Clinical trial results:
A Phase III, Open-label, Randomized, Multi-center Study of the Effects of Leukocyte Interleukin, Injection [Multikine] Plus Standard of Care (Surgery + Radiotherapy or Surgery + Concurrent Chemoradiotherapy) in Subjects with Advanced Primary Squamous Cell Carcinoma of the Oral Cavity / Soft Palate Versus Standard of Care Only.

Summary

EudraCT number	2010-019952-35
Trial protocol	HU PL GB AT RO HR ES IT
Global end of trial date	04 December 2020

Results information

Result version number	v1 (current)
This version publication date	20 April 2025
First version publication date	20 April 2025
Summary attachment (see zip file)	CS001P3_Synopsis CSR (CS001P3_Clinical Study Report_Synopsis_16Jan2025_Redacted.pdf)

Trial information

Trial identification

Sponsor protocol code	CS001P3

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01265849
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CEL-SCI Corporation
Sponsor organisation address	: 8229 Boone Boulevard, Suite 802, Vienna/Virginia, United States, 22182
Public contact	John Cipriano, CEL-SCI Corporation, 001 703-506-9460, jcipriano@cel-sci.com
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2020
Global end of trial reached?	Yes
Global end of trial date	04 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary endpoint of the study is OS. After Multikine injection (with or without CIZ (cyclophosphamide indometacin and zinc)) followed by standard of care (SOC) treatment, subjects will be monitored on a regular basis by clinical and radiographic criteria and will be followed for 30-36 months after completion of study drug + SOC until the required number of deaths are observed.

Protection of trial subjects:

all treatments for minimizing pain and distress to subjects per medical standard of care

Background therapy:

standard of care therapy (surgery followed by radiotherapy or concurrent radiochemotherapy)

Evidence for comparator:

standard of Care (control): surgical excision of tumor and involved lymph nodes followed by radiotherapy +/- concurrent chemotherapy

Actual start date of recruitment	15 December 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	Philippines: 2
Country: Number of subjects enrolled	Taiwan: 40
Country: Number of subjects enrolled	Thailand: 2
Country: Number of subjects enrolled	India: 86
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Sri Lanka: 46
Country: Number of subjects enrolled	Bosnia and Herzegovina: 40
Country: Number of subjects enrolled	Serbia: 183
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	Belarus: 46
Country: Number of subjects enrolled	Russian Federation: 178
Country: Number of subjects enrolled	Ukraine: 158
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Poland: 46

Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Croatia: 55
Country: Number of subjects enrolled	Romania: 2
Worldwide total number of subjects	923
EEA total number of subjects	125

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)	720
From 65 to 84 years	202
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients recruited by investigators in their research sites from the database or by means of website advertisement or reference from other doctors. Patients underwent screening procedures and were required to meet all the inclusion criteria and none of the exclusion criteria. Recruitment period throughout the study course

Pre-assignment

Screening details:

There are 3 arms group 1 (multikine+CIZ+SOC); group 2 (multikine+SOC) and group 3(SOC). In total 928 patients started and 802 completed the study. 126 patients were withdrawn from the study for various reasons. ITT population consists of 923 patients, which is used as baseline.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	LI+CIZ+SOC

Arm description:

LI plus CIZ (cyclophosphamide,indomethacin and zinc) is given as adjuvant therapy prior to standard of care (SOC)

Arm type	Experimental
Investigational medicinal product name	LI 400 IU
Investigational medicinal product code	
Other name	Multikine
Pharmaceutical forms	Injection
Routes of administration	Intralymphatic use, Peritumoral use, Subcutaneous use

Dosage and administration details:

Multikine is provided frozen in a vial containing 2.2 mL of drug at 200 IU (as IL-2) per mL for peritumoral, intra-tumoral, peri-lymphatic or subcutaneous administration. The drug is stored frozen in the pharmacy at –20o C until needed. The vial contents may be thawed at
ambient temperature just before use, and the drug is allowed to reach ambient temperature before injection. If thawed at ambient temperature, the drug must be injected within 4 hours. Subjects randomized to one of the Multikine treatment groups, Multikine, 400 IU (2 mL) is injected each day of study drug administration, 1/2 dose (1 mL) peri-tumorally and 1/2 dose (1 mL) peri-lymphatically at the jugular lymphatic chain ipsilaterally to the injected tumor site inferior to the tip of the mastoid process in the area of the sternomastoid
muscle sequentially and during the same visit.Both injections (peri-tumorally and peri-lymphatically) are administered 5 times per week for 3 weeks.

Investigational medicinal product name	cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Cyclophosphamidie is administered IV bolus (one time only) at a dose of 300mg/m^2 three days prior to beginning treatment with LI. Standard of care (SOC) for previously untreated squamouscell carcinoma of the head and neck is currently surgery followed by radiotherapy (60-70Gy in30 to 35 fractions over 6 to 7 weeks) for higher risk subjects (subjects determined at surgery to have adverse features per the NCCN guidelines, such as, positive surgical margins, 2 or more clinically positive nodes or extracapsular nodal spread, etc. that would pre-dispose them for higher risk of recurrence)

radiotherapy is combined with concurrent chemotherapy (cisplatin100mg/m^2 intravenously 1x weekly for 3 weeks on day 1 of weeks 1, 4 and 7 of radiotherapy

Investigational medicinal product name	indometacine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One 25mg capsule of indomethacin is administered orally beginning on day one of LI treatment daily until the day before surgery

Investigational medicinal product name	Zinc
Investigational medicinal product code	
Other name	multivatimines
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule daily beginning on day one of treatment with LI until one day before surgery

Investigational medicinal product name	cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin is administered 100mg/m^2 IV concurrent with radiotherapy. The chemotherapy agent(cisplatin 100mg/m^2) is administered intravenously 1x weekly for 3 weeks on day 1 of weeks1, 4 and 7 of radiotherapy

Arm title	LI+SOC

Arm description:

LI is administered without CIZ to determine the contribution of CIZ to the effects of LI

Arm type	Experimental
Investigational medicinal product name	LI 400 IU
Investigational medicinal product code	
Other name	Multikine
Pharmaceutical forms	Injection
Routes of administration	Intralymphatic use, Peritumoral use, Subcutaneous use

Dosage and administration details:

Multikine is provided frozen in a vial containing 2.2 mL of drug at 200 IU (as IL-2) per mL for peritumoral, intra-tumoral, peri-lymphatic or subcutaneous administration. The drug is stored frozen in the pharmacy at –20o C until needed. The vial contents may be thawed at
ambient temperature just before use, and the drug is allowed to reach ambient temperature before injection. If thawed at ambient temperature, the drug must be injected within 4 hours. Subjects randomized to one of the Multikine treatment groups, Multikine, 400 IU (2 mL) is injected each day of study drug administration, 1/2 dose (1 mL) peri-tumorally and 1/2 dose (1 mL) peri-lymphatically at the jugular lymphatic chain ipsilaterally to the injected tumor site inferior to the tip of the mastoid process in the area of the sternomastoid
muscle sequentially and during the same visit.Both injections (peri-tumorally and peri-lymphatically) are administered 5 times per week for 3 weeks.

Investigational medicinal product name	cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin is administered 100mg/m^2 IV concurrent with radiotherapy. The chemotherapy agent(cisplatin 100mg/m^2) is administered intravenously 1x weekly for 3 weeks on day 1 of weeks1, 4

7 of radiotherapy

Arm title	Standard of care

Arm description:

SOC for previously untreated SCCHN patients is currently surgery followed by either radiotherapy or combined radiochemotherapy depending the patient's risk status for relapse determined at surgery

Arm type	Active comparator
Investigational medicinal product name	cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin is administered 100mg/m^2 IV concurrent with radiotherapy. The chemotherapy agent(cisplatin 100mg/m^2) is administered intravenously 1x weekly for 3 weeks on day 1 of weeks1, 4 and 7 of radiotherapy

Number of subjects in period 1	LI+CIZ+SOC	LI+SOC	Standard of care
Started	395	134	394
Intent to Treat Population	395	134	394
Completed	350	115	337
Not completed	45	19	57
Physician decision	1	-	2
Consent withdrawn by subject	25	13	34
treatment not initiated	1	-	4
Lost to follow-up	17	5	11
not specified	1	1	6

Baseline characteristics

Reporting groups	
Reporting group title	LI+CIZ+SOC
Reporting group description:	
LI plus CIZ (cyclophosphamide,indomethacin and zinc) is given as adjuvant therapy prior to standard of care (SOC)	
Reporting group title	LI+SOC
Reporting group description:	
LI is administered without CIZ to determine the contribution of CIZ to the effects of LI	
Reporting group title	Standard of care
Reporting group description:	
SOC for previously untreated SCCHN patients is currently surgery followed by either radiotherapy or combined radiochemotherapy depending the patient's risk status for relapse determined at surgery	

Reporting group values	LI+CIZ+SOC	LI+SOC	Standard of care
Number of subjects	395	134	394
Age categorical Units: Subjects			
Adults (18-64 years)	307	111	302
From 65-84 years	88	22	92
85 years and over	0	1	0
Age continuous Units: years			
arithmetic mean	56.5	55.9	57.0
full range (min-max)	26 to 82	20 to 86	22 to 84
Gender categorical Units: Subjects			
Female	83	29	79
Male	312	105	315
ethnicity Units: Subjects			
hispanic or latino	190	57	186
uknow or not reported	205	77	208
Race Units: Subjects			
asian	79	25	76
black or african	2	0	0
white	311	108	317
uknow or not reported	3	1	1
american indian	0	0	0
native hawaiian	0	0	0
more then one race	0	0	0
primary tumor location measure Units: Subjects			
cheek (buccal mucosa)	53	18	55
floor of mouth	111	37	116
oral tongue	182	63	178
soft palate	49	16	45

tumor code measure Units: Subjects			
T1	21	4	12
T2	94	28	95
T3	163	68	191
T4A	117	34	96
Number of nodes involved measure Units: Subjects			
missing	1	0	0
N0	190	62	180
N1	108	37	118
N2	96	35	96
TNM stage measure Units: Subjects			
III	218	75	228
IVA	177	59	166

Reporting group values	Total		
Number of subjects	923		
Age categorical Units: Subjects			
Adults (18-64 years)	720		
From 65-84 years	202		
85 years and over	1		
Age continuous Units: years arithmetic mean full range (min-max)	 -		
Gender categorical Units: Subjects			
Female	191		
Male	732		
ethnicity Units: Subjects			
hispanic or latino	433		
uknow or not reported	490		
Race Units: Subjects			
asian	180		
black or african	2		
white	736		
uknow or not reported	5		
american indian	0		
native hawaiian	0		
more then one race	0		
primary tumor location measure Units: Subjects			
cheek (buccal mucosa)	126		
floor of mouth	264		
oral tongue	423		
soft palate	110		

tumor code measure Units: Subjects			
T1	37		
T2	217		
T3	422		
T4A	247		
Number of nodes involved measure Units: Subjects			
missing	1		
N0	432		
N1	263		
N2	227		
TNM stage measure Units: Subjects			
III	521		
IVA	402		

End points

End points reporting groups

Reporting group title	LI+CIZ+SOC
Reporting group description:	
LI plus CIZ (cyclophosphamide,indomethacin and zinc) is given as adjuvant therapy prior to standard of care (SOC)	
Reporting group title	LI+SOC
Reporting group description:	
LI is administered without CIZ to determine the contribution of CIZ to the effects of LI	
Reporting group title	Standard of care
Reporting group description:	
SOC for previously untreated SCCHN patients is currently surgery followed by either radiotherapy or combined radiochemotherapy depending the patient's risk status for relapse determined at surgery	

Subject analysis set title	SOC low risk
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Per the NCCN Guidelines lower risk subjects to receive radiotherapy randomized to SOC	
Subject analysis set title	LI+CIZ+SOC low risk
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Per the NCCN Guidelines lower risk subjects to receive radiotherapy randomized to LI+CIZ+SOC	
Subject analysis set title	LI+SOC low risk
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Per the NCCN Guidelines lower risk subjects to receive radiotherapy randomized to LI+SOC	

Primary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
OS is assessed using Kaplan-Meier life-table and compared using a log rank test and confirmed further with tumor stage location and geographic stratified log rank tests. Both Stratified and unstratified log rank test are presented with the unstratified log rank test constituting the primary analysis. A two-sided p- value of 0.05 or less is considered statistically significant for comparing the two groups (i.e., Study comparator arms: LI+CIZ+SOC vs. SOC alone). Interim analyses is performed (by the iDMC) throughout the study to assess safety, sample size and futility	
End point type	Primary
End point timeframe:	
3-5 years	

End point values	LI+CIZ+SOC	LI+SOC	Standard of care	SOC low risk
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	395	134	394	168
Units: months				
median (confidence interval 95%)	46.3 (39.3 to 55)	58.1 (41.4 to 68.2)	52.9 (46.5 to 66.6)	55.2 (48.0 to 99.9)

End point values	LI+CIZ+SOC low risk	LI+SOC low risk		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	54		
Units: months				
median (confidence interval 95%)	101.7 (64.1 to 101.7)	68.2 (44.7 to 99.9)		

Statistical analyses

Statistical analysis title	LI + CIZ + SOC, Standard of Care (SOC)

Statistical analysis description:

The primary objective is to compare overall survival in the Multikine (LI) + CIZ + SOC group to that in the SOC alone group for superiority of the former

Comparison groups	LI+CIZ+SOC v Standard of care
Number of subjects included in analysis	789
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.4051 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.32

Notes:

[1] - For the primary efficacy measure a two-sided p-value of 0.05 or less is considered to be statistically significant in comparing the LI treatments vs. SOC alone for superiority.

[2] - For the primary efficacy measure a two-sided p-value of 0.05 or less is considered to be statistically significant in comparing the LI+CIZ+SOC treatment vs. SOC alone for superiority.

Statistical analysis title	LI+SOC vs SOC

Statistical analysis description:

The LI+SOC vs SOC comparison is not a part of the primary (OS) analysis

Comparison groups	LI+SOC v Standard of care
Number of subjects included in analysis	528
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7181
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.42

Statistical analysis title	LI+CIZ+SOC vs SOC low risk

Statistical analysis description:

The primary analysis is repeated for the 326 (41%) of subjects meeting the NCCN guideline for low risk.

Comparison groups	SOC low risk v LI+CIZ+SOC low risk
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0478
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.95

Notes:

[3] - For the primary efficacy measure a two-sided p-value of 0.05 or less is considered to be statistically significant in comparing the LI+CIZ+SOC treatment vs. SOC alone for superiority. This p value is uncorrected for multiplicity.

Statistical analysis title	LI+SOC vs SOC low risk
Comparison groups	LI+SOC low risk v SOC low risk
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.4115
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.29

Notes:

[4] - The comparison of LI+SOC vs SOC was not a part of the primary (OS) analysis. The unstratified logrank statistic for this comparison is p=0.4115, the stratified logrank is 0.2862.
The stratified hazard ratio for this comparison is 0.82 (0.52-1.29), p=0.3859.

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

PFS will be assessed using Kaplan-Meier life-table and compared using a logrank test and confirmed further with stage location and geographic stratified log rank tests. Both stratified and unstratified logrank test results are presented with the unstratified log rank test representing the primary analysis. A two-sided p-value of 0.05 or less will be considered statistically significant in comparing the groups. The Holm closed-sequential procedure will be used to control type 1 error probability to at most 0.05.

End point type	Secondary

End point timeframe:

3-5 years

End point values	LI+CIZ+SOC	LI+SOC	Standard of care	SOC low risk
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	395	134	394	168
Units: months				
median (confidence interval 95%)	32.4 (25.5 to 43.4)	45.5 (23.5 to 51.2)	45.5 (23.5 to 51.2)	51.5 (42.5 to 72.2)

End point values	LI+CIZ+SOC low risk	LI+SOC low risk		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	54		
Units: months				
median (confidence interval 95%)	66.4 (47.5 to 101.7)	68.2 (37.0 to 112.4)		

Statistical analyses

Statistical analysis title	LI+CIZ+SOC vs SOC

Statistical analysis description:

The secondary endpoint PFS is analyzed similar to OS and LRC.

Comparison groups	LI+CIZ+SOC v Standard of care
Number of subjects included in analysis	789
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.3303 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.31

Notes:

[5] - The unstratified log rank statistic for the LI+CIZ+SOC vs SOC is not adjusted for multiplicity.

[6] - P-values are reported unadjusted for multiplicity. The stratified log rank p-value for this comparison is 0.6669

Statistical analysis title	LI+SOC vs SOC

Statistical analysis description:

The p-values for LI+SOC to SOC comparison for unstratified and stratified logrank are 0.5739 and 0.8162, respectively. Hazard ratio (95%CI) for this comparison is 1.10 (0.84, 1.43)

Comparison groups	LI+SOC v Standard of care
Number of subjects included in analysis	528
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.478
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.43

Statistical analysis title	LI+CIZ+SOC vs SOC low risk

Statistical analysis description:

The population for this PFS analysis is low risk subjects by NCCN guidelines.

Comparison groups	SOC low risk v LI+CIZ+SOC low risk
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.04

Statistical analysis title	LI+SOC vs SOC low risk

Statistical analysis description:

The population for this PFS analysis is low risk subjects by NCCN guidelines

Comparison groups	LI+SOC low risk v SOC low risk

Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.4376 [8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.3

Notes:

[7] - The population for this PFS analysis is low risk subjects by NCCN guidelines.

[8] - the p-values for unstratified and stratified logrank are 0.5175 and 0.4530, respectively

Secondary: Time to LRC failure

End point title	Time to LRC failure

End point description:

LRC is assessed by classifying the first evidence of progression in local (defined as any reappearance or new disease above the clavicle) but not distal sites for the control groups and for the LI treated group. LRC failure includes progression of tumor(s) and nodes or appearance of new disease above the clavicle (but not distant metastases) the reappearance of tumor in the original tumor bed, development of cervical node metastases and new disease above the clavicle other than distant metastases not present at baseline. The total number and corresponding percent of subjects in each of the treated and untreated control groups as well as the time to LRC in days for each group will also be displayed for each group.

End point type	Secondary

End point timeframe:

2-3 years

End point values	LI+CIZ+SOC	LI+SOC	Standard of care	SOC low risk
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	395	134	394	168
Units: months				
median (confidence interval 95%)	99.9 (99.9 to 99.9)	99.9 (99.9 to 99.9)	99.9 (99.9 to 99.9)	99.9 (99.9 to 99.9)

End point values	LI+CIZ+SOC low risk	LI+SOC low risk		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	54		
Units: months				
median (confidence interval 95%)	99.9 (99.9 to 99.9)	99.9 (99.9 to 99.9)		

Statistical analyses

Statistical analysis title	LI+CIZ+SOC vs SOC

Statistical analysis description:

The secondary endpoint LRC failure is analyzed similar to the primary OS endpoint. The primary comparison is LI+CIZ+SOC vs SOC.

Comparison groups	LI+CIZ+SOC v Standard of care
Number of subjects included in analysis	789
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.7304 [10]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.36

Notes:

[9] - The secondary endpoint LRC failure is analyzed similar to the primary OS endpoint. The primary comparison is LI+CIZ+SOC vs SOC; LI+SOC vs SOC results are also reported

[10] - P-values are not adjusted for multiple comparisons. The p-value for the stratified logrank statistic is 0.7171

Statistical analysis title	LI+SOC vs SOC

Statistical analysis description:

The secondary endpoint LRC failure is analyzed similar to the primary OS endpoint. The comparison is LI+SOC vs SOC results are reported.

Comparison groups	LI+SOC v Standard of care
Number of subjects included in analysis	528
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.394 [11]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.69

Notes:

[11] - P-values are not adjusted for multiple comparisons.The p-value for the stratified logrank statistic is 0.7171.

Statistical analysis title	LI+CIZ+SOC vs SOC low risk

Statistical analysis description:

Population is low-risk subjects by NCCN Guidelines. Median time-to-LRC failure has not yet been reach for any of the treatments.

Comparison groups	SOC low risk v LI+CIZ+SOC low risk
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.6142 [13]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.28

Notes:

[12] - Population is low-risk subjects by NCCN Guidelines.The stratified hazard ratio is in the direction favoring LI+CIZ+SOC. The p-value for this comparison is 0.4082

[13] - P-values are reported unadjusted for multiplicity.The p-value for the stratified logrank statistic for this comparison is 0.3024

Statistical analysis title	LI+SOC vs SOC low risk

Statistical analysis description:

Median time-to-LRC failure has not yet been reach for any of the treatments. Population is low-risk subjects by NCCN Guidelines.

Comparison groups	SOC low risk v LI+SOC low risk
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8131 [14]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.65

Notes:

[14] - The LI+SOC vs SOC comparison unstratified logrank statistic is p=0.9784; stratified the p-value is 0.8461.

Secondary: EORTC Quality of Life Questionnaire (QLQ) - Head & Neck Cancer Module: QLQ-H&N35

End point title	EORTC Quality of Life Questionnaire (QLQ) - Head & Neck Cancer Module: QLQ-H&N35

End point description:

EORTC Quality of Life Questionnaire (QLQ) - Head & Neck Cancer Module: QLQ-H&N35. Pain item on the QLQ-H&N35 ranges from 0 to 100 with lower scores representing better (less) Head and Neck pain. If reporting a score on a scale, please include the unabbreviated scale title, the minimum and maximum values, and whether higher scores mean a better or worse outcome. Approximately 30% of participants completed this QoL instrument.

End point type	Secondary

End point timeframe:

3 years

End point values	LI+CIZ+SOC	LI+SOC	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	44	120	
Units: score on scale				
arithmetic mean (standard error)				
month 2	-2.75 (± 1.66)	-2.8 (± 2.77)	-3.81 (± 1.67)	
Months 36	-9.47 (± 1.66)	-8.63 (± 2.61)	-8.42 (± 1.64)	

Statistical analyses

Statistical analysis title	LI+CIZ+SOC vs SOC

Statistical analysis description:

P-values are not adjusted for multiplicity. This is a repeated measures ANCOVA with the fixed effects of treatment, visit, treatment by visit interaction, tumor location, tumor stage, geographic region, and baseline score. Results are reported for the first (Month 2) and last (Month 36) administration of this QoL instrument.For H&N pain a lower score is better. Planned analysis focus is on LI+CIZ+SOC.

Comparison groups	LI+CIZ+SOC v Standard of care
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.7452 [16]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.03
upper limit	5.63
Variability estimate	Standard error of the mean
Dispersion value	2.465

Notes:

[15] - Approximately 30% of the participants completed this QoL instrument. This is a completer analysis.
[16] - P-value is not adjusted for multiplicity. Analysis is a repeated measures ANCOVA with treatment, visit, treatment by visit interaction, tumor location, tumor stage, geographic region, and baseline score.

Secondary: EORTC Quality of Life Questionnnaire (QLQ) C30 QOL:	
End point title	EORTC Quality of Life Questionnnaire (QLQ) C30 QOL:
End point description:	
EORTC QOQ-C30 was completed by approximately 30% of participants. This is a completer analysis. If reporting a score on a scale, please include the unabbreviated scale title, the minimum and maximum values, and whether higher scores mean a better or worse outcome	
End point type	Secondary
End point timeframe:	
3 years	

End point values	LI+CIZ+SOC	LI+SOC	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	44	119	
Units: score on a scale				
least squares mean (standard error)				
Month 2	0.28 (± 1.82)	7.95 (± 3.03)	3.29 (± 1.83)	
Month 36	7.64 (± 1.82)	10.79 (± 2.85)	6.33 (± 1.8)	

Statistical analyses

Statistical analysis title	Quality of Life (QOL) in LI + CIZ + SOC vs. SOC
Statistical analysis description:	
Approximately 30% of participants completed the QOL instrument at first (Month2) and last (Month 36) administration. This study was not powered for QoL comparisons. These completer analyses are descriptive only.	
Comparison groups	LI+CIZ+SOC v Standard of care
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21 [17]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.79
upper limit	1.69
Variability estimate	Standard error of the mean
Dispersion value	2.395

Notes:

[17] - P-values are unadjusted for multiplicity

Secondary: EORTC Quality of Life Questionnaire - Head & Neck 35 QOL: H&N Swallowing

End point title	EORTC Quality of Life Questionnaire - Head & Neck 35 QOL: H&N Swallowing

End point description:

Difficulty swallowing item on the QLQ-H&N35 ranges from 0 to 100 with lower scores representing better (less) difficulty swallowing.
If reporting a score on a scale, please include the unabbreviated scale title, the minimum and maximum values, and whether higher scores mean a better or worse outcome.

End point type	Secondary

End point timeframe:

3 years

End point values	LI+CIZ+SOC	LI+SOC	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	44	120	
Units: score on a scale				
least squares mean (standard error)				
Month 2	8.11 (± 1.88)	6.29 (± 3.13)	7.31 (± 1.89)	
Month 36	6.9 (± 1.89)	1.66 (± 2.96)	8.94 (± 1.86)	

Statistical analyses

Statistical analysis title	LI + CIZ + SOC, Standard of Care (SOC)

Statistical analysis description:

Approximately 30% of the participants completed this QoL instrument. This is a completer analysis.

Comparison groups	LI+CIZ+SOC v Standard of care
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.7452 [19]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.03
upper limit	5.63
Variability estimate	Standard error of the mean
Dispersion value	2.465

Notes:

[18] - Approximately 30% of the participants completed this QoL instrument. This is a completer analysis.
[19] - P-value is not adjusted for multiplicity. Analysis is a repeated measures ANCOVA with treatment, visit, treatment by visit interaction, tumor location, tumor stage, geographic region, and baseline score.

Secondary: Prognoses Using Histopathology (HP) Markers

End point title	Prognoses Using Histopathology (HP) Markers[20]

End point description:

OS, PFS, and LRC were examined using a proportional hazards model to assess the interactions between HP levels, risk group (low, high), and treatment (LI+CIZ+SOC, SOC Alone). Twenty (20) HP markers were classified as (low, medium, high), 2 HP ratios as (low, medium, high) and 14 HP combinations as (low, high) resulting in 94 possible treatment comparisons for OS, PFS and LRC. Significance (two-sided $p<0.05$ always favoring Group 1 vs Group 3) was observed for OS (14/60, 2/6, and 9/28), PFS (11/60, 1/6, and 5/28), and LRC (9/60, 1/6, and 6/28) in support of robust efficacy outcomes, only seen in the low risk population. Combined, significance was reached for 20.9% (59/282) possible comparisons; the one-sided 97.5% confidence bound on the fraction significant was 16.3% which exceeds 5% chance alone.

End point type	Secondary

End point timeframe:

Duration of the study

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis included only LI+CIZ+SOC and SOC arms, due to small numbers in the LI+SOC arm this arm was not included.

End point values	LI+CIZ+SOC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	394		
Units: percentage of treatment comparison				
number (confidence interval 95%)	20.9 (16.3 to 26.1)	0 (0 to 1.3)		

Statistical analyses

Statistical analysis title	LI + CIZ + SOC

Statistical analysis description:

LI plus CIZ (cyclophosphamide, indomethacin and zinc) is given as adjuvant therapy prior to standard of care (SOC).

Comparison groups	Standard of care v LI+CIZ+SOC
Number of subjects included in analysis	789
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	< 0.0001
Method	N% of significant test results
Parameter estimate	N % of significant results
Point estimate	20.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.3
upper limit	26.1

Notes:

[21] - Treatment comparisons of LI+CIZ+SOC v. SOC were repeated at all levels of HP, HP ratios, and HP combinations for endpoints OS, PFS, and LRC. Significant outcomes (two-sided $p<0.05$ favoring LI+CIZ+SOC) were accumulated. Fifty-nine (59) of the 282 possible comparisons favored LI+CIZ+SOC, well above the 5% of statistically significant results to be expected assuming no treatment effect. There

were no significant test results that favored SOC. All significant (P<0.05) were in the low risk group.

Post-hoc: Multikine Response (Pre-surgery)	
End point title	Multikine Response (Pre-surgery)
End point description: Pre-surgery tumor response was assessed by RECIST 1.0 criteria, see Protocol Appendix 10.	
End point type	Post-hoc
End point timeframe: Initation of treatment through surgery	

End point values	LI+CIZ+SOC	LI+SOC	Standard of care	SOC low risk
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	395	134	394	168
Units: participants				
number (not applicable)	32	23	0	0

End point values	LI+CIZ+SOC low risk	LI+SOC low risk		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	54		
Units: participants				
number (not applicable)	24	10		

Statistical analyses

Statistical analysis title	LI + CIZ + SOC, Standard of Care (SOC), LI + SOC
Statistical analysis description: Pre-surgery tumor response was assessed by RECIST 1.0 criteria, see Protocol Appendix 10.	
Comparison groups	LI+CIZ+SOC v LI+SOC v Standard of care
Number of subjects included in analysis	923
Analysis specification	Post-hoc
Analysis type	superiority[22]
Parameter estimate	mean %
Point estimate	8.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	5
upper limit	11

Notes:

[22] - Response Rates (95%CI) are given for each treatment group [ITTpopulation]: LI+CIZ+SOC (n=395) is 8.1% (5.0%, 11.0%),LI+SOC (n=134) is 9.7% (5.0%, 16.0%), SOC (n=394) is 0 (-)

Statistical analysis title	Multikine response-low risk participants

Statistical analysis description:

Intent-to-treat population who are low risk by NCCN guideline

Comparison groups	SOC low risk v LI+CIZ+SOC low risk v LI+SOC low risk
Number of subjects included in analysis	380
Analysis specification	Post-hoc
Analysis type	superiority[23]
Parameter estimate	mean %
Point estimate	16
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.4
upper limit	21.7

Notes:

[23] - A total of 34 low risk participants received LI with or without CIZ and were responders. Low risk LI+CIZ+SOC Response Rate (95%CI) is 15.2% (11.8, 25.5), LI+SOC is 18.5% (11.5, 37.8), SOC is 0(--,--)

Post-hoc: Overall Survival (OS) by Response (RECIST 1.0)

End point title	Overall Survival (OS) by Response (RECIST 1.0)

End point description:

Survival was assessed for subjects responding (RECIST 1.0) to Multikine treatment

End point type	Post-hoc

End point timeframe:

Duration of the study

End point values	LI+CIZ+SOC	LI+SOC	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	395	134	394	
Units: count of participants				
number (not applicable)				
non-responder and alive	166	56	204	
non-responder and dead	197	65	190	
responder and alive	25	10	0	
responder and dead	7	3	0	

Statistical analyses

Statistical analysis title	LI + CIZ + SOC, Standard of Care (SOC), LI + SOC

Statistical analysis description:

The null hypothesis that survival is unrelated to MK response versus the alternative hypothesis that MK response is predictive of survival.

Comparison groups	LI+CIZ+SOC v LI+SOC v Standard of care
Number of subjects included in analysis	923
Analysis specification	Post-hoc
Analysis type	superiority[24]
P-value	< 0.0001
Method	Fisher exact

Notes:

[24] - Fishers Exact Test (FET) for response and survival is reported as p<0.0001 for treatment group LI+CIZ+SOC. The FET p-value for response and survival for treatment group LI+SOC is 0.0434. No results are given for SOC as there are no responses.

Statistical analysis title	LI + CIZ + SOC,SOC, LI + SOC low risk

Statistical analysis description:

The null hypothesis that survival is unrelated to MK response versus the alternative hypothesis that MK response is predictive of survival for low risk participants

Comparison groups	LI+CIZ+SOC v LI+SOC v Standard of care
Number of subjects included in analysis	923
Analysis specification	Post-hoc
Analysis type	superiority[25]
P-value	= 0.0067 [26]
Method	mean %

Notes:

[25] - Fishers Exact Test (FET) for response and survival among low risk participants is reported as p=0.0101 for treatment group LI+CIZ+SOC. The FET p-value for response and survival among low risk participants for treatment group LI+SOC is 0.4832. No results are given for SOC as there are no responses.

[26] - Fishers Exact Test (FET) for response and survival among low risk participants is reported as p=0.0067 for subjects receiving either LI+CIZ+SOC or LI+SOC.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the signing of the ICF to the end of the study treatment follow up in each group and through the end of the study. For this study, there was an end of study follow-up for AEs 30 and 60 days following the last study treatment component.

Adverse event reporting additional description:

All AEs occurring during the study period were recorded. The clinical course of each event was followed until resolution, stabilization, or until it was determined that the study treatment or participation was not the cause. All unresolved SAEs were followed by the investigator until the events were resolved, the subject was lost to follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Li+CIZ+SOC

Reporting group description:

LI plus CIZ (cyclophosphamide, indomethacin and zinc) is given as adjuvant therapy prior to standard of care (SOC)

Reporting group title	Standard of Care (SOC)

Reporting group description:

SOC for previously untreated SCCHN patients is currently surgery followed by either radiotherapy or combined radiochemotherapy depending the patient's risk status for relapse determined at surgery

Reporting group title	LI + SOC

Reporting group description:

LI is administered without CIZ to determine the contribution of CIZ to the effects of LI

Serious adverse events	Li+CIZ+SOC	Standard of Care (SOC)	LI + SOC
Total subjects affected by serious adverse events			
subjects affected / exposed	216 / 383 (56.40%)	187 / 367 (50.95%)	70 / 129 (54.26%)
number of deaths (all causes)	204	190	68
number of deaths resulting from adverse events	165	139	49
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenoma benign			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Colon cancer			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Epiglottic cancer			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Hepatic cancer			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lip and/or oral cavity cancer			
subjects affected / exposed	2 / 383 (0.52%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lip and/or oral cavity cancer recurrent			
subjects affected / exposed	18 / 383 (4.70%)	18 / 367 (4.90%)	6 / 129 (4.65%)
occurrences causally related to treatment / all	0 / 18	0 / 18	0 / 6
deaths causally related to treatment / all	0 / 11	0 / 9	0 / 3
Lip and/or oral cavity cancer stage IV			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung cancer metastatic			
subjects affected / exposed	3 / 383 (0.78%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	2 / 383 (0.52%)	2 / 367 (0.54%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Malignant melanoma			

subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Malignant neoplasm progression			
subjects affected / exposed	100 / 383 (26.11%)	74 / 367 (20.16%)	32 / 129 (24.81%)
occurrences causally related to treatment / all	3 / 103	0 / 74	1 / 34
deaths causally related to treatment / all	3 / 89	0 / 68	1 / 29
Malignant pleural effusion			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Metastases to bone			
subjects affected / exposed	1 / 383 (0.26%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metastases to central nervous system			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	2 / 129 (1.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Metastases to lung			
subjects affected / exposed	8 / 383 (2.09%)	5 / 367 (1.36%)	2 / 129 (1.55%)
occurrences causally related to treatment / all	0 / 8	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 5	0 / 1	0 / 1
Metastases to lymph nodes			
subjects affected / exposed	6 / 383 (1.57%)	9 / 367 (2.45%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 8	0 / 9	0 / 1
deaths causally related to treatment / all	0 / 4	0 / 3	0 / 1
Metastases to salivary gland			

subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic neoplasm			
subjects affected / exposed	1 / 383 (0.26%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nasal cavity cancer			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal sinus cancer			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Neoplasm progression			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Non-small cell lung cancer			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Oesophageal carcinoma			
subjects affected / exposed	2 / 383 (0.52%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Oesophageal squamous cell carcinoma			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Oral cavity cancer metastatic			

subjects affected / exposed	2 / 383 (0.52%)	4 / 367 (1.09%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 4	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Second primary malignancy			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Small cell lung cancer			
subjects affected / exposed	0 / 383 (0.00%)	2 / 367 (0.54%)	0 / 129 (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
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 383 (0.26%)	1 / 367 (0.27%)	0 / 129 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Squamous cell carcinoma of the hypopharynx			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Squamous cell carcinoma of the oral cavity			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Tongue cancer metastatic			

subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Tongue cancer recurrent			
subjects affected / exposed	1 / 383 (0.26%)	2 / 367 (0.54%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	2 / 129 (1.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsil cancer			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal cancer			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tumour haemorrhage			
subjects affected / exposed	4 / 383 (1.04%)	3 / 367 (0.82%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Laryngeal cancer			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Vascular disorders			
Arterial haemorrhage			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Deep vein thrombosis			

subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Jugular vein thrombosis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Lymphoedema			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Lymphorrhoea			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Peripheral artery thrombosis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Venous thrombosis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
General disorders and administration site conditions			
Accidental death			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Asthenia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Complication associated with device			

subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	18 / 383 (4.70%)	17 / 367 (4.63%)	4 / 129 (3.10%)
occurrences causally related to treatment / all	0 / 18	0 / 17	0 / 4
deaths causally related to treatment / all	0 / 18	0 / 17	0 / 4
Face oedema			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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 physical health deterioration			
subjects affected / exposed	0 / 383 (0.00%)	5 / 367 (1.36%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Implant site ulcer			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Localised oedema			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			

subjects affected / exposed	1 / 383 (0.26%)	2 / 367 (0.54%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Organ failure			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Pyrexia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Sudden cardiac death			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Sudden death			
subjects affected / exposed	0 / 383 (0.00%)	3 / 367 (0.82%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Dysphonia			

subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Epistaxis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Obstructive airways disorder			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Oropharyngeal swelling			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Pleural effusion			
subjects affected / exposed	2 / 383 (0.52%)	2 / 367 (0.54%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia aspiration			
subjects affected / exposed	2 / 383 (0.52%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Pulmonary embolism			
subjects affected / exposed	2 / 383 (0.52%)	3 / 367 (0.82%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 0
Pulmonary oedema			

subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Respiratory failure			
subjects affected / exposed	2 / 383 (0.52%)	1 / 367 (0.27%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Upper airway obstruction			
subjects affected / exposed	2 / 383 (0.52%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	3 / 383 (0.78%)	0 / 367 (0.00%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Weight decreased			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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

Flap necrosis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Humerus fracture			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Jaw fracture			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoradionecrosis			
subjects affected / exposed	1 / 383 (0.26%)	2 / 367 (0.54%)	2 / 129 (1.55%)
occurrences causally related to treatment / all	0 / 1	0 / 7	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			
subjects affected / exposed	1 / 383 (0.26%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	4 / 383 (1.04%)	4 / 367 (1.09%)	2 / 129 (1.55%)
occurrences causally related to treatment / all	1 / 4	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative adhesion			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Postoperative wound complication			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation mucositis			

subjects affected / exposed	1 / 383 (0.26%)	1 / 367 (0.27%)	0 / 129 (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
Radiation skin injury			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Rib fracture			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Scar			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Seroma			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Skin flap necrosis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Skin graft contracture			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Wound dehiscence			

subjects affected / exposed	3 / 383 (0.78%)	2 / 367 (0.54%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 383 (0.26%)	2 / 367 (0.54%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	2 / 129 (1.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	2 / 383 (0.52%)	3 / 367 (0.82%)	2 / 129 (1.55%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 1
Cardiac failure			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	3 / 383 (0.78%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	2 / 129 (1.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Cardiovascular disorder			

subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Myocardial infarction			
subjects affected / exposed	1 / 383 (0.26%)	1 / 367 (0.27%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pericardial effusion			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Ventricular arrhythmia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Ventricular fibrillation			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Cerebrovascular accident			

subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cranial nerve palsies multiple			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Seizure			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 383 (0.78%)	5 / 367 (1.36%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	2 / 383 (0.52%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenectomy			
subjects affected / exposed	0 / 383 (0.00%)	2 / 367 (0.54%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Deafness unilateral			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Vertigo			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplopia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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			
Abdominal pain upper			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Ascites			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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

Diarrhoea			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer perforation			
subjects affected / exposed	2 / 383 (0.52%)	0 / 367 (0.00%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Enteritis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Gastric haemorrhage			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Gastric perforation			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingival bleeding			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glossitis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Haemorrhoids			

subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Hypoaesthesia oral			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Intestinal haemorrhage			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Intestinal obstruction			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Mouth ulceration			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Odynophagia			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal compression			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Oral cavity fistula			

subjects affected / exposed	6 / 383 (1.57%)	3 / 367 (0.82%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral mucosal hypertrophy			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Oroantral fistula			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Small intestinal haemorrhage			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Stomatitis			
subjects affected / exposed	2 / 383 (0.52%)	4 / 367 (1.09%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Submaxillary gland enlargement			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Tongue disorder			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Tongue movement disturbance			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue necrosis			

subjects affected / exposed	1 / 383 (0.26%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue oedema			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Vomiting			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Chronic hepatic failure			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Hepatic failure			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 383 (0.78%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Azotaemia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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 failure			

subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Costochondritis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Muscle contracture			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trismus			
subjects affected / exposed	1 / 383 (0.26%)	2 / 367 (0.54%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Abscess neck			
subjects affected / exposed	2 / 383 (0.52%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cellulitis			
subjects affected / exposed	5 / 383 (1.31%)	2 / 367 (0.54%)	2 / 129 (1.55%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ludwig angina			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Lung abscess			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Lymph gland infection			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Oral infection			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Osteomyelitis			

subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis acute			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Periorbital cellulitis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Peritonitis			
subjects affected / exposed	1 / 383 (0.26%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	9 / 383 (2.35%)	11 / 367 (3.00%)	2 / 129 (1.55%)
occurrences causally related to treatment / all	0 / 11	0 / 11	0 / 2
deaths causally related to treatment / all	0 / 7	0 / 0	0 / 2
Postoperative wound infection			
subjects affected / exposed	2 / 383 (0.52%)	4 / 367 (1.09%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas infection			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Pulmonary tuberculosis			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			

subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Sepsis			
subjects affected / exposed	4 / 383 (1.04%)	3 / 367 (0.82%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
Sepsis syndrome			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Septic shock			
subjects affected / exposed	2 / 383 (0.52%)	0 / 367 (0.00%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Streptococcal sepsis			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	2 / 383 (0.52%)	0 / 367 (0.00%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Urinary tract infection			

subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Wound abscess			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	2 / 383 (0.52%)	1 / 367 (0.27%)	0 / 129 (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
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Dehydration			
subjects affected / exposed	1 / 383 (0.26%)	2 / 367 (0.54%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 383 (0.26%)	2 / 367 (0.54%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypernatraemia			
subjects affected / exposed	1 / 383 (0.26%)	1 / 367 (0.27%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Hyperuricaemia			

subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Hypoalbuminaemia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Hypokalaemia			
subjects affected / exposed	0 / 383 (0.00%)	2 / 367 (0.54%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypomagnesaemia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	0 / 129 (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
Hyponatraemia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 367 (0.27%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypophagia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 367 (0.00%)	0 / 129 (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
Malnutrition			
subjects affected / exposed	0 / 383 (0.00%)	0 / 367 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Li+CIZ+SOC	Standard of Care (SOC)	LI + SOC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	354 / 383 (92.43%)	352 / 367 (95.91%)	124 / 129 (96.12%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	27 / 383 (7.05%)	25 / 367 (6.81%)	8 / 129 (6.20%)
occurrences (all)	32	28	9
Lymphocyte count decreased			
subjects affected / exposed	23 / 383 (6.01%)	26 / 367 (7.08%)	6 / 129 (4.65%)
occurrences (all)	50	53	10
Weight decreased			
subjects affected / exposed	169 / 383 (44.13%)	168 / 367 (45.78%)	56 / 129 (43.41%)
occurrences (all)	265	252	94
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	48 / 383 (12.53%)	11 / 367 (3.00%)	13 / 129 (10.08%)
occurrences (all)	50	11	13
Injury, poisoning and procedural complications			
Incision site pain			
subjects affected / exposed	31 / 383 (8.09%)	37 / 367 (10.08%)	13 / 129 (10.08%)
occurrences (all)	39	44	20
Radiation injury			
subjects affected / exposed	47 / 383 (12.27%)	49 / 367 (13.35%)	13 / 129 (10.08%)
occurrences (all)	64	77	20
Radiation mucositis			
subjects affected / exposed	28 / 383 (7.31%)	30 / 367 (8.17%)	15 / 129 (11.63%)
occurrences (all)	38	44	24
Radiation skin injury			
subjects affected / exposed	71 / 383 (18.54%)	77 / 367 (20.98%)	31 / 129 (24.03%)
occurrences (all)	80	87	48
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	64 / 383 (16.71%)	68 / 367 (18.53%)	26 / 129 (20.16%)
occurrences (all)	116	115	49
Leukopenia			
subjects affected / exposed	36 / 383 (9.40%)	32 / 367 (8.72%)	12 / 129 (9.30%)
occurrences (all)	58	45	14
Neutropenia			
subjects affected / exposed	33 / 383 (8.62%)	36 / 367 (9.81%)	8 / 129 (6.20%)
occurrences (all)	59	54	10
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	29 / 383 (7.57%)	39 / 367 (10.63%)	16 / 129 (12.40%)
occurrences (all)	44	46	19
Mucosal inflammation			
subjects affected / exposed	121 / 383 (31.59%)	117 / 367 (31.88%)	43 / 129 (33.33%)
occurrences (all)	162	166	56
Pyrexia			
subjects affected / exposed	43 / 383 (11.23%)	36 / 367 (9.81%)	16 / 129 (12.40%)
occurrences (all)	78	64	30
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	29 / 383 (7.57%)	22 / 367 (5.99%)	9 / 129 (6.98%)
occurrences (all)	45	34	13
Dry mouth			
subjects affected / exposed	40 / 383 (10.44%)	48 / 367 (13.08%)	11 / 129 (8.53%)
occurrences (all)	44	48	11
Dysphagia			
subjects affected / exposed	48 / 383 (12.53%)	40 / 367 (10.90%)	17 / 129 (13.18%)
occurrences (all)	55	45	22
Nausea			
subjects affected / exposed	38 / 383 (9.92%)	34 / 367 (9.26%)	16 / 129 (12.40%)
occurrences (all)	57	53	24
Oral pain			
subjects affected / exposed	31 / 383 (8.09%)	32 / 367 (8.72%)	18 / 129 (13.95%)
occurrences (all)	45	34	22
Stomatitis			

subjects affected / exposed	50 / 383 (13.05%)	63 / 367 (17.17%)	22 / 129 (17.05%)
occurrences (all)	74	108	40
Vomiting			
subjects affected / exposed	29 / 383 (7.57%)	24 / 367 (6.54%)	14 / 129 (10.85%)
occurrences (all)	41	38	20
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	25 / 383 (6.53%)	17 / 367 (4.63%)	4 / 129 (3.10%)
occurrences (all)	35	21	4
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	48 / 383 (12.53%)	43 / 367 (11.72%)	12 / 129 (9.30%)
occurrences (all)	55	50	15
Scar pain			
subjects affected / exposed	28 / 383 (7.31%)	20 / 367 (5.45%)	7 / 129 (5.43%)
occurrences (all)	29	20	9
Psychiatric disorders			
Insomnia			
subjects affected / exposed	25 / 383 (6.53%)	21 / 367 (5.72%)	5 / 129 (3.88%)
occurrences (all)	36	21	8
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	18 / 383 (4.70%)	21 / 367 (5.72%)	7 / 129 (5.43%)
occurrences (all)	22	25	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2011	Change in time to surgery to subject randomized to standard of care only

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 September 2016	Patricia Keegan, M.D., Director of the Division of Oncology Products 2, notified you through the September 26, 2016, telephone conversation that Protocol CS001P3 is on clinical hold and may not be continued except as specified below: Patients enrolled on Protocol CS001P3 prior to September 26, 2016, may continue to receive protocol-specified treatment at the discretion of the treating physician with written confirmation of their consent to remain on study after receiving an updated informed consent document, i.e., a consent document that describes the higher rate of deaths in the Multikine treatment arms identified in interim analyses	10 August 2017

Notes:

Limitations and caveats

None reported