

# **Local Application of Pilocarpine for Relieving Dry Mouth Complaints: A randomized controlled pilot trial**

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Can locally administered pilocarpine drops relieve dry mouth (xerostomia) in the elderly at cost of minimal side-effects?

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## LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

<b>ABR</b>	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
<b>AE</b>	Adverse Event
<b>AR</b>	Adverse Reaction
<b>CA</b>	Competent Authority
<b>CAT</b>	COPD Assessment Test
<b>CCMO</b>	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
<b>CV</b>	Curriculum Vitae
<b>COPD</b>	Chronic Obstructive Pulmonary Disease
<b>DSMB</b>	Data Safety Monitoring Board
<b>EU</b>	European Union
<b>EudraCT</b>	European drug regulatory affairs Clinical Trials
<b>FNA</b>	Formularium Nederlandse Apothekers
<b>GCP</b>	Good Clinical Practice
<b>IB</b>	Investigator's Brochure
<b>IC</b>	Informed Consent
<b>IMP</b>	Investigational Medicinal Product
<b>IMPD</b>	Investigational Medicinal Product Dossier
<b>METC</b>	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
<b>NRS</b>	Numeric Rating Scale
<b>(S)AE</b>	(Serious) Adverse Event
<b>SPC</b>	Summary of Product Characteristics (in Dutch: officiële productinformatie IB1-tekst)
<b>Sponsor</b>	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.

<b>SUSAR</b>	Suspected Unexpected Serious Adverse Reaction
<b>Wbp</b>	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens)
<b>WMO</b>	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)



**SUMMARY****Rationale:**

Xerostomia, the subjective feeling of dry mouth, is a frequent symptom in the elderly. Xerostomia leads to functional alterations and has disabling social consequences and reduces quality of life.

**Objectives**

The objective of this study is to deliver the “proof-of-concept” that locally administered pilocarpine drops are effective in a population of elderly with xerostomia at expense of a minimum of side effects.

**Study design:**

Open-label randomised controlled pilot study

**Study population:**

Patients of advanced age ( $\geq 70$  years) with a clinical diagnosis of chronic dry mouth (NRS score of  $\geq 5$ ) visiting the outpatient clinic of MUMC+.

**Intervention:**

Local administration of pilocarpine (eye)drops orally in a low dose or a high dose for 14 days.

**Main study parameters/endpoints:**

Change in xerostomia score

Change in oral health-related quality of life

**Secondary study parameters/endpoints**

- Adverse effects
- Other symptoms
- Global perceived effect

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:**

The extent of the burden associated with participation in this study is considered to be low. Total follow up will last a total of 3 weeks. In these 3 weeks the patient will visit the hospital twice and will be contacted through phone calls twice. Local oral administration of pilocarpine is reported to have none or only minor side effects. During the two hospital visits whole resting saliva will be collected, and blood pressure will be measured. The burden of both these procedures is considered low. The patient will also be asked to complete a total of four questionnaires in these 3 weeks. These questionnaires consists of 45 questions, which will take 20 minutes, the level of burden is low.

## 1. INTRODUCTION AND RATIONALE

### Introduction

Xerostomia is the subjective feeling of dry mouth, a symptom associated with alterations in the quality and quantity of saliva. Xerostomia leads to functional alterations such as halitosis, burning sensations, altered taste perception, pain, and difficulties of chewing, swallowing, speaking and sleeping.[1, 2] Also, xerostomia has disabling social consequences[3] and reduces quality of life.[2, 4-8]

Xerostomia has been associated with radiation therapy, the use of medications, various chronic diseases and/or poor health.[2] Reported prevalence rates among patients with cancer, Chronic Obstructive Pulmonary Disease (COPD) or heart failure are about 50%.[9-11] The prevalence among community-dwelling elderly ranges from 17% to 40%.[2] In a cohort of vulnerable elderly the prevalence of xerostomia was estimated at 100%, with low, moderate, and high xerostomia according to the xerostomia index at a rate of 49.3%, 30.3%, and 20.4%, respectively.[8]

In the elderly, xerostomia is mostly caused by side effects of chronic drug treatment in combination with a 30%-40% decrease of acinar cells of salivary glands between the ages of 34 and 75 years.[1]

Withdrawal or substitution of xerostomia-inducing drugs is the most effective treatment. However, this does not always outweighs the drug's benefits, e.g. with treatment of depression or pain.

