



## Clinical trial results:

### Mesenchymal stem cells for radiation-induced hyposalivation and xerostomia in previous head and neck cancer patients (MESRIX-II)

#### Summary

EudraCT number	2018-000348-24
Trial protocol	DK
Global end of trial date	22 February 2024

#### Results information

Result version number	v1 (current)
This version publication date	27 June 2025
First version publication date	27 June 2025

#### Trial information

##### Trial identification

Sponsor protocol code	CVB2018-1
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04776538
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Rigshospitalet
Sponsor organisation address	Inge Lehmannsvej 7, København Ø, Denmark, 2100 København
Public contact	Christian Von Buchwald, Rigshospitalet, Department of Otorhinolaryngology, Head and Neck Surgery & Audiology, 0045 35452370, christian.von.buchwald@regionh.dk
Scientific contact	Christian Von Buchwald, Rigshospitalet, Department of Otorhinolaryngology, Head and Neck Surgery & Audiology, 0045 35452370, christian.von.buchwald@regionh.dk

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 February 2023
Global end of trial reached?	Yes
Global end of trial date	22 February 2024
Was the trial ended prematurely?	No

Notes:

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## General information about the trial

Main objective of the trial:

The objective is to examine whether enrichment of the submandibular glands with injections of allogeneic ASCs will improve the salivary function in radiation-induced salivary damage.

Protection of trial subjects:

Description of Measures to Protect Trial Subjects:

To ensure the safety and well-being of participants in this trial investigating adipose-derived mesenchymal stem/stromal cell (ASC) therapy for radiation-induced xerostomia, several protective measures were implemented:

- Direct Access to Clinical Oversight: All participants were provided with a direct phone number to the principal investigator, ensuring they had 24/7 access to medical guidance or assistance throughout the trial period.
- Minimization of Pain and Distress: All injections were performed under ultrasound guidance to enhance precision and minimize discomfort or procedural complications. The procedure was conducted by trained personnel in a controlled clinical setting.
- Blinding and Randomization: The study employed a double-blind, placebo-controlled design to prevent bias and protect participants from psychological distress associated with knowing their treatment allocation.
- Monitoring and Follow-up: Participants were closely monitored for adverse events and treatment outcomes, with structured follow-up visits at 4 months and again at 1 year post-treatment. These follow-ups included clinical assessments, patient-reported outcomes, and blood sample analysis to detect potential immune responses.
- Adverse Event Recording: A structured protocol was in place for the documentation and evaluation of adverse events, allowing prompt identification and management of any treatment-related complications.
- Ethical Oversight: The study protocol received approval from an independent ethics committee, and all patients provided informed consent prior to enrollment, ensuring they were fully aware of the procedures, potential risks, and their right to withdraw at any time.

Background therapy:

In this trial, no additional treatments beyond the investigational product (adipose-derived mesenchymal stem/stromal cells, ASCs) and the placebo comparator were systematically administered across all arms or groups. All participants continued with their usual standard of care for radiation-induced xerostomia as prescribed by their treating clinicians, but no specific supportive therapies (e.g., sialogogues, saliva substitutes, or other interventions) were mandated or applied as part of the trial protocol.

Evidence for comparator:

The comparator used in this trial was a placebo consisting of CryoStor10 (BioLifeSolutions) supplemented with 10% dimethyl sulfoxide (DMSO), which served as the vehicle solution for the adipose-derived mesenchymal stem/stromal cells (MSCs). This specific formulation was chosen to match the composition of the investigational product, minus the active cellular component. By using the same vehicle solution as the treatment arm, the design ensured that any observed therapeutic differences could be attributed specifically to the MSCs.

Actual start date of recruitment	19 January 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 120
Worldwide total number of subjects	120
EEA total number of subjects	120

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	80
From 65 to 84 years	40
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patients are accessible for inclusion if they have been treated with radiotherapy for a head and neck cancer in Denmark. Patients will be recruited from the Department of Otorhinolaryngology, Head and Neck Surgery & Audiology, Rigshospitalet, by referral from other departments, e.g. Oncology Departments or can be self-referred

### Pre-assignment

Screening details:

Patients were initially contacted by phone to assess interest and answer questions. Those interested received written study information and were invited to a screening visit, where informed consent was obtained. Eligibility was assessed through clinical exams, labs, sialometry, and questionnaires. Only eligible patients were randomized.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The sponsor, investigators, study staff (except for staff involved in stem cell preparation and staff involved in bioanalytical analyses), and patients will be blinded to treatment assignment. A project nurse will thaw the frozen suspension of ASCs or placebo just before injection, and the syringes are covered in sterile green tape to ensure that neither the patients nor the study staff can see the suspension injected.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	adipose-derived mesenchymal stem cell (ASC)

Arm description:

adipose-derived mesenchymal stem cell (ASC) injection to the submandibular gland

Arm type	Experimental
Investigational medicinal product name	adipose-derived mesenchymal stem cell (ASC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Injection

Dosage and administration details:

A total of 0.5 mL of ASCs or placebo was injected without anaesthesia into each submandibular gland, and for the patients receiving ASCs, this corresponded to a dose of approximately  $25 \times 10^6$  cells per gland.

<b>Arm title</b>	Placebo
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Arm description:

Placebo consisted of CryoStor10 (BiolifeSolutions) supplemented with 10% DMSO

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection/infusion
Routes of administration	Injection

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Dosage and administration details:

0.5 mL of placebo was injected without anaesthesia into each submandibular gland,

Number of subjects in period 1	adipose-derived mesenchymal stem cell (ASC)	Placebo
Started	60	60
Completed	60	60

## Baseline characteristics

### Reporting groups

Reporting group title	adipose-derived mesenchymal stem cell (ASC)
Reporting group description: adipose-derived mesenchymal stem cell (ASC) injection to the submandibular gland	
Reporting group title	Placebo
Reporting group description: Placebo consisted of CryoStor10 (BiolifeSolutions) supplemented with 10% DMSO	

Reporting group values	adipose-derived mesenchymal stem cell (ASC)	Placebo	Total
Number of subjects	60	60	120
Age categorical Units: Subjects			
18-75 year old	60	60	120
Age continuous Units: years median standard deviation	61.0 ± 7.4	61.8 ± 6.8	-
Gender categorical Units: Subjects			
Female	19	13	32
Male	41	47	88

### Subject analysis sets

Subject analysis set title	ASC injection
Subject analysis set type	Intention-to-treat
Subject analysis set description: This analysis set includes all randomized participants who were allocated to the adipose-derived mesenchymal stem/stromal cell (ASC) injection group and received one injection of the investigational product. Data from these 60 subjects were analyzed according to the intention-to-treat principle, meaning all participants were analyzed in the group to which they were originally assigned	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: This analysis set includes all randomized participants who were allocated to the placebo group and received one injection of the placebo solution (CryoStor10 supplemented with 10% DMSO). Data from these 60 subjects were analyzed according to the intention-to-treat principle, meaning all participants were included in the analysis based on their original randomization assignment	

Reporting group values	ASC injection	Placebo	
Number of subjects	60	60	
Age categorical Units: Subjects			
18-75 year old	60	60	
Age continuous Units: years median	61.0	61.8	

standard deviation	$\pm 7.4$	$\pm 6.8$	
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Gender categorical Units: Subjects			
Female	19	13	
Male	41	47	

## End points

### End points reporting groups

Reporting group title	adipose-derived mesenchymal stem cell (ASC)
Reporting group description: adipose-derived mesenchymal stem cell (ASC) injection to the submandibular gland	
Reporting group title	Placebo
Reporting group description: Placebo consisted of CryoStor10 (BiolifeSolutions) supplemented with 10% DMSO	
Subject analysis set title	ASC injection
Subject analysis set type	Intention-to-treat
Subject analysis set description: This analysis set includes all randomized participants who were allocated to the adipose-derived mesenchymal stem/stromal cell (ASC) injection group and received one injection of the investigational product. Data from these 60 subjects were analyzed according to the intention-to-treat principle, meaning all participants were analyzed in the group to which they were originally assigned	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: This analysis set includes all randomized participants who were allocated to the placebo group and received one injection of the placebo solution (CryoStor10 supplemented with 10% DMSO). Data from these 60 subjects were analyzed according to the intention-to-treat principle, meaning all participants were included in the analysis based on their original randomization assignment	

### Primary: Unstimulated saliva flow rate

End point title	Unstimulated saliva flow rate
End point description: The primary efficacy objective: To compare the effect of ASC injection, relative to placebo, on changes in unstimulated salivary gland function from baseline to month 4, in patients with previous head and neck cancer. i.e., effectiveness: change in salivary gland function is measured by 4 months change in unstimulated whole saliva flow rate between ASC and placebo (consisting of CryoStor10 (BiolifeSolutions), the freeze media for ASCs).	
End point type	Primary
End point timeframe: 4 months	

End point values	adipose-derived mesenchymal stem cell (ASC)	Placebo	ASC injection	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	60	60	60	60
Units: mL/min				
number (not applicable)	0.04	0.01	0.04	0.01

Attachments (see zip file)	Unstimulated salivary flow rate/UWS plot.png
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## Statistical analyses

<b>Statistical analysis title</b>	Change in unstimulated salivary flow rate
Statistical analysis description: Effectiveness: Saliva gland function measured as the change in unstimulated whole saliva flow rate in the group receiving ASCs compared with the group of participants receiving placebo. Timeframe: 4 months. The saliva flow rate will be measured as ml/min.	
Comparison groups	adipose-derived mesenchymal stem cell (ASC) v Placebo v ASC injection v Placebo
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)

## Secondary: 1. Effectiveness: Stimulated salivary gland function measured by 4 months change in stimulated whole saliva flow rate.

End point title	1. Effectiveness: Stimulated salivary gland function measured by 4 months change in stimulated whole saliva flow rate.
End point description: Effectiveness: Stimulated salivary gland function measured by 4 months change in stimulated whole saliva flow rate.	
End point type	Secondary
End point timeframe: 4 months	

End point values	adipose-derived mesenchymal stem cell (ASC)	Placebo	ASC injection	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	60	60	60	60
Units: ml/min				
number (not applicable)	0.07	0.12	0.07	0.12

<b>Attachments (see zip file)</b>	Stimulated salivary flow rate/Stimulated salivary flow rate.png
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## Statistical analyses

<b>Statistical analysis title</b>	Change in saliva flow rate
Statistical analysis description: The change in saliva flow rate from baseline to the four-month follow-up visit will be presented as ml/min. Continuous outcome measures (change from baseline) will be analysed using an analysis of covariance (ANCOVA) model with randomised treatment group as a class variable and the baseline value as a continuous covariate.	
Comparison groups	ASC injection v Placebo

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)

### Secondary: Patient-Reported Outcome of xerostomia - XQ

End point title	Patient-Reported Outcome of xerostomia - XQ
End point description:	
Key secondary objectives are: To compare the effect of ASC injection, relative to placebo, from baseline to month 4 on all of the following outcome measures:	
Patient-Reported Outcome of xerostomia: Xerostomia Questionnaire (XQ).	
End point type	Secondary
End point timeframe:	
4 months	

End point values	adipose-derived mesenchymal stem cell (ASC)	Placebo	ASC injection	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	58	59	58	59
Units: Score				
number (not applicable)	-5.90	-5.12	-5.90	-5.12

<b>Attachments (see zip file)</b>	Table 2/Tabel 2.docx
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Patient-Reported Outcome of xerostomia: The European organisation for research and treatment of cancer quality of life questionnaire, head and neck-35 (EORTC QLQ-H&N35)

End point title	Patient-Reported Outcome of xerostomia: The European organisation for research and treatment of cancer quality of life questionnaire, head and neck-35 (EORTC QLQ-H&N35)
End point description:	
To compare the effect of ASC injection, relative to placebo, from baseline to month 4 on all of the following outcome measures: Patient-Reported Outcome of xerostomia: The European organisation for research and treatment of cancer quality of life questionnaire, head and neck-35 (EORTC QLQ-H&N35):	
a. Domains for dry mouth (HNDR) b. Domains for sticky saliva (HNSS) c. Domains for swallowing (HNSW)	
End point type	Secondary

End point timeframe:

The primary endpoint, as well as the key secondary outcomes will all be evaluated based on the 4 months assessment.

End point values	ASC injection	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	59		
Units: Score				
number (not applicable)	-13.60	-7.74		

Attachments (see zip file)	Tabel 2.docx
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### Statistical analyses

Statistical analysis title	Change in symptom score
Comparison groups	Placebo v ASC injection
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANCOVA

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Safety was monitored throughout the study period of 4 months

Adverse event reporting additional description:

Safety was evaluated by registration of treatment-related adverse events, serious adverse events (SAE), or death. Evaluation of the immune response to ASC was measured by the development of de novo HLA antibodies

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTC AE 5.0
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Dictionary version	5.0
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### Reporting groups

Reporting group title	Mesenchymal stem cells
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Mesenchymal stem cells	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 60 (1.67%)	2 / 60 (3.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma	Additional description: One patient who received ASCs had a malignant melanoma removed from his chest three months after his ASC treatment. The patient had a history of malignant melanoma.		
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea	Additional description: One patient was admitted to the intensive care unit for one day due to dyspnoea caused by secretion stagnation in the lungs, 2.5 months after the treatment.		
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection	Additional description: one patient underwent a planned knee operation (total knee alloplasty), however, the patient developed an infection in the knee and had to be hospitalized for 22 days to receive intravenous antibiotics and undergo knee revision surgery.		

subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

<b>Non-serious adverse events</b>	Mesenchymal stem cells	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 60 (18.33%)	3 / 60 (5.00%)	
Nervous system disorders			
Near syncope	Additional description: near syncope during the injection		
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Swelling of submandibular gland	Additional description: temporary swelling of the submandibular glands. The swelling remained for 1 day to 3 weeks, but thereafter, disappeared in all patients.		
subjects affected / exposed	9 / 60 (15.00%)	0 / 60 (0.00%)	
occurrences (all)	9	0	
haematoma after the injections	Additional description: Haematoma after the injections		
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	
occurrences (all)	1	1	
Soreness	Additional description: temporary soreness of submandibular glands for 1-2 days		
subjects affected / exposed	2 / 60 (3.33%)	1 / 60 (1.67%)	
occurrences (all)	2	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/37658468>