

Clinical trial results:

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis

EudraCT number	2014-000770-19		
Trial protocol	CZ SK HU DE ES BG PL RO		
Global end of trial date	04 October 2018		
Result version number v2 (current)			
This version publication date	15 January 2020		
First version publication date	31 October 2019		
Version creation reason			
Sponsor protocol code	D5740C00001		
ISRCTN number	-		
ClinicalTrials.gov id (NCT number)	NCT02174627		
WHO universal trial number (UTN)	-		
Notes:			
Sponsor organisation name	AstraZeneca		
Sponsor organisation address	101 Orchard Ridge Drive, Gaithersburg, Maryland, United States, 20878		
Public contact	Global Clinical Lead, AstraZeneca, +1 302 885 1180,		
Scientific contact	ClinicalTrialTransparency@astrazeneca.com Global Clinical Lead, AstraZeneca, +1 302 885 1180,		
Scientific contact	ClinicalTrialTransparency@astrazeneca.com		
Notes:			
-			
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		
1701/2000 apply to this that:	<u> </u>		

Analysis stage	Final
Date of interim/final analysis	04 October 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 October 2018
Was the trial ended prematurely?	No

Main objective of the trial:

To evaluate the efficacy and safety of roxadustat compared with placebo for the treatment of anemia in chronic kidney disease (CKD) participants not on dialysis.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Sample.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	26 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Country: Number of subjects enrolled	Argentina: 74	
Country: Number of subjects enrolled	Brazil: 85	
Country: Number of subjects enrolled	Bulgaria: 78	
Country: Number of subjects enrolled	Canada: 50	
Country: Number of subjects enrolled	Colombia: 4	
Country: Number of subjects enrolled	Czech Republic: 20	
Country: Number of subjects enrolled	Germany: 5	
Country: Number of subjects enrolled	Hungary: 50	
Country: Number of subjects enrolled	India: 205	
Country: Number of subjects enrolled	Korea, Republic of: 245	
Country: Number of subjects enrolled	Malaysia: 15	
Country: Number of subjects enrolled	Mexico: 101	
Country: Number of subjects enrolled	Peru: 147	
Country: Number of subjects enrolled	Philippines: 97	
Country: Number of subjects enrolled	Poland: 38	
Country: Number of subjects enrolled	Romania: 3	
Country: Number of subjects enrolled	Russian Federation: 102	
Country: Number of subjects enrolled	Slovakia: 9	
Country: Number of subjects enrolled	Spain: 15	

Country: Number of subjects enrolled	Taiwan: 129
Country: Number of subjects enrolled	Thailand: 89
Country: Number of subjects enrolled	Turkey: 32
Country: Number of subjects enrolled	Ukraine: 222
Country: Number of subjects enrolled	United States: 683
Country: Number of subjects enrolled	Vietnam: 263
Worldwide total number of subjects	2761
EEA total number of subjects	218

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)	1526
From 65 to 84 years	1137
85 years and over	98

Recruitment details:

This study was conducted at 385 centers in 25 countries worldwide across the United States (US), Canada, Latin America, Asia and Europe between 26 June 2014 and 04 October 2018. Participants with CKD who were not on dialysis were recruited in this study.

Screening details:

Study had a screening period (up to 6 weeks), treatment period (up to 4 years) and follow-up period (4 weeks after treatment period for those who completed treatment). 2781 participants were randomized, of which 2761 were included in the analysis and 20 were excluded. Only participants included in the analysis are presented in the participant flow.

Period 1 title	Overall Study (overall period)	
Is this the baseline period?	Yes	
Allocation method	Randomised - controlled	
Blinding used	Double blind	
Roles blinded Subject, Investigator, Monitor, Carer, Assessor		

Are arms mutually exclusive?	Yes
	Roxadustat

Arm description:

Participants received roxadustat tablets orally times a week (TIW). The initial dose was 70 milligrams (mg) TIW and was titrated to achieve and maintain haemoglobin (Hb) 11 ± 1 grams per deciliter (g/dL). Treatment started on Day 1 and treatment duration was variable for individual participants (estimated up to 4 years). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks until Week 52, every 8 weeks thereafter using a dose adjustment algorithm; all dose adjustments were based on Hb values.

Arm type	Experimental
Investigational medicinal product name	Roxadustat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The initial dose was 70 mg orally TIW. Dosing continued TIW throughout the treatment period (up to 4 years) unless downward dose adjustment required a change to twice or once weekly.

	Placebo
--	---------

Arm description:

Participants received treatment with placebo tablets orally TIW. Dosing instructions were matched to instructions provided for roxadustat (ie, initial dose matched 70 mg TIW). Treatment started on Day 1 and treatment duration was variable for individual participants (estimated up to 4 years). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks until Week 52, every 8 weeks thereafter using a dose adjustment algorithm; all dose adjustments were based on Hb values.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets matched to size and strength of roxadustat tablets, orally TIW. Dosing continued TIW

throughout the treatment period (up to 4 years) unless downward dose adjustment required a change to twice or once weekly.

	Roxadustat	Placebo
Started	1384	1377
Received treatment	1384	1376
Discontinued treatment	499 [1]	801 [2]
Completed	1300	1247
Not completed	84	130
Incorrect enrolment before randomization	-	1
Consent withdrawn by subject	84	128
Missing	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left. Either resolve this issue or provide a justification.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left. Either resolve this issue or provide a justification.

Reporting group title	Roxadustat

Reporting group description:

Participants received roxadustat tablets orally times a week (TIW). The initial dose was 70 milligrams (mg) TIW and was titrated to achieve and maintain haemoglobin (Hb) 11 ± 1 grams per deciliter (g/dL). Treatment started on Day 1 and treatment duration was variable for individual participants (estimated up to 4 years). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks until Week 52, every 8 weeks thereafter using a dose adjustment algorithm; all dose adjustments were based on Hb values.

Reporting group title	Placebo

Reporting group description:

Participants received treatment with placebo tablets orally TIW. Dosing instructions were matched to instructions provided for roxadustat (ie, initial dose matched 70 mg TIW). Treatment started on Day 1 and treatment duration was variable for individual participants (estimated up to 4 years). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks until Week 52, every 8 weeks thereafter using a dose adjustment algorithm; all dose adjustments were based on Hb values.

	Roxadustat	Placebo	Total
Number of subjects	1384	1377	2761
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0

Infants and toddlers (28 days-23

Units: Subjects			
Hispanic or Latino	344	357	701
Not Hispanic or Latino	1040	1020	2060
Unknown or Not Reported	0	0	0

Reporting group title Roxado	ustat

Reporting group description:

Participants received roxadustat tablets orally times a week (TIW). The initial dose was 70 milligrams (mg) TIW and was titrated to achieve and maintain haemoglobin (Hb) 11 ± 1 grams per deciliter (g/dL). Treatment started on Day 1 and treatment duration was variable for individual participants (estimated up to 4 years). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks until Week 52, every 8 weeks thereafter using a dose adjustment algorithm; all dose adjustments were based on Hb values.

|--|

Reporting group description:

Participants received treatment with placebo tablets orally TIW. Dosing instructions were matched to instructions provided for roxadustat (ie, initial dose matched 70 mg TIW). Treatment started on Day 1 and treatment duration was variable for individual participants (estimated up to 4 years). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks until Week 52, every 8 weeks thereafter using a dose adjustment algorithm; all dose adjustments were based on Hb values.

End point title	US Food and Drug Administration (FDA) Analysis: Mean Change
	From Baseline in Hb Averaged Over Week 28 to Week 52

End point description:

Baseline Hb was defined as the mean of the last 3 central laboratory Hb values from the screening and randomization visits. Mean change in Hb from baseline to mean value from Week 28 to Week 52 was analyzed using a missing at random (MAR) based multiple imputation analysis of covariance (ANCOVA) model with baseline Hb, baseline estimated glomerular filtration rate (eGFR), cardiovascular (CV) history, geographic region and treatment group as fixed effect covariates. The adjusted least squares (LS) mean estimates of change from baseline to mean during Week 28 to Week 52 are presented. The Intention-To-Treat (ITT) analysis set included all participants who were randomized to investigational product (IP) irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis.

End point type	Primary
End point timeframe:	
Baseline (Day 1, Week 0) and Week 28 t	to Week 52.

	Roxadustat	Placebo	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	1334	1330	
Units: g/dL			
least squares mean (standard error)	1.75 (± 0.033)	0.40 (± 0.034)	

Treatment Difference in Hb

Statistical analysis description:

Difference between groups (roxadustat minus placebo) in LS mean changes; MAR-based multiple

imputation ANCOVA model.

Comparison groups	Roxadustat v Placebo
Number of subjects included in analysis	2664
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.27
upper limit	1.43
Variability estimate	Standard error of the mean
Dispersion value	0.041

Notes:

[1] - Superiority of roxadustat compared with placebo would be declared if the lower bound of the 2-sided 95% confidence interval (CI) of the difference between roxadustat and placebo exceeded 0 g/dL.

End point title European Union (EU) Health Authorities Analysis: Percentage Participants With Hb Response During the First 24 Weeks of Treatment

End point description:

Hb response was defined as: - Hb \geq 11.0 g/dL and Hb increase from baseline by \geq 1.0 g/dL for participants with baseline Hb > 8.0 g/dL; or - Hb increase from baseline by \geq 2.0 g/dL, for participants with baseline Hb \leq 8.0 g/dL at 2 consecutive visits (with available data) separated at least 5 days during the first 24 weeks of treatment without having received rescue therapy (red blood cell [RBC] transfusion, erythropoietin analogue, or intravenous [IV] iron) prior to Hb response. The percentage of participants with an Hb response during the first 24 weeks of treatment is presented. The Full Analysis Set (FAS) included all participants in the ITT analysis set who received at least 1 dose of IP and had baseline Hb and at least 1 post-dose Hb assessment. Participants from the FAS, with data available for analysis are presented.

End point type	Primary
End point timeframe:	
Baseline (Day 1, Week 0) up to Week 24.	

	Roxadustat	Placebo	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	1371	1357	
Units: Percentage of participants			
number (not applicable)	77.0	8.5	

· · · · · · · · · · · · · · · · · · ·	
Treatment difference in Hb responders	

Statistical analysis description:

Comparison of the percentage of responders for roxadustat versus placebo was analysed using a Cochran-Mantel-Haenszel test adjusting for baseline Hb, baseline eGFR, geographic region and CV history.

Comparison groups	Roxadustat v Placebo
Number of subjects included in analysis	2728
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative Risk
Point estimate	9.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.63
upper limit	10.89

·	Mean Change From Baseline in Hb Averaged Over Week 28 to Week 52 in Participants With Baseline High Sensitivity C-Reactive Protein (hsCRP) Greater Than the Upper Limit of
	Normal (ULN)

End point description:

Baseline hsCRP was quantified from stored biomarker samples obtained at randomization. Baseline Hb was defined as the mean of the last 3 central laboratory Hb values from the screening and randomization visits. Mean change in Hb from baseline to mean value during Week 28 to Week 52 was analyzed using a MAR based multiple imputation ANCOVA model with baseline Hb, baseline eGFR, CV history, geographic region and treatment group as fixed effect covariates. The adjusted LS mean estimates of change from baseline in participants with baseline hsCRP >ULN to mean during Week 28 to Week 52 are presented. The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis. Only participants who consented to the use of donated biomarker samples and had baseline hsCRP >ULN were included in the analysis.

End point type	Secondary
End point timeframe:	
Raceline (Day 1, Week 0) and Week 28 to Week 52	

	Roxadustat	Placebo	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	213	198	
Units: g/dL			
least squares mean (standard error)	1.75 (± 0.087)	0.62 (± 0.091)	

	Treatment Difference in Hb	
Statistical analysis description:		
Difference between groups (roxadustat minus placebo) in LS mean changes; MAR-based multiple imputation ANCOVA model.		
Comparison groups	Roxadustat v Placebo	
Number of subjects included in analysis	411	
Analysis specification	Pre-specified	
Analysis type	superiority ^[2]	
P-value	< 0.001	
Method	ANCOVA	
Parameter estimate	LS Mean Difference	
oint estimate 1.13		
Confidence interval		
level	95 %	
sides	2-sided	
lower limit	0.91	
upper limit	1.35	
Variability estimate	cy estimate Standard error of the mean	

Dispersion value

[2] - Superiority of roxadustat compared with placebo would be declared if the lower bound of the 2-sided 95% CI of the difference between roxadustat and placebo exceeded 0 g/dL.

0.112

Proportion of Total Time of Interpolated Hb Values Greater Than or Equal To 10 g/dL From Week 28 to Week 52
Than or Equal to 10 g/dL From Week 28 to Week 52

End point description:

Proportion of total time of interpolated Hb values ≥ 10 g/dL was calculated as the time the linearly interpolated curve between measurements ≥ 10 g/dL divided by the time between measurements from Week 28 to Week 52. Proportion of total time was analyzed using an ANCOVA model with baseline Hb and baseline eGFR as covariates, and CV history, geographic region and treatment group as fixed effects. The adjusted LS mean estimates of change from Week 28 to Week 52 are presented. The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis. Participants without any Hb measurements from Week 28 were not included in the analysis.

End point type	Secondary
End point timeframe:	
Week 28 up to Week 52.	

	Roxadustat	Placebo	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	1220	1145	
Units: proportion of total time			
least squares mean (standard error)	0.82 (± 0.011)	0.33 (± 0.011)	

	Treatment Difference in Total Time of Hb	
Statistical analysis description:		
Difference between groups (roxadustat r	minus placebo) in LS mean changes; ANCOVA model.	
Comparison groups	Roxadustat v Placebo	
Number of subjects included in analysis	2365	
Analysis specification	Pre-specified	
Analysis type	superiority ^[3]	
P-value	< 0.001	
Method	ANCOVA	
Parameter estimate	LS Mean Difference	
Point estimate	0.5	
Confidence interval		
level	95 %	
sides	2-sided	
lower limit	0.47	
upper limit	0.52	
Variability estimate	Standard error of the mean	
Dispersion value	0.013	

[3] - Superiority of roxadustat compared with placebo would be declared if the lower bound of the 2-sided 95% CI of the difference between roxadustat and placebo exceeded 0.

Proportion of Total Time of Interpolated Hb Values Within the
Interval of 10 to 12 g/dL From Week 28 to Week 52

End point description:

Proportion of total time of interpolated Hb values within the interval of 10 to 12 g/dL was calculated as the time the linearly interpolated curve between measurements were within 10 to 12 g/dL divided by the time between measurements from Week 28 to Week 52. Proportion of total time was analyzed using an ANCOVA model with baseline Hb and baseline eGFR as covariates, and CV history, geographic region and treatment group as fixed effects. The adjusted LS mean estimates of change from Week 28 to Week 52 are presented. The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis. Participants without any Hb measurements from Week 28 were not included in the analysis.

End point type	Secondary
End point timeframe:	
Week 28 up to Week 52.	

	Roxadustat	Placebo	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	1220	1145	
Units: proportion of total time			
least squares mean (standard error)	0.70 (± 0.010)	0.28 (± 0.010)	

Treatment Difference in Total Time of Hb				
Statistical analysis description:				
Difference between groups (roxadustat r	minus placebo) in LS mean changes; ANCOVA model.			
Comparison groups	Roxadustat v Placebo			
Number of subjects included in analysis	2365			
Analysis specification	Pre-specified			
Analysis type	superiority ^[4]			
P-value	< 0.001			
Method	ANCOVA			
Parameter estimate	LS Mean Difference			
Point estimate	0.42			
Confidence interval				
level	95 %			
sides	2-sided			
lower limit 0.4				
upper limit	0.45			
Variability estimate Standard error of the mean				
Dispersion value	0.013			

[4] - Superiority of roxadustat compared with placebo would be declared if the lower bound of the 2-sided 95% CI of the difference between roxadustat and placebo exceeded 0.

Mean Change in Low-Density Lipoprotein (LDL) Cholesterol From Baseline to Week 24
Tom Baseline to Week 21

End point description:

Baseline LDL was defined as the last result obtained prior to randomization. Mean changes in LDL cholesterol from baseline to Week 24 was analyzed using an ANCOVA model with baseline LDL, baseline Hb and baseline eGFR as covariates, and CV history, geographic region and treatment group as fixed effects. The adjusted LS mean estimates of change from baseline to Week 24 are presented. The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis.

End point type	Secondary
End point timeframe:	
Baseline (Day 1, Week 0) and Week 24	

	Roxadustat	Placebo	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	1147	1133	
Units: millimole per liter			
least squares mean (standard error)	-0.38 (± 0.028)	-0.02 (± 0.027)	

Treatment Difference in LDL Cholesterol
Treatment Difference in LDL Cholesterol

Statistical analysis description:			
Difference between groups (roxadustat i	minus placebo) in LS mean changes; ANCOVA model.		
Comparison groups	Roxadustat v Placebo		
Number of subjects included in analysis	2280		
Analysis specification	Pre-specified		
Analysis type	superiority ^[5]		
P-value	< 0.001		
Method	ANCOVA		
Parameter estimate	LS Mean Difference		
Point estimate	-0.36		
Confidence interval			
level	95 %		
sides	2-sided		
lower limit	-0.42		
upper limit	-0.29		
Variability estimate	Standard error of the mean		
Dispersion value	0.033		

[5] - Superiority of roxadustat compared with placebo would be declared if the lower bound of the 2-sided 95% CI of the difference between roxadustat and placebo exceeded 0.

End point title	Time-To-First Instance of Receiving IV Iron, RBC Transfusion or
	Erythropoietin Analogue as Rescue Therapy

End point description:

Time-to-first rescue therapy (IV iron, RBC transfusion or erythropoietin analogue) was calculated as (date of first rescue therapy, or date of censoring if no rescue therapy was taken) minus (date of first dose of IP) +1. Event rate was calculated as (number of participants with event) divided by (the total number of days at risk for event across all participants in given group divided by 365.25) multiplied by 100. The event rate is presented for participants with events. The on-treatment plus 28 days (OT+28) analysis set included all participants who received at least 1 dose of randomized IP, except for those excluded from analysis. Participants were censored 28 days after last intake of IP.

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

End point timeframe:

Baseline (Day1, Week 0) up to End of Study (EOS) visit (4 weeks after the treatment period) (or up to date of first rescue therapy), with treatment duration up to 4 years.

	Roxadustat	Placebo	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	1384	1376	
Units: Events per 100 participant years			
number (not applicable)	11.90	39.76	

 Treatment Difference in Rescue Therapy

Statistical analysis description:

Treatments were compared using a Cox proportional hazards model, with baseline Hb and baseline eGFR

as continuous variables used as covariates, and treatment group, CV history and geographic region as fixed effects. The Efron method was used for ties and p-values were calculated using the Wald test.

Comparison groups	Roxadustat v Placebo		
Number of subjects included in analysis	2760		
Analysis specification	Pre-specified		
Analysis type	superiority ^[6]		
P-value	< 0.001		
Method	Regression, Cox		
Parameter estimate	Hazard ratio (HR)		
Point estimate	0.26		
Confidence interval			
level	95 %		
sides	2-sided		
lower limit	0.23		
upper limit	0.31		

Notes:

[6] - Superiority of roxadustat compared with placebo would be declared if the upper limit of the 2-sided 95% CI for the HR was \leq 1.0.

End point title	Time-To-First Instance of Receiving a RBC Transfusion As
	Rescue Therapy

End point description:

Time-to-first RBC rescue therapy was calculated as (date of first RBC rescue therapy, or date of censoring if no rescue therapy was taken) minus (date of first dose of IP) +1. Event rate was calculated as (number of participants with event) divided by (the total number of days at risk for event across all participants in given group divided by 365.25) multiplied by 100. The event rate is presented for participants with events. The OT+28 analysis set included all participants who received at least 1 dose of randomized IP, except for those excluded from analysis. Participants were censored 28 days after last intake of IP.

End point type	Secondary

End point timeframe:

Baseline (Day1, Week 0) up to EOS visit (4 weeks after the treatment period) (or up to date of first RBC rescue therapy), with treatment duration up to 4 years.

	Roxadustat	Placebo	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	1384	1376	
Units: Events per 100 participant years			
number (not applicable)	7.98	19.61	

Treatment Difference in RBC Transfusion

Statistical analysis description:

Treatments were compared using a Cox proportional hazards model, with baseline Hb and baseline eGFR as continuous variables used as covariates, and treatment group, CV history and geographic region as fixed effects. The Efron method was used for ties and p-values were calculated using the Wald test.

Comparison groups	Roxadustat v Placebo
-------------------	----------------------

Number of subjects included in analysis	2760	
Analysis specification	Pre-specified	
Analysis type	superiority ^[7]	
P-value	< 0.001	
Method	Regression, Cox	
Parameter estimate	Hazard ratio (HR)	
Point estimate	0.37	
Confidence interval		
level	95 %	
sides	2-sided	
lower limit	0.3	
upper limit	0.44	

[7] - Superiority of roxadustat compared with placebo would be declared if the upper limit of the 2-sided 95% CI for the HR was ≤ 1.0 .

End point title	Mean Change From Baseline in Short Form 36 (SF-36) Vitality
	Sub-Score From Week 12 to Week 28

End point description:

SF-36 is a Quality of Life (QoL) scale comprising 8 domains of health status: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health. Each domain score is on a scale from 0-100 (worst health possible to best health possible); higher scores indicate better health status. Mean change in SF-36 Vitality sub-score from baseline to mean from Week 12 to Week 28 was analyzed using a mixed model for repeated measures (MMRM) with terms for baseline score, treatment group, baseline Hb, baseline eGFR, CV history, geographic region, visit and treatment-by-visit interaction as fixed effects and participant as random effect. The adjusted LS mean estimates of change from baseline to mean score from Week 12 to Week 28 are presented. The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis.

End point type	Secondary
End point timeframe:	
Baseline (Day 1, Week 0) and Week 12 to Week 28.	

	Roxadustat	Placebo	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	1279	1235	
Units: scores on a scale			
least squares mean (standard error)	1.59 (± 0.231)	1.15 (± 0.233)	

	Treatment Difference in SF-36 Vitality		
Statistical analysis description:			
Difference between groups (roxadustat minus placebo) in LS mean changes; MMRM analysis.			
Comparison groups	parison groups Roxadustat v Placebo		

Number of subjects included in analysis	2514
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.12
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.99
Variability estimate	Standard error of the mean
Dispersion value	0.283

[8] - Superiority of roxadustat compared with placebo would be declared if the lower bound of the 2-sided 95% CI of the difference between roxadustat and placebo exceeded 0.

End point title	Annual Rate of eGFR Change From Baseline Prior to the
	Initiation of Dialysis or Kidney Transplant

Number of subjects included in analysis	2640
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.046 ^[9]
Method	Random Effects Analysis
Parameter estimate	Rate of Change Difference
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.01
Variability estimate	Standard error of the mean
Dispersion value	0.254

[9] - Nominal p-value (as prior sequential outcome measure p-value did not meet < 0.05.

End point title	Mean Change From Baseline in SF-36 Physical Functioning Sub-
	Score From Week 12 to Week 28

End point description:

SF-36 is a QoL scale comprising 8 domains of health status: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health. Each domain score is on a scale from 0-100 (worst health possible to best health possible); higher scores indicate better health status. Mean change in SF-36 Physical Functioning sub-score from baseline to mean from Week 12 to Week 28 was analyzed using a MMRM with terms for baseline score, treatment group, baseline Hb, baseline eGFR, CV history, geographic region, visit and treatment-by-visit interaction as fixed effects and participant as random effect. The adjusted LS mean estimates of change from baseline to mean score from Week 12 to Week 28 are presented. The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis.

End point type	Secondary
End point timeframe:	
Baseline (Day 1, Week 0) and Week 12 to Week 28.	

	Roxadustat	Placebo	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	1279	1234	
Units: scores on a scale			
least squares mean (standard error)	0.14 (± 0.222)	-0.39 (± 0.224)	

	Treatment Difference in SF-36 Physical Functioning
Statistical analysis description:	
Difference between groups (roxadustat minus placebo) in LS mean changes; MMRM analysis.	
Comparison groups	Roxadustat v Placebo

Number of subjects included in analysis	2513	
Analysis specification	Pre-specified	
Analysis type	superiority ^[10]	
P-value	= 0.051 [11]	
Method	Mixed models analysis	
Parameter estimate	LS Mean Difference	
Point estimate	0.52	
Confidence interval		
level	95 %	
sides	2-sided	
lower limit	0	
upper limit	1.05	
Variability estimate	Standard error of the mean	
Dispersion value	0.269	

^[10] - Superiority of roxadustat compared with placebo would be declared if the lower bound of the 2-sided 95% CI of the difference between roxadustat and placebo exceeded 0.

^{[11] -} Nominal p-value (as prior sequential outcome measure p-value did not meet < 0.05.

Timeframe for reporting adverse events:

From date of randomization up to EOS visit (4 weeks after the treatment period), with treatment duration up to 4 years.

Adverse event reporting additional description:

The ITT analysis set included all participants who were randomized to IP irrespective of their protocol adherence and continued participation in the study, except for those excluded from analysis.

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

Dictionary name	MedDRA
Dictionary version	20.0

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Participants received placebo tablets orally TIW. Dosing instructions were matched to instructions provided for roxadustat (ie, initial dose matched to 70 mg TIW). Treatment started on Day 1 and treatment duration was variable for individual participants (estimated up to 4 years). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks until Week 52, every 8 weeks thereafter using a dose adjustment algorithm; all dose adjustments were based on Hb values.

Reporting group title	Roxadustat
-----------------------	------------

Reporting group description:

Participants received roxadustat tablets orally TIW. The initial dose was 70 mg TIW and was titrated to achieve and maintain Hb 11 ± 1 g/dL. Treatment started on Day 1 and treatment duration was variable for individual participants (estimated up to 4 years). Dose adjustments were permitted starting at Week 4 and at intervals of every 4 weeks until Week 52, every 8 weeks thereafter using a dose adjustment algorithm; all dose adjustments were based on Hb values.

	Placebo	Roxadustat	
Total subjects affected by serious adverse events			
subjects affected / exposed	749 / 1377 (54.39%)	795 / 1384 (57.44%)	
number of deaths (all causes)	245	284	
number of deaths resulting from adverse events	213	262	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Die dalen een een		1
Bladder cancer subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 13 / (0.00%)	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Breast cancer female		ا ا
subjects affected / exposed	2 / 1377 (0.15%)	2 / 1384 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Breast cancer metastatic		
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Breast neoplasm		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cervix carcinoma		
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Colon adenoma		
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Colon cancer		I
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0/0
deaths causally related to treatment / all	0 / 0	0 / 0
Colon neoplasm	· · · · · · · · · · · · · · · · · · ·	
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Colorectal cancer metastatic	' ' ' ' ' ' ' ' ' ' ' ' ' ' ' ' ' ' '	,
colorectal carreer metastatic	l l	

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottic carcinoma			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Gastric adenoma			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0/0	0 / 0	
Gastric neoplasm			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Gastric cancer			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal tract adenoma			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Hepatic cancer	1		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma	[

subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leiomyoma			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip squamous cell carcinoma			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung carcinoma cell type unspecified stage IV]		
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 1377 (0.07%)	5 / 1384 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0/0	0 / 3	
Malignant melanoma			
•	•	•	•

subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelofibrosis			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm of appendix			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine tumour of the lung			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ovarian cancer			[
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
-	•	-	•

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	4 / 1377 (0.29%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate cancer			
subjects affected / exposed	0 / 1377 (0.00%)	5 / 1384 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the vagina			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
	•		•

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0/0	0/1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0/1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm		i I	
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Aortic rupture			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm rupture			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0/0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aortic stenosis		i i	
subjects affected / exposed	4 / 1377 (0.29%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arteriosclerosis	i -, - 	· - · - 	
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to	0 / 0	1/2	
treatment / all deaths causally related to	0 / 0	0 / 1	
treatment / all	0/0	0 / 1	
Arteriovenous fistula			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	4 / 1377 (0.29%)	15 / 1384 (1.08%)	
occurrences causally related to treatment / all	0 / 4	1 / 15	
deaths causally related to treatment / all	0 / 0	0 / 1	
Distributive shock			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dry gangrene			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism venous			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	4 / 1377 (0.29%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension	İ		
I The state of the	1	ı	

	subjects affected / exposed	16 / 1377 (1.16%)	17 / 1384 (1.23%)	
	occurrences causally related to treatment / all	1 / 16	0 / 19	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Hypertensive crisis			
	subjects affected / exposed	27 / 1377 (1.96%)	33 / 1384 (2.38%)	
	occurrences causally related to treatment / all	0 / 31	0 / 51	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Hypertensive emergency			
	subjects affected / exposed	21 / 1377 (1.53%)	21 / 1384 (1.52%)	
	occurrences causally related to treatment / all	0 / 23	0 / 24	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Hypotension			
	subjects affected / exposed	8 / 1377 (0.58%)	6 / 1384 (0.43%)	
	occurrences causally related to treatment / all	0 / 8	1 / 6	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Hypovolaemic shock			
	subjects affected / exposed	6 / 1377 (0.44%)	0 / 1384 (0.00%)	
	occurrences causally related to treatment / all	0 / 6	0 / 0	
	deaths causally related to treatment / all	0/3	0 / 0	
	Iliac artery perforation			
	subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Jugular vein thrombosis			
	subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Lymphocele			
	subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Malignant hypertension			
•			· ·	

	subjects affected / exposed	1 / 1377 (0.07%)	2 / 1384 (0.14%)	
	occurrences causally related to treatment / all	0 / 1	0 / 2	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Orthostatic hypotension			
	subjects affected / exposed	1 / 1377 (0.07%)	2 / 1384 (0.14%)	
	occurrences causally related to treatment / all	0 / 1	0 / 2	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Paget-Schroetter syndrome			
	subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Pallor			
	subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Peripheral arterial occlusive disease			
	subjects affected / exposed	2 / 1377 (0.15%)	5 / 1384 (0.36%)	
	occurrences causally related to treatment / all	0 / 2	0 / 5	
	deaths causally related to treatment / all	0 / 0	0 / 1	
	Peripheral artery occlusion			
	subjects affected / exposed	3 / 1377 (0.22%)	1 / 1384 (0.07%)	
	occurrences causally related to treatment / all	0 / 4	0 / 2	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Peripheral artery stenosis			
	subjects affected / exposed	1 / 1377 (0.07%)	2 / 1384 (0.14%)	
	occurrences causally related to treatment / all	0 / 2	0 / 2	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Peripheral artery thrombosis			
	subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Peripheral ischaemia			
•		•	-	

subjects affected / exposed	2 / 1377 (0.15%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 1377 (0.07%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral venous disease			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post thrombotic syndrome			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose ulceration			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular occlusion			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visceral congestion			[
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
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			
Asthenia			
subjects affected / exposed	9 / 1377 (0.65%)	13 / 1384 (0.94%)	
occurrences causally related to treatment / all	0 / 9	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	

Catheter site haemorrhage		
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0/0	0 / 0
Catheter site pain		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Chest pain		
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Death		
subjects affected / exposed	28 / 1377 (2.03%)	43 / 1384 (3.11%)
occurrences causally related to treatment / all	1 / 28	0 / 43
deaths causally related to treatment / all	1 / 28	0 / 43
Device related thrombosis		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Fatigue		
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Generalised oedema		
subjects affected / exposed	7 / 1377 (0.51%)	17 / 1384 (1.23%)
occurrences causally related to treatment / all	0 / 11	0 / 25
deaths causally related to treatment / all	0 / 0	0 / 0
Hernia pain	· 	·
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0/1	0/0
deaths causally related to treatment / all	0 / 0	0 / 0
Implant site extravasation	· 	·
-	1	

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site necrosis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 1377 (0.07%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	2 / 1377 (0.15%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	7 / 1377 (0.51%)	7 / 1384 (0.51%)	
occurrences causally related to treatment / all	0 / 7	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema due to renal disease			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	5 / 1377 (0.36%)	7 / 1384 (0.51%)	
occurrences causally related to treatment / all	0 / 10	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pacemaker generated arrhythmia			
	•	•	,

subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0/0	0 / 0	
Peripheral swelling			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 1377 (0.36%)	6 / 1384 (0.43%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stenosis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0/0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden death			
subjects affected / exposed	11 / 1377 (0.80%)	5 / 1384 (0.36%)	
occurrences causally related to treatment / all	0 / 11	0 / 5	
deaths causally related to treatment / all	0 / 11	0 / 5	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device allergy			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney transplant rejection			
subjects affected / exposed	1 / 1377 (0.07%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal transplant failure			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant rejection			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 1377 (0.07%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysfunctional uterine bleeding			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0/0	0 / 0	
Ovarian cyst			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst ruptured			

	_		
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst torsion			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian mass			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic prolapse			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic fibrosis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic mass			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatomegaly			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			

subjects affected / exposed	22 / 1377 (1.60%)	13 / 1384 (0.94%)	
occurrences causally related to treatment / all	0 / 25	0 / 13	
deaths causally related to treatment / all	0 / 2	0 / 1	
Acute respiratory distress syndrome	İ	i İ	
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0/0	
Acute respiratory failure			
subjects affected / exposed	20 / 1377 (1.45%)	12 / 1384 (0.87%)	
occurrences causally related to treatment / all	0 / 20	0 / 13	
deaths causally related to treatment / all	0 / 5	0 / 5	
Aspiration			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	3 / 1377 (0.22%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial fistula			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			

subjects affected / exposed	8 / 1377 (0.58%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	12 / 1377 (0.87%)	11 / 1384 (0.79%)	
occurrences causally related to treatment / all	0 / 14	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 2	
Dyspnoea exertional			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 1377 (0.07%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Laryngeal stenosis]	
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder	İ		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0/0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain	İ		
	I .	ı	!

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	16 / 1377 (1.16%)	15 / 1384 (1.08%)	
occurrences causally related to treatment / all	0 / 20	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural thickening			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 1377 (0.07%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 1377 (0.15%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonitis			
subjects affected / exposed	2 / 1377 (0.15%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 1377 (0.07%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary alveolar haemorrhage]	
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion]	
· -	•		i

subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	3 / 1377 (0.22%)	5 / 1384 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary hypertension			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	16 / 1377 (1.16%)	17 / 1384 (1.23%)	
occurrences causally related to treatment / all	0 / 16	0 / 17	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory alkalosis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			1
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure		[1
	•	•	1

subjects affected / exposed	9 / 1377 (0.65%)	5 / 1384 (0.36%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 6	0 / 2	
Tracheal stenosis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract inflammation			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar disorder			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Confusional state			j
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0/1	0/0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium		- 	
1	ı	Ī	1

subjects affected / exposed	1 / 1377 (0.07%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranoia			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular cognitive impairment			1
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure			
1	•	•	•

subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	2 / 1377 (0.15%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0/0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 1377 (0.07%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0/0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0/0	0 / 0	
Cholangitis acute			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0/0	0 / 0	
Cholecystitis]]	
subjects affected / exposed	1 / 1377 (0.07%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute	j		
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic	j	·	
•	- '		•

subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 1377 (0.07%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic hepatic failure			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cirrhosis alcoholic			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhagic hepatic cyst			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hepatitis acute			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis alcoholic			

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose abnormal			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure decreased			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood urine present			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulation factor decreased			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0/0	0/1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
1 ' '	I .	I	1

subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0/0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic stenosis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 1377 (0.07%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula occlusion			
subjects affected / exposed	4 / 1377 (0.29%)	7 / 1384 (0.51%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0/0	0 / 0	
Arteriovenous fistula site complication	<u> </u>	 	
subjects affected / exposed	4 / 1377 (0.29%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula thrombosis			
subjects affected / exposed	9 / 1377 (0.65%)	18 / 1384 (1.30%)	
	, , ,		4
occurrences causally related to treatment / all	1/9	1 / 19	

Cervical vertebral fracture		
subjects affected / exposed	0 / 1377 (0.00%)	3 / 1384 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Chemical peritonitis subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0/0	0/1
deaths causally related to treatment / all	0 / 0	0 / 0
Chemical poisoning		
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0/0
deaths causally related to treatment / all	0 / 0	0 / 0
Chest injury		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Comminuted fracture		
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Complications of transplanted kidney		
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Compression fracture		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Concussion	İ	İ
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Dialysis disequilibrium syndrome		ĺ
•	•	·

		,	
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dialysis related complication			
subjects affected / exposed	0 / 1377 (0.00%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	3 / 1377 (0.22%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 1377 (0.15%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
subjects affected / exposed occurrences causally related to treatment / all	1 / 1377 (0.07%) 0 / 1	0 / 1384 (0.00%) 0 / 0	
occurrences causally related to			

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heat stroke			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	6 / 1377 (0.44%)	5 / 1384 (0.36%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Joint dislocation			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
•	•	•	•

subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip injury			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle injury			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital haemorrhage			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal dialysis complication			
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Post procedural complication	l i		ĺ
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural hypotension			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 1377 (0.07%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt malfunction			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0/0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt occlusion	İ		
I .	I	I	1

subjects affected / exposed	2 / 1377 (0.15%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin injury			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord injury cervical			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal fracture			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spleen contusion			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma obstruction			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site haemorrhage			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
•	•	1	•

subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subdural haematoma			
subjects affected / exposed	2 / 1377 (0.15%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant dysfunction			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic liver injury			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture		1	
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access malfunction	İ	İ	
1	1	I	ı

subjects affected / exposed			
	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site thrombosis			
subjects affected / exposed	2 / 1377 (0.15%)	6 / 1384 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0/0	0 / 0	
Vascular graft complication			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Vascular graft occlusion			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haematoma			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (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			
Congenital cystic kidney disease			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
•	1	0.40	
occurrences causally related to treatment / all	0 / 3	0 / 0	
occurrences causally related to	0/3	0/0	

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	5 / 1377 (0.36%)	8 / 1384 (0.58%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute left ventricular failure	l	İ	
subjects affected / exposed	4 / 1377 (0.29%)	5 / 1384 (0.36%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myocardial infarction	l i	İ	
subjects affected / exposed	27 / 1377 (1.96%)	26 / 1384 (1.88%)	
occurrences causally related to treatment / all	1 / 31	0 / 28	
deaths causally related to treatment / all	0 / 6	0 / 6	
Angina pectoris			
subjects affected / exposed	9 / 1377 (0.65%)	10 / 1384 (0.72%)	
occurrences causally related to treatment / all	0/9	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable	l i	į į	
subjects affected / exposed	10 / 1377 (0.73%)	10 / 1384 (0.72%)	
occurrences causally related to treatment / all	0 / 11	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia		j	
subjects affected / exposed	3 / 1377 (0.22%)	6 / 1384 (0.43%)	
occurrences causally related to treatment / all	0/3	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 3	
Aortic valve stenosis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
	0 / 0	0 / 1	
occurrences causally related to treatment / all	0,0	-	
occurrences causally related to treatment / all deaths causally related to treatment / all	0/0	0/0	

subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial fibrillation		
subjects affected / exposed	12 / 1377 (0.87%)	10 / 1384 (0.72%)
occurrences causally related to treatment / all	1 / 15	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial flutter		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Atrioventricular block		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Atrioventricular block complete		
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bradyarrhythmia		
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bundle branch block left		
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bradycardia		
subjects affected / exposed	3 / 1377 (0.22%)	2 / 1384 (0.14%)
occurrences causally related to treatment / all	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac arrest		
•	•	'

subjects affected / exposed	4 / 1377 (0.29%)	9 / 1384 (0.65%)	
occurrences causally related to treatment / all	0 / 4	0 / 9	
deaths causally related to treatment / all	0 / 3	0 / 6	
Cardiac asthma			
subjects affected / exposed	0 / 1377 (0.00%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	32 / 1377 (2.32%)	25 / 1384 (1.81%)	
occurrences causally related to treatment / all	0 / 35	0 / 31	
deaths causally related to treatment / all	0 / 5	0 / 6	
Cardiac failure acute			
subjects affected / exposed	14 / 1377 (1.02%)	8 / 1384 (0.58%)	
occurrences causally related to treatment / all	0 / 16	0 / 8	
deaths causally related to treatment / all	0 / 7	0 / 3	
Cardiac failure chronic			
subjects affected / exposed	5 / 1377 (0.36%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	31 / 1377 (2.25%)	33 / 1384 (2.38%)	
occurrences causally related to treatment / all	1 / 42	0 / 41	
deaths causally related to treatment / all	0 / 5	0 / 7	
Cardiac tamponade			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (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	4 / 1377 (0.29%)	6 / 1384 (0.43%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 3	0 / 5	
Cardiogenic shock			

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 3	
Cardiomegaly			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 1377 (0.07%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 1377 (0.07%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0/3	
Chronic left ventricular failure			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive cardiomyopathy			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	7 / 1377 (0.51%)	12 / 1384 (0.87%)	
occurrences causally related to treatment / all	0 / 7	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery insufficiency			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery stenosis			

subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart valve incompetence			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart valve stenosis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive cardiomyopathy			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Left ventricular failure			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular hypertrophy			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0/0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic cardiomyopathy			
· · · · ·	1	1	

subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve disease			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	13 / 1377 (0.94%)	14 / 1384 (1.01%)	
occurrences causally related to treatment / all	0 / 13	0 / 14	
deaths causally related to treatment / all	0 / 9	0 / 6	
Myocardial ischaemia			
subjects affected / exposed	8 / 1377 (0.58%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 4	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 1377 (0.00%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity		ĺ	
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0/0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinoatrial block	İ	· 	
C.HOGGIGI DIOCK	I	l	1

	_	_	_
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrest			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles]		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0/0	0/1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation		· 	
1	•	•	•

subjects affected / exposed	3 / 1377 (0.22%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autonomic nervous system imbalance			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain injury			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar infarction			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar stroke		ĺ	
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma	I	· 	

	_	_	_
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral haemorrhage			
subjects affected / exposed	3 / 1377 (0.22%)	9 / 1384 (0.65%)	
occurrences causally related to treatment / all	0 / 3	1 / 9	
deaths causally related to treatment / all	0 / 3	0 / 4	
Cerebral infarction			
subjects affected / exposed	8 / 1377 (0.58%)	13 / 1384 (0.94%)	
occurrences causally related to treatment / all	1 / 9	0 / 14	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	11 / 1377 (0.80%)	15 / 1384 (1.08%)	
occurrences causally related to treatment / all	0 / 11	0 / 15	
deaths causally related to treatment / all	0 / 2	0 / 2	
Cerebrovascular disorder			
subjects affected / exposed	0 / 1377 (0.00%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0/3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical cord compression			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Coma uraemic]		
•	•	•	•

subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Dementia			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Demyelination			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Diabetic hyperglycaemic coma			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic hyperosmolar coma			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidotic hyperglycaemic coma			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0/0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetic neuropathy	i		
1	1	ı	ı

subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Dizziness			
subjects affected / exposed	2 / 1377 (0.15%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0/0	0 / 0	
Encephalopathy	1		
subjects affected / exposed	0 / 1377 (0.00%)	5 / 1384 (0.36%)	
occurrences causally related to treatment / all	0/0	0 / 5	
deaths causally related to treatment / all	0/0	0 / 0	
Facial paralysis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0/0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0/0	0 / 0	
Facial spasm			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0/0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0/0	1 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Haemorrhagic stroke	I		
subjects affected / exposed	6 / 1377 (0.44%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0/3	0 / 2	
Haemorrhage intracranial			

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headache			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 1377 (0.07%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive encephalopathy			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intercostal neuralgia			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	3 / 1377 (0.22%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic stroke			
subjects affected / exposed	7 / 1377 (0.51%)	9 / 1384 (0.65%)	
occurrences causally related to treatment / all	0 / 7	1/9	
deaths causally related to treatment / all	0 / 2	0 / 0	
Lacunar infarction	İ	I	
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0/0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar stroke			
Luculiai Sti Okc	1	I	I

subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	3 / 1377 (0.22%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myoclonus			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurodegenerative disorder			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neuroleptic malignant syndrome			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neuropathy peripheral			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occipital neuralgia			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			l
1	1	1	1

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Partial seizures			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Post stroke seizure			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0/0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0/0	0 / 0	
Seizure			
subjects affected / exposed	2 / 1377 (0.15%)	6 / 1384 (0.43%)	
occurrences causally related to treatment / all	0/3	0 / 6	
deaths causally related to treatment / all	0 / 0	0/0	
Senile dementia			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0/0	
Somnolence			
-	-	=	•

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 1377 (0.22%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic infarction			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thalamus haemorrhage			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transient ischaemic attack			
subjects affected / exposed	5 / 1377 (0.36%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uraemic encephalopathy			
subjects affected / exposed	2 / 1377 (0.15%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
VIth nerve paralysis			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular encephalopathy			
subjects affected / exposed	1 / 1377 (0.07%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	1/1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency	İ		
1	1	ı	ı

subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo CNS origin			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular migraine			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (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	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Evans syndrome			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic uraemic syndrome			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0/0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia		· 	
I	1	I	I

subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histiocytosis haematophagic			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocoagulable state			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 1377 (0.07%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			-
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0/0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia		İ	
	1	1	ı

subjects affected / exposed	1 / 1377 (0 070/)	2 / 1204 (0 220/)	l l
	1 / 1377 (0.07%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 1377 (0.22%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			[
subjects affected / exposed	1 / 1377 (0.07%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular ataxia			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0/0	0 / 0	
Vestibular disorder			
subjects affected / exposed	1 / 1377 (0.07%)	5 / 1384 (0.36%)	
occurrences causally related to treatment / all	0/1	0/5	
deaths causally related to treatment / all	0/0	0 / 0	
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy	j		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0/0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative keratitis	j		j
	•		·

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0/0	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Visual acuity reduced			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0/0	0 / 1	
Abdominal discomfort			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Abdominal pain			
subjects affected / exposed	4 / 1377 (0.29%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0/0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
•	•	•	•

subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gastroparesis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gastropathy			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 1377 (0.36%)	9 / 1384 (0.65%)	
occurrences causally related to treatment / all	0 / 5	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dieulafoy's vascular malformation			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagio	:		

subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 1377 (0.07%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis haemorrhagic			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (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	2 / 1377 (0.15%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
i	1	1	1

subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis haemorrhagic			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive duodenitis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral hernia incarcerated			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 1377 (0.00%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0/0	0 / 0	
Gastric polyps			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	2 / 1377 (0.15%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0/2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
1	I .	ı	ı

subjects affected / exposed	3 / 1377 (0.22%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	15 / 1377 (1.09%)	18 / 1384 (1.30%)	
occurrences causally related to treatment / all	1 / 18	0 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastritis haemorrhagic			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenitis haemorrhagic			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0/0	
Gastrointestinal haemorrhage		ĺ	
subjects affected / exposed	15 / 1377 (1.09%)	20 / 1384 (1.45%)	
occurrences causally related to treatment / all	0 / 16	1 / 20	
deaths causally related to treatment / all	0 / 0	1 / 3	
Gastrointestinal inflammation	İ		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
Gastrooesophagear reflux disease	1	l l	

subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic ascites			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic erosive gastritis			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0/0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0/0	
Hiatus hernia			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation	İ		
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0/1	0/0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus	Ì		
1 11003	1	1	I

	subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Impaired gastric emptying			
	subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
	occurrences causally related to treatment / all	0 / 1	0 / 2	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Incarcerated umbilical hernia			
	subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Inguinal hernia			
	subjects affected / exposed	3 / 1377 (0.22%)	4 / 1384 (0.29%)	
	occurrences causally related to treatment / all	0 / 4	0 / 5	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Inguinal hernia strangulated			
	subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Intestinal haemorrhage			
	subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Intestinal obstruction			
	subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
	occurrences causally related to treatment / all	0 / 2	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Large intestine perforation			
	subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
İ	Lower gastrointestinal haemorrhage			
•		•	-	

5 / 1377 (0.36%)	1 / 1384 (0.07%)	
0 / 5	0 / 1	
0 / 0	0 / 0	
0 / 1377 (0.00%)	1 / 1384 (0.07%)	
0 / 0	0 / 1	
0 / 0	0 / 0	
1 / 1377 (0.07%)	0 / 1384 (0.00%)	
0 / 1	0 / 0	
0 / 0	0 / 0	
0 / 1377 (0.00%)	1 / 1384 (0.07%)	
0 / 0	0 / 1	
0 / 0	0 / 0	
2 / 1377 (0.15%)	1 / 1384 (0.07%)	
0 / 2	0 / 1	
0 / 0	0 / 0	
1 / 1377 (0.07%)	1 / 1384 (0.07%)	
0 / 1	0 / 2	
0 / 0	0 / 0	
0 / 1377 (0.00%)	1 / 1384 (0.07%)	
0 / 0	0 / 1	
0 / 0	0 / 0	
]	
0 / 1377 (0.00%)	2 / 1384 (0.14%)	
0 / 0	0 / 2	
0 / 0	0 / 0	
	0 / 5 0 / 0 0 / 1377 (0.00%) 0 / 0 0 / 0 1 / 1377 (0.07%) 0 / 1 0 / 0 0 / 0 0 / 0 2 / 1377 (0.00%) 0 / 0 1 / 1377 (0.07%) 0 / 2 0 / 0 1 / 1377 (0.00%) 0 / 0 0 / 0 0 / 1377 (0.00%) 0 / 0 0 / 0 0 / 0 0 / 0	0/5 0/1 0/0 0/0 0/1377 (0.00%) 1/1384 (0.07%) 0/0 0/1 0/0 0/0 1/1377 (0.07%) 0/1384 (0.00%) 0/1 0/0 0/0 0/0 0/1377 (0.00%) 1/1384 (0.07%) 0/2 0/1 0/0 0/0 1/1377 (0.07%) 1/1384 (0.07%) 0/1 0/2 0/0 0/0 1/1377 (0.00%) 1/1384 (0.07%) 0/0 0/1 0/0 0/0 0/1377 (0.00%) 1/1384 (0.07%) 0/0 0/1 0/0 0/1 0/0 0/0

			_
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic cyst			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 1377 (0.00%)	5 / 1384 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	4 / 1377 (0.29%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	3 / 1377 (0.22%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer haemorrhage			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer perforation			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal adhesions]		
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal cloudy effluent			
•			•

subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	4 / 1377 (0.29%)	11 / 1384 (0.79%)	
occurrences causally related to treatment / all	0 / 4	0 / 11	
deaths causally related to treatment / all	0 / 1	0 / 2	
Uraemic gastropathy]	
•	•	•	•

Subjects affected / exposed occurrences causally related to treatment / all deaths causally related to deaths causally related to deaths causally related to deaths causally related to deaths causally related to deaths causally related to	
treatment / all deaths causally related to treatment / all occurrences causally related to treatment / all o/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0	
treatment / all	
Subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all o/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0	
occurrences causally related to treatment / all deaths causally related to treatment / all occurrences causally related to occurrences causally related to occ	
treatment / all deaths causally related to deaths causally related to death	
Treatment / all	
Blister subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Decubitus ulcer subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Diabetic ulcer subjects affected / exposed occurrences causally related to 0 / 1 0 / 0 Diabetic ulcer subjects affected / exposed occurrences causally related to 0 / 1 0 / 1 0 / 0	
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Decubitus ulcer subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Diabetic foot subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Diabetic foot subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Diabetic ulcer subjects affected / exposed occurrences causally related to treatment / all Diabetic ulcer subjects affected / exposed occurrences causally related to 0 / 1 0 / 0	
occurrences causally related to treatment / all deaths causally related to treatment / all occurrences causally related to treatment / all occurrences causally related to treatment / all occurrences causally related to treatment / all deaths causally related to treatment / all occurrences causally related to treatment / all occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all occurrences causally related to treatment / all deaths causally related to treatment / all occurrences causally related to treatment / all occurrences causally related to treatment / all occurrences causally related to treatment / all occurrences causally related to treatment / all occurrences causally related to treatment / all occurrences causally related to	
treatment / all deaths causally related to treatment / all Decubitus ulcer subjects affected / exposed Occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Dermatitis atopic subjects affected / exposed Occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Diabetic foot subjects affected / exposed Occurrences causally related to treatment / all deaths causally related to treatment / all Diabetic foot subjects affected / exposed Occurrences causally related to treatment / all Diabetic ulcer subjects affected / exposed Occurrences causally related to treatment / all Diabetic ulcer subjects affected / exposed Occurrences causally related to Occurrences causally re	
treatment / all	
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Dermatitis atopic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Diabetic foot subjects affected / exposed O / 1377 (0.00%) O / 0 3 / 1384 (0.22%) O / 0 0 / 4 0 / 0 0 / 4 Diabetic foot subjects affected / exposed O / 0 O / 0 Diabetic foot subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Diabetic ulcer subjects affected / exposed occurrences causally related to of 0 O / 0	
occurrences causally related to treatment / all deaths causally related to treatment / all Dermatitis atopic subjects affected / exposed occurrences causally related to treatment / all Determatitis atopic subjects affected / exposed occurrences causally related to treatment / all Diabetic foot subjects affected / exposed occurrences causally related to treatment / all Diabetic foot subjects affected / exposed occurrences causally related to treatment / all Diabetic ulcer subjects affected / exposed occurrences causally related to treatment / all Diabetic ulcer subjects affected / exposed occurrences causally related to treatment / all Diabetic ulcer subjects affected / exposed occurrences causally related to occurrenc	
treatment / all deaths causally related to treatment / all Dermatitis atopic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Diabetic foot subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all oly 1 Oly 0 O	
treatment / all	
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Diabetic foot subjects affected / exposed occurrences causally related to treatment / all occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all objects affected / exposed occurrences causally related to treatment / all objects affected / exposed occurrences causally related to o / 1 Diabetic ulcer subjects affected / exposed occurrences causally related to occurrences causally related to occurrences causally related to occurrences causally related to occurrences causally related to occurrences causally related to	
occurrences causally related to treatment / all deaths causally related to treatment / all Diabetic foot subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Diabetic ulcer subjects affected / exposed occurrences causally related to treatment / all Diabetic ulcer subjects affected / exposed occurrences causally related to occurren	
treatment / all deaths causally related to treatment / all Diabetic foot subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Diabetic ulcer subjects affected / exposed occurrences causally related to 0 / 0 0 / 0 0 / 0 0 / 0 0 / 0 0 / 0 0 / 0 0 / 0 0 / 0 0 / 0	
treatment / all 0 / 0 0 / 0 Diabetic foot subjects affected / exposed 5 / 1377 (0.36%) 6 / 1384 (0.43%) 0 ccurrences causally related to treatment / all deaths causally related to treatment / all 0 / 1 0 / 0 Diabetic ulcer subjects affected / exposed 1 / 1377 (0.07%) 0 / 1384 (0.00%) 0 ccurrences causally related to 0 / 1 0 / 0	
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Diabetic ulcer subjects affected / exposed occurrences causally related to 1 / 1377 (0.07%) 0 / 1384 (0.00%) 0 / 1384 (0.00%) 0 / 0	
occurrences causally related to treatment / all deaths causally related to treatment / all	
treatment / all deaths causally related to treatment / all Diabetic ulcer subjects affected / exposed occurrences causally related to 1 / 1377 (0.07%) 0 / 1384 (0.00%) 0 / 0	
treatment / all 0 / 1 0 / 0 Diabetic ulcer subjects affected / exposed 1 / 1377 (0.07%) 0 / 1384 (0.00%) occurrences causally related to 0 / 1 0 / 0	
subjects affected / exposed $1/1377 (0.07\%)$ $0/1384 (0.00\%)$ occurrences causally related to $0/1$ $0/0$	
occurrences causally related to $0/1$ $0/0$	
deaths causally related to treatment / all 0 / 0 0 / 0	
Papule	
subjects affected / exposed 1 / 1377 (0.07%) 0 / 1384 (0.00%)	
occurrences causally related to treatment / all	
deaths causally related to treatment / all 0 / 0 0 / 0	
Necrobiosis lipoidica diabeticorum	

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Rash			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 1377 (0.07%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic epidermal necrolysis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	32 / 1377 (2.32%)	41 / 1384 (2.96%)	
occurrences causally related to treatment / all	0 / 33	0 / 48	
deaths causally related to treatment / all	0 / 1	0 / 1	
Anuria			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Azotaemia			
subjects affected / exposed	60 / 1377 (4.36%)	61 / 1384 (4.41%)	
occurrences causally related to treatment / all	0 / 79	0 / 73	
deaths causally related to treatment / all	0 / 10	0 / 14	
Chronic kidney disease			

subjects affected / exposed	7 / 1377 (0.51%)	8 / 1384 (0.58%)
occurrences causally related to treatment / all	0 / 7	0 / 8
deaths causally related to treatment / all	0 / 5	0 / 7
Cystitis haemorrhagic	1	
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0/0	0 / 0
Diabetic nephropathy		
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
End stage renal disease		
subjects affected / exposed	201 / 1377	199 / 1384
occurrences causally related to treatment / all	(14.60%) 0 / 211	(14.38%) 1 / 211
deaths causally related to treatment / all	0 / 11	0 / 11
Glomerulonephritis	1	
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0/0	0/0
Glomerulonephritis chronic		

subjects affected / exposed

subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedematous kidney			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyuria			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelocaliectasis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal atrophy			

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst haemorrhage subjects affected / exposed	3 / 1377 (0.22%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 4	0/1	
deaths causally related to treatment / all	0 / 0	0/0	
Renal failure			
subjects affected / exposed	1 / 1377 (0.07%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 1377 (0.07%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal pain			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal papillary necrosis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal pelvis fistula			

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary fistula			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 1377 (0.07%)	5 / 1384 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract inflammation			
	•	•	•

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Goitre			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism secondary			
subjects affected / exposed	0 / 1377 (0.00%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0/3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain		
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cervical spinal stenosis subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Flank pain		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gouty arthritis		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Haemarthrosis		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intervertebral disc protrusion		
subjects affected / exposed	1 / 1377 (0.07%)	3 / 1384 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Lumbar spinal stenosis		
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Muscular weakness	ļ	ĺ
subjects affected / exposed	2 / 1377 (0.15%)	2 / 1384 (0.14%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Musculoskeletal chest pain		

subjects affected / exposed	1 / 1377 (0.07%)	5 / 1384 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 1377 (0.15%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 1377 (0.00%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0/3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 1377 (0.07%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis	- 	· 	
subjects affected / exposed	3 / 1377 (0.22%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0/3	0/3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylitis		· 	
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0/0	0/1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus			
•	•		•

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to	0/0	0 / 1	
treatment / all	0,0	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
nfections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0/0	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Abscess			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0/0	0/1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	3 / 1377 (0.22%)	3 / 1384 (0.22%)	
occurrences causally related to		, ,	
treatment / all deaths causally related to	0 / 3	0 / 3	
treatment / all	0/0	0/0	
Acute hepatitis B			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Appendicitis			
subjects affected / exposed	5 / 1377 (0.36%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 5	0/3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated	j		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to		0.40	
treatment / all	0/0	0 / 0	

subjects affected / exposed	3 / 1377 (0.22%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0/3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous graft site infection			
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 1377 (0.07%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone tuberculosis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	9 / 1377 (0.65%)	7 / 1384 (0.51%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbuncle			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac valve abscess			

subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site cellulitis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	8 / 1377 (0.58%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 9	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	13 / 1377 (0.94%)	24 / 1384 (1.73%)	
occurrences causally related to treatment / all	0 / 13	0 / 27	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis gangrenous			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	2 / 1377 (0.15%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Clostridium difficile infection			
subjects affected / exposed	2 / 1377 (0.15%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
1	•	1	1

subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis bacterial			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus nephritis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	5 / 1377 (0.36%)	14 / 1384 (1.01%)	
occurrences causally related to treatment / all	0 / 6	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	5 / 1377 (0.36%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetic foot infection]	
subjects affected / exposed	4 / 1377 (0.29%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gangrene]	
	1	1	t .

subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	4 / 1377 (0.29%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	3 / 1377 (0.22%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysematous cystitis			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysematous pyelonephritis			
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 1377 (0.07%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endotoxic shock			
-	•	•	•

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Enteritis infectious			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter sepsis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0/0	
Enterococcal sepsis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0/0	
Epiglottitis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0/1	
deaths causally related to treatment / all	0 / 0	0 / 0	
- Fungaemia	İ	İ	
1	1	I .	ı

subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal oesophagitis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal peritonitis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	7 / 1377 (0.51%)	10 / 1384 (0.72%)	
occurrences causally related to treatment / all	0 / 9	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	8 / 1377 (0.58%)	13 / 1384 (0.94%)	
occurrences causally related to treatment / all	0 / 8	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis bacterial			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 1377 (0.07%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			

subjects affected / exposed	2 / 1377 (0.15%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter gastritis			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B reactivation			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			

	_	_	_
subjects affected / exposed	5 / 1377 (0.36%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	3 / 1377 (0.22%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node tuberculosis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	0 / 1377 (0.00%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0/0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
	'		

	subjects affected / exposed	2 / 1377 (0.15%)	3 / 1384 (0.22%)	
	occurrences causally related to treatment / all	0 / 3	0 / 3	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Osteomyelitis acute			
	subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Osteomyelitis chronic			
	subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
	occurrences causally related to treatment / all	0 / 0	0 / 2	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Otitis media chronic			
	subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Parvovirus infection			
	subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
	Perineal abscess			
	subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
1	Perinephric abscess			
	subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
1	Peritonitis			
	subjects affected / exposed	14 / 1377 (1.02%)	15 / 1384 (1.08%)	
	occurrences causally related to treatment / all	0 / 19	0 / 17	
	deaths causally related to treatment / all	0 / 0	0 / 1	
	Peritonitis bacterial			
		•	-	•

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Peritonsillar abscess		
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0/0
Pharyngitis		
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pleural infection		
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia		
subjects affected / exposed	88 / 1377 (6.39%)	113 / 1384 (8.16%)
occurrences causally related to treatment / all	1 / 107	0 / 149
deaths causally related to treatment / all	0 / 10	0 / 12
Pneumonia bacterial		
subjects affected / exposed	3 / 1377 (0.22%)	2 / 1384 (0.14%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 1
Pneumonia influenzal		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia klebsiella		
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia mycoplasmal		
, p		-

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural cellulitis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural pneumonia			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	2 / 1377 (0.15%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection	İ		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis	İ	İ	
,	1	I	I

subjects affected / exposed	2 / 1377 (0.15%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purulence			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	5 / 1377 (0.36%)	8 / 1384 (0.58%)	
occurrences causally related to treatment / all	0 / 5	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	4 / 1377 (0.29%)	6 / 1384 (0.43%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	11 / 1377 (0.80%)	11 / 1384 (0.79%)	
occurrences causally related to treatment / all	0 / 14	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyoderma			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyonephrosis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst infection			
subjects affected / exposed	1 / 1377 (0.07%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
	•		•

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	23 / 1377 (1.67%)	49 / 1384 (3.54%)	
occurrences causally related to treatment / all	0 / 24	0 / 51	
deaths causally related to treatment / all	0 / 8	0 / 26	
Septic shock			
subjects affected / exposed	15 / 1377 (1.09%)	18 / 1384 (1.30%)	
occurrences causally related to treatment / all	0 / 15	0 / 19	
deaths causally related to treatment / all	0 / 9	0 / 14	
Sinusitis			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 1377 (0.00%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Staphylococcal sepsis	İ		
subjects affected / exposed	3 / 1377 (0.22%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0/3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stenotrophomonas sepsis	İ	· · · · · · · · · · · · · · · · · · ·	
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0/0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia	1 7, 7		!
on ephotocical pacteraelilla	1	I	

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal endocarditis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	4 / 1377 (0.29%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Taeniasis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	3 / 1377 (0.22%)	5 / 1384 (0.36%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Typhoid fever			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

1		
subjects affected / exposed	26 / 1377 (1.89%)	36 / 1384 (2.60%)
occurrences causally related to treatment / all	0 / 32	0 / 38
deaths causally related to treatment / all	0 / 0	0 / 1
Urinary tract infection bacterial		
subjects affected / exposed	0 / 1377 (0.00%)	3 / 1384 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Urosepsis		
subjects affected / exposed	6 / 1377 (0.44%)	8 / 1384 (0.58%)
occurrences causally related to treatment / all	0 / 6	0 / 11
deaths causally related to treatment / all	0 / 1	0 / 1
Vascular access site infection		
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Vestibular neuronitis		
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Viral infection		
subjects affected / exposed	3 / 1377 (0.22%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Metabolism and nutrition disorders		
Acidosis		
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Adult failure to thrive		
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Calciphylaxis		

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	2 / 1377 (0.15%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	4 / 1377 (0.29%)	8 / 1384 (0.58%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetes mellitus			
subjects affected / exposed	3 / 1377 (0.22%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetes mellitus inadequate control			
subjects affected / exposed	3 / 1377 (0.22%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	10 / 1377 (0.73%)	6 / 1384 (0.43%)	
occurrences causally related to treatment / all	0 / 12	0 / 10	
deaths causally related to treatment / all	0 / 2	0 / 1	
Diabetic metabolic decompensation			
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Electrolyte imbalance]		
subjects affected / exposed	3 / 1377 (0.22%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0/3	0/1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
T	ı	ı	ı

subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Fluid overload		
subjects affected / exposed	22 / 1377 (1.60%)	20 / 1384 (1.45%)
occurrences causally related to treatment / all	0 / 27	0 / 28
deaths causally related to treatment / all	0 / 0	0 / 0
Fluid retention		
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Food aversion		
subjects affected / exposed	2 / 1377 (0.15%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gout		
subjects affected / exposed	1 / 1377 (0.07%)	4 / 1384 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Hypercalcaemia		
subjects affected / exposed	3 / 1377 (0.22%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hyperglycaemia		
subjects affected / exposed	9 / 1377 (0.65%)	16 / 1384 (1.16%)
occurrences causally related to treatment / all	0 / 10	0 / 17
deaths causally related to treatment / all	0 / 1	0 / 0
Hyperglycaemic hyperosmolar nonketotic syndrome		ĺ
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hyperinsulinaemic hypoglycaemia		
'	•	

1 .	1		I
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (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	25 / 1377 (1.82%)	41 / 1384 (2.96%)	
occurrences causally related to treatment / all	0 / 35	2 / 53	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hypernatraemia			
subjects affected / exposed	0 / 1377 (0.00%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	2 / 1377 (0.15%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypervolaemia			
subjects affected / exposed	0 / 1377 (0.00%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	2 / 1377 (0.15%)	2 / 1384 (0.14%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	26 / 1377 (1.89%)	32 / 1384 (2.31%)	
occurrences causally related to treatment / all	0 / 27	0 / 38	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 1377 (0.07%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyponatraemia		ĺ	
1	•		•

subjects affected / exposed	6 / 1377 (0.44%)	7 / 1384 (0.51%)	
occurrences causally related to treatment / all	0 / 9	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hypovolaemia			
subjects affected / exposed	4 / 1377 (0.29%)	3 / 1384 (0.22%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketoacidosis			
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketosis			
subjects affected / exposed	1 / 1377 (0.07%)	0 / 1384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	4 / 1377 (0.29%)	4 / 1384 (0.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 0	
Metabolic acidosis			
subjects affected / exposed	3 / 1377 (0.22%)	7 / 1384 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 3	
Type 1 diabetes mellitus			
subjects affected / exposed	2 / 1377 (0.15%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
•	•	•	-

subjects affected / exposed	1 / 1377 (0.07%)	1 / 1384 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Frequency threshold for reporting non-se			
	Placebo	Roxadustat	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	757 / 1377 (54.97%)	839 / 1384 (60.62%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	117 / 1377 (8.50%)	148 / 1384 (10.69%)	
occurrences (all)	151	190	
Nervous system disorders			
Dizziness			
subjects affected / exposed	86 / 1377 (6.25%)	74 / 1384 (5.35%)	
occurrences (all)	113	91	
Headache			
subjects affected / exposed	82 / 1377 (5.95%)	93 / 1384 (6.72%)	
occurrences (all)	96	122	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	106 / 1377 (7.70%)	144 / 1384 (10.40%)	
occurrences (all)	135	192	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	88 / 1377 (6.39%)	91 / 1384 (6.58%)	
occurrences (all)	101	126	
Diarrhoea			
subjects affected / exposed	117 / 1377 (8.50%)	 138 / 1384 (9.97%)	
occurrences (all)	156	190	
Nausea			
subjects affected / exposed	103 / 1377 (7.48%)	124 / 1384 (8.96%)	
occurrences (all)	127	171	
Vomiting			

subjects affected / exposed occurrences (all)	67 / 1377 (4.87%) 85	75 / 1384 (5.42%) 90	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	69 / 1377 (5.01%)	105 / 1384 (7.59%)	
occurrences (all)	91	123	
Dyspnoea			
subjects affected / exposed	64 / 1377 (4.65%)	70 / 1384 (5.06%)	
occurrences (all)	80	85	

subjects affected / exposed occurrences (all)	106 / 1377 (7.70%) 152	101 / 1384 (7.30%) 159	
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	75 / 1377 (5.45%) 86	86 / 1384 (6.21%) 105	

EU-CTR publication date: 15 January 2020

26 September 2014

Tiered weight-based start doses changed to fixed 70 mg TIW start dose: 120 and 350 mg dose steps removed. Dose algorithm adjusted to reflect results of pharmacometric modeling and simulation using the simplified dosing regimen. Dose cap lowered as additional modeling/simulation indicated this dose would be sufficient. Definition of excessive erythropoiesis simplified. Visit 1 changed to a phone call. Removed visits at Weeks 3, 5, and 7. Visits every 8 weeks (not 4 weeks) after Week 52. Visit window from ±2 days to -4 days to 2 days. Priority order of secondary objectives changed. Rescue therapy objective prioritized before self-reported health status. Inclusion criteria: #3 reworded to clarify that qualifying eGFR was by central laboratory calculation; #5 and #6: Ferritin raised to \geq 50 nanograms/mL and transferrin saturation raised to \geq 15%. Exclusion criteria: #9 changed from Bosniak category II to IIF; #13 added "that is determined to be the principal cause of anemia". Removed "or their quardian/legal representative" for participant consent. Deleted IP discontinuation for thrombocytopenia or bleeding. Rescue medication: IV iron guidance adjusted to align with guidelines. Added recommendation for oral iron supplementation. Inclusion of statins text to ask Investigators to consider roxadustat-statin interactions and local prescribing information when deciding on appropriate statin dose for individual participants. Inclusion of text on phosphate binders. Efficacy analysis set: Participants were not to be censored 96 hours after their last dose in the OT+28 population; ITT analysis set for major adverse cardiovascular event (MACE) instead. ANCOVA changed to MMRM for efficacy analysis. Added: "In subjects who do not experience a MACE event, the time-to-event will be censored at the EOT visit for analyses based both on the safety analysis population and on FAS". Removed annual study discontinuation rate of 8.5% and changed estimated time from 1.5 years to 1.4 years.

31 August 2018

To harmonize D5740C00001 with other studies in the CKD-non-dialysis-dependent Phase 3 program, to serve as a pivotal study for confirming efficacy and safety and to facilitate assessment of pooled efficacy and safety data across the Phase 3 program, the following changes were implemented: Previous primary objective changed to primary safety objective (with CV safety analyses now being pooled across the study program). Addition of 2 primary efficacy objectives: one objective for the US FDA and one for the EU health authority. Previous primary objective text moved to new sub-section. Inclusion of text on pooled CV safety analyses and the pooled statistical analysis plan. Previous secondary objectives split out by objective type (efficacy and safety) and updated and new secondary objectives added. Study duration extended. Enrollment anticipated to occur over approximately a 3 year period. Text on sample size determination revised, including addition of text on sample size estimation for the primary efficacy objective. Study end date changed (extension of study into Q3 2018) to reflect a common end date across the Phase 3 studies when the required number of participants with adjudicated CV endpoints was anticipated. Additional criteria (participants requiring a third course of erythropoietin analogue rescue therapy, or those initiating dialysis who required erythropoietin analogue rescue therapy) for permanent discontinuation from the IP were added. Text added to state that hepcidin and hsCRP were to be analyzed from biomarker samples. Added definition of treatment emergent AE. FAS was renamed to the ITT and a new subsection was added describing the new FAS. Changes were made to the criteria, treatment groups and censoring rules of the analysis sets. A new sub-section was added on participants who will not be included in any analysis set.

Notes:

Were there any global interruptions to the trial? No

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

20 participants were excluded from the analysis due to GCP violations or system technical issues (9 in the roxadustat group and 11 in the placebo group). Higher IP discontinuation was observed in placebo group versus in roxadustat group.

Notes:

EU-CTR publication date: 15 January 2020