Clinical trial results:
Phase IV study on the feasibility of a preventative/therapeutic approach with Benzydamine Oromucosal solution in radiation-induced Oral Mucositis (OM) in patients with head and neck cancer (HNC)

Summary

EudraCT number	2020-003306-32
Trial protocol	HU PL
Global end of trial date	05 September 2022
Results information	
Result version number	v1 (current)
This version publication date	30 September 2023
First version publication date	30 September 2023

Trial information

Trial identification	
Sponsor protocol code	030(Z)WO19247
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05055726
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Angelini Pharma S.p.A.
Sponsor organisation address	Via Amelia 70, Rome, Italy, 00181
Public contact	Valeria Tellone, Angelini Pharma S.p.A., +39 3452493461, valeria.tellone@angelinipharma.com
Scientific contact	Valeria Tellone, Angelini Pharma S.p.A., +39 3452493461, valeria.tellone@angelinipharma.com

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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 September 2022
Global end of trial reached?	Yes
Global end of trial date	05 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effectiveness of benzydamine oromucosal solution (mouthwash) in the prevention/treatment of radiation-induced oral mucositis, in Head and Neck Cancer (HNC) patients, from first day of radiation therapy (RT) through end of RT/Early Treatment Termination visit (ETTV).

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, GCP principals and all applicable regulatory requirement. The clinical trial was initiated when a written and dated positive opinion by all relevant Regulatory Authorities and Ethics Committees of the country involved was obtained.
Before entering the study, a written and signed informed consent form (ICF) and the Declaration of Consent for Processing of Personal Data (DCPPD) were obtained from all patients. Patients were enrolled only if both the ICF and DCPPD were obtained in writing.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable.
This was a Phase IV, multicentre, international, open label, single-group study. The single-group design was chosen since there was no other comparable product with the same mechanism of action as benzydamine in this indication, nor a standard of care recognised at the European level. Moreover, placebo or similar mouthwash solutions were not selected as comparators due to ethical reasons related to the importance of treating the severe symptomatology that characterises RT-induced OM.

Actual start date of recruitment	06 December 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hungary: 31
Country: Number of subjects enrolled	Poland: 58
Worldwide total number of subjects	89
EEA total number of subjects	89

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	58
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 89 patients diagnosed with stages III or IV NHC, who were candidates and about to start RT, were enrolled into the study and 67 of the patients included in the enrolled population completed the study per protocol from 7 sites (4 sites in Hungary and 3 sites in Poland).

Pre-assignment

Screening details:

At the screening visit, patients with prior head and neck RT (in the previous 6 months), or patients who received a palliative treatment; patients with distant metastatic disease and/or severe cognitive impairment and/or clinically symptomatic brain metastases and/or patients with significant comorbid conditions; or patients with mucositis due to o

Period 1

Period 1 title	OVERALL PERIOD (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study: both the Investigator and patient were aware of the assigned medication.

Arms

Arm title	Benzydamine HCl 0.15% w/v oromucosal solution

Arm description:

Treatment of 15 ml (1 tablespoon) of concentrated or diluted (with water) solution was taken at home, 2-3 times a day, but not more than 5 times a day. Patients were asked to wash the mouth and throat for 20-30 seconds, according to the Investigator’s indications and the local product’s SmPC.
In Hungary, at the first treatment, the therapy was advised to be started with diluted product (15 ml of water + 15 ml of concentrated solution). After that, gargling could continue with 15 ml (1 tablespoon) of concentrated benzydamine oromucosal solution (mouthwash), generally 2 to 3 times a day, but not more than 5 times a day.
In Poland, the solution was to be used 2 to 3 times daily; at a single time, approximately 15 ml of concentrated or diluted benzydamine oromucosal solution (mouthwash) with a small amount of water, wash the mouth and throat for 20 to 30 seconds.

Arm type	Experimental
Investigational medicinal product name	Benzydamine Hydrochloride 0.15%
Investigational medicinal product code	030
Other name	
Pharmaceutical forms	Oromucosal solution
Routes of administration	Oromucosal use

Dosage and administration details:

Treatment of 15 ml (1 tablespoon) of concentrated or diluted (with water) solution was taken at home, 2-3 times a day, but not more than 5 times a day. Patients were asked to wash the mouth and throat for 20-30 seconds, according to the Investigator’s indications and the local product’s SmPC.

Number of subjects in period 1	Benzydamine HCl 0.15% w/v oromucosal solution
Started	89
Completed	67
Not completed	22
Protocol deviation	22

Baseline characteristics

Reporting groups

Reporting group title	OVERALL PERIOD

Reporting group description: -

Reporting group values	OVERALL PERIOD	Total	
Number of subjects	89	89	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	58	58	
From 65-84 years	31	31	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	61.36		
standard deviation	± 8.37	-	
Gender categorical Units: Subjects			
Female	17	17	
Male	72	72	

Subject analysis sets

Subject analysis set title	Safety population (SP)
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population (SP)was defined as all the patients who took at least one dose of the study medication.

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population was defined as all the patients with a treatment compliance to the study medication ≥ 80% and all NRS evaluations, from first day of RT through 4 weeks, with no major protocol violations

Reporting group values	Safety population (SP)	Per Protocol Population	
Number of subjects	89	67	
Age categorical Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over	58 31	42 25	
Age continuous Units: years			
arithmetic mean	61.36	61.97	
standard deviation	± 8.37	± 8.49	
Gender categorical Units: Subjects			
Female	17	13	
Male	72	54	

End points

End points reporting groups

Reporting group title	Benzydamine HCl 0.15% w/v oromucosal solution

Reporting group description:

Treatment of 15 ml (1 tablespoon) of concentrated or diluted (with water) solution was taken at home, 2-3 times a day, but not more than 5 times a day. Patients were asked to wash the mouth and throat for 20-30 seconds, according to the Investigator's indications and the local product's SmPC.
In Hungary, at the first treatment, the therapy was advised to be started with diluted product (15 ml of water + 15 ml of concentrated solution). After that, gargling could continue with 15 ml (1 tablespoon) of concentrated benzydamine oromucosal solution (mouthwash), generally 2 to 3 times a day, but not more than 5 times a day.
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Primary: Percentage of responders

End point title	Percentage of responders[1]

End point description:

The number of responders is defined as the number of HNC patients with OM pain intensity <5 (numerical rating scale [NRS]), expressed in percentage, at Visits 0 to 7/ETTV.

End point type	Primary

End point timeframe:

Visits from 0 to 7/ETTV.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the nature of the single-arm study, all statistical analysis was descriptive.

End point values	Benzydamine HCl 0.15% w/v oromucosal solution	Safety population (SP)	Per Protocol Population	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	89	89	67	
Units: number	30	30	20	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of compliant patients

End point title	Number of compliant patients

End point description:

The compliance was calculated at the end of the study by the Sponsor using relevant data entered by the Investigator into the eCRF.
A patient was considered compliant to the benzydamine treatment if he/she took ≥80% of the total dose assigned by the Investigator.

The number of compliant patients was expressed in percentage,

End point type	Secondary

End point timeframe:

At Visits 0 to 7/ETTV.

End point values	Benzydamine HCl 0.15% w/v oromucosal solution	Safety population (SP)	Per Protocol Population	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	89	89	67	
Units: Percentage	86	86	100	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were monitored through the whole study period from the signature of the informed consent form (6th December 2021) to the last visit scheduled in the protocol (5th September 2022).

Adverse event reporting additional description:

In the SP (m-ITT), there were 135 TEAEs reported during the study. Of the 135 TEAEs, two were adverse drug reactions (ADRs) occurred in two separate patients. Nearly all (n=126, 93.3%) of the TEAEs were reported as unlikely to have a correlation with the IMP. There were two that were reported as possibly correlated, and seven were reported as unas

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Adverse Events

Reporting group description: -

Serious adverse events	Adverse Events		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 89 (4.49%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Neutropenic sepsis			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
COVID-19			

subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Adverse Events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 89 (35.96%)		
Investigations			
C-reactive protein increased			
subjects affected / exposed	6 / 89 (6.74%)		
occurrences (all)	7		
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	9 / 89 (10.11%)		
occurrences (all)	9		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 89 (6.74%)		
occurrences (all)	7		
Odynophagia			
subjects affected / exposed	9 / 89 (10.11%)		
occurrences (all)	9		
Infections and infestations			
Oral fungal infection			
subjects affected / exposed	9 / 89 (10.11%)		
occurrences (all)	9		
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed occurrences (all)	6 / 89 (6.74%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2021	The present substantial Study Amendment no. 2 of May 24th, 2021 proposes changes relevant to the AJCC staging system version to be used in the trial, prohibited medications and administrative changes. Applicable sections in the Study Protocol were modified in accordance with this amendment. The changes proposed must be applied to all sites/Countries where the study has been already submitted/approved. The present Study Amendment is submitted to the applicable Regulatory Authorities and Ethics Committees in accordance with the local regulation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not applicable

Notes: