Clinical trial results:
Therapeutic drug monitoring (TDM) for personalized antibiotic treatment with piperacillin-tazobactam (PipTaz) in patients with febrile neutropenia after myelo-suppressive cytostatic chemotherapy

Summary

EudraCT number	2016-002388-33
Trial protocol	DE
Global end of trial date	06 June 2018

Results information

Result version number	v1 (current)
This version publication date	09 December 2020
First version publication date	09 December 2020
Summary attachment (see zip file)	Study Report (TARGET-FN_Ergebnisbericht_Final_20190529_sign.pdf)

Trial information

Trial identification

Sponsor protocol code	ZKSJ0086

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Friedrich-Schiller University Jena
Sponsor organisation address	Bachstraße 18, Jena, Germany, 07743
Public contact	Prof. Marie von Lilienfeld-Toal, Jena University Hospital , +49 364193924210, marie.von_lilienfeld-toal@med.uni-jena.de
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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	07 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 June 2018
Global end of trial reached?	Yes
Global end of trial date	06 June 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary goal of the study is to examine if and in which extent the effect of a dose adjusted administration of piperacillin/tazobactam after therapeutic drug monitoring has a benefit on a stable fever recovery without changing the anti infective therapy in patients with neutropenia after myelo-suppressive cytostatic chemotherapy

Protection of trial subjects:

(S)AEs have been documented and reported as appropriate. According to protocol, patients were followed up.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 November 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: 38
Worldwide total number of subjects	38
EEA total number of subjects	38

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)	26
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment: 25.11.2016 to 07.05.2018 only in Jena (Germany)

Pre-assignment

Screening details:

153 patients were pre-screened. Of those 77 patients were screened. 38 patients could be randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pip/Taz with dose adjustment

Arm description:

The dose adjustment of piperacillin/tazobactam follows a predefined scheme depending on the measured plasma concentration after half of the application interval (usually after 4 hours).

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

Dosage and administration details:

First 4/0.5g Pip/Taz bolus over 15-30 minutes for all participants, then adjust dose according to 4-hour plasma levels for piperacillin. Daily for the first three days of treatment with Pip/Taz according to the measured plasma levels after the first application of the day or the first application in the study, further therapy is performed with the dose after the last dose adjustment

In case of plasma levels >160mg/l (10xMHK), dose adjustment is made until the levels are <160mg/l after 4 hours.
In case of a delayed result (6-8h after administration), the next administration is continued as before and the dose adjustment is only implemented with the next but one administration.
Maximum dose 24g piperacillin (plus 3g tazobactam) in 24 hours.

Arm title	Pip/Taz without dose adjustment

Arm description:

Piperacillin/tazobactam is also administered in this study arm, but no dose adjustment is made. In accordance with in-house standards, 4/0.5g Pip/Taz is administered 3x/day. The maximum dose is 12g piperacillin in 24h.

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

Dosage and administration details:

According to in-house standard 4/0.5g Pip/Taz are applied 3x/day. The maximum dose is 12g Piperacillin in 24h.

Number of subjects in period 1	Pip/Taz with dose adjustment	Pip/Taz without dose adjustment
Started	19	19
Completed	18	19
Not completed	1	0
investigational product not received	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Pip/Taz with dose adjustment
Reporting group description:	
The dose adjustment of piperacillin/tazobactam follows a predefined scheme depending on the measured plasma concentration after half of the application interval (usually after 4 hours).	
Reporting group title	Pip/Taz without dose adjustment
Reporting group description:	
Piperacillin/tazobactam is also administered in this study arm, but no dose adjustment is made. In accordance with in-house standards, 4/0.5g Pip/Taz is administered 3x/day. The maximum dose is 12g piperacillin in 24h.	

Reporting group values	Pip/Taz with dose adjustment	Pip/Taz without dose adjustment	Total
Number of subjects	19	19	38
Age categorical Units: Subjects			
Adults (18-64 years)	13	13	26
From 65-84 years	6	6	12
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	55.1	58.1	
standard deviation	± 11.9	± 11.6	-
Gender categorical Units: Subjects			
Female	10	9	19
Male	9	10	19

Subject analysis sets	
Subject analysis set title	primary analysis
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomized patients with at least one drug administration.	
Subject analysis set title	secondary analysis
Subject analysis set type	Per protocol
Subject analysis set description:	
All randomized patients which are adherent to the protocol.	

Reporting group values	primary analysis	secondary analysis	
Number of subjects	36	22	
Age categorical Units: Subjects			
Adults (18-64 years)	24	16	
From 65-84 years	12	6	
85 years and over	0	0	

Age continuous Units: years			
arithmetic mean	55.3	58.1	
standard deviation	± 12.3	± 11.6	
Gender categorical Units: Subjects			
Female	17	10	
Male	19	12	

End points

End points reporting groups

Reporting group title	Pip/Taz with dose adjustment
Reporting group description:	
The dose adjustment of piperacillin/tazobactam follows a predefined scheme depending on the measured plasma concentration after half of the application interval (usually after 4 hours).	
Reporting group title	Pip/Taz without dose adjustment
Reporting group description:	
Piperacillin/tazobactam is also administered in this study arm, but no dose adjustment is made. In accordance with in-house standards, 4/0.5g Pip/Taz is administered 3x/day. The maximum dose is 12g piperacillin in 24h.	

Subject analysis set title	primary analysis
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomized patients with at least one drug administration.	
Subject analysis set title	secondary analysis
Subject analysis set type	Per protocol
Subject analysis set description:	
All randomized patients which are adherent to the protocol.	

Primary: freedom of fever after 5 consecutive days

End point title	freedom of fever after 5 consecutive days
End point description:	

End point type	Primary
End point timeframe:	
30 days after randomization	

End point values	Pip/Taz with dose adjustment	Pip/Taz without dose adjustment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: number of patients				
yes	5	8		
no	12	11		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Pip/Taz with dose adjustment v Pip/Taz without dose adjustment

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.429
Method	Chi-squared

Secondary: number of antibiotica free days during hospital stay

End point title	number of antibiotica free days during hospital stay

End point description:

End point type	Secondary

End point timeframe:

Day 30 after randomization

End point values	Pip/Taz with dose adjustment	Pip/Taz without dose adjustment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: days				
median (inter-quartile range (Q1-Q3))	12 (10 to 14)	14 (11 to 19)		

Statistical analyses

Statistical analysis title	Mann-Whitney U Test
Comparison groups	Pip/Taz with dose adjustment v Pip/Taz without dose adjustment
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.167
Method	Wilcoxon (Mann-Whitney)

Secondary: Admission to Intensive Care

End point title	Admission to Intensive Care

End point description:

End point type	Secondary

End point timeframe:

Day 30 after randomization

End point values	Pip/Taz with dose adjustment	Pip/Taz without dose adjustment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: number of patients				
yes	1	0		
no	16	19		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Pip/Taz without dose adjustment v Pip/Taz with dose adjustment
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.472
Method	Chi-squared

Secondary: hospital stay

End point title	hospital stay

End point description:

End point type	Secondary

End point timeframe:

Day 30 after randomization

End point values	Pip/Taz with dose adjustment	Pip/Taz without dose adjustment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: days				
median (inter-quartile range (Q1-Q3))	23 (20 to 32)	29 (24 to 35)		

Statistical analyses

Statistical analysis title	Mann-Whitney U Test
Comparison groups	Pip/Taz with dose adjustment v Pip/Taz without dose adjustment
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.146
Method	Wilcoxon (Mann-Whitney)

Secondary: Duration of antibiotica therapy

End point title	Duration of antibiotica therapy

End point description:

End point type	Secondary

End point timeframe:

Day 30 after randomization

End point values	Pip/Taz with dose adjustment	Pip/Taz without dose adjustment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: days				
median (inter-quartile range (Q1-Q3))	6.3 (3.6 to 8.5)	5.9 (3.7 to 8.6)		

Statistical analyses

Statistical analysis title	Mann-Whitney U Test
Comparison groups	Pip/Taz without dose adjustment v Pip/Taz with dose adjustment
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.924
Method	Wilcoxon (Mann-Whitney)

Secondary: Cumulative dose piperacillin day 1 to day 3

End point title	Cumulative dose piperacillin day 1 to day 3

End point description:

End point type	Secondary

End point timeframe:
Day 1 to 3 after randomization

End point values	Pip/Taz with dose adjustment	Pip/Taz without dose adjustment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: gram(s)				
median (inter-quartile range (Q1-Q3))	36 (36 to 40)	36 (36 to 36)		

Statistical analyses

Statistical analysis title	Mann-Whitney U Test
Comparison groups	Pip/Taz with dose adjustment v Pip/Taz without dose adjustment
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.397
Method	Wilcoxon (Mann-Whitney)

Secondary: Cumulative dose tazobactam day 1 to day 3

End point title	Cumulative dose tazobactam day 1 to day 3

End point description:

End point type	Secondary

End point timeframe:
Day 1 to day 3 after randomization

End point values	Pip/Taz with dose adjustment	Pip/Taz without dose adjustment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: gram(s)				
median (inter-quartile range (Q1-Q3))	4.5 (4.5 to 5)	4.5 (4.5 to 4.5)		

Statistical analyses

Statistical analysis title	Mann-Whitney U Test
Comparison groups	Pip/Taz with dose adjustment v Pip/Taz without dose adjustment
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.397
Method	Wilcoxon (Mann-Whitney)

Secondary: SIRS: temperature >= 38° or <=36° at final visit

End point title	SIRS: temperature >= 38° or <=36° at final visit
End point description:	

End point type	Secondary
End point timeframe:	
Day 30 after randomization	

End point values	Pip/Taz with dose adjustment	Pip/Taz without dose adjustment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: number of patients				
yes	0	0		
no	17	19		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Pip/Taz with dose adjustment v Pip/Taz without dose adjustment
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Chi-squared

Secondary: SIRS: tachycardia (heart rate >= 90 per minute) at final visit

End point title	SIRS: tachycardia (heart rate >= 90 per minute) at final visit
End point description:	

End point type	Secondary

End point timeframe:
Day 30 after randomization

End point values	Pip/Taz with dose adjustment	Pip/Taz without dose adjustment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: number of patients				
yes	6	7		
no	11	12		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Pip/Taz with dose adjustment v Pip/Taz without dose adjustment
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Chi-squared

Secondary: SIRS: Leucocytosis (>=12.000/mm³) or Leucopenia (<=4.000/mm³)

End point title	SIRS: Leucocytosis (>=12.000/mm³) or Leucopenia (<=4.000/mm³)

End point description:

End point type	Secondary

End point timeframe:
Day 30 after randomization

End point values	Pip/Taz with dose adjustment	Pip/Taz without dose adjustment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: number of patients				
yes	8	12		
no	9	7		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Pip/Taz with dose adjustment v Pip/Taz without dose adjustment
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.493
Method	Chi-squared

Secondary: Ampicillin resistance

End point title	Ampicillin resistance

End point description:

End point type	Secondary

End point timeframe:

Day 30 after randomization

End point values	Pip/Taz with dose adjustment	Pip/Taz without dose adjustment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: number of patients				
yes	6	4		
no	11	15		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Pip/Taz with dose adjustment v Pip/Taz without dose adjustment

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Chi-squared

Secondary: Piperacillin resistance

End point title	Piperacillin resistance

End point description:

End point type	Secondary

End point timeframe:

Day 30 after randomization

End point values	Pip/Taz with dose adjustment	Pip/Taz without dose adjustment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: number of patients				
yes	0	0		
no	17	19		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Pip/Taz with dose adjustment v Pip/Taz without dose adjustment
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The detection of AEs begins with randomization. The end of AE detection is reached 24h after the 5th day of stable defibrillation or, if this is not achieved with Pip/Taz alone, 24h after the end of monotherapy with Pip/Taz in patients receivi

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Pip/Taz with dose adjustment

Reporting group description:

The dose adjustment of piperacillin/tazobactam follows a predefined scheme depending on the measured plasma concentration after half of the application interval (usually after 4 hours).

Reporting group title	Pip/Taz without dose adjustment

Reporting group description:

Piperacillin/tazobactam is also administered in this study arm, but no dose adjustment is made. In accordance with in-house standards, 4/0.5g Pip/Taz is administered 3x/day. The maximum dose is 12g piperacillin in 24h.

Serious adverse events	Pip/Taz with dose adjustment	Pip/Taz without dose adjustment	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	
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	Pip/Taz with dose adjustment	Pip/Taz without dose adjustment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 19 (26.32%)	6 / 19 (31.58%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Pericardial effusion			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Nervous system disorders			
Intercostal neuralgia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	2 / 19 (10.53%)	2 / 19 (10.53%)	
occurrences (all)	2	2	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	2 / 19 (10.53%)	0 / 19 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2016	The requirements of the Ethics Committee and the comments of the BfArM were integrated into the trial protocol and patient information after the initial application. Changes in the protocol included additional signature lines for the responsible analyst at the Institute for Clinical Chemistry and Laboratory Diagnostics and the supplier of the investigational product to the UKJ pharmacy, information on the dosage and application of Pip/Taz and the indication that patient consent must be obtained before the onset of fever. In addition, further information was provided on the criteria for discontinuation. Changes in the patient information included the revision of some of the contents (including terms understood by laypersons, optional information for the family doctor, dosage/application according to in-house standards). The approval or approving assessment is dated 24.10.2016 and 10.10.2016.
24 October 2017	Substantial Amendment regarding an additional deputy of the PI.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported