Clinical trial results:
Prospective, randomized, multicenter clinical trial on the impact of Therapeutic Drug Monitoring (TDM) of piperacillin on organ functions and survival in the treatment of severe sepsis or septic shock

Summary

EudraCT number	2016-000136-17
Trial protocol	DE
Global end of trial date	06 January 2020

Results information

Result version number	v1 (current)
This version publication date	02 October 2021
First version publication date	02 October 2021

Trial information

Trial identification

Sponsor protocol code	Target_ZKSJ0085

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Friedrich-Schiller-Universität Jena
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 January 2020
Global end of trial reached?	Yes
Global end of trial date	06 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

As the primary goal of the study, it needs to be established whether an optimisation of antimicrobial therapy by individual dose adjustment of the test substance Piperacillin has a beneficial impact on organ function in severe sepsis or septic shock and whether it is superiour to dosage following prescribing information. This should be examined on the basis of global morbidity measurement (mean total SOFA-score).

Protection of trial subjects:

(S)AEs have been documend and reported as appropriate. According to protocol, patients were followed up.
Pre-determined safety-relevant data were submitted to the DSMB at regular intervals, on the basis of which recommendations for the continuation of the study were made. Furthermore, adverse events and serious adverse events were reported in both study arms.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2016
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	Germany: 253
Worldwide total number of subjects	253
EEA total number of subjects	253

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)	98

From 65 to 84 years	155
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment: 26.01.2017 to 09.12.2020 in 10 study Centers, all in Germany

Pre-assignment

Screening details:

1020 patients were screened. 254 patients could be randomized. There was no declaration of consent for a patient who had already been randomized to the TDM group, so that a total of 253 patients were included in the analysis .

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Masking: open-Label; Doctor open, Patient blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	PipTDM (Experimental Group)

Arm description:

In the experimental group, the continuous intravenous infusion of the test substance (Piperacillin / Tazobactam (TZP)) was carried out after bolus administration with regular determination of the serum concentration of piperacillin with subsequent, patient-specific dose adjustment of piperacillin / tazobactam, in relation to the sepsis pathogen. Continuous infusion of piperacillin/tazobactam is guided by an algorithm-based daily TDM at the 4xMIC of the infecting organism, starting 24 hours after the loading dose.
Starting on day 1 after randomization up to and including day 10 or ending of the therapy with piperacillin, the daily determination of the serum concentration of piperacillin was carried out with an individual dose adjustment tailored to the minimum inhibitory concentration of the pathogen causing the sepsis.

Arm type	Experimental
Investigational medicinal product name	Piperacillin/Tazobactam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

- Patients without pretretement with piperacillin: After randomization a bolus of TZP (4.5g) over 30 minutes and immediately afterwards continuous intravenous infusion of TZP, depending on the current kidney function in the following dosage (running rate perfusor, 4.5g.) / 50ml NaCl 0.9%):
• eGFR ≥ 20 ml / min 13.5 g / 24 h (6.3 ml / h)
• eGFR <20 ml / min 9 g / 24 h (4.2 ml / h)
- Patients with pretrement with piperacillin within the last 24 hours: bolus administration was omitted, after randomization continuous intravenous infusion of piperacillin / tazobactam, depending on the current kidney function in the following dosage (flow rate perfusor, 4.5g / 50ml NaCl 0.9%):
• eGFR ≥ 20 ml / min 13.5 g / 24 h (6.3 ml / h)
• eGFR < 20 ml/min 9g/24h (4.2 ml / h)

Arm title	PipKon (Control Group)

Arm description:

In the control group, the continuous intravenous infusion of the test substance after bolus administration in the dose according to the technical information. In the case of renal insufficiency, the dosage was adjusted according to the product information.

