ACADEMISCH CENTRUM TANDHEELKUNDE AMSTERDAM

Subject information for participation in a medical-scientific study

Dutch title: 'Evaluatie van de effecten van een prebiotische mondspoeling op het ecosysteem van de mond- de INORE-studie.'

English title: 'The evaluation of the effects of a prebiotic mouth rinse on the oral ecosystem - the INORE study'

Introduction

Dear Sir/Madam,

You are being asked to take part in a medical-scientific study. Participation is voluntary. In order to participate, your written consent is required. You are receiving this letter because you are interested in the above-mentioned study. Before you decide whether you want to take part in this study, you will be given an explanation about what the study involves. Please take your time to read this information and ask the investigator if you have any questions. You can also ask the independent expert, mentioned at the bottom of this letter, for additional information. You can also discuss it with your partner, friends or family.
Further information about participating in such a study is found in the enclosed brochure 'Medical scientific research'.

1. General information

This study is being conducted by the Academic Center for Dentistry Amsterdam (ACTA). It is supported by the Dutch Ministry of Economic Affairs, within the foundation 'LSH-TKI' with a contribution of ACTA, TNO (the Dutch Organisation for Applied Scientific Research) and Philips. For this study, 62 subjects from the Netherlands are required. The Medical Ethics Review Committee of the Amsterdam University Medical Centre, location AMC has approved this study (CCMO reference number NL72143.018.19). General information about the assessment of research can be found in the brochure 'Medical scientific research'.

2. Purpose of the study

The purpose of this study is to investigate the potential changes in the composition of the oral bacteria in (tongue / tooth) plaque after two weeks of using a 10% inulin-containing mouth rinse (wash-in period), followed by two weeks of no oral hygiene in combination with the mouth rinse (experimental gingivitis period) and then a two-week recovery period with resumed regular oral hygiene combined with the mouth rinse (recovery period). We will compare the effect of rinsing with inulin with the effect of rising with a placebo solution. A placebo is an agent without an active substance, a "fake agent". In this study this is a 0.5% table salt solution. We aim to publish the results in an international scientific journal.

3. Background of the study

Based on previous research, we expect that rinsing with an inulin-containing mouth rinse will strengthen the resilience of the mouth. If the resilience of the mouth is sufficient, the mouth will be healthier and also, it will recover faster once inflammation occurs in the mouth. We will test these expectations during the rinsing and the non-brushing periods of this study.

4. What does participation involve

If you participate, it will take in total approximately 10 weeks, of which 7 weeks will be the study itself. The first visit is to determine whether you are suitable to participate (the screening visit). During this screening visit we will perform an oral examination that is comparable to a periodic check-up by your dentist. The researcher will also ask about your medical history using a standard medical-health questionnaire, because some medical conditions can influence the results of the study. Occasionally we find something during the screening that needs more in-depth examination. We will always inform you if this is applicable to you and we will refer you for additional examination to your dentist or physician. The costs for the additional examinations are on your own account. It can also appear that, even though you are healthy, you are not suitable for participation in this study.

You will use a mouth rinse for six weeks. Half of the participants will receive the test rinse that contains inulin, while the other half will receive the placebo rinse with table salt. The choice of the rinse will be designated by drawing lots. The clinical researchers will not know which group you are in and will perform the measurements blindly. Both mouth rinses have very mild and neutral taste. During the last visit we will ask you which of the two rinses you think you were using.

Corona

We apply the standard infection prevention measures during all visits as described in the Dutch guidelines for oral care. Except during the actual measurements, we will keep a distance of one and a half meters between each other, between the participants and between the investigators and the participants. If you have a positive test, we ask you to let us know. We will discuss with you the possible influence on the study participation.

Visits and tests

The investigation requires that you visit ACTA seven times. You will receive a reminder via WhatsApp prior to each visit. If you object to receiving WhatsApp reminders, you can indicate this beforehand. Each visit will take a maximum of 30 minutes and will consist of a short oral examination and the following procedures:

- photos will be taken of your teeth with a fluorescence-detecting camera, so that we can record the property of your dental plaque to fluoresce. Old and mature dental plaque, associated with inflammation, fluoresces red when exposed to blue light.
- saliva will be collected to determine the acidity (pH) of the saliva
- dental plaque will be collected using a plastic scraper, tongue plaque will be collected by sweeping over the tongue with a small brush, in order to determine the microbial composition using DNA sequencing technique. With this method we can follow how the bacterial composition changes in time;

- light-absorption recordings will be taken of your gums in order to measure the health of the gums. This method is new and may in the future replace other gum-health assessment tests;
- gum-health tests will be performed (comparable to a regular six-monthly check-up by your dentist) to measure the health-status of your gums.

Dit schema is niet VMBO/13 jaar niveau

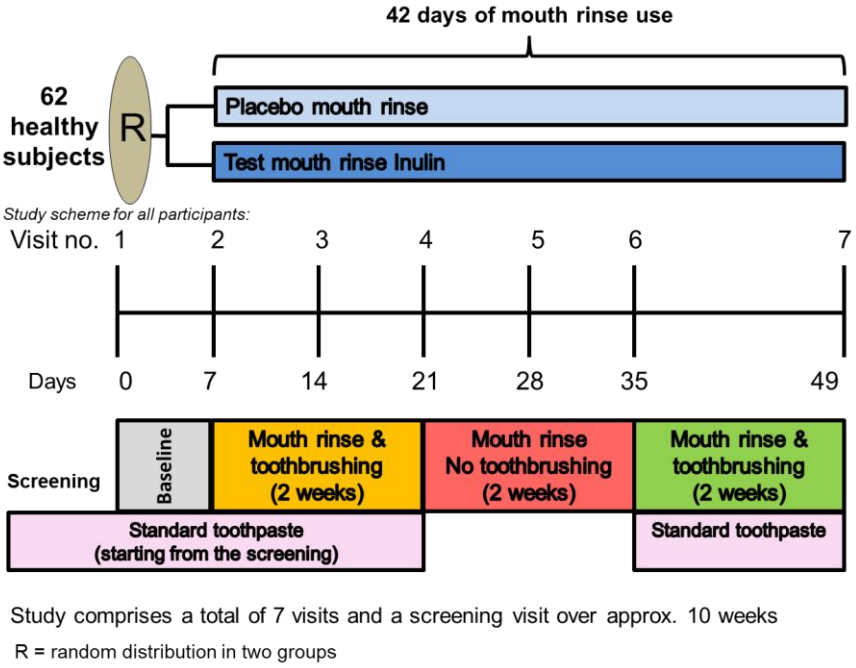

Figure above gives a schematic overview of the study.

5. What will be expected of you

For the study to run smoothly, it is important that you agree to the following study rules.

The rules are that you:

- use the mouth rinse according to the instructions;
- only use the standard toothpaste (which will be provided) during the study, from the screening up until the last visit of the study, except the two weeks of abstaining from the toothbrushing;
- follow the instructions of the study;
- do not participate in another medical-scientific study;
  show up at the planned study visits.

It is important that you contact the investigator:

- when you start taking any prescribed medicine.
- when you start taking any non-prescribed medicine such as homeopathic medicine, natural medicine, vitamins and/or over the counter medicines;
- if you are hospitalised or treated in a hospital;
- if you suddenly experience any health complaints;
- if you no longer wish to participate in the study;

- if your contact details change.

Women who are pregnant or breastfeeding, may not take part in this study. If you do become pregnant during the study, please inform the investigator about this right away.

More rules for the entire investigation:

If you participate in this study, we will ask you

- to visit ACTA once to determine whether you are suitable to participate in the study (the screening-visit);
- to visit ACTA seven times at set days for an oral examination that will last at most 30 minutes;
- to use the standard toothpaste when asked to do so during the study, we will give this toothpaste to you;
- not to use any other mouth rinse (mouthwash) and do not clean your tongue for the duration of the study;
- not to brush or otherwise clean your teeth 24 hours before each visit. This means you may no longer brush or clean between the teeth on the evening and the following morning of each appointment;
- not to eat or drink anything with the exception of tap water 1 hour before a visit;
- not to schedule any dental treatments (including periodic check-ups) for the duration of the study.

Additional rules:

- For two weeks you will be asked to rinse four times a day with a mouth rinse. You will rinse three times after the main meals and once before bedtime. Each time, you will take a fresh mouth rinse and rinse twice for 30 seconds. We ask you not to rinse your mouth, eat or drink anything and / or brush your teeth for an hour since you have rinsed with the mouth rinse.
- After two weeks of using the mouth rinse, we will ask you not to clean your mouth in the following two weeks and to continue to use the mouth rinse. This means that you cannot brush your teeth during these weeks, and cannot clean your tongue, use another mouth rinse (apart from the one from the study) or clean between your teeth.
- After in total of four weeks of rinsing, of which the last two weeks without any cleaning of the mouth, you will clean your mouth again as you were used to and you will continue to use the mouth rinse for another two weeks.
- In total you will use the mouth rinse for six weeks.

Location of the investigation

This research is conducted at ACTA, Gustav Mahlerlaan 3004, 1081 LA Amsterdam.

6. Possible side effects and discomforts

We do not expect any side effects from using the mouth rinse, although you may experience a minor aftertaste in your mouth for a short time. When performing measurements to check the health of your gums (a procedure that is regularly performed by a dentist during a check-up), it is normal to experience some sensitivity. Your gums may become a bit sensitive during the non-

brushing period, though this does not happen always. This possible sensitivity will disappear when you will start cleaning your teeth again.

7. Possible advantages and disadvantages

It is important that you properly consider the possible advantages and disadvantages before you decide to participate. You will not personally receive any advantage from taking part in this study. Your participation though may contribute to more knowledge about the use of inulin as substance to keep the mouth healthy. Disadvantages of participation in the study are that you have to visit ACTA in total eight times and that there are rules that you must adhere to. All of these things are described under points 4, 5 and 6.

8. If you do not want to participate or would like to stop participating in the study

You decide for yourself whether you want to participate in the study. Participation is voluntary. If you do participate, you can always change your mind and stop, even during the study. The data obtained thus far will be used for the study. If there is any new information about the study that is important for you, the investigator will inform you on that. You will then be asked if you wish to continue to participate.

9. End of the study

Your participation in the study ends when

- all visits according to the schedule/such as described under the point 4 have been completed;
- you personally choose to stop;
- you become pregnant;
- the investigator decides that it is better for you to stop;
- the research consortium, the government or the assessing Medical Ethics Review Committee, decide to stop the study.

After processing all the data, the investigator will inform you about the most important outcomes of the study. This will happen approximately one year after your participation.
The investigator will also tell in which group you participated. If you prefer not to know, you can tell the investigator who will then not tell this to you.

10. Use and storage of your data and body material

For this study, your personal data and tongue and dental-plaque samples will be collected, used and stored. It involves information about your name, address, date of birth and information about your health. The collection, use and storage of your data and your tongue and dental-plaque samples is required in order to answer the questions asked in this study and to be able to publish the results. We ask your consent for the use of your data and tongue and dental-plaque samples.

Confidentiality of your data and body material

To protect your privacy, your data and your tongue and dental-plaque samples receive a code. Your name and other information that could directly lead to your identity are thus omitted. This information can only identify you by using a key. This key will be stored securely in the research facility. Research partners TNO and Philips are bound to respect your privacy rights and therefore will not receive any traceable personal data from you. Other research partners do not receive any data from you at all. Only tongue and dental-plaque samples (here defined as bodily materials) labelled with a code will be sent to TNO for the DNA analyses. The results of the analyses of the tongue and dental-plaque samples will be subsequently shared with ACTA using the same code.

As part of this study, a subset of your data will be shared with Philips. This will be done using the codes, without any traceable information to you. No bodily materials and no contact details (name, telephone number, etc.) will be shared with Philips. Philips is a worldwide operating healthcare company and is committed to protecting your privacy. For details on how Philips protects your personal data as part of this study, please consult the document 'Philips Privacy Notice INORE Study'.

In reports or publications on this study, the data will also be non-traceable to you.

Access to your data for review

Some individuals may have full access to your data at the study site, also to the data without a code. This is needed in order to check whether the study is decently performed. Individuals who have access to your data for review are: the Health Care and Youth Inspectorate, a controller hired by the sponsor of the study, and the researchers who are directly involved. They will keep your data confidential. We ask your consent for this access.

Retention period of data

Your data must be stored for 20 years at the ACTA study site. Your body material (tongue and plaque samples) will be destroyed immediately after use.

Information about incidental findings

During this study, there may be incidental findings that are not relevant for the study, but could be relevant for you. If this is important for your health, you will be notified by the researcher. You can then discuss with your own dentist what needs to be done. You give us permission to inform your dentist that you are participating in this study.

Withdrawal of consent

You can always withdraw your consent for the use of your personal data. The study data that have been collected until the time you withdraw your consent may still be used in the study.

More information about your rights concerning the processing of data

For general information about your rights concerning the processing of your personal data, please consult the website of the Dutch Data Protection Authority. If you have any questions

about your rights, please contact the principal investigator at ACTA. If you have any questions or complaints regarding the processing of your personal information, we recommend that you contact the study site. You can also contact the Data Protection Officer of ACTA or the Dutch Data Protection Authority.

Registration of the study

Information about this study is also included in a summary of medical research i.e. the Nederlands Trial Register (www.trialregister.nl). No data that can be traced back to you is included. After the study, the website may contain a summary of the results of this study. You can find this study under registration numberNL8428.

11. Insurance for subjects

Everyone who participates in this study is insured. The insurance covers damage resulting from the study. Not all damage is covered. In appendix 4 you can find more information about the insurance and the exceptions. It also states who you should report any damage to.

12. Informing dentist

We will always send your dentist a letter to let them know that you are taking part in the study. This is for your own safety. If you do not agree to this, you cannot participate in this study. If there are unexpected findings during the study, for example concerning your oral health, we will provide you with the correct advice. For treatment you may be referred to your own dentist. You cannot take part in the study if you do not have your own dentist.

13. Compensation for participation

You will receive reimbursement for your participation, which includes travel related costs. If you participate in the study and complete all the instructions and research visits, you will receive € 400 after the study. If you stop during the study, you will receive € 25 per completed visit. If you want to participate in the study, but during the screening visit it appears that you are not suitable for participation, you will receive a reimbursement of € 15.

14. Do you have any questions?

If you have any questions, please contact the principal investigator. If you would like an independent advice about participation in this study, please get in touch with the independent expert. She is very well informed about the study, but does not take part in this study.
If you have any complaints about the study, you can discuss this with the investigator or your dentist. If you would rather not do that, you can contact the complaints' officer of ACTA. All data can be found in a**ppendix 1**: Contact information.

15. Signing of informed consent form

When you have had enough time to think all this information over, you will be asked to decide about participation in this study. If you consent, you will be asked to confirm this on the corresponding consent form, in writing. With your written consent, you indicate that you have

understood the information and agree to participate in the study. Both you and the investigator will receive a signed version of this consent form. Before signing the consent form there will be ample time to ask additional questions.

16. Appendices to this information

Appendices in this document:

1. Contact details ACTA
2. Contact details Philips
3. Informed consent form

Appendices as separate documents:

4. Information about insurance
5. Brochure "Medical research. General information for subjects "(March 2016 version)
6. Privacy notice Philips “INORE”

Appendix 1: contact details ACTA

Principal investigator:
Prof. dr. E. (Egija) Zaura
Academisch Centrum Tandheelkunde Amsterdam |Preventive Dentistry |
Gustav Mahlerlaan 3004 | 1081 LA Amsterdam | T +31 (0)20 - 5980 684 | e.zaura@acta.nl

Coordinating investigator:
Dr. C.M.C. (Catherine) Volgenant | T +31 20 59 80 596 | c.volgenant@acta.nl

Independent expert:
Dr. C.C. Bonifacio
Academisch Centrum Tandheelkunde Amsterdam | Pediatric Dentistry |
Gustav Mahlerlaan 3004 | 1081 LA Amsterdam | T +31 20 59 80 597 | c.bonifacio@acta.nl

Complaints’ officer ACTA:
Ms A.G. Buis – de Vos
Academisch Centrum Tandheelkunde Amsterdam | Zorginstituut |
Gustav Mahlerlaan 3004 | 1081 LA Amsterdam | T +31 6 2153 84 75 | a.g.buis-de.vos@acta.nl

Data Protection Officer ACTA:
Mr. drs. M.A. Verkijk
Academisch Centrum Tandheelkunde Amsterdam | ACTA bestuur en management |
Gustav Mahlerlaan 3004 | 1081 LA Amsterdam | T +31 20 59 80636 | fg@acta.nl

Responsible for the processing of your personal data:
ACTA, a joint venture of UvA and Stichting VU. For more information about your rights you can contact the principal investigator or visit https://www.acta.nl/nl/patientenzorg/bescherming-persoonsgegevens/index.aspx

Appendix 2: contact details Philips

Responsible for the processing of your personal data:
Philips Electronics Nederland B.V. ("Philips")
High Tech Campus 52, 5656AG, Eindhoven, Nederland

Contact details Data Protection Officer Philips:
If you have any questions about the way Philips uses your data, please contact our Data Protection Officer via our contact form
(www.philips.com/contactprivacy) or at
Philips Center HBT 16
Attn.: Data Protection Officer
P.O. Box 77900, 1070 MX, Amsterdam, The Netherlands

The ACTA Data Protection Officer is your first point of contact.

Thank you for your attention!

Appendix 3: Informed consent form for the clinical study:

'The evaluation of the effects of a prebiotic mouth rinse on the oral ecosystem - the INORE study '

- I have read the information letter. I was also able to ask questions. My questions have been answered sufficiently. I have had enough time to decide whether or not to participate.
- I understand that participation is voluntary. I also know that I may decide at any time to not participate or to stop participating in the study. Without having to provide any reason.
- I give consent for my dentist to be informed of my participation in this study.
- I give consent for my dentist to be informed of unexpected findings which are or may be of interest for my health.
- I give consent to collect and use my data and body material (plaque samples) for answering the research question in this study.
- I know that for study monitoring purposes some individuals could have access to all my data. Those people are listed in this information letter. I consent to that access by these persons.
- I give consent that after the study the coded research data will be stored for 20 years.
- I **give/ do not give*** consent to being contacted again after this study for a follow-up study.
- I **would like** / **would not like*** to be informed about in which group I was.
- **I give / do not give*** consent to the parties mentioned in the information letter to use my research data in the future for research and development purposes in oral healthcare.
- I want to participate in this study.

Name of subject: ……..

Signature: Date : __ / __ / __

I certify that I have fully informed this subject about the said study. If information becomes known during the study that could influence the consent of the subject, I will inform him/her of this on time.

Name of investigator (or his/her representative): ……

Signature: Date: __ / __ / __

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* Strikethrough what is not applicable.

The subject will receive a complete information letter, together with a signed version of the informed consent form.