Clinical trial results:
EARLY ORAL SWITCH THERAPY IN LOW-RISK STAPHYLOCOCCUS AUREUS BLOODSTREAM INFECTION
ACRONYM: SABATO (Staphylococcus Aureus Bacteremia Antibiotic Treatment Options)

Summary

EudraCT number	2013-000577-77
Trial protocol	DE ES NL
Global end of trial date	26 April 2020

Results information

Result version number	v1 (current)
This version publication date	04 October 2022
First version publication date	04 October 2022
Summary attachment (see zip file)	Result Report (SABATO_Ergebnisbericht_v1.4.pdf)

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-1400

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01792804
WHO universal trial number (UTN)	-
Other trial identifiers	German Clinical Trials Register identifier: DRKS00004741

Notes:

Sponsors

Sponsor organisation name	Heinrich-Heine University Düsseldorf
Sponsor organisation address	Universitätsstr. 1, Düsseldorf, Germany, 40225
Public contact	Institute of Medical Microbiology and Hospital Hygiene, Otto-von-Guericke University Magdeburg, 49 3916713392, kerstin.brennecke@med.ovgu.de
Scientific contact	Institute of Medical Microbiology and Hospital Hygiene, Otto-von-Guericke University Magdeburg, 49 3916713392, kerstin.brennecke@med.ovgu.de
Sponsor organisation name	University of Cologne
Sponsor organisation address	Gleueler Str. 269, Cologne, Germany, 50935
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Scientific contact	Institute of Medical Microbiology and Hospital Hygiene, Otto-von-Guericke-University Magdeburg, 49 3916713392, kerstin.brennecke@med.ovgu.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric	No

investigation plan (PIP)	
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	07 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 April 2020
Global end of trial reached?	Yes
Global end of trial date	26 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that in patients with low-risk S. aureus bloodstream infection (SAB) a switch from intravenous to oral antimicrobial therapy (oral switch therapy, OST) is non-inferior to a conventional course of intravenous therapy (intravenous standard therapy, IST).

Protection of trial subjects:

To protect trial subjects a Data Monitoring Committee (DMC) was implemented that regularly discussed trial safety. Furthermore, stopping rules for the trial were defined.

Background therapy:

Before start of the intervention all participants received 5-7 days of adequate intravenous antibiotic therapy.

Evidence for comparator:

Comparator drugs are the current standard of care for Staphylococcus aureus bacteremia. To reduce variability the following licensed drugs were allowed as intravenous treatment: flucloxacillin (cloxacillin in Spain and France), cefazolin, vancomycin, daptomycin.

Actual start date of recruitment	20 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Spain: 64
Country: Number of subjects enrolled	France: 69
Country: Number of subjects enrolled	Germany: 73
Worldwide total number of subjects	213
EEA total number of subjects	213

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)	100
From 65 to 84 years	97
85 years and over	16

Subject disposition

Recruitment

Recruitment details:

Recruitment periods:
Germany: 20 Dec 2013 to 26 Apr 2021
The Netherlands: 17 Jun 2015 to 26 Apr 2021
Spain: 10 Oct 2014 to 26 Apr 2021
France: 12 Jun 2017 to 26 Apr 2021

Pre-assignment

Screening details:

5,330 patients with Staphylococcus aureus bacteremia were screened (5,063 patients with complete basic information). The main inclusion criterion was 5-7 days of adequate intravenous therapy. Main exclusion criteria were polymicrobial bloodstream infection, signs and symptoms of complicated bacteremia, foreign bodies, and severe comorbidity

Period 1

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

Blinding implementation details:

The assessors of the endpoint, the adjudication committee (clinical review committee), were masked regarding treatment arm.

Arms

Are arms mutually exclusive?	Yes
Arm title	OST (oral switch therapy)

Arm description:

Oral Switch Therapy

Arm type	Experimental
Investigational medicinal product name	Trimethoprim-Sulfamethoxazol
Investigational medicinal product code	J01EE51
Other name	Cotrimoxazol; 723-46-6; SUB10711MIG; SUB11310MIG
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

160/800 mg twice daily per os

Investigational medicinal product name	Clindamycin
Investigational medicinal product code	D10AF01
Other name	SUB06665MIG
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Daily dose: 1800 mg in three doses per os

Investigational medicinal product name	Linezolid
Investigational medicinal product code	J01XX08
Other name	SUB08520MIG
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Daily dose: 1200 mg in two doses per os

Arm title	IST (intravenous standard therapy)

Arm description:	
Intravenous Standard Therapy	
Arm type	Active comparator
Investigational medicinal product name	Flucloxacillin
Investigational medicinal product code	J01CF05
Other name	CAS-Nr 5250-39-5; EV code SUB07673MIG
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details:	
recommended daily dose: 8.000 mg i.v. in 4 doses	
Investigational medicinal product name	Cloxacillin
Investigational medicinal product code	J01CF02
Other name	CAS 61-72-3; EV SUB06780MIG
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Recommended daily dose: 8.000 mg in 4 doses	
Investigational medicinal product name	Cefazolin
Investigational medicinal product code	J01DB04
Other name	CAS 25953-19-9; EV SUB07379MIG
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Recommended daily dose: 6.000 mg in 3 doses	
Investigational medicinal product name	Vancomycin
Investigational medicinal product code	A07AA09
Other name	CAS 1404-90-6; EV SUB05076MIG
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Recommended daily dosing: 2.000 mg in 2 doses	
Investigational medicinal product name	Daptomycin
Investigational medicinal product code	J01XX09
Other name	CAS 103060-53-3; EV SUB06910MIG
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Solution for infusion
Dosage and administration details:	
Daily dose: 10 mg/kilogram once per day	

Number of subjects in period 1	OST (oral switch therapy)	IST (intravenous standard therapy)
Started	108	105
Completed	86	79
Not completed	22	26
non-evaluable in per protocol population	22	26

Baseline characteristics

Reporting groups	
Reporting group title	OST (oral switch therapy)
Reporting group description:	
Oral Switch Therapy	
Reporting group title	IST (intravenous standard therapy)
Reporting group description:	
Intravenous Standard Therapy	

Reporting group values	OST (oral switch therapy)	IST (intravenous standard therapy)	Total
Number of subjects	108	105	213
Age categorical			
Units: Subjects			
Adults (18-64 years)	48	52	100
From 65-84 years	50	47	97
85 years and over	10	6	16
Age continuous			
Units: years			
arithmetic mean	64.35	62.56	
standard deviation	± 16.78	± 17.56	-
Gender categorical			
Units: Subjects			
Female	37	28	65
Male	71	77	148
Charlson Comorbidity Index			
Measure for the presence of comorbidities (values = 0 to 21)			
Units: arbitrary			
median	3.00	3.00	
inter-quartile range (Q1-Q3)	1.00 to 5.00	1.00 to 4.00	-

Subject analysis sets	
Subject analysis set title	Per Protocol Analysis
Subject analysis set type	Per protocol
Subject analysis set description:	
The per protocol set includes all study subjects who were essentially treated according to protocol and reached a defined endpoint in the trial (SAB-unrelated deaths will be excluded).	
Subject analysis set title	Intention-to-treat 1
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The intention-to-treat dataset includes all randomized study subjects, analyzed as assigned, with indeterminate and missing outcomes counted as failures. For time-to-event outcomes these cases are censored. The ITT population will be analysed as (ITT-1) any patient randomized, (ITT-2) only patients that were randomized AND received study drug without patients in whom a major inclusion criterion was violated.	
Subject analysis set title	Intention-to-treat 2
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The intention-to-treat dataset includes all randomized study subjects, analyzed as assigned, with	

indeterminate and missing outcomes counted as failures. For time-to-event outcomes these cases are censored. The ITT population will be analysed as (ITT-1) any patient randomized, (ITT-2) only patients that were randomized AND received study drug without patients in whom a major inclusion criterion was violated.

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety set includes all study subjects who received any study drug as treated. Specifically, patients who ever received an oral antibiotic are compared to patients who never received an oral antibiotic.

Reporting group values	Per Protocol Analysis	Intention-to-treat 1	Intention-to-treat 2
Number of subjects	165	213	206
Age categorical Units: Subjects			
Adults (18-64 years)	81	100	96
From 65-84 years	75	97	95
85 years and over	9	16	15
Age continuous Units: years			
arithmetic mean	62.22	63.47	63.50
standard deviation	± 17.41	± 17.15	± 17.16
Gender categorical Units: Subjects			
Female	48	65	62
Male	117	148	144
Charlson Comorbidity Index			
Measure for the presence of comorbidities (values = 0 to 21)			
Units: arbitrary			
median	2.00	3.00	3.00
inter-quartile range (Q1-Q3)	1.0 to 4.0	1.0 to 5.0	1.0 to 5.0

Reporting group values	Safety Set		
Number of subjects	210		
Age categorical Units: Subjects			
Adults (18-64 years)	99		
From 65-84 years	95		
85 years and over	16		
Age continuous Units: years			
arithmetic mean	63.42		
standard deviation	± 17.20		
Gender categorical Units: Subjects			
Female	65		
Male	145		
Charlson Comorbidity Index			
Measure for the presence of comorbidities (values = 0 to 21)			
Units: arbitrary			
median	3.00		
inter-quartile range (Q1-Q3)	1.00 to 5.00		

End points

End points reporting groups

Reporting group title	OST (oral switch therapy)
Reporting group description: Oral Switch Therapy	
Reporting group title	IST (intravenous standard therapy)
Reporting group description: Intravenous Standard Therapy	
Subject analysis set title	Per Protocol Analysis
Subject analysis set type	Per protocol
Subject analysis set description: The per protocol set includes all study subjects who were essentially treated according to protocol and reached a defined endpoint in the trial (SAB-unrelated deaths will be excluded).	
Subject analysis set title	Intention-to-treat 1
Subject analysis set type	Intention-to-treat
Subject analysis set description: The intention-to-treat dataset includes all randomized study subjects, analyzed as assigned, with indeterminate and missing outcomes counted as failures. For time-to-event outcomes these cases are censored. The ITT population will be analysed as (ITT-1) any patient randomized, (ITT-2) only patients that were randomized AND received study drug without patients in whom a major inclusion criterion was violated.	
Subject analysis set title	Intention-to-treat 2
Subject analysis set type	Intention-to-treat
Subject analysis set description: The intention-to-treat dataset includes all randomized study subjects, analyzed as assigned, with indeterminate and missing outcomes counted as failures. For time-to-event outcomes these cases are censored. The ITT population will be analysed as (ITT-1) any patient randomized, (ITT-2) only patients that were randomized AND received study drug without patients in whom a major inclusion criterion was violated.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: The safety set includes all study subjects who received any study drug as treated. Specifically, patients who ever received an oral antibiotic are compared to patients who never received an oral antibiotic.	

Primary: SAB-related complications

End point title	SAB-related complications
End point description: Staphylococcus aureus bloodstream infection-related complications is a composite endpoint consisting of relapsing SAB, deep-seated infection with S. aureus, or attributable mortality all within 90 days.	
End point type	Primary
End point timeframe: Follow-up period of 90 days	

End point values	OST (oral switch therapy)	IST (intravenous standard therapy)	Per Protocol Analysis	Intention-to-treat 1
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	108	105	165	213
Units: patients	14	13	7	27

End point values	Intention-to-treat 2			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: patients	22			

Statistical analyses

Statistical analysis title	Zhao's test

Statistical analysis description:

The primary endpoint SAB-related complications (relapsing SAB, deep-seated infection with S. aureus, or mortality attributable to SAB) within 90 days will be evaluated regarding non-inferiority of oral vs. intravenous antimicrobial therapy by Zhao's test (test 1) of non-null hypothesis on proportions stratified by study center at one-sided level 5% and with a non-inferiority margin of 10%.

Comparison groups	OST (oral switch therapy) v IST (intravenous standard therapy)
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.013 [2]
Method	Zhao's test 1
Parameter estimate	Risk difference (RD)
Point estimate	0.0065
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0666
upper limit	0.0797

Notes:

[1] - (A) (null hypothesis) H0: pOST > pIST + 0.10 vs (alternative hypothesis) Ha: pOST ≤ pIST + 0.10
If this null hypothesis can be rejected (alpha=5%, one-sided), the above hypothesis (A) will be tested again at one-sided alpha=2.5%.
(B) If the above second null hypothesis can also be rejected, the non-inferiority margin of 5% will be applied.
If the null hypothesis can be rejected (alpha=5%, one-sided), the hypothesis will be tested again at one-sided alpha=2.5%.
[2] - (A) ITT-1; (B) p=0.2075, ITT-1 (PP: (A) p<0.0001, (B) p=0.0095; ITT-2: (A) p=0.0024, (B) p=0.0882)

Secondary: Length of hospital stay

End point title	Length of hospital stay

End point description:

Length of hospital stay

End point type	Secondary

End point timeframe:

90 days

End point values	OST (oral switch therapy)	IST (intravenous standard therapy)	Per Protocol Analysis	Intention-to-treat 1
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	108	105	165	213
Units: days				
arithmetic mean (standard deviation)	17.38 (± 15.80)	18.76 (± 14.58)	16.49 (± 14.11)	18.06 (± 15.19)

End point values	Intention-to-treat 2			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: days				
arithmetic mean (standard deviation)	18.04 (± 15.37)			

Statistical analyses

Statistical analysis title	Time-to-event analysis

Statistical analysis description:

Kaplan-Meier curves and log-rank test. Patients who died in hospital or were discharged counted as event.

Comparison groups	OST (oral switch therapy) v IST (intravenous standard therapy)
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0551 [3]
Method	Wilcoxon test

Notes:

[3] - ITT-1, two-sided (PP: p=0.0199; ITT-2: p=0.0295)

Secondary: 14-day survival

End point title	14-day survival

End point description:

Survival at 14 days

End point type	Secondary

End point timeframe:

14 days

End point values	OST (oral switch therapy)	IST (intravenous standard therapy)	Per Protocol Analysis	Intention-to-treat 1
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	108	105	165	213
Units: patients	2	0	1	2

End point values	Intention-to-treat 2			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: patients	1			

Statistical analyses

Statistical analysis title	Time-to-event analysis
Statistical analysis description: Kaplan-Meier curves and log-rank test	
Comparison groups	OST (oral switch therapy) v IST (intravenous standard therapy)
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1633 [4]
Method	Logrank

Notes:
[4] - ITT-1, two-sided (PP: p=0.3378; ITT-2: p=0.3268)

Secondary: Complications of intravenous therapy

End point title	Complications of intravenous therapy
End point description: Complications of intravenous therapy, such as thrombophlebitis	
End point type	Secondary
End point timeframe: 90 days	

End point values	OST (oral switch therapy)	IST (intravenous standard therapy)	Per Protocol Analysis	Intention-to-treat 1
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	108	105	165	213
Units: persons	20	22	19	42

End point values	Intention-to-treat 2			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: persons	38			

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	IST (intravenous standard therapy) v OST (oral switch therapy)
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7314 [5]
Method	Fisher exact

Notes:

[5] - ITT-1, two-sided (PP: p=0.0856; ITT-2: p=0.7200)

Secondary: 30-day survival

End point title	30-day survival
End point description: Survival at 14, 30, and 90 days	
End point type	Secondary
End point timeframe: 30 days	

End point values	OST (oral switch therapy)	IST (intravenous standard therapy)	Per Protocol Analysis	Intention-to-treat 1
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	108	105	165	213
Units: patients	6	4	2	10

End point values	Intention-to-treat 2			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: patients	9			

Statistical analyses

Statistical analysis title	Time-to-event analysis
Statistical analysis description: Kaplan-Meier curves and log-rank test	
Comparison groups	OST (oral switch therapy) v IST (intravenous standard therapy)
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5362 [6]
Method	Logrank

Notes:
[6] - ITT-1, two-sided (PP: p=0.9552; ITT-2: p=0.7579)

Secondary: 90-day survival

End point title	90-day survival
End point description:	
End point type	Secondary
End point timeframe: 90 days	

End point values	OST (oral switch therapy)	IST (intravenous standard therapy)	Per Protocol Analysis	Intention-to-treat 1
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	108	105	165	213
Units: patients	17	11	10	28

End point values	Intention-to-treat 2			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: patients	27			

Statistical analyses

Statistical analysis title	Time-to-event analysis
Statistical analysis description: Kaplan-Meier curves and log-rank test	
Comparison groups	IST (intravenous standard therapy) v OST (oral switch therapy)
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2614 [7]
Method	Logrank

Notes:
[7] - ITT-1, two-sided (PP: p=0.6155; ITT-2: p=0.3546)

Other pre-specified: Clostridium difficile associated diarrhea

End point title	Clostridium difficile associated diarrhea
End point description: Clostridium difficile associated diarrhea	
End point type	Other pre-specified
End point timeframe: 90 days	

End point values	OST (oral switch therapy)	IST (intravenous standard therapy)	Per Protocol Analysis	Intention-to-treat 1
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	108	105	165	213
Units: patients	14	12	3	26

End point values	Intention-to-treat 2			
Subject group type	Subject analysis set			
Number of subjects analysed	206			
Units: patients	22			

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	IST (intravenous standard therapy) v OST (oral switch therapy)

Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8351 [8]
Method	Fisher exact

Notes:

[8] - ITT-1, two-sided (PP: p=1.0000; ITT-2: p=0.8229)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE were systematically assessed at 30 days and 90 days. Additionally, adverse events were reported to the study sites by the patients when the AE occured.

Adverse event reporting additional description:

Adverse events were recorded from CTCAE grade 3 or higher. Relatedness was classified as "related" (classification terms used in the study: certain, probably/likely, possible, conditional/unclassified, unassessable/unclassifiable) and "unrelated" (study term: unlikely).
Analysis of adverse was events based on the safety set.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	OST (oral switch therapy)
Reporting group description: -	
Reporting group title	IST (intravenous standard therapy)

Reporting group description: -

Serious adverse events	OST (oral switch therapy)	IST (intravenous standard therapy)	
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 107 (38.32%)	32 / 103 (31.07%)	
number of deaths (all causes)	18	12	
number of deaths resulting from adverse events	18	12	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma	Additional description: B-cell lymphoma		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma	Additional description: Bronchial carcinoma		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma stage IV	Additional description: Malignant melanoma stage IV		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatocellular carcinoma	Additional description: Hepatocellular carcinoma		

subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ovarian cancer metastatic	Additional description: Ovarian cancer metastatic		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer	Additional description: Prostate cancer		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic neoplasm	Additional description: Pancreatic neoplasm		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Aortic dissection	Additional description: Aortic dissection		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Peripheral arterial occlusive disease	Additional description: Peripheral arterial occlusive disease		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic	Additional description: Shock haemorrhagic		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia	Additional description: Asthenia		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Disease progression	Additional description: Disease progression		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise	Additional description: Malaise		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing	Additional description: Impaired healing		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema	Additional description: Generalised oedema		
subjects affected / exposed	2 / 107 (1.87%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration	Additional description: General physical health deterioration		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain	Additional description: Pain		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (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			
Bronchospasm	Additional description: Bronchospasm		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease	Additional description: Chronic obstructive pulmonary disease		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal fistula	Additional description: Pharyngeal fistula		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism	Additional description: Pulmonary embolism		
subjects affected / exposed	1 / 107 (0.93%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia aspiration	Additional description: Pneumonia aspiration		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure	Additional description: Respiratory failure		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Fall	Additional description: Fall		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture	Additional description: Facial bones fracture		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Toxicity to various agents	Additional description: Toxicity to various agents		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction	Additional description: Acute myocardial infarction		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial flutter	Additional description: Atrial flutter		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest	Additional description: Cardiac arrest		
subjects affected / exposed	1 / 107 (0.93%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure	Additional description: Cardiac failure		
subjects affected / exposed	1 / 107 (0.93%)	3 / 103 (2.91%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	1 / 1	0 / 3	
Cardio-respiratory arrest	Additional description: Cardio-respiratory arrest		
subjects affected / exposed	3 / 107 (2.80%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Myocardial ischaemia	Additional description: Myocardial ischaemia		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Left ventricular failure	Additional description: Left ventricular failure		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			

Syncope	Additional description: Syncope		
subjects affected / exposed	1 / 107 (0.93%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy	Additional description: Hepatic encephalopathy		
subjects affected / exposed	1 / 107 (0.93%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	2 / 107 (1.87%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal lymphadenopathy	Additional description: Retroperitoneal lymphadenopathy		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sickle cell anaemia with crisis	Additional description: Sickle cell anaemia with crisis		
subjects affected / exposed	1 / 107 (0.93%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenic purpura	Additional description: Thrombocytopenic purpura		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis	Additional description: Gastritis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (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: Intestinal ischaemia		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Vomiting	Additional description: Vomiting		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage	Additional description: Upper gastrointestinal haemorrhage		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage	Additional description: Rectal haemorrhage		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis acute	Additional description: Hepatitis acute		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic hepatitis	Additional description: Ischaemic hepatitis		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Petechiae	Additional description: Petechiae		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure	Additional description: Renal failure		

subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess	Additional description: Anal abscess		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess	Additional description: Abscess		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial	Additional description: Arthritis bacterial		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis	Additional description: Clostridium difficile colitis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis	Additional description: Endocarditis		
subjects affected / exposed	0 / 107 (0.00%)	2 / 103 (1.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis	Additional description: Osteomyelitis		
subjects affected / exposed	1 / 107 (0.93%)	2 / 103 (1.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection	Additional description: Klebsiella infection		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (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: Infection		

subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (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: Peritonitis	
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Pneumonia	Additional description: Pneumonia	
subjects affected / exposed	1 / 107 (0.93%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Postoperative wound infection	Additional description: Postoperative wound infection	
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory tract infection	Additional description: Respiratory tract infection	
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Pseudomembranous colitis	Additional description: Pseudomembranous colitis	
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Sepsis	Additional description: Sepsis	
subjects affected / exposed	4 / 107 (3.74%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0
Septic shock	Additional description: Septic shock	
subjects affected / exposed	2 / 107 (1.87%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Skin bacterial infection	Additional description: Skin bacterial infection	

subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia	Additional description: Staphylococcal bacteraemia		
subjects affected / exposed	1 / 107 (0.93%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection staphylococcal	Additional description: Urinary tract infection staphylococcal		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection	Additional description: Wound infection		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus	Additional description: Diabetes mellitus		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
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: 0 %

Non-serious adverse events	OST (oral switch therapy)	IST (intravenous standard therapy)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 107 (18.69%)	17 / 103 (16.50%)	
Vascular disorders			
Hypertension	Additional description: Hypertension		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	

Phlebitis	Additional description: Phlebitis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Poor venous access	Additional description: Poor venous access		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia	Additional description: Asthenia		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Oedema	Additional description: Oedema		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	3 / 107 (2.80%)	1 / 103 (0.97%)	
occurrences (all)	3	1	
Pain	Additional description: Pain		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Transplant rejection	Additional description: Transplant rejection		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease	Additional description: Chronic obstructive pulmonary disease		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Pulmonary oedema	Additional description: Pulmonary oedema		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Pulmonary embolism	Additional description: Pulmonary embolism		

subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Pleurisy	Additional description: Pleurisy		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Hypoxia	Additional description: Hypoxia		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Investigations			
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme increased	Additional description: Hepatic enzyme increased		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Cardiac disorders			
Coronary artery disease	Additional description: Coronary artery disease		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Depressed level of consciousness	Additional description: Depressed level of consciousness		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Ischaemic stroke	Additional description: Ischaemic stroke		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	1 / 107 (0.93%)	2 / 103 (1.94%)	
occurrences (all)	1	2	
Eye disorders			
Cataract	Additional description: Cataract		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Colitis ulcerative	Additional description: Colitis ulcerative		

subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Constipation	Additional description: Constipation		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Diverticulum intestinal	Additional description: Diverticulum intestinal		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis atopic	Additional description: Dermatitis atopic		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Urinary retention	Additional description: Urinary retention		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Back pain		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Gouty arthritis	Additional description: Gouty arthritis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Erysipelas	Additional description: Erysipelas		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Cystitis	Additional description: Cystitis		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	

Influenza	Additional description: Influenza		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	1 / 107 (0.93%)	1 / 103 (0.97%)	
occurrences (all)	1	1	
Wound infection	Additional description: Wound infection		
subjects affected / exposed	1 / 107 (0.93%)	1 / 103 (0.97%)	
occurrences (all)	1	1	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	4 / 107 (3.74%)	1 / 103 (0.97%)	
occurrences (all)	4	1	
Pseudomonas infection	Additional description: Pseudomonas infection		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Malnutrition	Additional description: Malnutrition		
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences (all)	0	1	
Electrolyte imbalance	Additional description: Electrolyte imbalance		
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 December 2014	In amendment I, in- and exclusion criteria were relaxed to facilitate enrolment.
20 July 2016	Amendment II, change of sponsor
20 March 2018	Amendment III, adjustment of sample size, conversion of interim analysis to final analysis
18 July 2019	Amendment IV, extension of the recruitment period

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 June 2018	The trial was suspended on advice from the Data Monitoring Committee (DMC). After a more detailed data analysis, the DMC recommended to proceed with enrolment.	18 July 2018

Notes:

Limitations and caveats

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

Sample size was adjusted during the trial and the initially planned interim analysis was converted into the final analysis.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26452342

http://www.ncbi.nlm.nih.gov/pubmed/32051007