Arm type	Active comparator
Investigational medicinal product name	Piperacillin/Tazobactam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

- Patients without pretreatment with piperacillin: After randomization, a bolus of piperacillin / tazobactam (4.5g) was given over 30 minutes and immediately afterwards continuous intravenous infusion of TZP, depending on the renal function, in the following dosage (FRP, 4.5g / 50ml NaCl 0.9%), was started:
• eGFR ≥ 20 ml / min 13.5g / 24 h (6.3 ml / h)
• eGFR <20 ml / min 9g / 24 h (4.2 ml / h)
- Patients with pretreatment with piperacillin: bolus administration was omitted, after randomization the cont. intrav. infusion of TZP was carried out, depending on the kidney function in the follow. dosage (FRP, 4.5g / 50ml NaCl 0.9%):
• eGFR ≥ 20 ml / min 13.5g / 24 h (6.3 ml / h)
• eGFR <20 ml / min 9g / 24 h (4.2 ml/h)
If the kidney function changed in the further course of therapy, the dosage of TZP in the control group was adjusted according to the following specifications:
• eGFR ≥ 20 ml/min or cont. RRT: 13.5g/24 h (6,3 ml/h)
• eGFR < 20 ml/min or iHD: 9g/24 h (4,2 ml/h)

Number of subjects in period 1	PipTDM (Experimental Group)	PipKon (Control Group)
Started	126	127
Completed	125	124
Not completed	1	3
Adverse event, serious fatal	-	1
Lost to follow-up	1	-
Protocol deviation	-	2

Baseline characteristics

Reporting groups

Reporting group title	PipTDM (Experimental Group)

Reporting group description:

In the experimental group, the continuous intravenous infusion of the test substance (Piperacillin / Tazobactam (TZP)) was carried out after bolus administration with regular determination of the serum concentration of piperacillin with subsequent, patient-specific dose adjustment of piperacillin / tazobactam, in relation to the sepsis pathogen. Continuous infusion of piperacillin/tazobactam is guided by an algorithm-based daily TDM at the 4xMIC of the infecting organism, starting 24 hours after the loading dose.
Starting on day 1 after randomization up to and including day 10 or ending of the therapy with piperacillin, the daily determination of the serum concentration of piperacillin was carried out with an individual dose adjustment tailored to the minimum inhibitory concentration of the pathogen causing the sepsis.

Reporting group title	PipKon (Control Group)

Reporting group description:

In the control group, the continuous intravenous infusion of the test substance after bolus administration in the dose according to the technical information. In the case of renal insufficiency, the dosage was adjusted according to the product information.

Reporting group values	PipTDM (Experimental Group)	PipKon (Control Group)	Total
Number of subjects	126	127	253
Age categorical Units: Subjects			
Adults (18-64 years)	44	54	98
85 years and over	0	0	0
>= 65 years	82	73	155
Age continuous Units: years			
median	69.5	66	
inter-quartile range (Q1-Q3)	59 to 78	57 to 76	-
Gender categorical Units: Subjects			
Female	46	35	81
Male	80	92	172

Subject analysis sets

Subject analysis set title	primary analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Primary and secondary outcomes were evaluated in the intent-to-treat population, to which all randomized patients belong according to their randomly assigned group membership. Base data and target values were group-specific described by suitable statistical parameters (mean value, standard deviation, 25th, 50th, 75th percentile, interquartile range, absolute and relative frequencies). The primary outcome measure is the SOFA score. It is included in the analysis as an individual mean over the course of day 1 after randomization until discharge from the ITS or until death, but no more than day 10. The difference between the intervention arms was evaluated confirmatory using a mixed linear model. Fixed factors are intervention and the SOFA score at the time of randomization (baseline).

Reporting group values	primary analysis		
Number of subjects	253		
Age categorical Units: Subjects			
Adults (18-64 years)	98		
85 years and over	0		
>= 65 years	155		
Age continuous Units: years			
median	68		
inter-quartile range (Q1-Q3)	57 to 78		
Gender categorical Units: Subjects			
Female	81		
Male	172		

End points

End points reporting groups

Reporting group title	PipTDM (Experimental Group)

Reporting group description:

In the experimental group, the continuous intravenous infusion of the test substance (Piperacillin / Tazobactam (TZP)) was carried out after bolus administration with regular determination of the serum concentration of piperacillin with subsequent, patient-specific dose adjustment of piperacillin / tazobactam, in relation to the sepsis pathogen. Continuous infusion of piperacillin/tazobactam is guided by an algorithm-based daily TDM at the 4xMIC of the infecting organism, starting 24 hours after the loading dose.
Starting on day 1 after randomization up to and including day 10 or ending of the therapy with piperacillin, the daily determination of the serum concentration of piperacillin was carried out with an individual dose adjustment tailored to the minimum inhibitory concentration of the pathogen causing the sepsis.

Reporting group title	PipKon (Control Group)

Reporting group description:

In the control group, the continuous intravenous infusion of the test substance after bolus administration in the dose according to the technical information. In the case of renal insufficiency, the dosage was adjusted according to the product information.

Subject analysis set title	primary analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Primary and secondary outcomes were evaluated in the intent-to-treat population, to which all randomized patients belong according to their randomly assigned group membership. Base data and target values were group-specific described by suitable statistical parameters (mean value, standard deviation, 25th, 50th, 75th percentile, interquartile range, absolute and relative frequencies). The primary outcome measure is the SOFA score. It is included in the analysis as an individual mean over the course of day 1 after randomization until discharge from the ITS or until death, but no more than day 10. The difference between the intervention arms was evaluated confirmatory using a mixed linear model. Fixed factors are intervention and the SOFA score at the time of randomization (baseline).

Primary: SOFA-Score

End point title	SOFA-Score

End point description:

It should be determined whether and to what extent the TDM-based piperacillin therapy represents a benefit for the patient's organ function.

End point type	Primary

End point timeframe:

individually averaged from day 1 after randomization to discharge from ITS or until death, but no more than day 10

End point values	PipTDM (Experimental Group)	PipKon (Control Group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: Points				
arithmetic mean (confidence interval 95%)	7.9 (7.1 to 8.8)	8.2 (7.4 to 9.1)		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	PipKon (Control Group) v PipTDM (Experimental Group)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.389
Method	Chi-squared

Secondary: 28-days Mortality

End point title	28-days Mortality
End point description:	
End point type	Secondary
End point timeframe:	
28 days	

End point values	PipTDM (Experimental Group)	PipKon (Control Group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: days	27	32		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	PipTDM (Experimental Group) v PipKon (Control Group)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.435
Method	Chi-squared

Secondary: length of hospital stay	
End point title	length of hospital stay
End point description:	
End point type	Secondary
End point timeframe: up to 28 days	

End point values	PipTDM (Experimental Group)	PipKon (Control Group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: days				
median (inter-quartile range (Q1-Q3))	24 (15 to 28)	25 (15 to 28)		

Statistical analyses

Statistical analysis title	kaplan-Meier analysis
Comparison groups	PipKon (Control Group) v PipTDM (Experimental Group)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.486
Method	Logrank

Secondary: length of ICU stay	
End point title	length of ICU stay
End point description:	
End point type	Secondary
End point timeframe: up to 28 days	

End point values	PipTDM (Experimental Group)	PipKon (Control Group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: days				
median (inter-quartile range (Q1-Q3))	9 (4 to 15)	11 (7 to 17)		

Statistical analyses

Statistical analysis title	kaplan-Meier analysis
Comparison groups	PipTDM (Experimental Group) v PipKon (Control Group)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.698
Method	Logrank

Secondary: SOFA Subscore: Respiratory

End point title	SOFA Subscore: Respiratory
End point description:	
End point type	Secondary
End point timeframe: day 1 to 10	

End point values	PipTDM (Experimental Group)	PipKon (Control Group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: points				
median (inter-quartile range (Q1-Q3))	2.5 (2 to 3)	2.5 (2 to 2.9)		

Statistical analyses

Statistical analysis title	Mann-Whitney-U test
Comparison groups	PipTDM (Experimental Group) v PipKon (Control Group)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.445
Method	Wilcoxon (Mann-Whitney)

Secondary: SOFA Subscore: central nervous system

End point title	SOFA Subscore: central nervous system

End point description:

End point type	Secondary

End point timeframe:

day 1 to 10

End point values	PipTDM (Experimental Group)	PipKon (Control Group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: points				
median (inter-quartile range (Q1-Q3))	0.1 (0 to 1.2)	0.3 (0 to 1.3)		

Statistical analyses

Statistical analysis title	Mann-Whitney-U test
Comparison groups	PipTDM (Experimental Group) v PipKon (Control Group)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	Wilcoxon (Mann-Whitney)

