Clinical trial results:
A Randomized, Open-Label, Multi-Center, International Phase 2 Study of TAS-114 in Combination with S-1 in Patients with Advanced or Metastatic
Non-Small Cell Lung Cancer

Summary

EudraCT number	2016-001806-40
Trial protocol	ES PL
Global end of trial date	30 November 2017

Results information

Result version number	v1 (current)
This version publication date	19 October 2020
First version publication date	19 October 2020
Summary attachment (see zip file)	2016-001806-40 - TAS-114-201 CSR Summary (TO-TAS-114-201_aCSR_Summary.pdf)

Trial information

Trial identification

Sponsor protocol code	TO-TAS-114-201

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Taiho Oncology, Inc.
Sponsor organisation address	202 Carnegie Center, Suite 100, Princeton, United States, 08540
Public contact	Clinical Trials Information, Medpace Spain S.L, 0034 918534105, Spain.Regulatory@medpace.com
Scientific contact	Clinical Trials Information, Medpace Spain S.L, 0034 918534105, Spain.Regulatory@medpace.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2017
Global end of trial reached?	Yes
Global end of trial date	30 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the progression-free survival (PFS) of patients with advanced or metastatic non-small cell lung cancer NSCLC, when treated with TAS-114/S-1 combination versus S-1 in patients with advanced solid tumor for which no standard therapy exists

Protection of trial subjects:

All considerations regarding the protection of human subjects were carried out in accordance with the protocol, GCP, ICH Guidelines, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements.

The investigator (according to applicable regulatory requirements) or a person designated by the investigator and under the investigator's responsibility fully informed patients of all pertinent aspects of the clinical trial. All participants were informed to the fullest extent possible about the study in a language and in terms they are able to understand. Before participation in the trial, the written ICF were signed and personally dated by the patient or by the patient's legal representative and by the person who conducted the ICF discussion.

The study was approved by an appropriately constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC), as required in Chapter 3 of the ICH E6 Guidelines, applicable local regulations, and, for studies conducted under an Investigational New Drug (IND) application, the United States (US) Code of Federal Regulations Title 21 part 56.

Randomization took place once the consented patient completed all the necessary baseline procedures and was deemed eligible for study entry. Treatment assignment was done centrally using a dynamic allocation method (biased coin) via an interactive voice/web response system (IXRS) stratified by: 1) geographical region (Region 1: Asian; Region 2: Western); and 2) histological subtypes (non-squamous cell carcinoma [including mixed] and squamous cell carcinoma).

Patients continued to receive study therapy until documentation of progressive disease (PD), intolerable toxicity, withdrawal of consent, or other discontinuation criteria were met.

Background therapy: -

Evidence for comparator:

Chemotherapy regimens containing 5-fluorouracil (5-FU) drugs as the backbone are mainstays for the treatment of many cancers including breast, colorectal, and gastric cancer. Many combination chemotherapies employing 5-FU with chemical modulators such as leucovorin and other anti-malignant tumor agents have been investigated and have demonstrated efficacy against a variety of carcinomas to date. Oral fluoropyrimidines such as S-1, a fixed dose combination of tegafur, a prodrug of 5-FU, gimeracil, a dihydropyrimidine dehydrogenase (DPD) inhibitor that prevents degradation of 5-FU by the body and maintains 5-FU exposure, and oteracil potassium, an orotate phosphoribosyltransferase (OPRT) inhibitor that decreases the activity of 5-FU in normal gastrointestinal (GI) mucosa have been developed

Actual start date of recruitment	15 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	United States: 8
Country: Number of subjects enrolled	Japan: 60
Worldwide total number of subjects	128
EEA total number of subjects	60

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)	61
From 65 to 84 years	67
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was planned to enroll approximately 124 patients with advanced or metastatic NSCLC.
A total of 128 patients were randomized (64 to each study arm) at 26 study sites located in 5 countries and made up the intent-to-treat (ITT) population.

Pre-assignment

Screening details:

All patients completed the following study procedures prior to a confirmation of eligibility: Medical History, ECOG performance status , 12-lead electrocardiogram (ECG), Blood and urine sample assessment, Physical Examination, Baseline Signs and Symptoms, Height, Vital Signs, Weight, Pregnancy testing, CT scan and bone scan and so on...

Pre-assignment period milestones

Number of subjects started	165[1]
Number of subjects completed	128

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen Failure: 37

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 165 patients started screening and out of 165 patients, 37 patients screened failed and therefore 128 patients were randomized

Period 1

Period 1 title	Baseline Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Baseline

Arm description:

Baseline period; screening for participation in the study

Arm type	Screening
Investigational medicinal product name	TAS-114
Investigational medicinal product code	TAS-114
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAS-114, supplied as 100 mg tablets packaged in kits containing 20 tablets for Europe and the US and 120 tablets for Japan.

TAS-114 (400 mg per dose) was administered to patients in the TAS-114/S-1 arm orally BID, with a glass of water within 1 hour after completion of morning and evening meals, for 14 days, followed by a 7-day rest period.

Investigational medicinal product name	S-1
Investigational medicinal product code	L01BC53
Other name	Tegafur/gimeracil/oteracil
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

S-1 is an immediate release dosage form contained in hard gelatin capsules in which tegafur (FT), gimeracil (CDHP), and oteracil as monopotassium salt (Oxo) are combined at a molar ratio of 1:0.4:1. Study drug was packaged in kits containing 28 capsules (15-mg or 20-mg capsules) for all regions. Patients in both arms received S-1 at a dose of 30 mg/m2 BID, with a glass of water within 1 hour after completion of morning and evening meals, for 14 days, followed by a 7-day rest period.

Number of subjects in period 1	Baseline
Started	128
Sign ICF	128
Inclusion/Exclusion	128
Assign Patient Number	128
Medical History	128
Baseline Signs and Symptoms	128
Physical Exam	128
Height	128
Vital Signs/Weight	128
Performance Status	128
ECG	128
Hematology	128
Serum Chemistry	128
Coagulation	128
Urinalysis	128
Pregnancy test	128
Concomitant Medications	128
Tumor Assessment	128
Completed	128

Period 2	
Period 2 title	Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes

Arm title	TAS-114/S-1

Arm description:

Experimental arm, evaluating the efficacy, safety and tolerability of TAS-114 in combination with S-1 regimen in patients with advanced or metastatic non-small cell lung cancer (NSCLC).

Arm type	Experimental
Investigational medicinal product name	TAS-114
Investigational medicinal product code	TAS-114
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAS-114, supplied as 100 mg tablets packaged in kits containing 20 tablets for Europe and the US and 120 tablets for Japan.

TAS-114 (400 mg per dose) was administered to patients in the TAS-114/S-1 arm orally BID, with a glass of water within 1 hour after completion of morning and evening meals, for 14 days, followed by a 7-day rest period.

Investigational medicinal product name	S-1
Investigational medicinal product code	L01BC53
Other name	Tegafur/gimeracil/oteracil
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

S-1 is an immediate release dosage form contained in hard gelatin capsules in which tegafur (FT), gimeracil (CDHP), and oteracil as monopotassium salt (Oxo) are combined at a molar ratio of 1:0.4:1. Study drug was packaged in kits containing 28 capsules (15-mg or 20-mg capsules) for all regions. Patients in both arms received S-1 at a dose of 30 mg/m2 BID, with a glass of water within 1 hour after completion of morning and evening meals, for 14 days, followed by a 7-day rest period.

Arm title	S-1 control

Arm description:

Control arm, evaluating the efficacy, safety and tolerability of the S-1 regimen in patients with advanced or metastatic non-small cell lung cancer (NSCLC).

Arm type	Active comparator
Investigational medicinal product name	S-1
Investigational medicinal product code	L01BC53
Other name	Tegafur/gimeracil/oteracil
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

S-1 is an immediate release dosage form contained in hard gelatin capsules in which tegafur (FT), gimeracil (CDHP), and oteracil as monopotassium salt (Oxo) are combined at a molar ratio of 1:0.4:1. Study drug was packaged in kits containing 28 capsules (15-mg or 20-mg capsules) for all regions. Patients in both arms received S-1 at a dose of 30 mg/m2 BID, with a glass of water within 1 hour after completion of morning and evening meals, for 14 days, followed by a 7-day rest period.

Number of subjects in period 2	TAS-114/S-1	S-1 control
Started	64	64
Inclusion/Exclusion	64	64
Baseline Signs and Symptoms	64	64
Physical Exam	64	64

Vital Signs/Weight	64	64
Performance Status	64	64
Hematology	64	64
Serum Chemistry	64	64
Coagulation	64	64
Concomitant Medications	64	64
AE/Toxicity Assessment	64	64
Tumor Assessment	64	64
TAS-114/S-1 or S-1 treatment	64	64
PGx Sampling	64	64
Survival Status	64	64
Completed	64	63
Not completed	0	1
Physician decision	-	1

Period 3	
Period 3 title	End of Treatment Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	TAS-114/S-1
Arm description: End of Treatment/Study	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	S-1 control
Arm description: End of Treatment/Study	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	TAS-114/S-1	S-1 control
Started	64	63
Physical Exam	64	63
Vital Signs/Weight	64	63
Performance Status	64	63

ECG	64	63
Hematology	64	63
Serum Chemistry	64	63
Coagulation	64	63
Urinalysis	64	63
Concomitant Medications	64	63
AE/Toxicity Assessment	64	63
Tumor Assessment	64	63
PGx Sampling	64	63
Survival Status	64	63
Completed	9	11
Not completed	55	52
Consent withdrawn by subject	2	2
Physician decision	1	-
Adverse event, non-fatal	11	7
Lack of efficacy	41	43

Baseline characteristics

Reporting groups	
Reporting group title	Baseline Period
Reporting group description: -	

Reporting group values	Baseline Period	Total	
Number of subjects	128	128	
Age categorical Units: Subjects			
Adults (18-64 years)	61	61	
From 65-84 years	67	67	
Age continuous Units: years			
arithmetic mean	63.2		
full range (min-max)	43 to 80	-	
Gender categorical Units: Subjects			
Female	39	39	
Male	89	89	
Race Units: Subjects			
Asian/Oriental	60	60	
Caucasian/White	42	42	
Not Collected	24	24	
Other	2	2	
Ethnicity Units: Subjects			
Hispanic or Latino	13	13	
Not Hispanic or Latino	92	92	
Not Collected	23	23	
Weight Units: kg			
arithmetic mean	64.8		
full range (min-max)	38 to 104	-	
Height Units: cm			
arithmetic mean	165.6		
full range (min-max)	140 to 190	-	

Subject analysis sets	
Subject analysis set title	Intention to treat (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: ITT population - patients who were randomized	
Subject analysis set title	Intention to treat (ITT) - TAS-114/S-1
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to treat (ITT) population for the TAS-114/S-1 group

Subject analysis set title	Intention to treat (ITT) - S-1 control
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to treat (ITT) population for the S-1 control group

Reporting group values	Intention to treat (ITT)	Intention to treat (ITT) - TAS-114/S-1	Intention to treat (ITT) - S-1 control
Number of subjects	128	64	64
Age categorical Units: Subjects			
Adults (18-64 years)	61	28	33
From 65-84 years	67	36	31
Age continuous Units: years			
arithmetic mean	63.2	63.8	62.6
full range (min-max)	43 to 80	46 to 76	43 to 80
Gender categorical Units: Subjects			
Female	39	23	16
Male	89	41	48
Race Units: Subjects			
Asian/Oriental	60	30	30
Caucasian/White	42	21	21
Not Collected	24	12	12
Other	2	1	1
Ethnicity Units: Subjects			
Hispanic or Latino	13	8	5
Not Hispanic or Latino	92	45	47
Not Collected	23	11	12
Weight Units: kg			
arithmetic mean	64.8	63.5	66.0
full range (min-max)	38 to 104	39 to 92	38 to 104
Height Units: cm			
arithmetic mean	165.6	164.5	168.0
full range (min-max)	140 to 190	148 to 180	140 to 190

End points

End points reporting groups

Reporting group title	Baseline
Reporting group description:	
Baseline period; screening for participation in the study	
Reporting group title	TAS-114/S-1
Reporting group description:	
Experimental arm, evaluating the efficacy, safety and tolerability of TAS-114 in combination with S-1 regimen in patients with advanced or metastatic non-small cell lung cancer (NSCLC).	
Reporting group title	S-1 control
Reporting group description:	
Control arm, evaluating the efficacy, safety and tolerability of the S-1 regimen in patients with advanced or metastatic non-small cell lung cancer (NSCLC).	
Reporting group title	TAS-114/S-1
Reporting group description:	
End of Treatment/Study	
Reporting group title	S-1 control
Reporting group description:	
End of Treatment/Study	
Subject analysis set title	Intention to treat (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT population - patients who were randomized	
Subject analysis set title	Intention to treat (ITT) - TAS-114/S-1
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention to treat (ITT) population for the TAS-114/S-1 group	
Subject analysis set title	Intention to treat (ITT) - S-1 control
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention to treat (ITT) population for the S-1 control group	

Primary: Progression-Free Survival

End point title	Progression-Free Survival
End point description:	
Progression-Free Survival (PFS) was the primary endpoint of this study and was defined as the time from the day of randomization to the start of disease progression or death (any cause), whichever occurs first, based on the blinded radiological review assessment of response. PFS was compared between the 2 treatment groups using the stratified log-rank test with significance level of 1-sided 5%. The estimate of the hazard ratio and corresponding 90% and 95% confidence interval (CI) were provided using a Cox proportional hazards (CPH) model including treatment and the 2 stratification factors in the model; survival curves were estimated using the Kaplan-Meier method.	
End point type	Primary
End point timeframe:	
Time from the day of randomization to the start of disease progression or death (any cause), whichever occurs first, based on the blinded radiological review assessment of response.	

End point values	TAS-114/S-1	S-1 control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	64		
Units: months				
median (confidence interval 95%)	3.65 (2.69 to 5.16)	4.17 (2.60 to 6.60)		

Statistical analyses

Statistical analysis title	Progression-Free Survival

Statistical analysis description:

Progression-Free Survival (PFS) per central independent review in the Intent to Treat (ITT) population. PFS was compared between the 2 treatment groups using the stratified log-rank test with significance level of 1-sided 5%. The estimate of the hazard ratio and corresponding 90% and 95% confidence interval (CI) were provided using a Cox proportional hazards (CPH) model including treatment and the 2 stratification factors in the model.

Comparison groups	S-1 control v TAS-114/S-1
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2744
Method	t-test, 1-sided
Parameter estimate	Hazard ratio (HR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.88
Variability estimate	Standard deviation

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Survival (OS) was defined as the time from the day of randomization to the date of death by any cause. The estimate of the HR and corresponding 95% CI was provided using a univariate CPH model. Survival curves were estimated using the Kaplan-Meier method, and treatment arms were compared using an unstratified log-rank test.

End point type	Secondary

End point timeframe:

Overall Survival (OS) was defined as the time from the day of randomization to the date of death by any cause.

End point values	TAS-114/S-1	S-1 control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	64		
Units: months				
median (confidence interval 95%)	7.92 (6.28 to 10.78)	9.82 (7.66 to 13.40)		

Statistical analyses

Statistical analysis title	Overall Survival (months)
Statistical analysis description:	
Overall Survival (OS) in the Intent to Treat (ITT) population compared between the 2 treatment groups using an unstratified log-rank test.	
Comparison groups	TAS-114/S-1 v S-1 control
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.1431
Method	t-test, 2-sided
Parameter estimate	Hazard ratio (HR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	2.14
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded from the time a patient started receiving study treatment until 30 days after the last dose of study drug or until the start of new antitumor therapy, whichever was earlier.

Adverse event reporting additional description:

Events were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Safety assessments also included evaluation of laboratory test results, vital signs measurements, physical examination findings, and changes in ECOG performance status (ECOG PS).

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	TAS-114/S-1 (As Treated Population)

Reporting group description:

Adverse Events occurring in subjects within the TAS-114/S-1 (As Treated Population)

Reporting group title	S-1 (As Treated Population)

Reporting group description:

Adverse Events occurring in subjects within the S-1 (As Treated Population)

Serious adverse events	TAS-114/S-1 (As Treated Population)	S-1 (As Treated Population)	
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 64 (46.88%)	19 / 63 (30.16%)	
number of deaths (all causes)	36	29	
number of deaths resulting from adverse events	5	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			

subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 64 (6.25%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 64 (6.25%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Chronic obstructive pulmonary			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 64 (0.00%)	2 / 63 (3.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Hypoxia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory acidosis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Leptomeningeal carcinomatosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 64 (3.13%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Cholelithiasis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	3 / 64 (4.69%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purpura			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypopituitarism			

subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary-dependent Cushing's syndrome			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 64 (4.69%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic alkalosis			

subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	TAS-114/S-1 (As Treated Population)	S-1 (As Treated Population)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 64 (100.00%)	61 / 63 (96.83%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	2 / 64 (3.13%)	3 / 63 (4.76%)	
occurrences (all)	2	3	
Tumour associated fever			
subjects affected / exposed	3 / 64 (4.69%)	0 / 63 (0.00%)	
occurrences (all)	3	0	
Cancer pain			
subjects affected / exposed	0 / 64 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 64 (6.25%)	0 / 63 (0.00%)	
occurrences (all)	4	0	
Hot flush			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Deep vein thrombosis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Haematoma			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	

Intermittent claudication			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Orthostatic hypotension			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Subclavian artery thrombosis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Thrombophlebitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	19 / 64 (29.69%)	14 / 63 (22.22%)	
occurrences (all)	19	14	
Pyrexia			
subjects affected / exposed	14 / 64 (21.88%)	9 / 63 (14.29%)	
occurrences (all)	14	9	
Fatigue			
subjects affected / exposed	6 / 64 (9.38%)	11 / 63 (17.46%)	
occurrences (all)	6	11	
Malaise			
subjects affected / exposed	10 / 64 (15.63%)	5 / 63 (7.94%)	
occurrences (all)	10	5	
Non-cardiac chest pain			
subjects affected / exposed	6 / 64 (9.38%)	3 / 63 (4.76%)	
occurrences (all)	6	3	
Oedema peripheral			
subjects affected / exposed	5 / 64 (7.81%)	4 / 63 (6.35%)	
occurrences (all)	5	4	
Mucosal inflammation			

subjects affected / exposed	4 / 64 (6.25%)	3 / 63 (4.76%)	
occurrences (all)	4	3	
Chills			
subjects affected / exposed	2 / 64 (3.13%)	1 / 63 (1.59%)	
occurrences (all)	2	1	
Face oedema			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Gait disturbance			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
General physical health deterioration			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Hyperthermia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Localised oedema			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Xerosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	12 / 64 (18.75%)	10 / 63 (15.87%)	
occurrences (all)	12	10	
Cough			
subjects affected / exposed	8 / 64 (12.50%)	7 / 63 (11.11%)	
occurrences (all)	8	7	
Epistaxis			
subjects affected / exposed	5 / 64 (7.81%)	3 / 63 (4.76%)	
occurrences (all)	5	3	
Haemoptysis			

subjects affected / exposed	1 / 64 (1.56%)	4 / 63 (6.35%)	
occurrences (all)	1	4	
Oropharyngeal pain			
subjects affected / exposed	1 / 64 (1.56%)	2 / 63 (3.17%)	
occurrences (all)	1	2	
Hiccups			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Hypoxia			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Lung disorder			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Pleural effusion			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Productive cough			
subjects affected / exposed	0 / 64 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Wheezing			
subjects affected / exposed	0 / 64 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Dysphonia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Dyspnoea exertional			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Hyperoxia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Lung infiltration			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Pulmonary haemorrhage			

subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Pulmonary oedema			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Pulmonary pain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 64 (7.81%)	1 / 63 (1.59%)	
occurrences (all)	5	1	
Anxiety			
subjects affected / exposed	2 / 64 (3.13%)	3 / 63 (4.76%)	
occurrences (all)	2	3	
Depression			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Confusional state			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Hallucination			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Investigations			
White blood cell count decreased			
subjects affected / exposed	10 / 64 (15.63%)	5 / 63 (7.94%)	
occurrences (all)	10	5	
Platelet count decreased			

subjects affected / exposed	8 / 64 (12.50%)	6 / 63 (9.52%)		
occurrences (all)	8	6		
Neutrophil count decreased				
subjects affected / exposed	6 / 64 (9.38%)	7 / 63 (11.11%)		
occurrences (all)	6	7		
Aspartate aminotransferase increased				
subjects affected / exposed	4 / 64 (6.25%)	6 / 63 (9.52%)		
occurrences (all)	4	6		
Alanine aminotransferase increased				
subjects affected / exposed	3 / 64 (4.69%)	4 / 63 (6.35%)		
occurrences (all)	3	4		
Blood alkaline phosphatase increased				
subjects affected / exposed	3 / 64 (4.69%)	2 / 63 (3.17%)		
occurrences (all)	3	2		
Blood bilirubin increased				
subjects affected / exposed	0 / 64 (0.00%)	5 / 63 (7.94%)		
occurrences (all)	0	5		
Weight decreased				
subjects affected / exposed	5 / 64 (7.81%)	0 / 63 (0.00%)		
occurrences (all)	5	0		
Lymphocyte count decreased				
subjects affected / exposed	4 / 64 (6.25%)	0 / 63 (0.00%)		
occurrences (all)	4	0		
Blood creatine phosphokinase increased				
subjects affected / exposed	3 / 64 (4.69%)	0 / 63 (0.00%)		
occurrences (all)	3	0		
Blood creatinine increased				
subjects affected / exposed	2 / 64 (3.13%)	1 / 63 (1.59%)		
occurrences (all)	2	1		
White blood cell count increased				
subjects affected / exposed	1 / 64 (1.56%)	2 / 63 (3.17%)		
occurrences (all)	1	2		
Gamma-glutamyltransferase increased				

subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Hepatic enzyme increased			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Blood albumin decreased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Blood bicarbonate increased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Blood creatine increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Blood sodium decreased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Blood urine present			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Glucose urine present			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Neutrophil count increased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Protein total increased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Protein urine			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			

subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 64 (1.56%)	3 / 63 (4.76%)	
occurrences (all)	1	3	
Contusion			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Accidental overdose			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Eschar			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Fracture			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Head injury			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Multiple lentigines syndrome			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	3 / 64 (4.69%)	0 / 63 (0.00%)	
occurrences (all)	3	0	
Atrial fibrillation			

subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Angina pectoris			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Aortic valve stenosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Cyanosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 64 (6.25%)	3 / 63 (4.76%)	
occurrences (all)	4	3	
Headache			
subjects affected / exposed	4 / 64 (6.25%)	3 / 63 (4.76%)	
occurrences (all)	4	3	
Dysgeusia			
subjects affected / exposed	2 / 64 (3.13%)	4 / 63 (6.35%)	
occurrences (all)	2	4	
Neuralgia			
subjects affected / exposed	3 / 64 (4.69%)	0 / 63 (0.00%)	
occurrences (all)	3	0	
Syncope			
subjects affected / exposed	0 / 64 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Amnesia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Apraxia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	

Balance disorder			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Dysaesthesia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Epilepsy			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Neurotoxicity			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Presyncope			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Restless legs syndrome			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	42 / 64 (65.63%)	17 / 63 (26.98%)	
occurrences (all)	42	17	
Neutropenia			

subjects affected / exposed	5 / 64 (7.81%)	1 / 63 (1.59%)	
occurrences (all)	5	1	
Thrombocytopenia			
subjects affected / exposed	4 / 64 (6.25%)	2 / 63 (3.17%)	
occurrences (all)	4	2	
Leukopenia			
subjects affected / exposed	3 / 64 (4.69%)	1 / 63 (1.59%)	
occurrences (all)	3	1	
Leukocytosis			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Thrombocytosis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 64 (1.56%)	3 / 63 (4.76%)	
occurrences (all)	1	3	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	5 / 64 (7.81%)	5 / 63 (7.94%)	
occurrences (all)	5	5	
Blepharitis			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Dry eye			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Eye discharge			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Eye pain			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Visual impairment			

subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Conjunctival hyperaemia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Corneal disorder			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Dacryostenosis acquired			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Ocular icterus			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Retinal haemorrhage			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	20 / 64 (31.25%)	23 / 63 (36.51%)	
occurrences (all)	20	23	
Diarrhoea			
subjects affected / exposed	19 / 64 (29.69%)	18 / 63 (28.57%)	
occurrences (all)	19	18	
Vomiting			
subjects affected / exposed	12 / 64 (18.75%)	13 / 63 (20.63%)	
occurrences (all)	12	13	
Constipation			
subjects affected / exposed	9 / 64 (14.06%)	9 / 63 (14.29%)	
occurrences (all)	9	9	
Stomatitis			
subjects affected / exposed	10 / 64 (15.63%)	4 / 63 (6.35%)	
occurrences (all)	10	4	

Abdominal pain			
subjects affected / exposed	3 / 64 (4.69%)	5 / 63 (7.94%)	
occurrences (all)	3	5	
Abdominal pain upper			
subjects affected / exposed	4 / 64 (6.25%)	3 / 63 (4.76%)	
occurrences (all)	4	3	
Dry mouth			
subjects affected / exposed	1 / 64 (1.56%)	2 / 63 (3.17%)	
occurrences (all)	1	2	
Dyspepsia			
subjects affected / exposed	0 / 64 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Odynophagia			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Oesophagitis			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Abdominal distension			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Ascites			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Colitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Dental caries			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	

Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Oral lichen planus			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Oral pain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Peptic ulcer			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Tongue discolouration			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	0 / 64 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Cholestasis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation			
subjects affected / exposed	18 / 64 (28.13%)	12 / 63 (19.05%)	
occurrences (all)	18	12	
Rash maculo-papular			

subjects affected / exposed	18 / 64 (28.13%)	2 / 63 (3.17%)		
occurrences (all)	18	2		
Rash				
subjects affected / exposed	15 / 64 (23.44%)	4 / 63 (6.35%)		
occurrences (all)	15	4		
Pruritus				
subjects affected / exposed	10 / 64 (15.63%)	8 / 63 (12.70%)		
occurrences (all)	10	8		
Dry skin				
subjects affected / exposed	12 / 64 (18.75%)	5 / 63 (7.94%)		
occurrences (all)	12	5		
Erythema				
subjects affected / exposed	1 / 64 (1.56%)	3 / 63 (4.76%)		
occurrences (all)	1	3		
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	3 / 64 (4.69%)	1 / 63 (1.59%)		
occurrences (all)	3	1		
Dermatitis acneiform				
subjects affected / exposed	2 / 64 (3.13%)	1 / 63 (1.59%)		
occurrences (all)	2	1		
Hyperhidrosis				
subjects affected / exposed	1 / 64 (1.56%)	2 / 63 (3.17%)		
occurrences (all)	1	2		
Pigmentation disorder				
subjects affected / exposed	3 / 64 (4.69%)	0 / 63 (0.00%)		
occurrences (all)	3	0		
Melanoderma				
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)		
occurrences (all)	1	1		
Skin exfoliation				
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)		
occurrences (all)	2	0		
Blister				
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)		
occurrences (all)	0	1		

Dermatitis contact			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Erythema multiforme			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Hyperkeratosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Intertrigo			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Nail disorder			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Night sweats			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Pruritus generalised			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Rash erythematous			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Rash papular			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Proteinuria			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Acute kidney injury			

subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Cystitis noninfective			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Pollakiuria			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Renal aneurysm			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Renal failure			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Pulmonary embolism			
subjects affected / exposed	1 / 64 (1.56%)	2 / 63 (3.17%)	
occurrences (all)	1	2	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Hypopituitarism			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 64 (7.81%)	6 / 63 (9.52%)	
occurrences (all)	5	6	
Arthralgia			
subjects affected / exposed	4 / 64 (6.25%)	2 / 63 (3.17%)	
occurrences (all)	4	2	
Muscle spasms			
subjects affected / exposed	4 / 64 (6.25%)	1 / 63 (1.59%)	
occurrences (all)	4	1	
Myalgia			

subjects affected / exposed	2 / 64 (3.13%)	3 / 63 (4.76%)	
occurrences (all)	2	3	
Pain in extremity			
subjects affected / exposed	2 / 64 (3.13%)	3 / 63 (4.76%)	
occurrences (all)	2	3	
Bone pain			
subjects affected / exposed	1 / 64 (1.56%)	2 / 63 (3.17%)	
occurrences (all)	1	2	
Musculoskeletal pain			
subjects affected / exposed	2 / 64 (3.13%)	1 / 63 (1.59%)	
occurrences (all)	2	1	
Neck pain			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Flank pain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Polymyalgia rheumatica			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 64 (1.56%)	5 / 63 (7.94%)	
occurrences (all)	1	5	
Urinary tract infection			
subjects affected / exposed	3 / 64 (4.69%)	1 / 63 (1.59%)	
occurrences (all)	3	1	
Conjunctivitis			
subjects affected / exposed	2 / 64 (3.13%)	1 / 63 (1.59%)	
occurrences (all)	2	1	

Lung infection			
subjects affected / exposed	3 / 64 (4.69%)	0 / 63 (0.00%)	
occurrences (all)	3	0	
Nasopharyngitis			
subjects affected / exposed	1 / 64 (1.56%)	2 / 63 (3.17%)	
occurrences (all)	1	2	
Influenza			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Oral candidiasis			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Otitis externa			
subjects affected / exposed	0 / 64 (0.00%)	2 / 63 (3.17%)	
occurrences (all)	0	2	
Pneumonia			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	
occurrences (all)	1	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Bronchitis haemophilus			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Erysipelas			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis viral			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	

Gingivitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Hordeolum			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Oral infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Pharyngitis bacterial			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Pyelonephritis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Sputum purulent			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Urethritis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	29 / 64 (45.31%)	27 / 63 (42.86%)	
occurrences (all)	29	27	
Hyperglycaemia			
subjects affected / exposed	4 / 64 (6.25%)	1 / 63 (1.59%)	
occurrences (all)	4	1	
Hyperkalaemia			
subjects affected / exposed	2 / 64 (3.13%)	3 / 63 (4.76%)	
occurrences (all)	2	3	
Hyponatraemia			

subjects affected / exposed	3 / 64 (4.69%)	2 / 63 (3.17%)	
occurrences (all)	3	2	
Hypoalbuminaemia			
subjects affected / exposed	3 / 64 (4.69%)	1 / 63 (1.59%)	
occurrences (all)	3	1	
Hypophosphataemia			
subjects affected / exposed	3 / 64 (4.69%)	1 / 63 (1.59%)	
occurrences (all)	3	1	
Dehydration			
subjects affected / exposed	1 / 64 (1.56%)	2 / 63 (3.17%)	
occurrences (all)	1	2	
Hypercalcaemia			
subjects affected / exposed	0 / 64 (0.00%)	3 / 63 (4.76%)	
occurrences (all)	0	3	
Hypocalcaemia			
subjects affected / exposed	2 / 64 (3.13%)	1 / 63 (1.59%)	
occurrences (all)	2	1	
Hypokalaemia			
subjects affected / exposed	1 / 64 (1.56%)	2 / 63 (3.17%)	
occurrences (all)	1	2	
Diabetes mellitus			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Folate deficiency			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Hypomagnesaemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Malnutrition			
subjects affected / exposed	0 / 64 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2016	Addition of the following exclusion criterion: Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose/galactose malabsorption.
08 September 2017	Updated Appendix D - Supplemental Requirements for Japan Only

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported