

**Clinical trial results:****A Phase II, Multicentre, Randomised, Double-Blind, Placebo-Controlled Study Comparing the Efficacy and Safety of Clonidine Lauriad® 50-µg and 100-µg Mucoadhesive Buccal Tablet (MBT) Applied Once Daily to Those of Placebo in the Prevention and Treatment of Chemoradiation Therapy-Induced Oral Mucositis in Patients with Head and Neck Cancer Summary**

| | |
|--------------------------|------------------|
| EudraCT number | 2009-014870-16 |
| Trial protocol | FR ES DE HU |
| Global end of trial date | 25 November 2016 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 04 February 2018 |
| First version publication date | 29 July 2016 |
| Version creation reason | <ul style="list-style-type: none">• New data added to full data set Addition of the 2-year Overall Survival follow-up results |

Trial information**Trial identification**

| | |
|-----------------------|--------------|
| Sponsor protocol code | BA2009-28-01 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01385748 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Onxeo |
| Sponsor organisation address | 49 boulevard du Général Martial Valin, Paris, France, 75015 |
| Public contact | Olivier de Beaumont, MD, Onxeo, 33 145587600, |
| Scientific contact | Olivier de Beaumont, MD, Onxeo, 33 145587600, |

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 | 09 October 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 August 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 November 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of clonidine Lauriad® 50-µg and 100-µg mucoadhesive buccal tablet versus placebo in the prevention and treatment of chemoradiotherapy induced oral mucositis.

Protection of trial subjects:

The following measures were put in place to protect patients:

The doses of clonidine Lauriad used in the study (50 µg and 100 µg of clonidine) were lower than those normally taken for anti-hypertensive treatment in order to prevent hypotensive effects, as well as sedation and dry mouth.

After the treatment was completed, there was a 4-week follow-up period to assess oral mucositis resolution and to record adverse events (AEs) and serious adverse events (SAEs). There is also a follow-up period until 2 years after the last patient's last visit (until September 2016) to collect data on survival and tumor status in all patients.

Patients could have been discontinued from therapy or from the study for any of the following reasons:

1. Withdrawal of patient consent, or loss to follow-up, or inability to remain under medical observation including post-study examination.
2. Non-compliance by the patient or major deviation from the protocol by the investigator and/or the patient.
3. Occurrence of an SAE.
4. Any other situation where, in the opinion of the investigator, continuation of the study would not be in the interest of the patient, or could modify the benefits or the risks for the patients.
5. Discontinuation of the study.

Background therapy:

Patients received treatment with the study medication one day to 3 days before the beginning of chemoradiation therapy for head and neck cancer (active phase) for up to 8 weeks, depending on the subject's prescribed radiation plan.

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 20 April 2010 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 2 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Spain: 52 |
| Country: Number of subjects enrolled | France: 88 |
| Country: Number of subjects enrolled | Germany: 31 |

| | |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Hungary: 4 |
| Country: Number of subjects enrolled | Switzerland: 2 |
| Country: Number of subjects enrolled | United States: 6 |
| Worldwide total number of subjects | 183 |
| EEA total number of subjects | 175 |

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) | 151 |
| From 65 to 84 years | 32 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 35 study centres, including clinical study sites in the United States, Switzerland, France, Hungary, Germany and Spain, enrolled patients into the study.

The worldwide total number of subjects was the number of randomised patients (183). In total 202 patients were screened and 19 failed screening.

Pre-assignment

Screening details:

Selected patients were male or female, aged > 18 years and suffering from a newly diagnosed squamous cell carcinoma of the oral cavity, oropharynx, or larynx histologically-confirmed, having undergone resective surgery and eligible for concurrent chemoradiation.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Treatment 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 blinding status and the break of the randomisation code were ensured according to the sponsor's standard operating procedures (SOPs). Measures taken to ensure that test drug/investigational product and placebo were indistinguishable and evidence that they were indistinguishable were also ensured according to the sponsor's SOPs. Procedures used to carry out blinding were sealed code list/envelopes.

Arms

| | |
|--|-----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Clonidine Lauriad 50-µg MBT |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Clonidine Lauriad |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Muco-adhesive buccal tablet |
| Routes of administration | Gingival use |

Dosage and administration details:

Each patient received 1 mucoadhesive buccal tablet containing 50 µg of clonidine Lauriad by gingival application one day to 3 days before the beginning of the chemoradiation therapy for up to 8 weeks, depending on the subject's prescribed radiation plan.

| | |
|--|------------------------------|
| Arm title | Clonidine Lauriad 100-µg MBT |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Clonidine Lauriad |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Muco-adhesive buccal tablet |
| Routes of administration | Gingival use |

Dosage and administration details:

Each patient received 1 mucoadhesive buccal tablet containing 100 µg of clonidine Lauriad by gingival application one day to 3 days before the beginning of the chemoradiation therapy for up to 8 weeks, depending on the subject's prescribed radiation plan.

| | |
|--|-----------------------------|
| Arm title | Placebo MBT |
| Arm description: - | |
| Arm type | Placebo |
| Investigational medicinal product name | Matching placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Muco-adhesive buccal tablet |
| Routes of administration | Gingival use |

Dosage and administration details:

Each patient received 1 placebo mucoadhesive buccal tablet by gingival application one day to 3 days before the beginning of the chemoradiation therapy for up to 8 weeks, depending on the subject's prescribed radiation plan.

| Number of subjects in period 1 | Clonidine Lauriad 50-µg MBT | Clonidine Lauriad 100-µg MBT | Placebo MBT |
|---------------------------------------|--------------------------------|---------------------------------|-------------|
| Started | 56 | 65 | 62 |
| Completed | 41 | 51 | 49 |
| Not completed | 15 | 14 | 13 |
| Adverse event, serious fatal | 4 | 2 | 1 |
| Consent withdrawn by subject | 7 | 4 | 5 |
| Non compliance | 3 | 1 | 6 |
| Other reasons | 1 | 7 | 1 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | 2 year follow-up |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

The break of the randomisation code was ensured according to the sponsor's standard operating procedures (SOPs). No patient was under treatment during Period 2. The code break was carry out on Dec 2014 and the list of patients treatment was send to all investigators. The investigator was free to inform his patients.

Arms

| | |
|------------------------------|-----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Clonidine Lauriad 50-µg MBT |

Arm description:

Follow-up period until until 2-years after the date of Last Patient Completed, for patients who signed a specific inform consent form for survival data (OS)
Patients were not treated in the follow-up period.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|---|------------------------------|
| Investigational medicinal product name | Clonidine Lauriad |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Muco-adhesive buccal tablet |
| Routes of administration | Gingival use |
| Dosage and administration details: | |
| No patient was under treatment during Period 2 (follow-up period) | |
| Arm title | Clonidine Lauriad 100-µg MBT |

Arm description:

Follow-up period until until 2-years after the date of Last Patient Completed, for patients who signed a specific inform consent form for survival data (OS)
Patients were not treated in the follow-up period.

| | |
|---|-----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Clonidine Lauriad |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Muco-adhesive buccal tablet |
| Routes of administration | Gingival use |
| Dosage and administration details: | |
| No patient was under treatment during Period 2 (follow-up period) | |
| Arm title | Placebo MBT |

Arm description:

Follow-up period until until 2-years after the date of Last Patient Completed, for patients who signed a specific inform consent form for survival data (OS)
Patients were not treated in the follow-up period.

| | |
|--|-----------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Matching placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Muco-adhesive buccal tablet |
| Routes of administration | Gingival use |

Dosage and administration details:

No patient was under treatment during Period 2 (follow-up period)

| Number of subjects in period 2^[1] | Clonidine Lauriad 50-µg MBT | Clonidine Lauriad 100-µg MBT | Placebo MBT |
|---|-----------------------------|------------------------------|-------------|
| Started | 35 | 42 | 39 |
| Completed | 35 | 42 | 39 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Follow-up survival period was added in study protocol amendment 9 in 2013. A specific inform consent form for survival data collection was signed by 116 patients alive at time of the amendment. The collection of OS data during the follow-up period was not possible in near 35% of the patients alive due to the lack of the signed specific OS inform consent form. This justifies the difference between the number of patients who completed the treatment period and patients starting the follow up

period

Baseline characteristics

Reporting groups

| | |
|--------------------------------|------------------------------|
| Reporting group title | Clonidine Lauriad 50-µg MBT |
| Reporting group description: - | |
| Reporting group title | Clonidine Lauriad 100-µg MBT |
| Reporting group description: - | |
| Reporting group title | Placebo MBT |
| Reporting group description: - | |

| Reporting group values | Clonidine Lauriad 50-µg MBT | Clonidine Lauriad 100-µg MBT | Placebo MBT |
|--|--------------------------------|---------------------------------|-------------|
| Number of subjects | 56 | 65 | 62 |
| Age categorical | | | |
| All baseline characteristics were analysed in the intention-to-treat (ITT) population. | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 43 | 58 | 50 |
| From 65 to 84 years | 13 | 7 | 12 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| median | 58.8 | 55.7 | 56.6 |
| full range (min-max) | 30 to 79 | 22 to 75 | 33 to 72 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 16 | 16 | 13 |
| Male | 40 | 49 | 49 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Black | 1 | 0 | 0 |
| Caucasian | 53 | 61 | 59 |
| Other | 2 | 4 | 3 |
| ECOG | | | |
| All patients showed no signs of oral mucositis at baseline. There was no obvious difference in disease characteristics between treatment groups. | | | |
| The Eastern Cooperative Oncology Group (ECOG) scores of the treatment groups is provided. The majority of patients had an ECOG score of 2. | | | |
| Units: Subjects | | | |
| Score 0 | 42 | 41 | 42 |
| Score 1 | 14 | 22 | 20 |
| Score 2 | 0 | 2 | 0 |
| Disease location | | | |
| The location of the squamous cell carcinoma at baseline is provided. | | | |
| Units: Subjects | | | |
| Oral cavity | 26 | 37 | 30 |
| Oropharynx | 19 | 17 | 21 |
| Hypopharynx | 4 | 2 | 2 |
| Larynx | 4 | 6 | 5 |
| Oral cavity/oropharynx | 0 | 1 | 1 |

| | | | |
|--|--------------|--------------|--------------|
| Oral cavity/hypopharynx | 0 | 1 | 1 |
| Oral cavity/larynx | 1 | 0 | 0 |
| Oropharynx/hypopharynx | 2 | 1 | 1 |
| Oropharynx/larynx | 0 | 0 | 1 |
| Disease location in oral cavity or oropharynx | | | |
| The location of the squamous cell carcinoma (in oral cavity or oropharynx) is provided. | | | |
| Units: Subjects | | | |
| Yes | 48 | 57 | 55 |
| No | 8 | 8 | 7 |
| Mucosal irritation | | | |
| The number of patients with mucosal irritation at baseline is provided. | | | |
| Units: Subjects | | | |
| Yes | 2 | 2 | 1 |
| No | 53 | 63 | 61 |
| Missing | 1 | 0 | 0 |
| Tooth extraction | | | |
| Units: Subjects | | | |
| Yes | 30 | 32 | 32 |
| No | 25 | 32 | 30 |
| Missing | 1 | 1 | 0 |
| Oral infection | | | |
| The number of patients presenting with oral infection at baseline is provided. | | | |
| Units: Subjects | | | |
| Yes | 0 | 1 | 0 |
| No | 55 | 64 | 62 |
| Missing | 1 | 0 | 0 |
| Prior surgery | | | |
| The number of patients having undergone prior surgery is provided. | | | |
| Units: Subjects | | | |
| Yes | 55 | 64 | 61 |
| No | 1 | 1 | 1 |
| Patients previously treated with radiotherapy and/or chemotherapy | | | |
| The number of patients having been previously treated with radiotherapy and/or chemotherapy is provided. | | | |
| Units: Subjects | | | |
| Yes | 54 | 62 | 61 |
| No | 2 | 3 | 1 |
| Height | | | |
| Units: cm | | | |
| median | 171 | 170 | 172 |
| full range (min-max) | 153 to 182 | 147 to 186 | 145 to 190 |
| Weight | | | |
| Units: kg | | | |
| median | 71.3 | 66 | 69 |
| full range (min-max) | 44 to 130 | 43 to 123 | 48 to 115 |
| BMI | | | |
| Body Mass Index. | | | |
| Units: kg/m2 | | | |
| median | 23.7 | 23.66 | 23.23 |
| full range (min-max) | 16.1 to 44.4 | 16.8 to 40.3 | 16.9 to 43.8 |

| | | | |
|---|--------------|---------------|--------------|
| Alcohol consumption Units: g/day median full range (min-max) | 0 0 to 45 | 0 0 to 100 | 0 0 to 50 |
| Disease duration | | | |
| The duration of the squamous cell carcinoma at baseline is provided. | | | |
| Units: months median full range (min-max) | 2 1 to 14 | 2 1 to 99 | 2 0 to 7 |

| | | | |
|--|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 183 | | |
| Age categorical | | | |
| All baseline characteristics were analysed in the intention-to-treat (ITT) population. | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 151 | | |
| From 65 to 84 years | 32 | | |
| 85 years and over | 0 | | |
| Age continuous Units: years median full range (min-max) | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 45 | | |
| Male | 138 | | |
| Ethnicity Units: Subjects | | | |
| Black | 1 | | |
| Caucasian | 173 | | |
| Other | 9 | | |
| ECOG | | | |
| All patients showed no signs of oral mucositis at baseline. There was no obvious difference in disease characteristics between treatment groups. | | | |
| The Eastern Cooperative Oncology Group (ECOG) scores of the treatment groups is provided. The majority of patients had an ECOG score of 2. | | | |
| Units: Subjects | | | |
| Score 0 | 125 | | |
| Score 1 | 56 | | |
| Score 2 | 2 | | |
| Disease location | | | |
| The location of the squamous cell carcinoma at baseline is provided. | | | |
| Units: Subjects | | | |
| Oral cavity | 93 | | |
| Oropharynx | 57 | | |
| Hypopharynx | 8 | | |
| Larynx | 15 | | |
| Oral cavity/oropharynx | 2 | | |
| Oral cavity/hypopharynx | 2 | | |
| Oral cavity/larynx | 1 | | |
| Oropharynx/hypopharynx | 4 | | |

| | | | |
|--|-----|--|--|
| Oropharynx/larynx | 1 | | |
| Disease location in oral cavity or oropharynx | | | |
| The location of the squamous cell carcinoma (in oral cavity or oropharynx) is provided. | | | |
| Units: Subjects | | | |
| Yes | 160 | | |
| No | 23 | | |
| Mucosal irritation | | | |
| The number of patients with mucosal irritation at baseline is provided. | | | |
| Units: Subjects | | | |
| Yes | 5 | | |
| No | 177 | | |
| Missing | 1 | | |
| Tooth extraction | | | |
| Units: Subjects | | | |
| Yes | 94 | | |
| No | 87 | | |
| Missing | 2 | | |
| Oral infection | | | |
| The number of patients presenting with oral infection at baseline is provided. | | | |
| Units: Subjects | | | |
| Yes | 1 | | |
| No | 181 | | |
| Missing | 1 | | |
| Prior surgery | | | |
| The number of patients having undergone prior surgery is provided. | | | |
| Units: Subjects | | | |
| Yes | 180 | | |
| No | 3 | | |
| Patients previously treated with radiotherapy and/or chemotherapy | | | |
| The number of patients having been previously treated with radiotherapy and/or chemotherapy is provided. | | | |
| Units: Subjects | | | |
| Yes | 177 | | |
| No | 6 | | |
| Height | | | |
| Units: cm | | | |
| median | | | |
| full range (min-max) | - | | |
| Weight | | | |
| Units: kg | | | |
| median | | | |
| full range (min-max) | - | | |
| BMI | | | |
| Body Mass Index. | | | |
| Units: kg/m2 | | | |
| median | | | |
| full range (min-max) | - | | |
| Alcohol consumption | | | |
| Units: g/day | | | |
| median | | | |

| | | | |
|--|---|--|--|
| full range (min-max) | - | | |
| Disease duration | | | |
| The duration of the squamous cell carcinoma at baseline is provided. | | | |
| Units: months | | | |
| median | | | |
| full range (min-max) | - | | |

Subject analysis sets

| | |
|----------------------------|------------------------------|
| Subject analysis set title | Clonidine Lauriad MBT Pooled |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Pool of patients who received 50 µg or 100 µg of clonidine Lauriad MBT.

| | |
|----------------------------|---|
| Subject analysis set title | Overall study - Clonidine lauriad 50-µg MBT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Dataset including all patients who received at least 1 dose of investigational drug (ITT) in the Clonidine Lauriad 50 µg MBT arm, over a period of time going from the date of randomisation of the first patient until 2-years after the date of Last Patient Completed (Period 1 + Period 2)

| | |
|----------------------------|--|
| Subject analysis set title | Overall study - Clonidine lauriad 100-µg MBT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Dataset including all patients who received at least 1 dose of investigational drug (ITT) in the Clonidine Lauriad 100 µg MBT arm, over a period of time going from the date of randomisation of the first patient until 2-years after the date of Last Patient Completed (Period 1 + Period 2)

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | Overall study - Placebo MBT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Dataset including all patients who received at least 1 dose of investigational drug (ITT) in the Placebo MBT arm, over a period of time going from the date of randomisation of the first patient until 2-years after the date of Last Patient Completed (Period 1 + Period 2)

| Reporting group values | Clonidine Lauriad MBT Pooled | Overall study - Clonidine lauriad 50-µg MBT | Overall study - Clonidine lauriad 100-µg MBT |
|--|------------------------------|---|--|
| Number of subjects | 121 | 56 | 65 |
| Age categorical | | | |
| All baseline characteristics were analysed in the intention-to-treat (ITT) population. | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 101 | | |
| From 65 to 84 years | 20 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| median | 57.6 | | |
| full range (min-max) | 22 to 79 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 32 | | |
| Male | 89 | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Black | 1 | | |
| Caucasian | 114 | | |

| | | | |
|--|-----|--|--|
| Other | 6 | | |
| ECOG | | | |
| All patients showed no signs of oral mucositis at baseline. There was no obvious difference in disease characteristics between treatment groups. | | | |
| The Eastern Cooperative Oncology Group (ECOG) scores of the treatment groups is provided. The majority of patients had an ECOG score of 2. | | | |
| Units: Subjects | | | |
| Score 0 | 83 | | |
| Score 1 | 36 | | |
| Score 2 | 2 | | |
| Disease location | | | |
| The location of the squamous cell carcinoma at baseline is provided. | | | |
| Units: Subjects | | | |
| Oral cavity | 63 | | |
| Oropharynx | 36 | | |
| Hypopharynx | 6 | | |
| Larynx | 10 | | |
| Oral cavity/oropharynx | 1 | | |
| Oral cavity/hypopharynx | 1 | | |
| Oral cavity/larynx | 1 | | |
| Oropharynx/hypopharynx | 3 | | |
| Oropharynx/larynx | 0 | | |
| Disease location in oral cavity or oropharynx | | | |
| The location of the squamous cell carcinoma (in oral cavity or oropharynx) is provided. | | | |
| Units: Subjects | | | |
| Yes | 105 | | |
| No | 16 | | |
| Mucosal irritation | | | |
| The number of patients with mucosal irritation at baseline is provided. | | | |
| Units: Subjects | | | |
| Yes | 4 | | |
| No | 116 | | |
| Missing | 1 | | |
| Tooth extraction | | | |
| Units: Subjects | | | |
| Yes | 62 | | |
| No | 57 | | |
| Missing | 2 | | |
| Oral infection | | | |
| The number of patients presenting with oral infection at baseline is provided. | | | |
| Units: Subjects | | | |
| Yes | 1 | | |
| No | 119 | | |
| Missing | 1 | | |
| Prior surgery | | | |
| The number of patients having undergone prior surgery is provided. | | | |
| Units: Subjects | | | |
| Yes | 119 | | |
| No | 2 | | |
| Patients previously treated with radiotherapy and/or chemotherapy | | | |

| | | | |
|--|--------------|--|--|
| The number of patients having been previously treated with radiotherapy and/or chemotherapy is provided. | | | |
| Units: Subjects | | | |
| Yes | 116 | | |
| No | 5 | | |
| Height | | | |
| Units: cm | | | |
| median | 170 | | |
| full range (min-max) | 147 to 186 | | |
| Weight | | | |
| Units: kg | | | |
| median | 69 | | |
| full range (min-max) | 43 to 130 | | |
| BMI | | | |
| Body Mass Index. | | | |
| Units: kg/m2 | | | |
| median | 23.67 | | |
| full range (min-max) | 16.1 to 44.4 | | |
| Alcohol consumption | | | |
| Units: g/day | | | |
| median | 0 | | |
| full range (min-max) | 0 to 100 | | |
| Disease duration | | | |
| The duration of the squamous cell carcinoma at baseline is provided. | | | |
| Units: months | | | |
| median | 2 | | |
| full range (min-max) | 1 to 99 | | |

| | | | |
|--|--------------------------------|--|--|
| Reporting group values | Overall study - Placebo MBT | | |
| Number of subjects | 62 | | |
| Age categorical | | | |
| All baseline characteristics were analysed in the intention-to-treat (ITT) population. | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | | | |
| From 65 to 84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Units: years | | | |
| median | | | |
| full range (min-max) | | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | | | |
| Male | | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Black | | | |
| Caucasian | | | |
| Other | | | |
| ECOG | | | |
| All patients showed no signs of oral mucositis at baseline. There was no obvious difference in disease characteristics between treatment groups. | | | |

| | | | |
|--|--|--|--|
| The Eastern Cooperative Oncology Group (ECOG) scores of the treatment groups is provided. The majority of patients had an ECOG score of 2. | | | |
| Units: Subjects | | | |
| Score 0 | | | |
| Score 1 | | | |
| Score 2 | | | |
| Disease location | | | |
| The location of the squamous cell carcinoma at baseline is provided. | | | |
| Units: Subjects | | | |
| Oral cavity | | | |
| Oropharynx | | | |
| Hypopharynx | | | |
| Larynx | | | |
| Oral cavity/oropharynx | | | |
| Oral cavity/hypopharynx | | | |
| Oral cavity/larynx | | | |
| Oropharynx/hypopharynx | | | |
| Oropharynx/larynx | | | |
| Disease location in oral cavity or oropharynx | | | |
| The location of the squamous cell carcinoma (in oral cavity or oropharynx) is provided. | | | |
| Units: Subjects | | | |
| Yes | | | |
| No | | | |
| Mucosal irritation | | | |
| The number of patients with mucosal irritation at baseline is provided. | | | |
| Units: Subjects | | | |
| Yes | | | |
| No | | | |
| Missing | | | |
| Tooth extraction | | | |
| Units: Subjects | | | |
| Yes | | | |
| No | | | |
| Missing | | | |
| Oral infection | | | |
| The number of patients presenting with oral infection at baseline is provided. | | | |
| Units: Subjects | | | |
| Yes | | | |
| No | | | |
| Missing | | | |
| Prior surgery | | | |
| The number of patients having undergone prior surgery is provided. | | | |
| Units: Subjects | | | |
| Yes | | | |
| No | | | |
| Patients previously treated with radiotherapy and/or chemotherapy | | | |
| The number of patients having been previously treated with radiotherapy and/or chemotherapy is provided. | | | |
| Units: Subjects | | | |
| Yes | | | |

| | | | |
|----|--|--|--|
| No | | | |
|----|--|--|--|

| | | | |
|---|--|--|--|
| Height Units: cm median full range (min-max) | | | |
| Weight Units: kg median full range (min-max) | | | |
| BMI | | | |
| Body Mass Index. | | | |
| Units: kg/m2 median full range (min-max) | | | |
| Alcohol consumption Units: g/day median full range (min-max) | | | |
| Disease duration | | | |
| The duration of the squamous cell carcinoma at baseline is provided. | | | |
| Units: months median full range (min-max) | | | |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Clonidine Lauriad 50-µg MBT |
| Reporting group description: - | |
| Reporting group title | Clonidine Lauriad 100-µg MBT |
| Reporting group description: - | |
| Reporting group title | Placebo MBT |
| Reporting group description: - | |
| Reporting group title | Clonidine Lauriad 50-µg MBT |
| Reporting group description: | Follow-up period until until 2-years after the date of Last Patient Completed, for patients who signed a specific inform consent form for survival data (OS) Patients were not treated in the follow-up period. |
| Reporting group title | Clonidine Lauriad 100-µg MBT |
| Reporting group description: | Follow-up period until until 2-years after the date of Last Patient Completed, for patients who signed a specific inform consent form for survival data (OS) Patients were not treated in the follow-up period. |
| Reporting group title | Placebo MBT |
| Reporting group description: | Follow-up period until until 2-years after the date of Last Patient Completed, for patients who signed a specific inform consent form for survival data (OS) Patients were not treated in the follow-up period. |
| Subject analysis set title | Clonidine Lauriad MBT Pooled |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | Pool of patients who received 50 µg or 100 µg of clonidine Lauriad MBT. |
| Subject analysis set title | Overall study - Clonidine lauriad 50-µg MBT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | Dataset including all patients who received at least 1 dose of investigational drug (ITT) in the Clonidine Lauriad 50 µg MBT arm, over a period of time going from the date of randomisation of the first parient until 2-years after the date of Last Patient Completed (Period 1 + Period 2) |
| Subject analysis set title | Overall study - Clonidine lauriad 100-µg MBT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | Dataset including all patients who received at least 1 dose of investigational drug (ITT) in the Clonidine Lauriad 100 µg MBT arm, over a period of time going from the date of randomisation of the first parient until 2-years after the date of Last Patient Completed (Period 1 + Period 2) |
| Subject analysis set title | Overall study - Placebo MBT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | Dataset including all patients who received at least 1 dose of investigational drug (ITT) in the Placebo MBT arm, over a period of time going from the date of randomisation of the first parient until 2-years after the date of Last Patient Completed (Period 1 + Period 2) |
| Primary: Cumulative radiation dose at which severe oral mucositis (WHO score ≥ 3) was first observed | |
| End point title | Cumulative radiation dose at which severe oral mucositis (WHO score ≥ 3) was first observed |

End point description:

WHO score Grade 3 oral mucositis was defined as ulcers, extensive erythema, and the inability of the patient to swallow a solid diet. WHO score Grade 4 oral mucositis was defined as mucositis to the extent that alimentation was not possible. Each assessment of oral mucositis was associated with the actual cumulative dose of radiotherapy.

The primary analysis of the primary endpoint was conducted on the ITT population.

As EudraCT only allows numerical data entry, the value of 999 indicates "Not Reached" for the upper limit of the confidence intervals.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

The presence of Grade 3 or Grade 4 oral mucositis was assessed using the WHO score scale twice a week for up to 8 weeks during the active phase (radiotherapy).

| End point values | Clonidine Lauriad 50-µg MBT | Clonidine Lauriad 100-µg MBT | Placebo MBT | Clonidine Lauriad MBT Pooled |
|---------------------------------------|-----------------------------|------------------------------|-----------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 56 | 65 | 62 | 121 |
| Units: Cumulative radiation dose (Gy) | | | | |
| median (confidence interval 95%) | 66 (44 to 999) | 56 (44 to 999) | 48 (42 to 61.6) | 60 (48 to 999) |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Treatment effect of clonidine Lauriad 50-µg MBT |
|-----------------------------------|---|

Statistical analysis description:

For comparison of the three clonidine Lauriad groups, the log-rank test at 5% significance level was used. This was achieved within a model where treatment was coded with three levels (placebo, clonidine Lauriad 50-µg MBT, clonidine Lauriad 100-µg MBT) for the three pairwise comparisons. The treatment effect was estimated by the hazard ratio of the clonidine Lauriad 50-µg MBT to the placebo with its two-sided 95% confidence interval.

| | |
|---|---|
| Comparison groups | Placebo MBT v Clonidine Lauriad 50-µg MBT |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.165 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.677 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.387 |
| upper limit | 1.186 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Treatment effect of clonidine Lauriad 100-µg MBT |
| Comparison groups | Clonidine Lauriad 100-µg MBT v Placebo MBT |

| | |
|---|-------------------|
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.421 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.817 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.495 |
| upper limit | 1.35 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Treatment effect of clonidine Lauriad MBT pooled |
|-----------------------------------|--|

Statistical analysis description:

For comparison of the clonidine Lauriad MBT (both doses pooled) versus placebo, the log-rank test at 5% significance level was used. This was achieved within a model where treatment was coded with two levels (placebo, clonidine). The treatment effect was estimated by the hazard ratio of the clonidine Lauriad MBT (both doses pooled) to the placebo with its two-sided 95% confidence interval.

| | |
|---|--|
| Comparison groups | Placebo MBT v Clonidine Lauriad MBT Pooled |
| Number of subjects included in analysis | 183 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.211 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.754 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.484 |
| upper limit | 1.175 |

Secondary: Opioid use: At least one opioid (class 3 analgesic)

| | |
|-----------------|---|
| End point title | Opioid use: At least one opioid (class 3 analgesic) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Opioid use was recorded twice weekly for up to 8 weeks during the active phase (radiotherapy).

| End point values | Clonidine Lauriad 50-µg MBT | Clonidine Lauriad 100-µg MBT | Placebo MBT | Clonidine Lauriad MBT Pooled |
|-----------------------------|-----------------------------------|------------------------------------|-----------------|------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 54 | 64 | 62 | 118 |
| Units: Number of patients | | | | |
| Missing | 2 | 1 | 0 | 3 |
| Yes | 23 | 30 | 30 | 53 |
| No | 31 | 34 | 32 | 65 |

Statistical analyses

No statistical analyses for this end point

Secondary: Opioid use: Minimal total cumulative dose administered

| | |
|------------------------|--|
| End point title | Opioid use: Minimal total cumulative dose administered |
| End point description: | Sum of non missing total cumulative doses across all class 3 analgesics recorded for the considered patient. |
| End point type | Secondary |
| End point timeframe: | Opioid use was recorded twice weekly for up to 8 weeks during the active phase (radiotherapy). |

| End point values | Clonidine Lauriad 50-µg MBT | Clonidine Lauriad 100-µg MBT | Placebo MBT | Clonidine Lauriad MBT Pooled |
|--------------------------------------|-----------------------------------|------------------------------------|----------------------|------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 20 | 24 | 29 | 44 |
| Units: morphine dose equivalent | | | | |
| arithmetic mean (standard deviation) | 469.31 (± 633.51) | 415.49 (± 490.55) | 624.94 (± 958.81) | 439.95 (± 553.88) |

Statistical analyses

No statistical analyses for this end point

Secondary: Opioid use: Minimal total cumulative dose administered

| | |
|------------------------|--|
| End point title | Opioid use: Minimal total cumulative dose administered |
| End point description: | Sum of non missing total cumulative doses across all class 3 analgesics recorded for the considered patient. |
| End point type | Secondary |
| End point timeframe: | Opioid use was recorded twice weekly for up to 8 weeks during the active phase (radiotherapy). |

| End point values | Clonidine Lauriad 50-µg MBT | Clonidine Lauriad 100-µg MBT | Placebo MBT | Clonidine Lauriad MBT Pooled |
|---------------------------------|-----------------------------------|------------------------------------|------------------|------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 20 | 24 | 29 | 44 |
| Units: morphine dose equivalent | | | | |
| median (full range (min-max)) | 183.6 (12 to 2249.1) | 174 (15 to 1804) | 215 (20 to 3672) | 178.65 (12 to 2249.1) |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Clonidine Lauriad 50-µg MBT versus placebo |
| Comparison groups | Placebo MBT v Clonidine Lauriad 50-µg MBT |
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.807 ^[1] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[1] - Significance threshold = 5%

| | |
|---|---|
| Statistical analysis title | Clonidine Lauriad 100-µg MBT versus placebo |
| Comparison groups | Clonidine Lauriad 100-µg MBT v Placebo MBT |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.971 ^[2] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[2] - Significance threshold = 5%

Secondary: Death

| | |
|-----------------|-------|
| End point title | Death |
|-----------------|-------|

End point description:

Survival (patient alive or deceased) from the date of randomisation to the date of death from any cause. Patients without death at the time of the analysis were censored at the date they were last known to be alive.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During period 1 at each study visit and in the follow-up period (for patients who consented), around every 6 months for 2 years after last subject completed.

| End point values | Overall study - Clonidine lauriad 50-µg MBT | Overall study - Clonidine lauriad 100-µg MBT | Overall study - Placebo MBT | |
|-----------------------------|--|---|--------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 56 | 65 | 62 | |
| Units: Number of death | 18 | 13 | 18 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

| | |
|-----------------|------------------|
| End point title | Overall survival |
|-----------------|------------------|

End point description:

OS was defined as the time from the date of randomisation to the date of death from any cause. Patients without death at the time of the analysis were censored at the date they were last known to be alive.

As EudraCT only allows numerical data entry, the value of 999 indicates "Not Reached" for the upper limit of the confidence intervals.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During period 1 at each study visit and in the follow-up period (for patients who consented), around every 6 months for 2 years after last subject completed.

| End point values | Overall study - Clonidine lauriad 50-µg MBT | Overall study - Clonidine lauriad 100-µg MBT | Overall study - Placebo MBT | |
|----------------------------------|--|---|--------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 56 | 65 | 62 | |
| Units: months | | | | |
| median (confidence interval 95%) | 47 (17.3 to 999) | 58.8 (35.9 to 999) | 41.8 (27.7 to 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cause of death

| | |
|-----------------|----------------|
| End point title | Cause of death |
|-----------------|----------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During period 1 at each study visit and in the follow-up period (for patients who consented), around every 6 months for 2 years after last subject completed.

| End point values | Overall study - Clonidine lauriad 50-µg MBT | Overall study - Clonidine lauriad 100-µg MBT | Overall study - Placebo MBT | |
|-----------------------------|--|---|--------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 18 | 13 | 18 | |
| Units: Number of patients | | | | |
| Progressive disease | 13 | 9 | 16 | |
| Unknown | 2 | 2 | 2 | |
| Other | 3 | 2 | 0 | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to onset of severe oral mucositis

| | |
|---|--|
| End point title | Time to onset of severe oral mucositis |
| End point description: | |
| Time to onset is the duration until first Severe Oral Mucositis. Severe Oral Mucositis was defined as a Grade 3 or Grade 4 WHO score. | |
| As EudraCT only allows numerical data entry, the value of 999 indicates "Not Reached" for the upper limit of the confidence intervals. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| The presence of Grade 3 or Grade 4 oral mucositis was assessed using the WHO score scale twice a week for up to 8 weeks during the active phase (radiotherapy). | |

| End point values | Clonidine Lauriad 50-µg MBT | Clonidine Lauriad 100-µg MBT | Placebo MBT | Clonidine Lauriad MBT Pooled |
|----------------------------------|-----------------------------------|------------------------------------|------------------|------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 56 | 65 | 62 | 121 |
| Units: weeks | | | | |
| median (confidence interval 95%) | 6.4 (4.6 to 999) | 6 (4.6 to 8) | 5.1 (4.4 to 6.9) | 6.4 (5.1 to 999) |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Treatment effect of clonidine Lauriad 50-µg MBT |
| Comparison groups | Clonidine Lauriad 50-µg MBT v Placebo MBT |

| | |
|---|------------------------|
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.199 ^[3] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.698 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.398 |
| upper limit | 1.223 |

Notes:

[3] - Significance threshold = 5%

| | |
|---|--|
| Statistical analysis title | Treatment effect of clonidine Lauriad 100-µg MBT |
| Comparison groups | Clonidine Lauriad 100-µg MBT v Placebo MBT |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.424 ^[4] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.817 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.493 |
| upper limit | 1.353 |

Notes:

[4] - Significance threshold = 5%

| | |
|---|--|
| Statistical analysis title | Treatment effect of clonidine Lauriad MBT pooled |
| Comparison groups | Placebo MBT v Clonidine Lauriad MBT Pooled |
| Number of subjects included in analysis | 183 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.235 ^[5] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.764 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.489 |
| upper limit | 1.193 |

Notes:

[5] - Significance threshold = 5%

Other pre-specified: The maximum severity of oral mucositis

| | |
|------------------------|--|
| End point title | The maximum severity of oral mucositis |
| End point description: | The maximum severity of oral mucositis was the maximum score observed during the active phase. |
| End point type | Other pre-specified |
| End point timeframe: | The presence of oral mucositis was assessed twice weekly for up to 8 weeks during the active phase (radiotherapy). |

| End point values | Clonidine Lauriad 50-µg MBT | Clonidine Lauriad 100-µg MBT | Placebo MBT | Clonidine Lauriad MBT Pooled |
|--------------------------------------|-----------------------------------|------------------------------------|-----------------|------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 56 | 65 | 62 | 121 |
| Units: Number of patients | | | | |
| Grade 0 | 7 | 6 | 4 | 13 |
| Grade 1 | 9 | 7 | 9 | 16 |
| Grade 2 | 15 | 20 | 11 | 35 |
| Grade 3 | 17 | 20 | 30 | 37 |
| Grade 4 | 6 | 10 | 6 | 16 |
| No value during the concerned period | 2 | 2 | 2 | 4 |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Clonidine Lauriad 50-µg MBT versus placebo |
| Statistical analysis description: | 114 subjects were included in this analysis. |
| Comparison groups | Clonidine Lauriad 50-µg MBT v Placebo MBT |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.176 ^[6] |
| Method | Kruskal-wallis |

Notes:

[6] - Significance threshold = 5%

| | |
|---|---|
| Statistical analysis title | Clonidine Lauriad 100-µg MBT versus placebo |
| Statistical analysis description: | 123 subjects were included in the analysis. |
| Comparison groups | Clonidine Lauriad 100-µg MBT v Placebo MBT |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.61 ^[7] |
| Method | Kruskal-wallis |

Notes:

[7] - Significance threshold = 5%

| | |
|--|---|
| Statistical analysis title | Clonidine Lauriad MBT pooled versus placebo |
| Statistical analysis description: 177 subjects were included in the analysis. | |
| Comparison groups | Placebo MBT v Clonidine Lauriad MBT Pooled |
| Number of subjects included in analysis | 183 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.295 [8] |
| Method | Kruskal-wallis |

Notes:

[8] - Significance threshold = 5%

Other pre-specified: The overall incidence of Grade 3/4 mucositis during the active phase

| | |
|---|--|
| End point title | The overall incidence of Grade 3/4 mucositis during the active phase |
| End point description: Number of patients with at least one grade 3/4 mucositis. | |
| End point type | Other pre-specified |
| End point timeframe: Assessed during the active phase (radiotherapy). | |

| End point values | Clonidine Lauriad 50-µg MBT | Clonidine Lauriad 100-µg MBT | Placebo MBT | Clonidine Lauriad MBT Pooled |
|-----------------------------|-----------------------------|------------------------------|-----------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 56 | 65 | 62 | 121 |
| Units: Number of patients | | | | |
| Missing | 2 | 2 | 2 | 4 |
| No | 31 | 33 | 24 | 64 |
| Yes | 23 | 30 | 36 | 53 |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Clonidine Lauriad 50-µg MBT versus placebo |
| Comparison groups | Clonidine Lauriad 50-µg MBT v Placebo MBT |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.063 [9] |
| Method | Chi-squared |

Notes:

[9] - Significance threshold = 5%

| | |
|---|---|
| Statistical analysis title | Clonidine Lauriad 100-µg MBT versus placebo |
| Comparison groups | Clonidine Lauriad 100-µg MBT v Placebo MBT |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.169 ^[10] |
| Method | Chi-squared |

Notes:

[10] - Significance threshold = 5%

| | |
|---|---|
| Statistical analysis title | Clonidine Lauriad MBT pooled versus placebo |
| Comparison groups | Placebo MBT v Clonidine Lauriad MBT Pooled |
| Number of subjects included in analysis | 183 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.064 ^[11] |
| Method | Chi-squared |

Notes:

[11] - Significance threshold = 5%

Other pre-specified: Salivary flow assessment using the NCI-CTC scale (Xerostomia): Time to first grade 2 or more

| | |
|-----------------|--|
| End point title | Salivary flow assessment using the NCI-CTC scale (Xerostomia): Time to first grade 2 or more |
|-----------------|--|

End point description:

Apparition of a grade 2 or more on the following 4-point scoring scale: 0 = normal; 1 = symptomatic (dry or thick saliva) without significant dietary alteration (unstimulated saliva low > 0.2 mL/minute); 2 = symptomatic and significant oral intake alterations (e.g. copious water, other lubricants, diet limited to purees and/or soft, moist foods) (unstimulated saliva 0.1 to 0.2 mL/minute); and 3 = symptoms leading to inability to adequately aliment orally, intravenous fluids, tube feedings, or total parenteral nutrition indicated (unstimulated saliva < 0.1 mL/minute).

As EudraCT only allows numerical data entry, the value of 999 indicates "Not Reached" for the upper limit of the confidence intervals.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Assessed and scored by the investigator weekly for up to 8 weeks during the active phase (radiotherapy). This analysis was performed on the safety population.

| End point values | Clonidine Lauriad 50-µg MBT | Clonidine Lauriad 100-µg MBT | Placebo MBT | Clonidine Lauriad MBT Pooled |
|----------------------------------|-----------------------------|------------------------------|------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 55 | 64 | 62 | 119 |
| Units: weeks | | | | |
| median (confidence interval 95%) | 6 (4.9 to 9.4) | 7.4 (6 to 999) | 5.1 (4.1 to 7.1) | 7.1 (5.7 to 9.4) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Treatment effect of clonidine Lauriad 50-µg MBT |
| Comparison groups | Clonidine Lauriad 50-µg MBT v Placebo MBT |
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.388 ^[12] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.824 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.484 |
| upper limit | 1.401 |

Notes:

[12] - Significance threshold = 5%

| | |
|---|--|
| Statistical analysis title | Treatment effect of clonidine Lauriad 100-µg MBT |
| Statistical analysis description: 126 subjects were included in this analysis. | |
| Comparison groups | Clonidine Lauriad 100-µg MBT v Placebo MBT |
| Number of subjects included in analysis | 126 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.054 ^[13] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.601 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.357 |
| upper limit | 1.012 |

Notes:

[13] - Significance threshold = 5%

| | |
|-----------------------------------|--|
| Statistical analysis title | Treatment effect of clonidine Lauriad MBT pooled |
| Comparison groups | Placebo MBT v Clonidine Lauriad MBT Pooled |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 181 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.102 ^[14] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.692 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.444 |
| upper limit | 1.078 |

Notes:

[14] - Significance threshold = 5%

Other pre-specified: Overall treatment compliance according to the patient diary

| | |
|---|---|
| End point title | Overall treatment compliance according to the patient diary |
| End point description: | |
| Compliance = [nb tablets / (end date of treatment - start date treatment + 1)] * 100 The "number of tablets" is the number of days with a tablet applied and treatment start and end dates are the first and last dates of the patient diary with a tablet applied. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| All patients completed a daily questionnaire during the active phase (radiotherapy). | |

| End point values | Clonidine Lauriad 50-µg MBT | Clonidine Lauriad 100-µg MBT | Placebo MBT | Clonidine Lauriad MBT Pooled |
|--------------------------------------|-----------------------------------|------------------------------------|-----------------|------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 55 | 64 | 62 | 119 |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 94.28 (± 8.23) | 93.12 (± 11.89) | 96.12 (± 5.59) | 93.66 (± 10.34) |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall treatment compliance according to the patient diary

| | |
|---|---|
| End point title | Overall treatment compliance according to the patient diary |
| End point description: | |
| Compliance = [nb tablets / (end date of treatment - start date treatment + 1)] * 100 The "number of tablets" is the number of days with a tablet applied and treatment start and end dates are the first and last dates of the patient diary with a tablet applied. | |
| End point type | Other pre-specified |

End point timeframe:

All patients completed a daily questionnaire during the active phase (radiotherapy).

| End point values | Clonidine Lauriad 50-µg MBT | Clonidine Lauriad 100-µg MBT | Placebo MBT | Clonidine Lauriad MBT Pooled |
|-------------------------------|-----------------------------------|------------------------------------|----------------------|------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 55 | 64 | 62 | 119 |
| Units: percent | | | | |
| median (full range (min-max)) | 96.97 (63.2 to 100) | 98.02 (42.9 to 100) | 98.15 (72 to 100) | 97.78 (42.9 to 100) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded during the treatment period, and for 4 weeks after treatment was completed.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------------|
| Reporting group title | Clonidine Lauriad 50-µg MBT |
|-----------------------|-----------------------------|

| | |
|--------------------------------|--|
| Reporting group description: - | |
|--------------------------------|--|

| | |
|-----------------------|------------------------------|
| Reporting group title | Clonidine Lauriad 100-µg MBT |
|-----------------------|------------------------------|

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|--------------------------------|--|
| Reporting group description: - | |
|--------------------------------|--|

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|-----------------------|-------------|
| Reporting group title | Placebo MBT |
|-----------------------|-------------|

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|--------------------------------|--|
| Reporting group description: - | |
|--------------------------------|--|

| | |
|-----------------------|------------------------------|
| Reporting group title | Clonidine Lauriad MBT Pooled |
|-----------------------|------------------------------|

| | |
|--------------------------------|--|
| Reporting group description: - | |
|--------------------------------|--|

| | |
|-----------------------|--------------|
| Reporting group title | All patients |
|-----------------------|--------------|

| | |
|--------------------------------|--|
| Reporting group description: - | |
|--------------------------------|--|

| Serious adverse events | Clonidine Lauriad 50-µg MBT | Clonidine Lauriad 100-µg MBT | Placebo MBT |
|---|-----------------------------|------------------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 55 (29.09%) | 21 / 64 (32.81%) | 14 / 62 (22.58%) |
| number of deaths (all causes) | 1 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 64 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to liver | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 64 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypotension | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 55 (3.64%) | 0 / 64 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 64 (1.56%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 64 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 4 / 55 (7.27%) | 1 / 64 (1.56%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthenia | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 64 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Localised oedema | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 64 (1.56%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 1 / 64 (1.56%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 64 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Testicular oedema | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 64 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 1 / 64 (1.56%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary mass | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 64 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 64 (1.56%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 64 (1.56%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound complication | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 64 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 64 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 55 (1.82%) | 1 / 64 (1.56%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 64 (1.56%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemolytic anaemia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 64 (1.56%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 64 (1.56%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 64 (1.56%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Stomatitis | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 4 / 64 (6.25%) | 2 / 62 (3.23%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 2 / 64 (3.13%) | 2 / 62 (3.23%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 3 / 64 (4.69%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 55 (0.00%) | 2 / 64 (3.13%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Odynophagia | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 64 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oral pain | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 64 (1.56%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 3 / 64 (4.69%) | 3 / 62 (4.84%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 64 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 64 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Infection | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 1 / 64 (1.56%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 64 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Bronchopneumonia | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 64 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis viral | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 64 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 64 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 64 (1.56%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 64 (1.56%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 64 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 2 / 64 (3.13%) | 3 / 62 (4.84%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 2 / 64 (3.13%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abnormal loss of weight | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 64 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cachexia | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 64 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 64 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 64 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 64 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Clonidine Lauriad MBT Pooled | All patients | |
|---|---------------------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 37 / 119 (31.09%) | 51 / 181 (28.18%) | |
| number of deaths (all causes) | 1 | 1 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to liver | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |

| | | | |
|--|-----------------|-----------------|--|
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 2 / 181 (1.10%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 5 / 119 (4.20%) | 5 / 181 (2.76%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 2 / 181 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised oedema | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 2 / 181 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 2 / 181 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Reproductive system and breast disorders | | | |
| Testicular oedema | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 2 / 181 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary mass | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 2 / 181 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound complication | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Neutropenia | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 2 / 181 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemolytic anaemia | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Stomatitis | | | |
| subjects affected / exposed | 6 / 119 (5.04%) | 8 / 181 (4.42%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 4 / 119 (3.36%) | 6 / 181 (3.31%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 4 / 119 (3.36%) | 4 / 181 (2.21%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 119 (1.68%) | 2 / 181 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Odynophagia | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral pain | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 4 / 119 (3.36%) | 7 / 181 (3.87%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Infection | | | |
| subjects affected / exposed | 3 / 119 (2.52%) | 3 / 181 (1.66%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Bronchopneumonia | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis viral | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 119 (2.52%) | 6 / 181 (3.31%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 2 / 119 (1.68%) | 3 / 181 (1.66%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abnormal loss of weight | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cachexia | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 119 (0.00%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 119 (0.84%) | 1 / 181 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Clonidine Lauriad 50-µg MBT | Clonidine Lauriad 100-µg MBT | Placebo MBT |
|---|--------------------------------|---------------------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 48 / 55 (87.27%) | 60 / 64 (93.75%) | 61 / 62 (98.39%) |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 4 / 64 (6.25%) | 1 / 62 (1.61%) |
| occurrences (all) | 4 | 4 | 1 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 9 / 55 (16.36%) | 11 / 64 (17.19%) | 14 / 62 (22.58%) |
| occurrences (all) | 12 | 14 | 18 |
| Mucosal inflammation | | | |

| | | | |
|--|-----------------------|------------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 8 / 55 (14.55%) 21 | 11 / 64 (17.19%) 19 | 6 / 62 (9.68%) 12 |
| Fatigue subjects affected / exposed occurrences (all) | 5 / 55 (9.09%) 5 | 5 / 64 (7.81%) 6 | 8 / 62 (12.90%) 10 |
| Pyrexia subjects affected / exposed occurrences (all) | 5 / 55 (9.09%) 5 | 10 / 64 (15.63%) 13 | 3 / 62 (4.84%) 3 |
| Pain subjects affected / exposed occurrences (all) | 3 / 55 (5.45%) 3 | 2 / 64 (3.13%) 3 | 4 / 62 (6.45%) 4 |
| General physical health deterioration subjects affected / exposed occurrences (all) | 3 / 55 (5.45%) 4 | 1 / 64 (1.56%) 2 | 2 / 62 (3.23%) 2 |
| Oedema subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 4 / 64 (6.25%) 4 | 0 / 62 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 3 / 55 (5.45%) 3 | 5 / 64 (7.81%) 6 | 8 / 62 (12.90%) 8 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 4 / 55 (7.27%) 4 | 3 / 64 (4.69%) 6 | 3 / 62 (4.84%) 4 |
| Dysphonia subjects affected / exposed occurrences (all) | 3 / 55 (5.45%) 3 | 3 / 64 (4.69%) 3 | 3 / 62 (4.84%) 3 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 5 / 55 (9.09%) 5 | 1 / 64 (1.56%) 1 | 3 / 62 (4.84%) 4 |
| Investigations Blood creatinine increased subjects affected / exposed occurrences (all) | 7 / 55 (12.73%) 7 | 3 / 64 (4.69%) 3 | 7 / 62 (11.29%) 7 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|------------------------|------------------------|------------------------|
| Radiation skin injury subjects affected / exposed occurrences (all) | 14 / 55 (25.45%) 24 | 22 / 64 (34.38%) 45 | 24 / 62 (38.71%) 35 |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 5 / 55 (9.09%) 6 | 2 / 64 (3.13%) 2 | 9 / 62 (14.52%) 9 |
| Dizziness subjects affected / exposed occurrences (all) | 2 / 55 (3.64%) 2 | 6 / 64 (9.38%) 10 | 2 / 62 (3.23%) 3 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 9 / 55 (16.36%) 11 | 12 / 64 (18.75%) 16 | 11 / 62 (17.74%) 12 |
| Leukopenia subjects affected / exposed occurrences (all) | 10 / 55 (18.18%) 17 | 12 / 64 (18.75%) 19 | 8 / 62 (12.90%) 11 |
| Neutropenia subjects affected / exposed occurrences (all) | 7 / 55 (12.73%) 9 | 12 / 64 (18.75%) 15 | 8 / 62 (12.90%) 9 |
| Lymphopenia subjects affected / exposed occurrences (all) | 7 / 55 (12.73%) 10 | 8 / 64 (12.50%) 12 | 5 / 62 (8.06%) 10 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 6 / 55 (10.91%) 13 | 6 / 64 (9.38%) 11 | 4 / 62 (6.45%) 4 |
| Ear and labyrinth disorders | | | |
| Tinnitus subjects affected / exposed occurrences (all) | 2 / 55 (3.64%) 2 | 4 / 64 (6.25%) 5 | 3 / 62 (4.84%) 3 |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 29 / 55 (52.73%) 63 | 29 / 64 (45.31%) 41 | 44 / 62 (70.97%) 82 |
| Dysphagia subjects affected / exposed occurrences (all) | 18 / 55 (32.73%) 25 | 19 / 64 (29.69%) 23 | 29 / 62 (46.77%) 40 |

| | | | |
|-----------------------------|------------------|------------------|------------------|
| Dry mouth | | | |
| subjects affected / exposed | 22 / 55 (40.00%) | 17 / 64 (26.56%) | 17 / 62 (27.42%) |
| occurrences (all) | 26 | 21 | 22 |
| Vomiting | | | |
| subjects affected / exposed | 14 / 55 (25.45%) | 15 / 64 (23.44%) | 24 / 62 (38.71%) |
| occurrences (all) | 26 | 20 | 32 |
| Constipation | | | |
| subjects affected / exposed | 18 / 55 (32.73%) | 17 / 64 (26.56%) | 16 / 62 (25.81%) |
| occurrences (all) | 20 | 19 | 16 |
| Oral pain | | | |
| subjects affected / exposed | 16 / 55 (29.09%) | 19 / 64 (29.69%) | 16 / 62 (25.81%) |
| occurrences (all) | 40 | 70 | 40 |
| Dysgeusia | | | |
| subjects affected / exposed | 14 / 55 (25.45%) | 11 / 64 (17.19%) | 12 / 62 (19.35%) |
| occurrences (all) | 15 | 13 | 12 |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 55 (12.73%) | 14 / 64 (21.88%) | 13 / 62 (20.97%) |
| occurrences (all) | 15 | 22 | 22 |
| Odynophagia | | | |
| subjects affected / exposed | 7 / 55 (12.73%) | 14 / 64 (21.88%) | 8 / 62 (12.90%) |
| occurrences (all) | 11 | 21 | 22 |
| Stomatitis | | | |
| subjects affected / exposed | 6 / 55 (10.91%) | 8 / 64 (12.50%) | 8 / 62 (12.90%) |
| occurrences (all) | 15 | 18 | 17 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 6 / 64 (9.38%) | 6 / 62 (9.68%) |
| occurrences (all) | 1 | 6 | 6 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 2 / 64 (3.13%) | 5 / 62 (8.06%) |
| occurrences (all) | 2 | 3 | 5 |
| Aptyalism | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 4 / 64 (6.25%) | 3 / 62 (4.84%) |
| occurrences (all) | 1 | 5 | 4 |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 0 / 64 (0.00%) | 2 / 62 (3.23%) |
| occurrences (all) | 3 | 0 | 2 |

| | | | | |
|---|-----------------------------|------------------|------------------|------------------|
| Skin and subcutaneous tissue disorders | Dermatitis | | | |
| | subjects affected / exposed | 11 / 55 (20.00%) | 9 / 64 (14.06%) | 8 / 62 (12.90%) |
| | occurrences (all) | 27 | 17 | 17 |
| | Erythema | | | |
| Renal and urinary disorders | subjects affected / exposed | 4 / 55 (7.27%) | 4 / 64 (6.25%) | 3 / 62 (4.84%) |
| | occurrences (all) | 5 | 4 | 3 |
| | Renal failure | | | |
| | subjects affected / exposed | 3 / 55 (5.45%) | 2 / 64 (3.13%) | 1 / 62 (1.61%) |
| Musculoskeletal and connective tissue disorders | occurrences (all) | 3 | 2 | 1 |
| | Musculoskeletal pain | | | |
| | subjects affected / exposed | 3 / 55 (5.45%) | 1 / 64 (1.56%) | 2 / 62 (3.23%) |
| | occurrences (all) | 3 | 1 | 3 |
| Infections and infestations | Oral candidiasis | | | |
| | subjects affected / exposed | 3 / 55 (5.45%) | 10 / 64 (15.63%) | 9 / 62 (14.52%) |
| | occurrences (all) | 4 | 11 | 13 |
| | Fungal infection | | | |
| | subjects affected / exposed | 2 / 55 (3.64%) | 2 / 64 (3.13%) | 7 / 62 (11.29%) |
| | occurrences (all) | 2 | 2 | 7 |
| | Candida infection | | | |
| | subjects affected / exposed | 2 / 55 (3.64%) | 2 / 64 (3.13%) | 4 / 62 (6.45%) |
| | occurrences (all) | 2 | 2 | 4 |
| Metabolism and nutrition disorders | Abnormal loss of weight | | | |
| | subjects affected / exposed | 4 / 55 (7.27%) | 11 / 64 (17.19%) | 17 / 62 (27.42%) |
| | occurrences (all) | 4 | 13 | 19 |
| | Decreased appetite | | | |
| | subjects affected / exposed | 6 / 55 (10.91%) | 8 / 64 (12.50%) | 5 / 62 (8.06%) |
| | occurrences (all) | 8 | 11 | 6 |

| Non-serious adverse events | Clonidine Lauriad MBT Pooled | All patients | |
|---|---------------------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 108 / 119 (90.76%) | 169 / 181 (93.37%) | |
| Vascular disorders | | | |

| | | | |
|---|-------------------------|-------------------------|--|
| Hypotension subjects affected / exposed occurrences (all) | 7 / 119 (5.88%) 8 | 8 / 181 (4.42%) 9 | |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 20 / 119 (16.81%) 26 | 34 / 181 (18.78%) 44 | |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 19 / 119 (15.97%) 40 | 25 / 181 (13.81%) 52 | |
| Fatigue subjects affected / exposed occurrences (all) | 10 / 119 (8.40%) 11 | 18 / 181 (9.94%) 21 | |
| Pyrexia subjects affected / exposed occurrences (all) | 15 / 119 (12.61%) 18 | 18 / 181 (9.94%) 21 | |
| Pain subjects affected / exposed occurrences (all) | 5 / 119 (4.20%) 6 | 9 / 181 (4.97%) 10 | |
| General physical health deterioration subjects affected / exposed occurrences (all) | 4 / 119 (3.36%) 6 | 6 / 181 (3.31%) 8 | |
| Oedema subjects affected / exposed occurrences (all) | 4 / 119 (3.36%) 4 | 4 / 181 (2.21%) 4 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 8 / 119 (6.72%) 9 | 16 / 181 (8.84%) 17 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 7 / 119 (5.88%) 10 | 10 / 181 (5.52%) 14 | |
| Dysphonia subjects affected / exposed occurrences (all) | 6 / 119 (5.04%) 6 | 9 / 181 (4.97%) 9 | |
| Psychiatric disorders | | | |

| | | | |
|---|---|--|--|
| Anxiety subjects affected / exposed occurrences (all) | 6 / 119 (5.04%) 6 | 9 / 181 (4.97%) 10 | |
| Investigations Blood creatinine increased subjects affected / exposed occurrences (all) | 10 / 119 (8.40%) 10 | 17 / 181 (9.39%) 17 | |
| Injury, poisoning and procedural complications Radiation skin injury subjects affected / exposed occurrences (all) | 36 / 119 (30.25%) 69 | 60 / 181 (33.15%) 104 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) | 7 / 119 (5.88%) 8 8 / 119 (6.72%) 12 | 16 / 181 (8.84%) 17 10 / 181 (5.52%) 15 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) | 21 / 119 (17.65%) 27 22 / 119 (18.49%) 36 19 / 119 (15.97%) 24 15 / 119 (12.61%) 22 12 / 119 (10.08%) 24 | 32 / 181 (17.68%) 39 30 / 181 (16.57%) 47 27 / 181 (14.92%) 33 20 / 181 (11.05%) 32 16 / 181 (8.84%) 28 | |
| Ear and labyrinth disorders | | | |

| | | | |
|-----------------------------|-------------------|--------------------|--|
| Tinnitus | | | |
| subjects affected / exposed | 6 / 119 (5.04%) | 9 / 181 (4.97%) | |
| occurrences (all) | 7 | 10 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 58 / 119 (48.74%) | 102 / 181 (56.35%) | |
| occurrences (all) | 104 | 186 | |
| Dysphagia | | | |
| subjects affected / exposed | 37 / 119 (31.09%) | 66 / 181 (36.46%) | |
| occurrences (all) | 48 | 88 | |
| Dry mouth | | | |
| subjects affected / exposed | 39 / 119 (32.77%) | 56 / 181 (30.94%) | |
| occurrences (all) | 47 | 69 | |
| Vomiting | | | |
| subjects affected / exposed | 29 / 119 (24.37%) | 53 / 181 (29.28%) | |
| occurrences (all) | 46 | 78 | |
| Constipation | | | |
| subjects affected / exposed | 35 / 119 (29.41%) | 51 / 181 (28.18%) | |
| occurrences (all) | 39 | 55 | |
| Oral pain | | | |
| subjects affected / exposed | 35 / 119 (29.41%) | 51 / 181 (28.18%) | |
| occurrences (all) | 110 | 150 | |
| Dysgeusia | | | |
| subjects affected / exposed | 25 / 119 (21.01%) | 37 / 181 (20.44%) | |
| occurrences (all) | 28 | 40 | |
| Diarrhoea | | | |
| subjects affected / exposed | 21 / 119 (17.65%) | 34 / 181 (18.78%) | |
| occurrences (all) | 37 | 59 | |
| Odynophagia | | | |
| subjects affected / exposed | 21 / 119 (17.65%) | 29 / 181 (16.02%) | |
| occurrences (all) | 32 | 54 | |
| Stomatitis | | | |
| subjects affected / exposed | 14 / 119 (11.76%) | 22 / 181 (12.15%) | |
| occurrences (all) | 33 | 50 | |
| Dyspepsia | | | |

| | | | |
|---|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 7 / 119 (5.88%) 7 | 13 / 181 (7.18%) 13 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 4 / 119 (3.36%) 5 | 9 / 181 (4.97%) 10 | |
| Aptyalism subjects affected / exposed occurrences (all) | 5 / 119 (4.20%) 6 | 8 / 181 (4.42%) 10 | |
| Salivary hypersecretion subjects affected / exposed occurrences (all) | 3 / 119 (2.52%) 3 | 5 / 181 (2.76%) 5 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis subjects affected / exposed occurrences (all) | 20 / 119 (16.81%) 44 | 28 / 181 (15.47%) 61 | |
| Erythema subjects affected / exposed occurrences (all) | 8 / 119 (6.72%) 9 | 11 / 181 (6.08%) 12 | |
| Renal and urinary disorders | | | |
| Renal failure subjects affected / exposed occurrences (all) | 5 / 119 (4.20%) 5 | 6 / 181 (3.31%) 6 | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 4 / 119 (3.36%) 4 | 6 / 181 (3.31%) 7 | |
| Infections and infestations | | | |
| Oral candidiasis subjects affected / exposed occurrences (all) | 13 / 119 (10.92%) 15 | 22 / 181 (12.15%) 28 | |
| Fungal infection subjects affected / exposed occurrences (all) | 4 / 119 (3.36%) 4 | 11 / 181 (6.08%) 11 | |
| Candida infection subjects affected / exposed occurrences (all) | 4 / 119 (3.36%) 4 | 8 / 181 (4.42%) 8 | |

| | | | |
|------------------------------------|-------------------|-------------------|--|
| Metabolism and nutrition disorders | | | |
| Abnormal loss of weight | | | |
| subjects affected / exposed | 15 / 119 (12.61%) | 32 / 181 (17.68%) | |
| occurrences (all) | 17 | 36 | |
| Decreased appetite | | | |
| subjects affected / exposed | 14 / 119 (11.76%) | 19 / 181 (10.50%) | |
| occurrences (all) | 19 | 25 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 26 November 2009 | Added 2 exclusion criteria: hypotension and orthostatic hypotension; added dosage of cytokine levels in serum and saliva to evaluate mechanism of action of clonidine and added forbidden concomitant treatments aiming to prevent or treat oral mucositis (e.g. GM-CSF, IL-11, Pilocarpine). |
| 26 February 2010 | Added sedation assessment at each visit; clarified that SAE reporting is not requested in case of planned hospitalisation; deleted the cytokines dosage because not feasible. |
| 14 January 2011 | Deleted 1 exclusion criterion excluding patients with unknown primary cancer. |
| 07 April 2011 | Only applicable to Germany: added that in case of a positive HIV test at screening, notification had to be done to Robert-Koch-Institute anonymously. |
| 09 September 2011 | Updated the total number of centres and prolonged the study duration extension; deleted the sedation assessment because not feasible. |
| 03 July 2012 | Added 1 inclusion criterion authorising previous neoadjuvant chemotherapy; modified 1 inclusion criterion authorising other chemotherapy in combination with cisplatin or carboplatin instead of cisplatin (or carboplatin) alone; prolonged study duration. |
| 12 October 2012 | Added administrative information following the submission in the United States; clarified that oral mucositis WHO score ≥ 3 was to be done by treatment. |
| 15 March 2013 | Harmonised NCI-CTC-AE classification between Europe and the United States. |
| 09 October 2013 | Added a follow-up period of 2 years to collect information on overall survival and progression; modified the primary endpoint to clarify and propose that in the situation where some patients would not reach the cumulative dose of 50 Gy, the cumulative dose at onset of an oral mucositis WHO score ≥ 3 was to be analysed using the Kaplan-Meier method; added that a severe oral mucositis should be considered as an event based on one evaluation instead of two successive evaluations showing a severe oral mucositis; revised the timelines of the study including the follow-up period. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported