During a 4-week break period, it is recommended to consume regularly tolerated amount of cow's milk proteins in previously tested form, according to the following rules:*

- The child should received 1 portion of the tolerated amount of cow's milk protein at home, at least three times a week, in the same form and dose as tested during the last negative OFC.
- The tolerated dose may be divided into 2-3 portions and administered throughout the day.
- The introduced products should optimally be administered when the child returns from nursery or kindergarten, in the early afternoon, to allow you to observe your child's reaction after consuming the entire dose of the tested meal. The tested product should not be administered later than 2 hours before the child goes to sleep.
- Children are advised to consume cow's milk proteins only in the form tested during the OFC, e.g. in the case of home-baked milk, only muffins or cakes prepared according to the given recipe should be administered; serving ready-made products from stores is prohibited.
- During the administration of the tested product, the child should be on a strict cow's milk-free diet, which includes avoiding milk and products of other ungulates (e.g. goat's milk, sheep's milk).
- Before you give the test product to your child, please ensure that all medications listed in the adverse event instruction are available at home.
- You will be asked to monitor the number of portions and the frequency of allergen administration during break period at home and report this information in the Milk Ladder Monitoring Diary developed by the study authors.

*What to avoid while administering the test product?*

- The tested product should not be administered on an empty stomach.

- Children should avoid strenuous physical exercise, exposure to significant airborne allergens (dust, pollen), and hot baths for the next 2-4 hours after consumption.

*These factors, known as cofactors, may change child's tolerance to consumed cow's milk proteins.*

*Can the dose of the tested product be increased?*

- If the child demonstrates good tolerance to the specified amount of cow's milk proteins during the first two weeks of break period, the daily portion may be increased to 2-3 servings in the following two weeks. A minimum interval of 2 hours between servings should be maintained.
- For participants at a higher level of milk ladder (after more than one negative OFC), during break period child can consume at home both the amount of cow's milk proteins in a form tolerated during the last OFC and 1-2 additional portions of CMPs from a previous step of the milk ladder. The child should not consume more than 3 products containing cow's milk proteins per day.

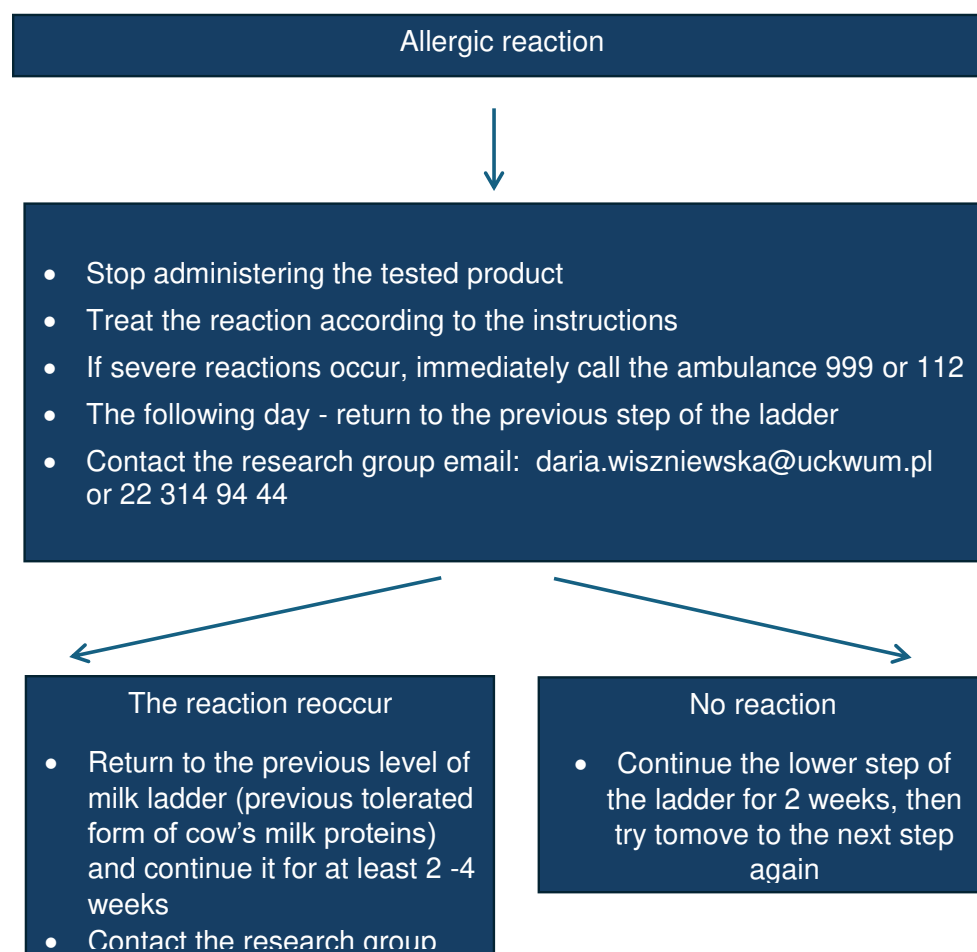
*Should cow's milk protein reintroduction be continued after a longer break?*

- If the allergen is not administered for more than a week, the interval between subsequent OFCs should be extended by a period proportional to the length of the break. A break in the administration of the product with cow's milk proteins for more than a week should be reported to a doctor from the research team who will set a new date for the next OFC.
- This incident should be noticed in Milk Ladder Monitoring Diary.

*Adverse effects at home:*

- Despite a negative OFC in the hospital setting, adverse effects may occur while administering cow's milk proteins in a similar amount and form at home.
- Possible adverse effects include:
  - hives, skin itching, angioedema,
  - diarrhoea, stomach pain, vomiting,
  - increased runny nose, sneezing, breathing difficulties,
  - weakness, fainting, loss of consciousness with hypovolemia,
  - urinary incontinence.

**If adverse effects occur, follow the instructions ( Figure 1.).**



**Figure 1. Management of adverse reactions.**

**Treatment:**

- **IF SYMPTOMS OF AN ANAPHYLACTIC REACTION OCCUR:**

- fainting, weakness, spots before the eyes, dizziness
- shortness of breath, difficulty breathing
- difficulty swallowing (regardless of co-occurring skin lesions)

**OR**

\* in case of urticaria, sudden redness of the skin, itching of the skin, swelling of the face, lips WITH ACCOMPANYING symptoms: from the digestive system - vomiting,

diarrhea, stomach pain or respiratory system - shortness of breath, cough, inspiratory/expiratory wheezing or accompanied by fainting/urinary incontinence

**YOU MUST PROVIDE:**

- **adrenaline intramuscularly (Epipen® Junior) 0.15mg - injection into the anterolateral part of the thigh,**
- prednisone (Encorton®) 1mg/kg (orally, crush),
- cetirizine (Zyrtec®) 20 drops orally.

**Immediately call the ambulance on 999 or the emergency number 112.**

- If only skin and/or respiratory symptoms occur (upper respiratory tract):  
(hives, itchy skin, facial swelling; runny nose, sneezing)

You must provide:

- prednisone (Encorton®) 1mg/kg (orally, crush),
- cetirizine (Zyrtec®) 20 drops orally.

**The research team should be immediately informed of the occurrence of adverse symptoms. The incident should be also noticed in Milk Ladder Monitoring Diary.**