Clinical trial results:
Prospective, randomised, controlled, double-blind, multi-centre, multinational study on the safety and efficacy of 6% Hydroxyethyl starch (HES) solution versus an electrolyte solution in patients undergoing elective abdominal surgery (PHOENICS)

Summary

EudraCT number	2016-002162-30
Trial protocol	BE CZ NL ES FR AT HR RO
Global end of trial date	06 July 2022

Results information

Result version number	v1 (current)
This version publication date	04 August 2023
First version publication date	04 August 2023

Trial information

Trial identification

Sponsor protocol code	HC-G-H-1504

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03278548
WHO universal trial number (UTN)	-
Other trial identifiers	Fresenius Kabi ID: VOLU-024-CP4

Notes:

Sponsors

Sponsor organisation name	Fresenius Kabi Deutschland GmbH
Sponsor organisation address	Else-Kröner-Str. 1, Bad Homburg, Germany, 61352
Public contact	Medical Scientific Affairs Pharma and Nutrition, Fresenius Kabi Deutschland GmbH, Trial-Disclosure@Fresenius-Kabi.com
Scientific contact	Medical Scientific Affairs Pharma and Nutrition, Fresenius Kabi Deutschland GmbH, Trial-Disclosure@Fresenius-Kabi.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective was to investigate non-inferiority regarding the safety of a 6% HES solution for infusion (Volulyte 6%) compared to an electrolyte solution for infusion (Ionolyte) in patients with acute blood loss undergoing elective abdominal surgery

Protection of trial subjects:

Subject protection was ensured by medical and ethical standards in accordance with Declaration of Helsinki, Good Clinical Practice and applicable national and local laws and regulation. The signed informed consent was obtained prior to inclusion in the study. The patients were informed in writing about their right to withdraw from the study at any time. Furthermore, a data safety monitoring board was established to protect the patients participating in the study

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 September 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 133
Country: Number of subjects enrolled	Poland: 83
Country: Number of subjects enrolled	Romania: 24
Country: Number of subjects enrolled	Spain: 896
Country: Number of subjects enrolled	Croatia: 17
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 144
Country: Number of subjects enrolled	Czechia: 235
Country: Number of subjects enrolled	France: 320
Country: Number of subjects enrolled	Germany: 490
Worldwide total number of subjects	2346
EEA total number of subjects	2346

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1056
From 65 to 84 years	1279
85 years and over	11

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Potential candidates for study participation were considered for the screening period. Before enrolling into screening informed consent had to be provided in writing.
A patient was randomized only after eligibility was proven by checking the inclusion and exclusion criteria

Period 1

Period 1 title	Overall trial without 1 year follow-up (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Volulyte

Arm description:

Started = Number of patients randomised for this arm

Arm type	Experimental
Investigational medicinal product name	Volulyte 6% solution for infusion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosing was individualised to the patient’s volume needs and guided by a volume algorithm based on either mean arterial pressure or other haemodynamic parameters. The daily dose of 30 ml/kg should not have been exceeded.
If patients were still hypotensive during administration of the investigational test product, they could also receive vasoactive/inotropic drugs, if regarded necessary due to the patient’s clinical condition.
Since HES preparations may rarely cause allergic reactions, the first 10-20 ml of the solution should have been infused slowly. In case of an allergic reaction, the infusion had to be stopped immediately, and appropriate treatment given.

Arm title	Ionolyte

Arm description:

Started = Number of patients randomised for this arm

Arm type	Active comparator
Investigational medicinal product name	Ionolyte solution for infusion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosing was individualised to the patient’s volume needs and guided by a volume algorithm based on either mean arterial pressure or other haemodynamic parameters.
The daily dose of 30 ml/kg should not have been exceeded.
If patients were still hypotensive during administration of the investigational reference product, they could also receive vasoactive/inotropic drugs, if regarded necessary due to the patient’s clinical condition.

Number of subjects in period 1[1]	Volulyte	Ionolyte
Started	1147	1142
Completed	852	861
Not completed	295	281
Adverse event, serious fatal	32	31
Consent withdrawn by subject	57	42
Adverse event, non-fatal	2	-
Other	187	189
Lost to follow-up	15	18
Protocol deviation	2	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: In 'period 1' only the eligible and randomized subjects are mentioned whereas under 'population of trial subjects' and 'subjects enrolled per age group' all patients enrolled (including screen failures) are mentioned.

Baseline characteristics

Reporting groups	
Reporting group title	Volulyte
Reporting group description:	
Started = Number of patients randomised for this arm	
Reporting group title	Ionolyte
Reporting group description:	
Started = Number of patients randomised for this arm	

Reporting group values	Volulyte	Ionolyte	Total
Number of subjects	1147	1142	2289
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	64.9	64.9	
standard deviation	± 9.51	± 9.92	-
Gender categorical Units: Subjects			
Female	414	446	860
Male	733	696	1429

Subject analysis sets	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients with at least one administration of study medication were included in the SAF.	
Subject analysis set title	Full analysis set for the primary endpoint (FASpEP)
Subject analysis set type	Full analysis
Subject analysis set description:	
The FASpEP comprised all patients from the SAF reaching the post-operative period and being monitored at least once with respect to the changes in cystatin C-based eGFR at POD1, POD2 or POD3.	
Subject analysis set title	Full analysis set for efficacy analyses (FASEff)
Subject analysis set type	Full analysis
Subject analysis set description:	
The FASEff comprised all patients from the SAF providing any efficacy data after IP start.	
Subject analysis set title	Per-protocol set for the primary endpoint (PPSpEP)

Subject analysis set type	Per protocol

Subject analysis set description:

The PPSpEP comprised all subjects from the FASpEP who did not have any major protocol deviations with regard to the primary endpoint.

Subject analysis set title	Per-protocol set for the key secondary endpoint (PPSKScEP)
Subject analysis set type	Per protocol

Subject analysis set description:

The PPSKScEP comprised all subjects from the SAF who did not have any major protocol deviations with regard to the key secondary endpoint.

Reporting group values	Safety analysis set (SAF)	Full analysis set for the primary endpoint (FASpEP)	Full analysis set for efficacy analyses (FASEff)
Number of subjects	1958	1946	1958
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	64.9	64.9	64.9
standard deviation	± 9.68	± 9.67	± 9.68
Gender categorical Units: Subjects			
Female	724	721	724
Male	1234	1225	1234

Reporting group values	Per-protocol set for the primary endpoint (PPSpEP)	Per-protocol set for the key secondary endpoint (PPSKScEP)	
Number of subjects	1857	1868	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			

Age continuous Units: years			
arithmetic mean	64.9	64.9	
standard deviation	± 9.59	± 9.60	
Gender categorical Units: Subjects			
Female	682	685	
Male	1175	1183	

End points

End points reporting groups

Reporting group title	Volulyte
Reporting group description: Started = Number of patients randomised for this arm	
Reporting group title	Ionolyte
Reporting group description: Started = Number of patients randomised for this arm	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description: All patients with at least one administration of study medication were included in the SAF.	
Subject analysis set title	Full analysis set for the primary endpoint (FASpEP)
Subject analysis set type	Full analysis
Subject analysis set description: The FASpEP comprised all patients from the SAF reaching the post-operative period and being monitored at least once with respect to the changes in cystatin C-based eGFR at POD1, POD2 or POD3.	
Subject analysis set title	Full analysis set for efficacy analyses (FASEff)
Subject analysis set type	Full analysis
Subject analysis set description: The FASEff comprised all patients from the SAF providing any efficacy data after IP start.	
Subject analysis set title	Per-protocol set for the primary endpoint (PPSpEP)
Subject analysis set type	Per protocol
Subject analysis set description: The PPSpEP comprised all subjects from the FASpEP who did not have any major protocol deviations with regard to the primary endpoint.	
Subject analysis set title	Per-protocol set for the key secondary endpoint (PPSKScEP)
Subject analysis set type	Per protocol
Subject analysis set description: The PPSKScEP comprised all subjects from the SAF who did not have any major protocol deviations with regard to the key secondary endpoint.	

Primary: Change in cystatin C-based estimated glomerular filtration rate (eGFR) from pre-operative baseline to eGFR value calculated from the highest cystatin C level measured during post-operative days 1–3 (POD1–3) (i.e., minimal eGFR during POD1–3)

End point title	Change in cystatin C-based estimated glomerular filtration rate (eGFR) from pre-operative baseline to eGFR value calculated from the highest cystatin C level measured during post-operative days 1–3 (POD1–3) (i.e., minimal eGFR during POD1–3)
End point description: The primary endpoint of this study was the change in cystatin C-based eGFR from pre-operative baseline to eGFR value calculated from the highest cystatin C level measured during post-operative days 1–3 (i.e., minimal eGFR during post-operative days 1–3). To calculate cystatin C-based eGFR the Chronic Kidney Disease Epidemiology Collaboration equation developed by Inker et al., 2012 was used.	
End point type	Primary
End point timeframe: From pre-operative baseline to post-operative days 1-3	

End point values	Volulyte	Ionolyte	Per-protocol set for the primary endpoint (PPSpEP)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	922[1]	935[2]	1857[3]	
Units: ml/min/1.73m²				
least squares mean (confidence interval 95%)	-1.713 (-3.274 to -0.153)	0.667 (-0.906 to 2.241)	-2.381 (-3.899 to -0.862)	

Notes:

[1] - PPS-pEP

[2] - PPS-pEP

[3] - 922 (Volulyte) + 935 (Ionolyte)
LS mean value below is the difference in LS means between groups

Statistical analyses

Statistical analysis title	Analysis of Primary Endpoint

Statistical analysis description:

This study was intended to test confirmatively the primary hypothesis that treatment with Volulyte is non-inferior to treatment with Ionolyte regarding the primary endpoint change in cystatin C-based eGFR from pre-operative baseline to eGFR value calculated from the highest cystatin C level measured during POD 1–3 (i.e., minimal eGFR during POD1–3) considering a non-inferiority margin of Δ = 8.1 ml/min/1.73 m² and a type I error rate of α = 2.5% one-sided

Comparison groups	Volulyte v Ionolyte
Number of subjects included in analysis	1857
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001 [4]
Method	ANCOVA

Notes:

[4] - The treatment group difference was -2.381 ml/min/1.73m² (95% CI: -3.899 to -0.862 ml/min/1.73 m²).
Since the lower limit of the 95% CI was greater than -Δ (i.e.,-8.1ml/min/1.73m²), non-inferiority to Ionolyte was demonstrated (p<0.0001)

Secondary: Key secondary endpoint: Mortality and major post-operative complications (including renal) until day 90

End point title	Key secondary endpoint: Mortality and major post-operative complications (including renal) until day 90

End point description:

This composite endpoint summarises the occurrence of death and major post-operative complications according to predefined criteria for the assessment of complications during the first 90 post-operative days.

End point type	Secondary

End point timeframe:

End of surgery - 90 post-operative days

End point values	Volulyte	Ionolyte		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	887[5]	907[6]		
Units: cases	324	322		

Notes:

[5] - SAF, N missing = 90

[6] - SAF, N missing = 74

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The reporting period for adverse events (AEs) started at T0 i.e. baseline (after randomization and prior induction of anaesthesia) and ended after T8 (90 days after surgery)

Adverse event reporting additional description:

Only treatment-emergent adverse events included

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Volulyte
Reporting group description: -	
Reporting group title	Ionolyte
Reporting group description: -	

Serious adverse events	Volulyte	Ionolyte	
Total subjects affected by serious adverse events			
subjects affected / exposed	296 / 977 (30.30%)	291 / 981 (29.66%)	
number of deaths (all causes)	32	31	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon neoplasm	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasm progression	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ovarian neoplasm			

subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiocarcinoma	Additional description: Cholangiocarcinoma		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant neoplasm progression	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	3 / 981 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Oesophageal carcinoma	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ureteral neoplasm	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial haemorrhage	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma	Additional description: Treatment-emergent		

subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage	Additional description: Treatment-emergent		
subjects affected / exposed	4 / 977 (0.41%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypotension	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lymphocele	Additional description: Treatment-emergent		
subjects affected / exposed	7 / 977 (0.72%)	9 / 981 (0.92%)	
occurrences causally related to treatment / all	0 / 7	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphorrhoea	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic	Additional description: Treatment-emergent		

subjects affected / exposed	9 / 977 (0.92%)	5 / 981 (0.51%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
Peripheral arterial occlusive disease	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Therapy cessation	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thyroid operation	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
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			
Chest pain	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

General physical health deterioration	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	

Multiple organ dysfunction syndrome	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	5 / 981 (0.51%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 2	1 / 5	

Pyrexia	Additional description: Treatment-emergent		
subjects affected / exposed	4 / 977 (0.41%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Systemic inflammatory response syndrome	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Impaired healing	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	3 / 981 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Inflammation	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Localised oedema	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sudden death	Additional description: Treatment-emergent

subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Contrast media allergy	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
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			
Vaginal fistula	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic haematoma	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome	Additional description: Treatment-emergent		
subjects affected / exposed	6 / 977 (0.61%)	3 / 981 (0.31%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Chronic obstructive pulmonary disease	Additional description: Treatment-emergent		

subjects affected / exposed	2 / 977 (0.20%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chylothorax	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion	Additional description: Treatment-emergent		
subjects affected / exposed	8 / 977 (0.82%)	9 / 981 (0.92%)	
occurrences causally related to treatment / all	1 / 9	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism	Additional description: Treatment-emergent		
subjects affected / exposed	9 / 977 (0.92%)	7 / 981 (0.71%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pulmonary oedema	Additional description: Treatment-emergent		

subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure	Additional description: Treatment-emergent		
subjects affected / exposed	7 / 977 (0.72%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine increased	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

International normalised ratio increased	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARS-CoV-2 test positive	Additional description: Treatment-emergent		
subjects affected / exposed	3 / 977 (0.31%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Transaminases increased	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic fistula	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic haemorrhage	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic leak	Additional description: Treatment-emergent		
subjects affected / exposed	26 / 977 (2.66%)	15 / 981 (1.53%)	
occurrences causally related to treatment / all	1 / 26	0 / 15	
deaths causally related to treatment / all	0 / 1	0 / 0	
Femoral nerve injury	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Flap necrosis	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	3 / 981 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic complication	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic leak	Additional description: Treatment-emergent		
subjects affected / exposed	7 / 977 (0.72%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal anastomosis complication	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic leak	Additional description: Treatment-emergent		
subjects affected / exposed	4 / 977 (0.41%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripancreatic fluid collection	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural bile leak	Additional description: Treatment-emergent		

subjects affected / exposed	1 / 977 (0.10%)	4 / 981 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fever	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	3 / 981 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage	Additional description: Treatment-emergent		
subjects affected / exposed	9 / 977 (0.92%)	8 / 981 (0.82%)	
occurrences causally related to treatment / all	0 / 9	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural pulmonary embolism	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural urine leak	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage	Additional description: Treatment-emergent		
subjects affected / exposed	4 / 977 (0.41%)	3 / 981 (0.31%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural intestinal perforation	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain	Additional description: Treatment-emergent		

subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural shock	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma complication	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suture related complication	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric injury	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal cuff dehiscence	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound evisceration	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	3 / 981 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haematoma	Additional description: Treatment-emergent		

subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wound dehiscence	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drain site complication	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fistula	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural stroke	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative renal failure	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative respiratory failure	Additional description: Treatment-emergent		

subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pneumothorax	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suture rupture	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava injury	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound necrosis	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arrhythmia	Additional description: Treatment-emergent		

subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation	Additional description: Treatment-emergent		
subjects affected / exposed	7 / 977 (0.72%)	3 / 981 (0.31%)	
occurrences causally related to treatment / all	0 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter	Additional description: Treatment-emergent		
subjects affected / exposed	3 / 977 (0.31%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bradyarrhythmia	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac arrest	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest	Additional description: Treatment-emergent		
subjects affected / exposed	4 / 977 (0.41%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 4	0 / 0	
Cardiovascular disorder	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial effusion	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia	Additional description: Treatment-emergent		

subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Torsade de pointes	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Embolic stroke	Additional description: Treatment-emergent		

subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hemiparesis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem syndrome	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia	Additional description: Treatment-emergent		

subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic haemorrhage	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea	Additional description: Treatment-emergent		

subjects affected / exposed	2 / 977 (0.20%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous fistula	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (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	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastric ulcer	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage	Additional description: Treatment-emergent		
subjects affected / exposed	6 / 977 (0.61%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemoperitoneum	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus	Additional description: Treatment-emergent		

subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic	Additional description: Treatment-emergent		
subjects affected / exposed	20 / 977 (2.05%)	21 / 981 (2.14%)	
occurrences causally related to treatment / all	0 / 21	0 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying	Additional description: Treatment-emergent		
subjects affected / exposed	6 / 977 (0.61%)	5 / 981 (0.51%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	5 / 981 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
Intestinal obstruction	Additional description: Treatment-emergent		
subjects affected / exposed	9 / 977 (0.92%)	3 / 981 (0.31%)	
occurrences causally related to treatment / all	0 / 9	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal fluid collection	Additional description: Treatment-emergent		
subjects affected / exposed	14 / 977 (1.43%)	15 / 981 (1.53%)	
occurrences causally related to treatment / all	0 / 14	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage	Additional description: Treatment-emergent		

subjects affected / exposed	3 / 977 (0.31%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jejunal perforation	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation	Additional description: Treatment-emergent		
subjects affected / exposed	3 / 977 (0.31%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus	Additional description: Treatment-emergent		
subjects affected / exposed	3 / 977 (0.31%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena	Additional description: Treatment-emergent		
subjects affected / exposed	3 / 977 (0.31%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric haemorrhage	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagopleural fistula	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic fistula	Additional description: Treatment-emergent		
subjects affected / exposed	4 / 977 (0.41%)	5 / 981 (0.51%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic pseudocyst	Additional description: Treatment-emergent		

subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer haemorrhage	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic hernia	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis	Additional description: Treatment-emergent		

subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenal haemorrhage	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal fistula	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haematoma	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic failure	Additional description: Treatment-emergent		

subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis necrotising	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth disorder	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cholangitis	Additional description: Treatment-emergent		

subjects affected / exposed	2 / 977 (0.20%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic artery aneurysm	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic vascular thrombosis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatorenal failure	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic hepatitis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis	Additional description: Treatment-emergent		

subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemobilia	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic artery occlusion	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haemorrhage	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Acute kidney injury	Additional description: Treatment-emergent		
subjects affected / exposed	21 / 977 (2.15%)	38 / 981 (3.87%)	
occurrences causally related to treatment / all	1 / 21	1 / 42	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder tamponade	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria	Additional description: Treatment-emergent		

subjects affected / exposed	3 / 977 (0.31%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postrenal failure	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric perforation	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	3 / 981 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction	Additional description: Treatment-emergent		

subjects affected / exposed	2 / 977 (0.20%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinoma	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder perforation	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urogenital fistula	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Compartment syndrome	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess	Additional description: Treatment-emergent		
subjects affected / exposed	5 / 977 (0.51%)	6 / 981 (0.61%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection	Additional description: Treatment-emergent		
subjects affected / exposed	4 / 977 (0.41%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abdominal sepsis	Additional description: Treatment-emergent		
subjects affected / exposed	3 / 977 (0.31%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19	Additional description: Treatment-emergent		

subjects affected / exposed	2 / 977 (0.20%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis infective	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection	Additional description: Treatment-emergent		
subjects affected / exposed	3 / 977 (0.31%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site abscess	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection	Additional description: Treatment-emergent		

subjects affected / exposed	6 / 977 (0.61%)	4 / 981 (0.41%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nosocomial infection	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraspinal abscess	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess	Additional description: Treatment-emergent		
subjects affected / exposed	4 / 977 (0.41%)	4 / 981 (0.41%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic infection	Additional description: Treatment-emergent		

subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perihepatic abscess	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perinephric abscess	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis	Additional description: Treatment-emergent		
subjects affected / exposed	7 / 977 (0.72%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Treatment-emergent		
subjects affected / exposed	8 / 977 (0.82%)	9 / 981 (0.92%)	
occurrences causally related to treatment / all	0 / 8	0 / 9	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia aspiration	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Post procedural infection	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess	Additional description: Treatment-emergent		

subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperativ wound infection	Additional description: Treatment-emergent		
subjects affected / exposed	17 / 977 (1.74%)	19 / 981 (1.94%)	
occurrences causally related to treatment / all	0 / 17	0 / 19	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pyelonephritis	Additional description: Treatment-emergent		
subjects affected / exposed	4 / 977 (0.41%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis	Additional description: Treatment-emergent		
subjects affected / exposed	8 / 977 (0.82%)	6 / 981 (0.61%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 0	
Septic shock	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	7 / 981 (0.71%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin infection	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdiaphragmatic abscess	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida	Additional description: Treatment-emergent		

subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection	Additional description: Treatment-emergent		
subjects affected / exposed	14 / 977 (1.43%)	11 / 981 (1.12%)	
occurrences causally related to treatment / all	0 / 14	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	3 / 981 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Empyema	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder abscess	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis	Additional description: Treatment-emergent		

subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic abscess	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	2 / 981 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural sepsis	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia	Additional description: Treatment-emergent		

subjects affected / exposed	2 / 977 (0.20%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 977 (0.10%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis	Additional description: Treatment-emergent		
subjects affected / exposed	2 / 977 (0.20%)	0 / 981 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dehydration	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 977 (0.00%)	1 / 981 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Volulyte	Ionolyte	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	617 / 977 (63.15%)	630 / 981 (64.22%)	
Injury, poisoning and procedural complications			
Procedural pain	Additional description: Treatment-emergent		
subjects affected / exposed	76 / 977 (7.78%)	79 / 981 (8.05%)	
occurrences (all)	78	83	
Vascular disorders			
Hypotension	Additional description: Treatment-emergent		
subjects affected / exposed	46 / 977 (4.71%)	55 / 981 (5.61%)	
occurrences (all)	46	56	
Blood and lymphatic system disorders			
Anaemia	Additional description: Treatment-emergent		
subjects affected / exposed	138 / 977 (14.12%)	136 / 981 (13.86%)	
occurrences (all)	178	168	
General disorders and administration site conditions			
Pain	Additional description: Treatment-emergent		
subjects affected / exposed	77 / 977 (7.88%)	73 / 981 (7.44%)	
occurrences (all)	79	81	
Gastrointestinal disorders			
Constipation	Additional description: Treatment-emergent		
subjects affected / exposed	53 / 977 (5.42%)	50 / 981 (5.10%)	
occurrences (all)	55	53	
Diarrhoea	Additional description: Treatment-emergent		
subjects affected / exposed	51 / 977 (5.22%)	53 / 981 (5.40%)	
occurrences (all)	53	57	
Nausea	Additional description: Treatment-emergent		
subjects affected / exposed	95 / 977 (9.72%)	95 / 981 (9.68%)	
occurrences (all)	102	101	
Vomiting	Additional description: Treatment-emergent		
subjects affected / exposed	58 / 977 (5.94%)	75 / 981 (7.65%)	
occurrences (all)	62	75	
Renal and urinary disorders			
Acute kidney injury	Additional description: Treatment-emergent		
subjects affected / exposed	91 / 977 (9.31%)	82 / 981 (8.36%)	
occurrences (all)	101	91	
Metabolism and nutrition disorders			

Hypocalcaemia	Additional description: Treatment-emergent		
subjects affected / exposed	91 / 977 (9.31%)	80 / 981 (8.15%)	
occurrences (all)	97	91	
Hypokalaemia	Additional description: Treatment-emergent		
subjects affected / exposed	91 / 977 (9.31%)	79 / 981 (8.05%)	
occurrences (all)	101	85	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2016	The main reasons for this amendment* were the following: - Adjustment of "concomitant medication", "duration per patient" and "duration of whole study" - Clarification that (serious) adverse events/ reactions are recorded and processed on timepoints T6-T8 - Addition of discontinuation criteria related to the study site and to the patient - Explanation of actions in case of a breach against the data protection. T6: post-operative day 8 until post-operative day 10 or hospital discharge, whatever occurs first T8: 90 days after surgery * Depending on the ethics committees' and national authorities' feedback and on timepoint of initial submission the number of amendments, the amendment dates, as well as the changes to the protocol may differ between the participating countries. As representative information, the overview of amendments in Germany is given here.
20 April 2017	The main reason for this amendment* was the addition of subgroup analysis for gender. * Depending on the ethics committees' and national authorities' feedback and on timepoint of initial submission the number of amendments, the amendment dates, as well as the changes to the protocol may differ between the participating countries. As representative information, the overview of amendments in Germany is given here.
27 February 2018	The main reason for this amendment* was to reflect the referral procedure in relation to risk-benefit-assessment. * Depending on the ethics committees' and national authorities' feedback and on timepoint of initial submission the number of amendments, the amendment dates, as well as the changes to the protocol may differ between the participating countries. As representative information, the overview of amendments in Germany is given here.
01 August 2019	The main reason for this amendment* was to reflect sponsor transfer from B. Braun to Fresenius Kabi. * Depending on the ethics committees' and national authorities' feedback and on timepoint of initial submission the number of amendments, the amendment dates, as well as the changes to the protocol may differ between the participating countries. As representative information, the overview of amendments in Germany is given here.
05 November 2019	The main reason for this amendment* was to adapt MAP-guided volume algorithm to increase patient recruitment. MAP=Mean arterial (blood) pressure. * Depending on the ethics committees' and national authorities' feedback and on timepoint of initial submission the number of amendments, the amendment dates, as well as the changes to the protocol may differ between the participating countries. As representative information, the overview of amendments in Germany is given here.

30 July 2021	The main reason for this amendment* was to clarify some statistical aspects. * Depending on the ethics committees' and national authorities' feedback and on timepoint of initial submission the number of amendments, the amendment dates, as well as the changes to the protocol may differ between the participating countries. As representative information, the overview of amendments in Germany is given here.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 January 2018	The study was set on temporary recruitment hold on 12.01.2018. The decision was taken after a meeting with the Pharmacovigilance Risk Assessment Committee (PRAC) and their recommendation to suspend the market authorisation of HES based on the off-label use in certain patient populations (e.g., critically ill or severe sepsis/septic shock patients). Although this did not directly affect the use of HES in the present study in abdominal surgery patients, where patient selection was controlled and in line with the SmPCs, the risk/benefit assessment of the study protocol and the ICF had to be adapted. Recruitment re-started in the respective countries after the approval of the updated protocol and ICF.	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35193648