

**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 | v2 (current) |
| This version publication date | 25 July 2020 |
| First version publication date | 08 July 2020 |
| Version creation reason | • Correction of full data set Description of arm A - control is updated. |

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

| | | | |
|---|--|--|--|
| Nervous system disorders Neuropathy peripheral subjects affected / exposed occurrences (all) Polyneuropathy subjects affected / exposed occurrences (all) Sciatica subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 2 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Pancytopenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) | 2 / 8 (25.00%) 2 2 / 8 (25.00%) 8 1 / 8 (12.50%) 1 2 / 8 (25.00%) 6 | | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | | |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Dysphagia subjects affected / exposed occurrences (all) | 2 / 8 (25.00%) 2 3 / 8 (37.50%) 5 4 / 8 (50.00%) 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 | 1 / 8 (12.50%) | | |
| occurrences (all) | 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 protocol could not be performed as trial was stopped prematurely due to low recruitment on 10-Jul-2019. |
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Notes: