Clinical trial results:
Randomized phase III study: Supplemental parenteral nutrition for patients with locally advanced inoperable tumors of the head and neck, receiving definitive radiotherapy with Cetuximab or Cisplatin

Summary

EudraCT number	2014-003833-24
Trial protocol	AT
Global end of trial date	10 July 2019

Results information

Result version number	v1
This version publication date	08 July 2020
First version publication date	08 July 2020

Trial information

Trial identification

Sponsor protocol code	AGMT_HNO_PN

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02236936
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AGMT
Sponsor organisation address	Gentzgasse 60/21, Vienna, Austria, 1180
Public contact	Daniela Wolkersdorfer, AGMT, +43 6626404412, d.wolkersdorfer@agmt.at
Scientific contact	Richard Greil, AGMT, +43 5725525801, r.greil@salk.at

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	19 May 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 July 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Loss of body weight by more than 5% at the end of radiotherapy, compared with weight at the beginning of therapy, will be scored as an event of critical weight loss

Protection of trial subjects:

Safety assessments were scheduled weekly during treatment and 3 months after end of radiation. Dose modifications in case of toxicity were described in the
protocol. Concomitant medications and therapies necessary for supportive care and safety of the patient were allowed. Only patients eligible for definitive curative radio-chemotherapy with Cisplatin or radio-immunotherapy with Cetuximab could have been included. The administration of concurrent other cancer therapy (chemotherapy, immunotherapy, antihormonal or biologic therapy) or concurrent treatment with an investigational drug was not permitted.
Women of childbearing potential must have a negative pregnancy test at screening and must use effective contraception.

Background therapy:

Standard of care (Immunotherapy with cetuximab; chemotherapy with cisplatin; radiation therapy)

Evidence for comparator: -

Actual start date of recruitment	20 April 2017
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	Austria: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	5
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient in (FPI): 20-Apr-2017; Last patient in (LPI): 02-Jul-2018; Recruitment was prematurely withdrawn on 10-July-2019 due to low recruitment.
Assessed for eligibility: 21 patients
Eligible and randomized: 8 patients, randomized at 3 different sites in Austria.

Pre-assignment

Screening details:

21 patients with histologically confirmed local advanced squamous cell carcinoma of the larynx, hypopharynx, oropharynx or cavum oris and definitly planned radiotherapy in combination with cisplatin or cetuximab were screened for eligibility. Only 8 patients met inclusion criteria and were willing to participate.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A - control

Arm description:

Standard of care without parenteral nutrition

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Arm B - intervention group

Arm description:

Parenteral overnight nutrition with ZentroOLIMEL® 5.7% with electrolytes, vitamins (Cernevit®) and micronutrients (Addel Trace® or Nutryelt®) 15 ml/kg body weight/day (weight loss >5% from baseline, parenteral nutrition has to be increased up to 25 ml/kg body weight per day)

Arm type	Experimental
Investigational medicinal product name	ZentroOLIMEL®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Parenteral overnight nutrition with ZentroOLIMEL® 5.7% with electrolytes, vitamins (Cernevit®) and micronutrients (Addel Trace® or Nutryelt®) starting with 15 ml/kg body weight/day. In case of weight loss of more than 5%, dose of ZentroOLIMEL® has to be increased up to 25 ml/kg/body weight/day. During the RTX period of 7 weeks, with a total of 49 days of parenteral nutritional support.

Investigational medicinal product name	Cernevit®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Parenteral overnight nutrition with ZentroOLIMEL® 5.7% with electrolytes, vitamins (Cernevit®) and micronutrients (Addel Trace®or Nutryelt®) starting with 15 ml/kg body weight/day. In case of weight loss of more than 5%, dose of ZentroOLIMEL® has to be increased up to 25 ml/kg/body weight/day. During the RTX period of 7 weeks, with a total of 49 days of parenteral nutritional support.

Investigational medicinal product name	Nutryelt® or Addel Trace®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Parenteral overnight nutrition with ZentroOLIMEL® 5.7% with electrolytes, vitamins (Cernevit®) and micronutrients (Addel Trace®or Nutryelt®) starting with 15 ml/kg body weight/day. In case of weight loss of more than 5%, dose of ZentroOLIMEL® has to be increased up to 25 ml/kg/body weight/day. During the RTX period of 7 weeks, with a total of 49 days of parenteral nutritional support.

Number of subjects in period 1	Arm A - control	Arm B - intervention group
Started	4	4
Completed	4	4

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	8	8	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	62		
full range (min-max)	47 to 77	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	7	7	

End points

End points reporting groups

Reporting group title	Arm A - control
Reporting group description:	
Standard of care without parenteral nutrition	
Reporting group title	Arm B - intervention group
Reporting group description:	
Parenteral overnight nutrition with ZentroOLIMEL® 5.7% with electrolytes, vitamins (Cernevit®) and micronutrients (Addel Trace® or Nutryelt®) 15 ml/kg body weight/day (weight loss >5% from baseline, parenteral nutrition has to be increased up to 25 ml/kg body weight per day)	

Primary: Critical weight loss (>5%)

End point title	Critical weight loss (>5%)[1]
End point description:	
Loss of body weight by more than 5% at the end of RTX, compared with weight at the beginning of therapy, is scored as an event of critical weight loss	
End point type	Primary
End point timeframe:	
Difference between baseline and week 8 (after end of radiotherapy)	

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: No statistical analyses have been specified, as recruitment was pematurely withdrawn and to less patients were recruited to perform statistical analyses.

End point values	Arm A - control	Arm B - intervention group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: Subjects				
Critical weight loss	3	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All patients having received at least one dose of the study medication were followed for adverse events for at least 28 days after discontinuing study treatment or completion of study treatment.

Adverse event reporting additional description:

Progression of disease (including death due to the underlying malignant disease) is not to be regarded as SAE.
Due to the seriousness of the disease in this study, certain conditions defined as SAEs were excluded from expedited reporting on a SAE report Form, i.e.:
Elective hospitalization and surgery for treatment of disease.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dysphagia			

subjects affected / exposed	2 / 8 (25.00%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vascular disorders			
Lymphoedema			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	8 / 8 (100.00%)		
occurrences (all)	19		

Oedema			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Investigations			
Blood creatine increased			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Blood magnesium decreased			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Hepatic enzyme increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	7		
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Lumbar vertebral fracture			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Radiation injury			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Radiation larynx injury			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Radiation skin injury			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Polyneuropathy			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Sciatica			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Leukopenia			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	8		
Pancytopenia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	6		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Dry mouth			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	5		
Dysphagia			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	8		

Nausea subjects affected / exposed occurrences (all)	4 / 8 (50.00%) 4		
Salivary gland calculus subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Hepatobiliary disorders Hepatobiliary disease subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 3		
Skin and subcutaneous tissue disorders Dermatitis subjects affected / exposed occurrences (all)	6 / 8 (75.00%) 14		
Onychomadesis subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Rash subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Scab subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Renal and urinary disorders Renal disorder subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 3		
Infections and infestations Device related infection subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 4		
Mucocutaneous candidiasis subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Pneumonia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		

Metabolism and nutrition disorders Hypocalcaemia subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2018	Due to low recruitment, procedures and questionnaires were removed to simplify protocol procedures. Many patients refused participation due to long hospital stays during treatment within the study. To increase acceptance of treatment home-care systems are allowed to be used. To get early information about feasibility, tolerability and efficacy of treatment also in case of persisting low recruitment, interim analysis was established after randomization of 40 patients.

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.

Statistical analyses according to protcol could not be performed as trial was stopped prematurely due to low recruitment on 10-Jul-2019.

Notes: