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	20 August 2014

Results information

Result version number	v1
This version publication date	29 July 2016
First version publication date	29 July 2016

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	Bérangère Vasseur, MD, Onxeo, b.vasseur@onxeo.com
Scientific contact	Bérangère Vasseur, MD, Onxeo, b.vasseur@onxeo.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	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	20 August 2014
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 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The 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

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

Reporting group values	Clonidine Lauriad MBT Pooled		
Number of subjects	121		
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 full range (min-max)	 57.6 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 full range (min-max)	 0 0 to 100		
Disease duration			
The duration of the squamous cell carcinoma at baseline is provided.			
Units: months median full range (min-max)	 2 1 to 99		

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: -	
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.	

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	Clonidine Lauriad 50-µg MBT v Placebo MBT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.165
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%

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

Radiation skin injury			
subjects affected / exposed	14 / 55 (25.45%)	22 / 64 (34.38%)	24 / 62 (38.71%)
occurrences (all)	24	45	35
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 55 (9.09%)	2 / 64 (3.13%)	9 / 62 (14.52%)
occurrences (all)	6	2	9
Dizziness			
subjects affected / exposed	2 / 55 (3.64%)	6 / 64 (9.38%)	2 / 62 (3.23%)
occurrences (all)	2	10	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 55 (16.36%)	12 / 64 (18.75%)	11 / 62 (17.74%)
occurrences (all)	11	16	12
Leukopenia			
subjects affected / exposed	10 / 55 (18.18%)	12 / 64 (18.75%)	8 / 62 (12.90%)
occurrences (all)	17	19	11
Neutropenia			
subjects affected / exposed	7 / 55 (12.73%)	12 / 64 (18.75%)	8 / 62 (12.90%)
occurrences (all)	9	15	9
Lymphopenia			
subjects affected / exposed	7 / 55 (12.73%)	8 / 64 (12.50%)	5 / 62 (8.06%)
occurrences (all)	10	12	10
Thrombocytopenia			
subjects affected / exposed	6 / 55 (10.91%)	6 / 64 (9.38%)	4 / 62 (6.45%)
occurrences (all)	13	11	4
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	2 / 55 (3.64%)	4 / 64 (6.25%)	3 / 62 (4.84%)
occurrences (all)	2	5	3
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	29 / 55 (52.73%)	29 / 64 (45.31%)	44 / 62 (70.97%)
occurrences (all)	63	41	82
Dysphagia			
subjects affected / exposed	18 / 55 (32.73%)	19 / 64 (29.69%)	29 / 62 (46.77%)
occurrences (all)	25	23	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			
subjects affected / exposed	4 / 55 (7.27%)	4 / 64 (6.25%)	3 / 62 (4.84%)
occurrences (all)	5	4	3
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	3 / 55 (5.45%)	2 / 64 (3.13%)	1 / 62 (1.61%)
occurrences (all)	3	2	1
Musculoskeletal and connective tissue disorders			
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	7 / 119 (5.88%)	8 / 181 (4.42%)	
occurrences (all)	8	9	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	20 / 119 (16.81%)	34 / 181 (18.78%)	
occurrences (all)	26	44	
Mucosal inflammation			
subjects affected / exposed	19 / 119 (15.97%)	25 / 181 (13.81%)	
occurrences (all)	40	52	
Fatigue			
subjects affected / exposed	10 / 119 (8.40%)	18 / 181 (9.94%)	
occurrences (all)	11	21	
Pyrexia			
subjects affected / exposed	15 / 119 (12.61%)	18 / 181 (9.94%)	
occurrences (all)	18	21	
Pain			
subjects affected / exposed	5 / 119 (4.20%)	9 / 181 (4.97%)	
occurrences (all)	6	10	
General physical health deterioration			
subjects affected / exposed	4 / 119 (3.36%)	6 / 181 (3.31%)	
occurrences (all)	6	8	
Oedema			
subjects affected / exposed	4 / 119 (3.36%)	4 / 181 (2.21%)	
occurrences (all)	4	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 119 (6.72%)	16 / 181 (8.84%)	
occurrences (all)	9	17	
Oropharyngeal pain			
subjects affected / exposed	7 / 119 (5.88%)	10 / 181 (5.52%)	
occurrences (all)	10	14	
Dysphonia			
subjects affected / exposed	6 / 119 (5.04%)	9 / 181 (4.97%)	
occurrences (all)	6	9	
Psychiatric disorders			

Anxiety			
subjects affected / exposed	6 / 119 (5.04%)	9 / 181 (4.97%)	
occurrences (all)	6	10	
Investigations			
Blood creatinine increased			
subjects affected / exposed	10 / 119 (8.40%)	17 / 181 (9.39%)	
occurrences (all)	10	17	
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	36 / 119 (30.25%)	60 / 181 (33.15%)	
occurrences (all)	69	104	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 119 (5.88%)	16 / 181 (8.84%)	
occurrences (all)	8	17	
Dizziness			
subjects affected / exposed	8 / 119 (6.72%)	10 / 181 (5.52%)	
occurrences (all)	12	15	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 119 (17.65%)	32 / 181 (17.68%)	
occurrences (all)	27	39	
Leukopenia			
subjects affected / exposed	22 / 119 (18.49%)	30 / 181 (16.57%)	
occurrences (all)	36	47	
Neutropenia			
subjects affected / exposed	19 / 119 (15.97%)	27 / 181 (14.92%)	
occurrences (all)	24	33	
Lymphopenia			
subjects affected / exposed	15 / 119 (12.61%)	20 / 181 (11.05%)	
occurrences (all)	22	32	
Thrombocytopenia			
subjects affected / exposed	12 / 119 (10.08%)	16 / 181 (8.84%)	
occurrences (all)	24	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	7 / 119 (5.88%)	13 / 181 (7.18%)	
occurrences (all)	7	13	
Abdominal pain upper			
subjects affected / exposed	4 / 119 (3.36%)	9 / 181 (4.97%)	
occurrences (all)	5	10	
Aptyalism			
subjects affected / exposed	5 / 119 (4.20%)	8 / 181 (4.42%)	
occurrences (all)	6	10	
Salivary hypersecretion			
subjects affected / exposed	3 / 119 (2.52%)	5 / 181 (2.76%)	
occurrences (all)	3	5	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	20 / 119 (16.81%)	28 / 181 (15.47%)	
occurrences (all)	44	61	
Erythema			
subjects affected / exposed	8 / 119 (6.72%)	11 / 181 (6.08%)	
occurrences (all)	9	12	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	5 / 119 (4.20%)	6 / 181 (3.31%)	
occurrences (all)	5	6	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	4 / 119 (3.36%)	6 / 181 (3.31%)	
occurrences (all)	4	7	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	13 / 119 (10.92%)	22 / 181 (12.15%)	
occurrences (all)	15	28	
Fungal infection			
subjects affected / exposed	4 / 119 (3.36%)	11 / 181 (6.08%)	
occurrences (all)	4	11	
Candida infection			
subjects affected / exposed	4 / 119 (3.36%)	8 / 181 (4.42%)	
occurrences (all)	4	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