Secondary: SOFA Subscore: liver function

End point title	SOFA Subscore: liver function

End point description:

End point type	Secondary

End point timeframe:

day 1 to 10

End point values	PipTDM (Experimental Group)	PipKon (Control Group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: points				
median (inter-quartile range (Q1-Q3))	0 (0 to 0.4)	0 (0 to 0.6)		

Statistical analyses

Statistical analysis title	Mann-Whitney-U test
Comparison groups	PipTDM (Experimental Group) v PipKon (Control Group)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.872
Method	Wilcoxon (Mann-Whitney)

Secondary: SOFA Subscore: cardiovascular system

End point title	SOFA Subscore: cardiovascular system
End point description:	
End point type	Secondary
End point timeframe: day 1 to 10	

End point values	PipTDM (Experimental Group)	PipKon (Control Group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: points				
median (inter-quartile range (Q1-Q3))	2 (1 to 3)	2 (1.2 to 3.2)		

Statistical analyses

Statistical analysis title	Mann-Whitney-U test
Comparison groups	PipTDM (Experimental Group) v PipKon (Control Group)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.808
Method	Wilcoxon (Mann-Whitney)

Secondary: SOFA Subscore: blood coagulation	
End point title	SOFA Subscore: blood coagulation
End point description:	

End point type	Secondary
End point timeframe:	
day 1 to 10	

End point values	PipTDM (Experimental Group)	PipKon (Control Group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: points				
median (inter-quartile range (Q1-Q3))	0.1 (0 to 1)	0 (0 to 0.8)		

Statistical analyses

Statistical analysis title	Mann-Whitney-U test
Comparison groups	PipTDM (Experimental Group) v PipKon (Control Group)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.541
Method	Wilcoxon (Mann-Whitney)

Secondary: SOFA Subscore: renal function	
End point title	SOFA Subscore: renal function
End point description:	

End point type	Secondary
End point timeframe:	
day 1 to 10	

End point values	PipTDM (Experimental Group)	PipKon (Control Group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: points				
median (inter-quartile range (Q1-Q3))	0.5 (0 to 1.5)	0.8 (0 to 2)		

Statistical analyses

Statistical analysis title	Mann-Whitney-U test
Comparison groups	PipTDM (Experimental Group) v PipKon (Control Group)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.404
Method	Wilcoxon (Mann-Whitney)

Secondary: Number of vasopressor free days

End point title	Number of vasopressor free days
End point description:	
End point type	Secondary
End point timeframe: up to day 14	

End point values	PipTDM (Experimental Group)	PipKon (Control Group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: points				
median (inter-quartile range (Q1-Q3))	11 (2 to 13)	9 (2 to 12)		

Statistical analyses

Statistical analysis title	Mann-Whitney-U test
Comparison groups	PipTDM (Experimental Group) v PipKon (Control Group)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.141
Method	Wilcoxon (Mann-Whitney)

Secondary: Number of mechanical ventilation free days	
End point title	Number of mechanical ventilation free days
End point description:	
End point type	Secondary
End point timeframe: up to day 28	

End point values	PipTDM (Experimental Group)	PipKon (Control Group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: points				
median (inter-quartile range (Q1-Q3))	20 (5 to 27)	18.5 (1 to 25)		

Statistical analyses

Statistical analysis title	Mann-Whitney-U test
Comparison groups	PipTDM (Experimental Group) v PipKon (Control Group)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	Wilcoxon (Mann-Whitney)

Secondary: Number of renal replacement therapy free days	
End point title	Number of renal replacement therapy free days
End point description:	
End point type	Secondary
End point timeframe: up to day 28	

End point values	PipTDM (Experimental Group)	PipKon (Control Group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: points				
median (inter-quartile range (Q1-Q3))	28 (21 to 28)	28 (10 to 28)		

Statistical analyses

Statistical analysis title	Mann-Whitney-U test
Comparison groups	PipTDM (Experimental Group) v PipKon (Control Group)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.329
Method	Wilcoxon (Mann-Whitney)

Secondary: cumultative dose Pip/Taz

End point title	cumultative dose Pip/Taz
End point description:	
End point type	Secondary
End point timeframe: from day 1 to day 10	

End point values	PipTDM (Experimental Group)	PipKon (Control Group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: mg				
median (inter-quartile range (Q1-Q3))	48296 (25803 to 79273)	58399 (28702 to 88452)		

Statistical analyses

Statistical analysis title	Mann-Whitney-U test
Comparison groups	PipTDM (Experimental Group) v PipKon (Control Group)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.35
Method	Wilcoxon (Mann-Whitney)

Secondary: cumultative dose Pip/Taz per day

End point title	cumultative dose Pip/Taz per day

End point description:

End point type	Secondary

End point timeframe:
dose of piperacillin / tazobactam per day

End point values	PipTDM (Experimental Group)	PipKon (Control Group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: mg				
median (inter-quartile range (Q1-Q3))	9106 (6486 to 12503)	10433 (8151 to 11700)		

Statistical analyses

Statistical analysis title	Mann-Whitney-U test
Comparison groups	PipTDM (Experimental Group) v PipKon (Control Group)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.119
Method	Wilcoxon (Mann-Whitney)

Secondary: duration of antibiotica therapy

End point title	duration of antibiotica therapy

End point description:
duration of antibiotika therapy

End point type	Secondary

End point timeframe:
day

End point values	PipTDM (Experimental Group)	PipKon (Control Group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: days	5	5		

Statistical analyses

Statistical analysis title	Mann-Whitney-U test
Comparison groups	PipTDM (Experimental Group) v PipKon (Control Group)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81
Method	Wilcoxon (Mann-Whitney)

Secondary: Number of antibiotics free days

End point title	Number of antibiotics free days
End point description:	
End point type	Secondary
End point timeframe: number of days without antibiotics (up to day 14)	

End point values	PipTDM (Experimental Group)	PipKon (Control Group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: days				
median (inter-quartile range (Q1-Q3))	8 (6 to 12)	8 (5 to 11)		

Statistical analyses

Statistical analysis title	Mann-Whitney-U test
Comparison groups	PipTDM (Experimental Group) v PipKon (Control Group)

Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.194
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The detection of AEs begins with the first dose of test medication after randomization. The end of AE detection is reached 24h after the last test medication (max. day 10)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	PipTDM group

Reporting group description:

The dose adjustment of piperacillin/tazobactam follows a predefined scheme depending on the measured Piperacillin concentration. Starting on day 1 after randomization, the daily determination of the piperacillin concentration is carried out, individually adjusted to the minimum inhibitory concentration (MIC) of the pathogen causing the sepsis.

Reporting group title	PipKon group

Reporting group description:

Piperacillin/tazobactam is also administered in this study arm, . In accordance with in-house Standards, depending on the kidney function in the following dosage (flow rate perfusor, 4.5g / 50ml NaCl 0.9%).

Serious adverse events	PipTDM group	PipKon group	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 126 (5.56%)	8 / 127 (6.30%)	
number of deaths (all causes)	27	32	
number of deaths resulting from adverse events	3	3	
Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	1 / 126 (0.79%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 126 (0.79%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	0 / 126 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Nervous system disorders			
Brain injury			
subjects affected / exposed	0 / 126 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Central nervous system haemorrhage			
subjects affected / exposed	0 / 126 (0.00%)	2 / 127 (1.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Multi-organ disorder			
subjects affected / exposed	1 / 126 (0.79%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	1 / 126 (0.79%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ulceration and perforation			
subjects affected / exposed	2 / 126 (1.59%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural disorder			
subjects affected / exposed	1 / 126 (0.79%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			

subjects affected / exposed	0 / 126 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 126 (0.00%)	1 / 127 (0.79%)	
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	PipTDM group	PipKon group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 126 (9.52%)	12 / 127 (9.45%)	
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	12 / 126 (9.52%)	12 / 127 (9.45%)	
occurrences (all)	12	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2017	Changes in the protocol included the deletion of the principal exclusion criteria "Renal insufficiency (acute or chronic) with renal replacement therapy or the need for renal replacement therapy expected within the following 6 hours after randomization" and the extension of the duration of the study from 18 Months to 36 Months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported