



## Clinical trial results:

### Pharmacokinetics and pharmacodynamics of Piperacillin-Tazobactam (PT) in pediatric oncology patients with fever and neutropenia

#### Summary

EudraCT number	2017-004281-10
Trial protocol	DK
Global end of trial date	30 June 2020

#### Results information

Result version number	v1 (current)
This version publication date	04 November 2021
First version publication date	04 November 2021

#### Trial information

##### Trial identification

Sponsor protocol code	PT/11/2017
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Boulevard 99, Aarhus N, Denmark, 8200
Public contact	Sabine Frølich Maarbjerg, Department of Pediatric Oncology, Aarhus University Hospital, Skejby, sabine.froelich@midt.rm.dk
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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:

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## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 February 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 June 2020
Was the trial ended prematurely?	No

Notes:

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## General information about the trial

Main objective of the trial:

With the overall objective of optimizing the dosing regimen of empirical piperacillin-tazobactam treatment in pediatric febrile neutropenia (FN), we investigated whether continuous piperacillin-tazobactam infusions provide antibiotic concentrations associated with maximal activity and optimal target attainment.

Protection of trial subjects:

The trial was conducted in accordance with the ethical standards described in the declaration of Helsinki. Approvals were obtained from the Central Denmark Region Committee on Health Research Ethics, the Danish Data Protection Agency and the Danish Medicines Agency. Written informed consent was obtained from both parents or legal guardians. Children aged 15 to 17 years were allowed to give written informed consent for themselves, in close collaboration with their parents or legal guardians.

Experienced nurses were handling the blood sampling and administration of study drug. Furthermore, all information regarding the trial was given by study nurses or doctors with large pediatric experience. Data was registered, saved and managed using REDCap (Research Electronic Data Capture), hosted at the Department of Clinical Medicine, Aarhus University. REDCap is a secure, web-based software platform designed to support data capture for research studies.

Background therapy:

As standard empirical therapy of pediatric FN, piperacillin-tazobactam (300 mg/kg/day) was prescribed as intermittent administration every eight hours by the treating physician. After study enrollment, the study participants received a piperacillin-tazobactam loading bolus (100 mg/kg) followed by continuous infusion of piperacillin-tazobactam (300 mg/kg/day) at a fixed rate over 24 hours by a CADD®-Solis VIP infusion pump. Blood sampling points covered peak concentration immediately after loading dose and prior to continuous infusion -initiation (2-30 minutes), distribution phase (0.5-1.5 hours), and C<sub>ss</sub> (12-24 hours).

Evidence for comparator:

Consensual PK/PD targets required for maximum efficacy of  $\beta$ -lactams in critically ill and neutropenic children remain to be established. For piperacillin, antibacterial effect is attained with a free drug concentration above MIC for 40%–70% of the time. However, a growing body of evidence recommends the use of higher PK/PD targets of 100% fT>MIC or even up to 100% fT>4-6xMIC to maximize the bactericidal effect and compensate for the reduced immunological response and limited post-antibiotic effect in neutropenic patients. Subsequently, the following PK/PD targets were evaluated in this trial: (1) 100% fT>MIC and (2) 50% fT>4xMIC. Although these targets are considered quite stringent, several other studies also evaluated these targets, and they are increasingly used among critically ill and neutropenic patients.

The PK/PD targets were evaluated in relation to the piperacillin MIC spectrum of blood stream infections in children with cancer at our institution, and the EUCAST MIC breakpoint for *Pseudomonas aeruginosa* (16 mg/L). In terms of antimicrobial susceptibility, *P. aeruginosa* represents a worst-case scenario and an increase in resistant *P. aeruginosa* strains has been reported during the last decades. Accordingly, it is recommended that empirical management of pediatric FN contain antipseudomonal coverage.

Actual start date of recruitment	01 August 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 76
Worldwide total number of subjects	76
EEA total number of subjects	76

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)	4
Children (2-11 years)	44
Adolescents (12-17 years)	28
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Study participants were recruited when they were admitted with FN and was prescribed piperacillin-tazobactam. Written informed consent was obtained from both parents or legal guardians. Children aged 15 to 17 years were allowed to give written informed consent for themselves, in close collaboration with their parents or legal guardians.

### Pre-assignment

Screening details:

Medical assessment

### Period 1

Period 1 title	Intervention (Overall study period) (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

OBS!!!!!! We have added an extra arm, due the system that can not manage single arm studies. The duplet arm contains identical information as the intervention arm. A total of 38 patients were included.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Total study population

Arm description:

Single-arm study

Arm type	Total study population
Investigational medicinal product name	Piperacillin-tazobactam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

As standard care, intravenous piperacillin-tazobactam was prescribed at 300 mg/kg/day and administered intermittently every eight hours. After study enrollment, eligible patients received an intravenous 2-5 minutes piperacillin-tazobactam loading dose of 100 mg/kg (not subtracted from the total daily dose) followed by continuous infusion of 300 mg/kg/day (piperacillin component, maximum of 16 000 mg/day) at a fixed rate over 24 hours.

A supplemental loading dose of 100 mg/kg (maximum four doses per day) was administered in case of a discontinued infusion for longer than 30 minutes.

<b>Arm title</b>	Total study population - duplet
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Arm description:

Duplet - total study population. This arm is made since the system does not accept single arm studies. This arm contains identical information.

Arm type	Experimental
Investigational medicinal product name	Piperacillin-tazobactam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

As standard care, intravenous piperacillin-tazobactam was prescribed at 300 mg/kg/day and administered intermittently every eight hours. After study enrollment, eligible patients received an intravenous 2-5 minutes piperacillin-tazobactam loading dose of 100 mg/kg (not subtracted from the

total daily dose) followed by continuous infusion of 300 mg/kg/day (piperacillin component, maximum of 16 000 mg/day) at a fixed rate over 24 hours.  
A supplemental loading dose of 100 mg/kg (maximum four doses per day) was administered in case of a discontinued infusion for longer than 30 minutes.

<b>Number of subjects in period 1</b>	Total study population	Total study population - duplet
Started	38	38
Completed	38	38

## Baseline characteristics

### Reporting groups

Reporting group title	Total study population
Reporting group description:	
Single-arm study	
Reporting group title	Total study population - duplet
Reporting group description:	
Duplet - total study population. This arm is made since the system does not accept single arm studies. This arm contains identical information.	

Reporting group values	Total study population	Total study population - duplet	Total
Number of subjects	38	38	76
Age categorical			
Median age			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	2	2	4
Children (2-11 years)	22	22	44
Adolescents (12-17 years)	14	14	28
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	14	14	28
Male	24	24	48
Underlying malignancy			
Units: Subjects			
Hematological malignancy	17	17	34
Solid tumors	21	21	42
Glomerular filtration rate (GFR)			
Units: ml/min/1.73m <sup>2</sup>			
median	175.5	175.5	
inter-quartile range (Q1-Q3)	133.3 to 209.3	133.3 to 209.3	-

## End points

### End points reporting groups

Reporting group title	Total study population
Reporting group description: Single-arm study	
Reporting group title	Total study population - duplet
Reporting group description: Duplet - total study population. This arm is made since the system does not accept single arm studies. This arm contains identical information.	

### Primary: Attainment of the target of 100% fT>MIC for the P. aeruginosa breakpoint

End point title	Attainment of the target of 100% fT>MIC for the P. aeruginosa breakpoint <sup>[1]</sup>
End point description: Attainment of the target of 100% fT>MIC for the P. aeruginosa breakpoint	
End point type	Primary
End point timeframe: Entire study period	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: The manuscript (containing statistics information) will be uploaded as soon as it is published.	

End point values	Total study population	Total study population - duplet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	38		
Units: %				
number (not applicable)				
Continuous infusion 400 mg/kg/day	99.4	99.4		
Continuous infusion 300 mg/kg/day	98.7	98.7		

### Statistical analyses

No statistical analyses for this end point

### Primary: Probability of target attainment of the target of 50% (100% for continuous infusion) fT>4xMIC

End point title	Probability of target attainment of the target of 50% (100% for continuous infusion) fT>4xMIC <sup>[2]</sup>
End point description: Probability of target attainment of the target of 50% (100% for continuous infusion) fT>4xMIC	
End point type	Primary
End point timeframe: Entire study period	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The manuscript (containing statistics information) will be uploaded as soon as it is published.

End point values	Total study population	Total study population - duplet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	38		
Units: %				
number (not applicable)				
Continuous infusion 400 mg/kg/day	39.8	39.8		
Continuous infusion 300 mg/kg/day	28.3	28.3		

## Statistical analyses

No statistical analyses for this end point

### Primary: Predictions of median steady state concentrations (95% percentiles) for continuous infusion of 300 mg/kg/day

End point title	Predictions of median steady state concentrations (95% percentiles) for continuous infusion of 300 mg/kg/day <sup>[3]</sup>
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End point description:

Predictions of median steady state concentrations (95% percentiles) for continuous infusion of 300 mg/kg/day

End point type	Primary
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End point timeframe:

Entire study period

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The manuscript (containing statistics information) will be uploaded as soon as it is published.

End point values	Total study population	Total study population - duplet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	38		
Units: mg/L				
median (confidence interval 95%)	47.6 (17.2 to 129.5)	47.6 (17.2 to 129.5)		

## Statistical analyses

No statistical analyses for this end point



## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

Time frame for reporting adverse events: 1 August 2018 - 30 June 2020.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	Product resume
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Dictionary version	06022021
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Frequency threshold for reporting non-serious adverse events: 5 %

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### Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No non-serious adverse events were reported.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Samples were collected in blood, which may represent an imprecise surrogate of drug concentrations at the infective site. To allow a further refinement of the dosing regimen for the youngest children, this age group should contain more children.
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Notes: