Study Code (CTC): SSHNC-1

PROTOCOL TITLE

Efficacy of GUM Hydral mouthwashes on symptoms of radiotherapy-induced xerostomia: a randomized, double-blind, crossover study.

Firma del PI

1. INTRODUCTION

1.1 BACKGROUND INFORMATION

Head and neck squamous cell carcinoma (HNSCC) accounts for more than 750,000 new cases per year (1) and its prognosis is still poor in terms of mortality and of morbidity and it causes approximately 350,000 deaths annually worldwide (2). The prognosis and therapy of this cancer are mainly related to the TNM stage and stage seems to be one of the most important prognostic features. Therefore, although advanced surgical techniques have increased the prognosis, it is still poor, with a survival rate which approximately varies between 25% and 45% in stages III and IV (3) (4) (5). Radiotherapy (RT) is an established treatment modality for HNSCC and other H&N tumors, either for treatment alone or as adjuvant (6) (7). Unfortunately, high-dose RT has significant adverse effects on the oral and maxillofacial tissues, both hard and soft, and dental management of these patients is based largely on individual and expert opinion, as few prospective studies have been performed to determine risk factors for adverse oral sequelae (8). In particular, when salivary glands are within the irradiated field, irreversible salivary glands damage occurs in 63–93% of the patients. Salivary gland damage typically manifests as reduced saliva secretion, which in turn can translate into a subjective sensation of dry mouth (xerostomia), oral discomfort, altered taste, difficulty with speaking, swallowing, chewing, and increased risk of dental disease. Overall hyposalivation and related xerostomia can cause a substantial reduction in quality-of-life (QoL). However there is currently little robust evidence to inform the management of hyposalivation and xerostomia in this population (9) (10). Although the treatment of xerostomia is very individual, a first-line medication is to ameliorate the dehydration in the mouth by substituting for the secretion of saliva. (11)

1.2 MEDICAL DEVICE DESCRIPTION

GUM Hydral (GUM Hydral: Sunstar Italiana SRL. Corso Italia 13 21047 Saronno, VA, Italy) is a product based on hyaluronic acid and sodium citrate. It helps in rehydrating and protecting the oral tissues, by forming a film on those tissues. It may be helpful in reducing the xerostomia symptoms.

1.3 FEATURES OF THE MEDICAL DEVICE

The device is a high-density liquid and it is used as a mouthwash. In this trial, the aim is to investigate if its efficacy in reducing the xerostomia symptoms is higher than placebo.

The placebo will be made of water with xylitol in addition. Xylitol is a is a sugar alcohol used as a sugar substitute, which does not increase the risk of tooth decay. In this formulation, its only role is to give a slight sweet flavor to water.

Water added with xylitol, in fact, may reduce, to a certain extent, the xerostomia symptoms, so it may be considered as a suitable comparator.

The device used for the clinical trial will be identified with visible marking stating “Exclusively for clinical investigations SSHNC-1 only”.

Funder will initiate the shipment of the medical device to the site upon the Principal Investigator received the Ethics Committee approval. Prior to any shipment, the site will be informed by the Funder/Sponsor on the upcoming shipment, expected arrival date and content of the shipment. The site should confirm receipt of the shipment.

Funder will also be encharged of the manifacturing and biological stabilization of placebo, whose composition is described above.

The placebo used for the clinical trial will be identified with visible marking stating "Exclusively for clinical investigations SSHNC-1 only".

Funder will also initiate the shipment of the placebo to the site upon the Principal Investigator received the Ethics Committee approval. Prior to any shipment, the site will be informed by the Funder/Sponsor on the upcoming shipment, expected arrival date and content of the shipment. The site should confirm receipt of the shipment.

For the risk analysis please refer to the IfU (Instruction for Use).

1.4 PURPOSES AND OBJECTIVES OF THE CLINICAL TRIAL

The aim of this study is to describe the effect of the administration of Hydral on reducing patients' xerostomia symptoms due to radiotherapy. (12)

1.5 EXPERIMENTAL DESIGN

The study will be conducted as a double-blind randomized clinical trial (RCT) and foresees a crossover design, so the population will be divided into two groups, receiving both the medical device and the placebo. The interventions will be described in paragraph 2.3.

2 MATERIALS AND METHODS

2.1 PATIENTS SELECTION

Inclusion criteria:

- Patients willing to sign the informed consent form
- Patients older than 18 years
- Patients with diagnosis of HNC, who had received local radiotherapy at least three months before the beginning of the study, involving the salivary glands, both for curative and palliative purpose, with or without chemotherapic treatment, reporting xerostomia symptoms
- Patients with diagnosis of HNC, who had received local radiotherapy as an adjuvant to surgical resection at least three months before the beginning of the study, with or without chemotherapic treatment, reporting xerostomia symptoms-

Exclusion criteria:

- Patients with documented contraindication to any of the components of GUM HYDRAL (there included eccipients)
- Patients with any neurological and psychiatric condition having an influence on the ability to self-apply the treatment
- Patients unwilling to complete the request diary card
- Patients unable to attend the ambulatory visits scheduled by the protocol
- Patients participating to other clinical studies
- Patients who had received antitumoral treatment during the previous three months
- Patients with concomitant Sjogren's syndrome
- Other causes of xerostomia (pharmacological treatment)

2.2 WITHDRAWAL PROCEDURES

The intervention will be stopped in any case of reported adverse event that can be attributed to GUM Hydral, or in case the patients will need a drug or a medication which could interfere with the xerostomia symptoms.

In order to improve the adherence of the patients to the protocol interventions, all the patients will be asked to update a diary card reporting the usage of the product.

During the duration of the treatment, the patients will be asked not to use any product analogue of Hydral.

2.3 INTERVENTIONS

The patients will be recruited in the Oral Medicine Department, in a 12 months period.

<u>Study design (see flow-chart)</u>
A baseline visit (T_0) will be conducted three months after the end of RT.
The investigational product GUM Hydral and the placebo will be each administered for a 30-days treatment period.
The patients will be divided into two groups: at **day 1 (baseline -** T_0**),** group A will receive treatment product, group B will receive a placebo.
At **day 15**, the compliance of the patient and any adverse effect will be evaluated by a phone call.
At **day 30**, the administration of the products will be stopped, and a 30 days washout phase will take part, followed by Phase 2 of the study.
At **day 61**, each group will be treated with the alternative product.
At **day 75**, the compliance of the patient and any adverse effect will be evaluated by a phone call.
At **day 90**, the final questionnaire will be administrated, and the investigation of all endpoints will take place.

Each Visit is described in the following flow-chart

Activities/Procedures	**Screening Visit** **(after 3 months from the end of the RT)** **From Day-3 to Day 0**	**Baseline Visit** **Day 1**	**DAY 15** **(± 2 gg)**	**DAY 30** **(± 7 gg)**	**DAY 31-60 Washout phase**	**DAY 61**	**DAY 75**	**DAY 90** **(End of Study Visit)** **(± 7 gg)**
	PHASE A					**PHASE B**		
Visit	**V1**	**V2**	**V3**	**V4**	**V5** **(Note 2)**		**V6**	**V7**
Informed Consent signature	X							
Inclusion/Exclusion Criteria verification	X							
Randomization		X						
Demography	X							
Medical and surgical history and underlying diseases	X							
Previous and concomitant treatments	X	X		X	X	X		X
Physical examinations	X			X		X		X
Salivary flow measurement	X			X		X		X
Oral swab for mycetes determination	X					X		X
Medical Device administration and accountability ***(pts compliance to treatment is assessed at each protocol visit)*** **(**Note 3)		X (Note 4)	X	X		X (Note 5)	X	X
Diary card dispensing and verification		X	X	X		X	X	X
QoLs administration	X (Note 6)		X	X		X	X	X
AEs monitoring	X	X	X	X	X		X	X

Note1: the screening visit might have a maximum duration of 1 day

Note 2: during the washout period a telephone contact will be conducted, in order to assess the safety profile of the patients, by specifically asking to refer any AE occurred and relevant concomitant medications administered (if applicable)

Note 3: an instruction procedure to standardize the products administration will be finalized. Patients will be asked to rinse with 15 ml of product, three times a day.

Note 4: PHASE A, Group A receives Hydral, Group B receives placebo

Note 5: PHASE B, Group A receives placebp, Group B receives Hydral

Note 6: this QoLS administration must be conducted after the ICF signature and before the first Medical Device administration

2.3.1 STUDY PROCEDURES

VISIT SCHEDULING

- Visit 1: DAY 1
- Visit 2: DAY 15
- Visit 3: DAY 30
- Washout phase: DAY 31-60
- Visit 4: DAY 61
- Visit 5: DAY 75
- Visit 6: DAY 90

DESCRIPTION OF VISITS AND ASSESSMENTS

VISIT 1:

- Informed consent signature
- Inclusion/Exclusion criteria verification
- Medical and surgical history and underlying diseases will be verified
- Previous and concomitant oral treatments will be checked out and proceed regularly, excluding any antitumoral therapy, both radio and chemotherapy
- Physical examination
- Oral swab for mycetes determination will be taken
- Salivary flow, both basal and stimulated, will be measured
- Three questionnaires for the assessment of xerostomia and of the quality of life will be administered:
  QLQ30
  QLQH&N35
  XQ questionnaire. In addition, one question by the Shortened Xerostomia Inventory (SXI-D) scale score will be used
- In addition, xerostomia will be assessed even through a NRS Scale
- Further, the patient's satisfaction in using each product will be evaluated by using a Likert scale
- Drug Administration and accountability: participants will be instructed to rinse with the mouthwash five times per day, especially before going to bed.

VISIT 2:

- Drug Administration and accountability: the compliance of the patient will be evaluated
- AEs monitoring

VISIT 3:

- Previous and concomitant oral treatments will be checked out and proceed regularly
- Physical examination
- Salivary flow measurement (both basal and stimulated)
- Drug Administration and accountability: the compliance of the patient will be evaluated
- Three questionnaires for the assessment of xerostomia and of the quality of life will be administered:
  QLQ 30
  QLQ H&N35
  XQ questionnaire. In addition, one question by the Shortened Xerostomia Inventory (SXI-D) scale score will be used
- In addition, xerostomia will be assessed even through a NRS Scale
- Further, the patient's satisfaction in using each product will be evaluated by using a Likert scale
- AEs monitoring

VISIT 4:

- Previous and concomitant oral treatments will be checked out and proceed regularly
- Physical examination
- Drug Administration and accountability: the compliance of the patient will be evaluated
- Three questionnaires for the assessment of xerostomia and of the quality of life will be administered:
  QLQ 30
  QLQ H&N35
  XQ questionnaire. In addition, one question by the Shortened Xerostomia Inventory (SXI-D) scale score will be used
- In addition, xerostomia will be assessed even through a NRS Scale
- Further, the patient's satisfaction in using each product will be evaluated by using a Likert scale

- Drug Administration and accountability: every patient will receive the product alternative to the one he used during the first phase of the trial
- Oral swab for mycetes determination will be taken
- AEs monitoring

VISIT 5:

- Drug Administration and accountability: the compliance of the patient will be evaluated
- AEs monitoring

VISIT 6:

- Previous and concomitant oral treatments will be checked out and proceed regularly
- Physical examination
- Salivary flow measurement (both basal and stimulated)
- Drug Administration and accountability: the compliance of the patient will be evaluated
- Three questionnaires for the assessment of xerostomia and of the quality of life will be administered:
  QLQ 30
  QLQ H&N35
  XQ questionnaire. In addition, one question by the Shortened Xerostomia Inventory (SXI-D) scale score will be used
- In addition, xerostomia will be assessed even through a NRS Scale
- Further, the patient's satisfaction in using each product will be evaluated by using a Likert scale

2.4 STUDY OBJECTIVES

The measurement of xerostomia is problematic. In contrast to hyposalivation, which can be objectively evaluated by using sialometry, xerostomia is comprised of a set of symptoms, and therefore can be assessed only by directly questioning individuals.

The questionnaire which will be used to this evaluation are Xerostomia Questionnaire (13) (14). To the XQ questionnaire, 1 further question was added from Xerostomia Inventory (XI) scale score (15).

The QLQ-C30 provides 30 questions, globally assessing patients' quality of life. The QLQ-H&N35 includes 35 questions, and addresses symptoms associated with specific tumor location, side effects associated with the oncologic treatment and additional QoL aspects modified by the disease or its treatment. The answers will be converted into a linear scoring scale, with values between 0 and 100, (16) (17) as per advocated by EORTC.

The modified XQ provides a measure of the severity of radiation -induced xerostomia that affects the patients' QoL. This questionnaire consists of 10 questions, associated with patient-reported dryness. Moreover, a general question "how dry is your mouth?" has been added to the questionnaire. The modified XQ is a self-administered tool and patients will be asked to rate each symptom on a 10-point NRS scale of 0-10, with higher scores indicating more severe dryness or discomfort due to dryness. Each item score is added, and the sum is linearly transformed to produce the final summary score ranging from 0 to 100, with higher scores representing higher levels of xerostomia.

Patients' compliance will be evaluated by the use of a diary card, in order to notice the amount of product used.

2.4.1 PRIMARY OBJECTIVE

To describe the results of the five questionnaires (listed below) at all the timepoints:

QLQ 30 (18)

QLQ H&N35 (19)

Xerostomia Inventory (XI) scale score (20) (21)

VAS scale

Xerostomia Questionnaire (22)

2.4.2 SECONDARY OBJECTIVES

- Evaluate Hydral treatment efficacy in reducing xerostomia's symptoms;
- Describe all the adverse events occurred during the study.

2.5 STUDY POPULATION

IDENTIFICATION PARAMETERS

Each patient will be identified with a univocal code (SSHNC-1_n°), which will be known only by the principal investigator.

2.6 RANDOMIZATION

Patients will be randomized to treatment groups using sequentially numbered, opaque sealed envelopes (SNOSE). (23)

The principal investigator will be encharged of generating the allocation sequence, of enrolling the participants and of assigning the interventions to the participants.

The co-workers who will administrate the therapies and the patients themselves will be blinded about the selected product.

Only in case of assessment of any adverse event, it will be possible for the P.I. to reveal the product used during the therapy.

2.7 DATA MANAGEMENT

The data will be collected by using a web based electronic Case Report Form (eCRF) which will be prepared on the basis of the flow chart included in Section 2.5. The data entry will be performed at site by the Investigator or a designee. The data will be cleared according to specific procedures by the Data Management team of the eCRF provider. The query flow will involve both the monitoring team and the Investigators.

All the details relevant to the data management will be described in the Data Management Plan, which will be prepared by the Data Manager in charge of the study.

2.8 STATISTICAL CONSIDERATIONS

2.8.1 SAMPLE SIZE

In order to detect a 30% difference, in a cross-over design, between the proportion of improved patients in the two groups, with an alpha=0.05 and a power of 80%, a sample size of N=40 is required.

2.8.2 DATA ANALYSIS

The sample will be described in its clinical and demographic features using descriptive statistics techniques. Quantitative variables will be described using the following measures: minimum, maximum, range, mean and standard deviation. Qualitative variables will be summarized with absolute and percentage frequency tables. Normality of continuous variables will be checked using Kolmogorov-Smirnov test.

The primary objective will be achieved using descriptive statistics techniques, summarizing questionnaires' results at the planned timepoints. Efficacy will be investigated considering an ANOVA mixed model. Adverse events will be described numerically (absolute frequency by type) and qualitatively. Comparison between the two groups in terms of adverse events will be done with a Chi-square test.

3. SAFETY AND TOLERABILITY EVALUATION

3.1 SAFETY AND TOLERABILITY PARAMETERS

Since GUM Hydral is intended for topical use only and its constituents are based on natural products, an evaluation of the vital signs is not necessary. The adverse events will be evaluated.

3.2 LABS PARAMETERS.

Oral swabs for mycetes will be taken in order to assess whether the presence of candida species can modify the perception of xerostomia.

3.3 VIGILANCE ACTIVITIES

DEFINITIONS

INCIDENT

Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or USER or of other persons or to a serious deterioration in their state of health.

FATAL INCIDENT

Incident where the Medical Device (MD) determined (or contributed to determine) the patient death (or user death). Factors such as potential risks in use of MD, characteristics of MD, patient health condition, etc. should be considered to assess the causality relationship between the MD and the death. The evaluation of the health professional who witnessed the fatal event should be also taken into account.

INCIDENT THAT HAS CAUSED A SERIOUS DETERIORATION IN THE HEALTH CONDITION

Incident in which the MD has caused a serious deterioration in the health condition of a patient or user or third person is to be intended as:

- an illness or life-threatening injury;
- an impairment of a body function;
- a condition requiring medical or surgical intervention to prevent an impairment of a body function or impairment of a body structure;
- a condition requiring hospitalization or prolongation of hospitalization.

NEAR INCIDENT

Near Incident is to be intended as:

- the condition where any malfunction or deterioration in the characteristics or performances, as well as any inadequacy in the labeling or instructions for use could result, if the MD had been used, a worsening of health condition or death of the patient or user, *or*
- the condition where any malfunction or deterioration in the characteristics or performances, as well as any inadequacy or in the labeling or instructions for use could cause during the procedure of use or following, if health personnel had not intervened, a worsening of health condition or death of the patient or user.

COMPLAINT

Health care professionals should report only to the manufacturer or authorized representative or distributor any non-compliance and / or events that are not listed above, concerning the use or pre-use procedures, related to a MD.

INVESTIGATOR REGULATORY OBLIGATIONS

The Investigator should submit any Incident/Near Incident to the Regulatory Authority (Ministero della Salute, Ufficio VI della Direzione Generale dei Dispositivi Medici e del Servizio Farmaceutico, DGDMF, dgfdm@postacert.sanita.it), to the EC (by e-mail or fax) and to the manufacturer/ authorized representative/distributor following the timelines indicated in the table herebelow:

REPORT	DEADLINE*

Incident	Within 10 calendar days from the date of knowledge by the Investigator
Near Incident	Within 30 calendar days from the date of knowledge by the Investigator

** to be applied also for Follow-Up reports and for claims to be reported to manufacturer/ authorized representative/distributor.*

This form must be filled in with all the available information, dated and signed.
Upon request by the Regulatory Authorities, the Investigator must complete his/her report with all available follow-up information.

SAFETY FOLLOW-UP

The safety information will be recorded by the Investigator starting from the date of the Informed Consent signature and will end-up at the End of Study Visit.

4. ETHICAL ISSUES

This trial will be carried out in compliance with the protocol, designed to ensure adherence to Good Clinical Practice, as described in:

1 ICH Harmonised Tripartite Guidelines for Good Clinical Practice, 1996. Note for Guidance on Good Clinical Practice CPMP/ICH/135/95
2 EU Directive 2001/20/EC, 2005/28/EC
3 Declaration of Helsinki (1964, and its amendments and subsequent clarification
4 UNI EN ISO 14155:2011

The Principal Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

4.1 PROTOCOL AMENDEMENTS

All significant deviations from the protocol will be documented. Any changes made after data analysis has begun will be documented as such and the rationale provided.

5. ADMINISTRATIVE PROCEDURES

5.1 ARCHIVING

The Principal Investigator will ensure the archiving of the essential documents of the study as specified by the GCP and in compliance with the applicable legislation. The Principal Investigator will adopt all the necessary measures to avoid accidental or premature destruction.
At the end of the study, all documents relating to the study should be retained for the period required by the applicable local regulatory requirement(s) or longer, if needed by the Sponsor.

6. INVESTIGATOR'S RESPONSIBILITY

The Investigator is aware of his responsibility for all the actions delegated by him/her to other members of his/her staff assigned to the conduct of the study. Except where specifically required. The Investigator is obliged to conduct the study in compliance with the study protocol and in adherence to the Good Clinical Practice (ICH-E6-R1, UNI EN ISO 14155:2011 and with the principles of the Declaration of Helsinki (1964) and successive revisions as well as in respect of the applicable legislation.

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