Therefore other treatment possibilities to effectively reduce xerostomia and improve quality of life should be considered.

Current symptomatic treatment options include local treatment with artificial saliva/mouthwashes or systemic or local administration of pilocarpine. The former has mainly been researched in advanced cancer patients[12, 13] and was not better than chewing gum.[14] The latter are the current mainstay treatment of patients in the palliative phase of their illness.[12] Pilocarpine is a parasympathomimetic drug that increases saliva production by activating muscarinic receptors.[12] Pilocarpine tablets (systemic treatment) are more effective than placebo in radiation-induced xerostomia,[15-18] Sjögren's disease, [19] tramadol induced oral dryness[20] and improved salivation in patients taking xerogenic medications.[21] However, systemic administration of pilocarpine has frequent side-effects such as sweating (20 -50%), flushing, rhinitis (12%), headaches (12%), increased frequency of urination (11-34%), flu-like symptoms (8%), asthenia (7%)[21-23] and, mainly in elderly patients, dizziness (17%) leading to dropout rates between 6% and 15% in clinical studies.[16] Local oral administration of pilocarpine (drops, lozenges and mouthwashes) are reported to have none [24, 25] or minor local side effects (irritation of mouth and tongue).[26] In addition, a 5 mg pilocarpine lozenge produced better clinical results than a 5 mg pilocarpine tablet in 33 head-and-neck cancer

patients.[27], Furthermore, pilocarpine eye drops 2% relieved xerostomia immediately in 19 patients with opioid-induced complaints of dry mouth.[25] However, inconclusive results have been reported about the effectiveness of these local formulations in other studies.[24, 28].

Literature is scarce on the effectiveness of pilocarpine in elderly patients with xerostomia.

Pilocarpine mouthwash relieved dry mouth in 19 elderly patients[26], whereas a systematic review evaluating the effectiveness of systemic pilocarpine in 242 elderly patients with xerostomia due to medication or unknown causes showed inconclusive results.[1] As our population is ageing and poly-pharmacy is common among elderly, more patients will be poly-medicated in the future. Hence, xerostomia will be a major problem and thus more research on this topic is necessary.

This study intends to deliver the “proof-of-concept” that locally administered pilocarpine drops are effective in reducing xerostomia complaints in a population of elderly (aged  $\geq 70$  years) with xerostomia at the expense of a minimum of side effects.

## 2. OBJECTIVES

### Objective

This study intends to deliver the “proof-of-concept” that locally administered pilocarpine drops in two doses are effective in a population of elderly (aged  $\geq 70$  years) with xerostomia at the expense of limited adverse events. To this end, the study aims to quantify the effect size of pilocarpine in two different dosages. In case we observe clinically meaningful changes in xerostomia through measured NRS, a sufficiently-powered RCT will be prepared to compare pilocarpine to placebo.

## 3. STUDY DESIGN

### DESIGN:

Open-label randomised controlled pilot study

### PARTICIPANTS

The study will be performed at the outpatient clinic internal medicine/elderly care of the Maastricht University Medical Centre+.

### INTERVENTION:

The intervention concerns the treatment of xerostomia in 2 treatment groups:

1. low dose pilocarpine = 3 x 2.0 mg = 3 x 2 drops of pilocarpine 20.0 mg/ml (2%) per day
2. high dose pilocarpine = 3 x 5.0 mg = 3 x 5 drops of pilocarpine 20.0 mg/ml (2%) per day

The study lasts 21 days of which the first 14 days with medication and the last 7 days without medication to measure a possible “switch-on” effect.

#### MEASUREMENTS

Xerostomia	Numeric Rating Scale (NRS) Geriatric Oral Health Assessment Index (GOHAI-NL)
Concurrent symptoms	Utrecht symptom Diary (USD)
Generic Health-Related Quality of Life (HRQoL)	EuroQoL 5D (EQ5D)
Global Perceived Effect (GPE)	GPE 7-point scale
Side effects	4-point Likert scale (flu-like symptoms, sweating, headache, urinary frequency, diarrhoea, nausea, vomiting, palpitations, dizziness, rhinitis, other)
Whole resting saliva	Total amount of unstimulated saliva measured in 5minutes

Patient characteristics that are collected at inclusion include gender, age, primary diagnosis, co-morbidity, medication and relevant history.

## 4. STUDY POPULATION

### 4.1 Population (base)

The study will be performed at the outpatient clinic internal medicine/elderly care of the Maastricht University Medical Centre+ (MUMC+). Potentially eligible patients will be identified on the outpatient clinic and will be invited to participate when meeting the inclusion criteria.

### 4.2 Inclusion criteria

- $\geq 70$  years of age
- Clinical diagnosis of chronic dry mouth defined as a Numeric Rating Scale (NRS) score  $\geq 5$  (scale 0 – 10, with 0 = no dry mouth and 10= worst possible dry mouth) on severity of xerostomia for more than 3 months.

### 4.3 Exclusion criteria

- Existence of cognitive impairment and/or diagnosis of dementia appraised by treating physician
- Inability to fill out the questionnaires due to other reasons
- Prior radiation therapy of the head-and-neck region

- Known m. Sjögren disease
- Contra-indications for parasympathomimetics (uncontrolled asthma, acute heart failure, active peptic ulceration, known hypersensitivity to pilocarpine, and when miosis is undesirable, e.g., in acute iritis and in narrow-angle (angle closure) glaucoma).

#### 4.4 Sample size calculation

For this study we will take a pragmatic approach, as too little is known of the mean and variance of xerostomia complaints, quantified using the NRS, and the effect size of pilocarpine. This study will provide input for the sample size calculation for a future study. It would be feasible to include at least 24 patients in a period of 6 months, or 12 per group, as suggested as a rule of thumb for pilot studies to obtain sufficient precision about the mean and variance .[29]

### 5. TREATMENT OF SUBJECTS

#### 5.1 Investigational product/treatment

Patients will receive regular clinical care and pilocarpine drops in unit dose vials (Pilocarpine Minims (*nitraat*), eye drops, Bausch & Lomb), 2%, two or five drops administered three times a day (6 or 15mg/24h). Patients will receive the study drug for 14 days.

#### 5.2 Use of co-intervention (if applicable)

Not applicable

#### 5.3 Escape medication (if applicable)

Not applicable

### 6. INVESTIGATIONAL PRODUCT

#### 6.1 Name and description of investigational product(s)

*Investigational product:*

Pilocarpine Minims (*nitraat*), eye drops, Bausch & Lomb, 20 mg/ml (2%), 0.5 ml  
(Oculoguttae pilocarpine sine conservans)

#### 6.2 Summary of findings from non-clinical studies

We refer to the Summary of Product Characteristics (SmPC)

#### 6.3 Summary of findings from clinical studies

Pilocarpine tablets are registered for dry mouth in Sjögrens disease and post radiation therapy.

Pilocarpine drops are registered for treatment of open-angle glaucoma and narrow-angle glaucoma and to antagonize mydriasis.

Pilocarpine tablets (systemic treatment) has proven to be effective in radiation-induced xerostomia,[15-18] Sjögrens disease, [19] tramadol induced oral dryness[20] and in patients taking xerogenic medications.[21] However, systemic administration of pilocarpine has frequent side-effects.

Off-label local oral administration of pilocarpine (drops, lozenges and mouthwashes) are reported to have none [24, 25] or minor local side effects (irritation of mouth and tongue).[26] In addition, a 5 mg pilocarpine lozenge produced better clinical results than a 5 mg pilocarpine tablet in 33 head-and-neck cancer patients.[27], Furthermore, pilocarpine eye drops 2% relieved xerostomia immediately in 19 patients with opioid-induced complaints of dry mouth.[25] However, inconclusive results have been reported about the effectiveness of these local formulations in other studies.[24, 28].

#### Dosing:

Post-radiation studies reveal an optimum oral dose of 5 mg 3 dd/day. Higher doses result in higher saliva flow but at the expense of more unacceptable adverse effects. Effect and side effects increase with increasing dosages.[15, 16] A trial with 2,5 mg 3dd/day showed an increase in salivary flow but not a subjective improvement.[18] Possibly this low dose is insufficient in damaged salivary glands. In this pilot study we will compare two doses (5 mg 3 dd/day and 2mg 3dd/day) in intact glands.

### **6.4 Summary of known and potential risks and benefits**

Pilocarpine is a cholinergic parasympathomimetic agent exerting a broad spectrum of pharmacologic effects with predominant muscarinic action.[30]

- In systemic use pilocarpine, in appropriate dosage, can increase secretion by the exocrine glands. The sweat, salivary, lacrimal, gastric, pancreatic, and intestinal glands and the mucous cells of the respiratory tract may be stimulated. Dose-related smooth muscle stimulation of the intestinal tract may cause increased tone, increased motility, spasm, and tenesmus. Bronchial smooth muscle tone may increase. The tone and motility of urinary tract, gallbladder, and biliary duct smooth muscle may be enhanced. Pilocarpine may have paradoxical effects on the cardiovascular system. The expected effect of a muscarinic agonist is vasodepression, but administration of pilocarpine may produce hypertension after a brief episode of hypotension. Bradycardia and tachycardia have both been reported with use of pilocarpine.

- In use as eye drops: systemic reactions rarely occur when treating chronic simple glaucoma at normal doses. However, in the treatment of acute closed-angle glaucoma the possibility of systemic reactions must be considered because of the higher doses given. Caution is particularly advised in patients with acute heart failure, bronchial asthma, peptic ulceration, hypertension, urinary tract obstruction, Parkinson's disease and corneal abrasions.[31]

**Contraindications:**

Pilocarpine HCl Tablets are contraindicated in patients with uncontrolled asthma, known hypersensitivity to pilocarpine, and when miosis is undesirable, e.g., in acute iritis and in narrow-angle (angle closure) glaucoma.

Pilocarpine eye drops are contraindicated in conditions where pupillary constriction is undesirable e.g. acute iritis, anterior uveitis and some forms of secondary glaucoma.

Pilocarpine eye drops are also contraindicated in case of hypersensitivity to the active substance or to any of the excipients thereof.

**6.5 Description and justification of route of administration and dosage**

Polypharmacy is common among elderly patients; patients may even object against more “pills”. In a crossover study in advanced cancer patients, pilocarpine tablets was found to be more effective than artificial saliva, however 50% of patients preferred the saliva. The commonest reason for preferring the artificial saliva was the fact that it was a spray, rather than a tablet.[32]

Patients don't experience local application as “pills”, which makes pilocarpine drops better acceptable. Moreover, local oral administration of pilocarpine (drops, lozenges and mouthwashes) are reported to have none [24, 25] or minor local side effects.[26]

**6.6 Dosages, dosage modifications and method of administration**

The two doses pilocarpine nitrate ( 3 x 2.0 mg = 3 x 2 drops or 3 x 5.0 mg = 3 x 5 drops) will be stable over the first 14 days of the study. Day 15 through day 21 patients will not receive medication. Drops will be administered left and right outside the molars and behind the front teeth under.

**6.7 Preparation and labeling of Investigational Medicinal Product**

The pilocarpine nitrate drops are commercially available (Bausch & Lomb), registered for treatment of open-angle glaucoma and narrow-angle glaucoma and to antagonize mydriasis.

**6.8 Drug accountability**

Drug accountability will be done at the Pharmacy.

## 7. NON-investigational products

NA

## 8. METHODS

### 8.1 Study parameters/endpoints

#### 8.1.1 Main study parameter/endpoint

- change in xerostomia score (NRS)
- change in oral health-related quality of life (GOHAI-NL)

#### 8.1.2 Secondary study parameters/endpoints

- Adverse effects
- Other symptoms
- Global perceived effect

#### 8.1.3 Other study parameters (if applicable)

- whole resting salivary flow

### 8.2 Randomisation, blinding and treatment allocation

Randomisation will be performed by a sealed envelope system.

In this participating clinicians are given treatment allocations randomly drawn from one of 24 sealed opaque envelopes that include 12 allocations to the low dose, and 12 to the high dose group to ensure perfect balance. Once a patient has consented to enter the study an envelope is opened and the patient is then offered the allocated treatment regimen.

### 8.3 Study procedures

The study will be performed at the outpatient clinic internal medicine/elderly care of the Maastricht University Medical Centre+. Potentially eligible patients will be identified on the outpatient clinic by answering the question if they have suffered from a dry mouth in the last three months. If the answer to this question is yes they will be invited to participate when meeting the inclusion criteria.

Each patient that participates in this study will receive a restaurant coupon and their travel expenses will be covered.

Randomisation will occur through a sealed envelope system. Once a patient has consented to the trial, a sealed opaque envelope is opened and the patient will receive the allocated treatment regime. This sealed opaque envelope will also contain a two digit number wherein the patient will be identified from this point forward in the database. The sealed opaque envelopes with all its content will be arranged by the researcher before start of the study.



Measures will be performed on day 0, 7, 14 and 21. Questionnaires on day 0, 7, 14 and 21, whole resting salivary flow on day 0 and 14, blood pressure will be measured on day 0 before and 1 hour after pilocarpine administration and on day 14.

	Day 0	Day 7	Day 14	Day 21
Hospital visit	X		X	
Patient characteristics	X			
Xerostomia NRS / GOHAI-NL	X	X	X	X
USD	X	X	X	X
EQ5D	X	X	X	X
GPE	X	X	X	X
Side effects	X	X	X	X
RR	X		X	
Whole resting saliva	X		X	

After inclusion the patient will visit the outpatient clinic twice on day 0 and day 14. On the first visit (day 0) after inclusion a questionnaire consisting of 45 questions, will be filled in, this will take 20 minutes. Also patient characteristics, including use of medication, will be accessed. Blood pressure and whole resting saliva will be measured. The blood pressure will be measured in sitting position using the Dinamap technology V100 care scape from general electric. The whole resting saliva will be measured by the doctor/research nurse. The patient will have to sit straight in a chair and will be asked to swallow the saliva that is currently in their mouth, in the next five minutes the patient will be asked to accumulate all the saliva that is spontaneously produced in their mouth. This whole resting saliva will be collected in a previously weighted cup and the result of each patient will be compared. The cups and the whole resting saliva will be measured with the SARTORIUS AC210p scale.

On day 14 all of these procedures but one (assessment of patient characteristic ) will be repeated. On day 7 and day 21 the patient will receive a phone call wherein the questionnaires will be taken by the doctor/research nurse. At the end of the study patients will be offered to continue the pilocarpine drops as off-label use. The reimbursement status for this indication is uncertain.

**Table 1:** Description of study procedures

	Procedure	Parameter	Description
Measurements	Whole resting saliva	Amount of saliva collected in 5 minutes	This procedure will be done twice during the study
	Blood pressure	mmHg	The sitting blood pressure will be measured using the Dinamap technology V100 care scape from general electric.
Questionnaires	0-10 Numeric Rating Scale (NRS)	Xerostomia	The NRS is used to quantify the level of severity of xerostomia using a 0-10 cm NRS ranging from 0 = no dry mouth to 10 = worst possible dry mouth.[28]
	Geriatric Oral Health Assessment Index (GOHAI-NL)	Xerostomia	Oral health-related quality of life (OHRQoL) of adults, in particular older people is measured 4 times during this study by the doctor/research nurse . It comprises of 12 items that measure three dimensions of OHRQoL: physical function items, psychosocial function and pain/discomfort. [33]
	Utrecht symptom Diary (USD)	concurrent symptoms	The USD asks patients to self-asses eleven symptoms and their wellbeing on a daily basis, by using a numerical rating scale ranging from 0 to 10. Patients can also indicate which symptom is a priority for them.[34, 35]
	EuroQoL 5D (EQ5D)	generic Health-Related Quality of Life (HRQoL)	Health-related quality of life is measured 4 times during this study by the doctor/research nurse, using five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[36]

	Global Perceived Effect (GPE 7-point scale)	Global Perceived Effect (GPE)	The GPE scale asks the patient to rate, on a numerical scale, how much their condition has improved or deteriorated since some predefined time point.[37]
	4-point Likert scale	Side effects	Patients are asked if they experienced flu-like symptoms, sweating, headache, urinary frequency, diarrhoea, nausea, vomiting, palpitations, dizziness, rhinitis, or other symptoms, while on the treatment.

## 8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

### 8.4.1 Specific criteria for withdrawal

Unacceptable adverse effects.

## 8.5 Replacement of individual subjects after withdrawal

Individual subjects will not be replaced after withdrawal.

## 8.6 Follow-up of subjects withdrawn from treatment

Patients will receive usual care after withdrawal

## 8.7 Premature termination of the study

Criteria for termination of the study prematurely: Since none or only minor side effects are expected, there is no specific criteria for premature termination of the study that can be stated beforehand. In the case of premature termination of the clinical trial, the investigator will inform

the reviewing accredited METC and the sponsor. Reasons for termination will be stated in writing.  
All participants will be informed. Participants will receive usual care.

## 9. SAFETY REPORTING

### 9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

### 9.2 AEs, SAEs and SUSARs

#### 9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

#### 9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
  - is life threatening (at the time of the event);
  - requires hospitalisation or prolongation of existing inpatients' hospitalisation;
  - results in persistent or significant disability or incapacity;
  - is a congenital anomaly or birth defect;
  - Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.
- An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the

initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

### 9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
  - Summary of Product Characteristics (SPC) for an authorised medicinal product;
  - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

### **9.3 Annual safety report**

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

### **9.4 Follow-up of adverse events**

All AEs will be followed until they have abated, or until a stable situation has been reached.

Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

### **9.5 Data Safety Monitoring Board (DSMB)**

Not applicable.

## **10. STATISTICAL ANALYSIS**

### **Primary and secondary study parameter(s)**

Baseline characteristics will be described in detail per group in order to assess any imbalance. In case of missing data, we will use stochastic regression imputation to produce a synthetic part of the data to allow for an intention to treat analysis.

Per group, the post-treatment xerostomia score will be described as mean and standard deviation, or median and interquartile range in case of severe skewness. Additionally, we will compute a change-from-baseline score for both groups, which will be described in a similar matter. All secondary

outcome measures will be described in full using either mean and standard deviation or median and interquartile range for continuous measures, and count and proportion for categorical measures. For exploratory purposes, we will use the independent-samples t-test to test for differences in xerostomia complaint scores (NRS) between the two groups. However, as this is a pilot study, the emphasis will lie on clinical interpretation of the effect sizes of both groups separately. Preliminary analyses on secondary outcome measures will be performed using the independent samples t-test and Fisher's Exact test, depending on the measurement level of each variable.

**Other study parameters**

Not applicable.

**Interim analysis**

No interim analysis will be performed.

**11. ETHICAL CONSIDERATIONS****11.1 Regulation statement**

The study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

**11.2 Recruitment and consent**

Patients who fulfill the inclusion criteria, will be informed about the study by their treating physician or physician assistant during a regular outpatient clinic visit. The treating physician or physician assistant will hand out the patient information leaflet and introduce the patient to the researcher.

The patient will have a minimum of 7 days period to decide if he or she wants to participate in the study. If a patient decides to participate, the researcher will plan a new appointment for the patient where additional questions can be answered and the informed consent can be signed.

This day will be considered day 0, and the start of the study for this patient.

Inclusion will take place on Tuesdays and Wednesdays in the outpatient clinic of internal medicine. On these days there are the largest amount of patients at the outpatient clinic. A total of 6 patients per doctor is expected to be seen. This means that on a Tuesday about 18 patients will be seen and on a Wednesday 12 patients.



**11.3 Objection by minors or incapacitated subjects**

Not applicable.

**11.4 Benefits and risks assessment, group relatedness**

**The risk to and burden for the subject will be in proportion to the potential value of the research because we expect possible less complaints of dry mouth at cost of minimal side effects of the drugs. Main burden of the patients will be 1 or 2 extra outpatient visits and time investment for filling in questionnaires.**

The sponsor/investigator has a liability insurance which is in accordance with article 7, of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

1. € 650.000,-- (i.e. six hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 5.000.000,-- (i.e. five million Euro) for death or injury for all subjects who participate in the Research;
3. € 7.500.000,-- (i.e. seven million five hundred thousand Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

**11.6 Incentives**

Patient will receive a restaurant coupon of €7.50 and their travel expenses will be covered.

**12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION****12.1 Handling and storage of data and documents**

Data will be handled confidentially and encoded. Only authorized personnel (researchers and monitor) will have access to these confidential files. Also the National Supervisory Authority can have access to these files. A subject identification code list will be used to trace data to an individual subject. The code (01, 02 etc.) will not be based on the patient initials and birth-date. The key to the code will be safeguarded by the investigator. General Data Protection Regulation

(GDPR) en de Uitvoeringswet AVG (UAVG; in het Engels: the Dutch Act on Implementation of the General Data Protection Regulation. Data will be saved for 15 years.

## **12.2 Monitoring and Quality Assurance**

Monitoring will be performed by the Clinical Trial Center Maastricht. Monitoring will follow the international ICH-GCP guidelines. Monitoring will consist of: site initiation visit; interim monitoring visits; and close out visit.

## **12.3 Amendments**

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given.

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will be notified to the accredited METC.

## **12.4 Annual progress report**

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

## **12.5 End of study report**

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

### **12.6 Public disclosure and publication policy**

The investigator will be responsible for the quality of the study performance, and he/she has the right to publish the results of this study in the appropriate well-accepted scientific journals. All publications will be confirming the basic principles of the CCMO publication policy ([www.ccmo.nl](http://www.ccmo.nl)). The study will be registered in the trial register ([www.trialregister.nl](http://www.trialregister.nl))

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