Clinical trial results:
CLINICAL PHARMACOKINETICS OF CASPOFUNGIN IN CRITICALLY ILL PATIENTS DURING CONTINUOUS VENO-VENOUS HEMOFILTRATION

Summary

EudraCT number	2006-004106-87
Trial protocol	AT
Global end of trial date	06 November 2014

Results information

Result version number	v1 (current)
This version publication date	27 September 2020
First version publication date	27 September 2020

Trial information

Trial identification

Sponsor protocol code	CAS CVVH

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Medical University Innsbruck
Sponsor organisation address	Christoph-Probst-Platz 1, Innrain 52 A, Innsbruck, Austria, 6020
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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	06 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 November 2014
Global end of trial reached?	Yes
Global end of trial date	06 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

to assess plasma pharmacokinetics in critically ill patients undergoing continuous veno-venous hemofiltration (CVVH), and to compare it with that of critically ill patients not requiring renal replacement therapy

Protection of trial subjects:

No additional risks for the patients during the study. Drawing blood from an arterial line, which is needed for ICU routine monitoring, is without significant addidonal risk.

Background therapy:

Subjects received treatment of an intensive care unit due to their medical history.

Evidence for comparator:

There was no evidence for a comparator in this trial.

Actual start date of recruitment	23 October 2007
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	Austria: 28
Worldwide total number of subjects	28
EEA total number of subjects	28

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)	21
From 65 to 84 years	7

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

We enrolled consecutive adult patients at a medical intensive care unit (ICU) with an indication for caspofungin.

Pre-assignment

Screening details:

We enrolled consecutive adult patients at a medical intensive care unit (ICU) with an indication for caspofungin.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CVVH patients

Arm description:

Caspofungin pharmacokinetics during continuous renal replacement therapy (CRRT), however, has been unknown so far. Therefore, we investigated the influence of continuous venovenous hemofiltration (CVVH) on the pharmacokinetics of caspofungin in critically ill patients in order to assess the appropriateness of standard dosage during CRRT.
Sampling was performed on day 1 of caspofungin treatment (single dose) and at steady state on day 4 or later. Two patients were already on caspofungin when admitted to the ICU, and thus, sampling after the first dose was missed. Five patients received only a single dose and for two subjects measurement was done on day 1 and at steady state.

Arm type	Experimental
Investigational medicinal product name	Cancidas
Investigational medicinal product code	
Other name	Caspofungin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

According to the manufacturer’s recommendation, the maintenance dose amounted to 50 mg per day in patients with a body weight of ≤ 80 kg and 70 mg once daily when body weight was > 80 kg. A loading dose of 70 mg was applied to all patients (infusion time, 1 h).

Arm title	CVVHD patients

Arm description:

Caspofungin pharmacokinetics during continuous renal replacement therapy (CRRT), however, has been unknown so far. Therefore, we investigated the influence of continuous venovenous hemodialysis (CVVHD) on the pharmacokinetics of caspofungin in critically ill patients in order to assess the appropriateness of standard dosage during CRRT.
Sampling was performed on day 1 of caspofungin treatment (single dose) and at steady state on day 4 or later. Four patients were already on caspofungin when admitted to the ICU, and thus, sampling after the first dose was missed. Four patients received only a single dose and for three subjects measurement was done on day 1 and at steady state.

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Arm title	Control

Arm description:

Caspofungin pharmacokinetics was assessed in 27 critically ill patients, including 13 patients not requiring continuous renal replacement therapy (CRRT).
Sampling was performed on day 1 of caspofungin treatment (single dose) and at steady state on day 4 or later. Twelve patients were already on caspofungin when admitted to the ICU, and thus, sampling after the first dose was missed. Four patients received only a single dose and for three subjects measurement was done on day 1 and at steady state.

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Number of subjects in period 1	CVVH patients	CVVHD patients	Control
Started	6	8	13
Completed	7	7	13
Not completed	0	1	0
Transferred to other arm/group	-	1	-
Joined	1	0	0
Transferred in from other group/arm	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	CVVH patients
Reporting group description:	
Caspofungin pharmacokinetics during continuous renal replacement therapy (CRRT), however, has been unknown so far. Therefore, we investigated the influence of continuous venovenous hemofiltration (CVVH) on the pharmacokinetics of caspofungin in critically ill patients in order to assess the appropriateness of standard dosage during CRRT. Sampling was performed on day 1 of caspofungin treatment (single dose) and at steady state on day 4 or later. Two patients were already on caspofungin when admitted to the ICU, and thus, sampling after the first dose was missed. Five patients received only a single dose and for two subjects measurement was done on day 1 and at steady state.	
Reporting group title	CVVHD patients
Reporting group description:	
Caspofungin pharmacokinetics during continuous renal replacement therapy (CRRT), however, has been unknown so far. Therefore, we investigated the influence of continuous venovenous hemodialysis (CVVHD) on the pharmacokinetics of caspofungin in critically ill patients in order to assess the appropriateness of standard dosage during CRRT. Sampling was performed on day 1 of caspofungin treatment (single dose) and at steady state on day 4 or later. Four patients were already on caspofungin when admitted to the ICU, and thus, sampling after the first dose was missed. Four patients received only a single dose and for three subjects measurement was done on day 1 and at steady state.	
Reporting group title	Control
Reporting group description:	
Caspofungin pharmacokinetics was assessed in 27 critically ill patients, including 13 patients not requiring continuous renal replacement therapy (CRRT). Sampling was performed on day 1 of caspofungin treatment (single dose) and at steady state on day 4 or later. Twelve patients were already on caspofungin when admitted to the ICU, and thus, sampling after the first dose was missed. Four patients received only a single dose and for three subjects measurement was done on day 1 and at steady state.	

Reporting group values	CVVH patients	CVVHD patients	Control
Number of subjects	7	8	13
Age categorical 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)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	7	9
From 65-84 years	2	1	4
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	60.6	53.1	51.2
standard deviation	± 7.87	± 12.54	± 18.09
Gender categorical Units: Subjects			
Female	4	2	6
Male	3	6	7

Reporting group values	Total		
Number of subjects	28		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	21		
From 65-84 years	7		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	12		
Male	16		

End points

End points reporting groups

Reporting group title	CVVH patients

Reporting group description:

Caspofungin pharmacokinetics during continuous renal replacement therapy (CRRT), however, has been unknown so far. Therefore, we investigated the influence of continuous venovenous hemofiltration (CVVH) on the pharmacokinetics of caspofungin in critically ill patients in order to assess the appropriateness of standard dosage during CRRT.
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Reporting group title	CVVHD patients

Reporting group description:

Caspofungin pharmacokinetics during continuous renal replacement therapy (CRRT), however, has been unknown so far. Therefore, we investigated the influence of continuous venovenous hemodialysis (CVVHD) on the pharmacokinetics of caspofungin in critically ill patients in order to assess the appropriateness of standard dosage during CRRT.
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Reporting group title	Control

Reporting group description:

Caspofungin pharmacokinetics was assessed in 27 critically ill patients, including 13 patients not requiring continuous renal replacement therapy (CRRT).
Sampling was performed on day 1 of caspofungin treatment (single dose) and at steady state on day 4 or later. Twelve patients were already on caspofungin when admitted to the ICU, and thus, sampling after the first dose was missed. Four patients received only a single dose and for three subjects measurement was done on day 1 and at steady state.

Primary: Total caspofungin body clearance

End point title	Total caspofungin body clearance[1]

End point description:

Sampling was performed on day 1 of caspofungin treatment (single dose).

End point type	Primary

End point timeframe:

Day 1

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 statistical significance of eventual differences in pharmacokinetic parameters between patients on and off CRRT was evaluated by the Mann-Whitney U test with Bonferroni’s correctionfor multiple testing. No statistical differences were found between the groups.

End point values	CVVH patients	CVVHD patients	Control	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	4	4	
Units: mL/ h/ kg				
arithmetic mean (standard deviation)	7.92 (± 1.675)	9.95 (± 4.560)	10.8 (± 4.986)	

Statistical analyses

No statistical analyses for this end point

Primary: Total caspofungin body clearence

End point title	Total caspofungin body clearence[2]

End point description:

Sampling was performed at steady state on day 4 or later.

End point type	Primary

End point timeframe:

Day 4- day 36

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 statistical significance of eventual differences in pharmacokinetic parameters between patients on and off CRRT was evaluated by the Mann-Whitney U test with Bonferroni's correctionfor multiple testing. No statistical differences were found between the groups.

End point values	CVVH patients	CVVHD patients	Control	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	7	12	
Units: mL/ h/ kg				
arithmetic mean (standard deviation)	6.53 (± 3.508)	4.01 (± 1.368)	6.24 (± 3.338)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Day 1- day 36

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	CVVH patients

Reporting group description:

Caspofungin pharmacokinetics during continuous renal replace-ment therapy (CRRT), however, has been unknown so far. Therefore, we investigated the influence of continuous venovenous hemofiltration (CVVH) on the pharmacokinetics of caspofungin in critically ill patients in order to assess the appropriateness of standard dosage during CRRT.
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Reporting group title	CVVHD patients

Reporting group description:

Caspofungin pharmacokinetics during continuous renal replace-ment therapy (CRRT), however, has been unknown so far. Therefore, we investigated the influence of continuous venovenous hemodialysis (CVVHD) on the pharmacokinetics of caspofungin in critically ill patients in order to assess the appropriateness of standard dosage during CRRT.
Sampling was performed on day 1 of caspofungin treatment (single dose) and at steady state on day 4 or later. Four patients were already on caspofungin when admitted to the ICU, and thus, sampling after the first dose was missed. Four patients received only a single dose and for three subjects measurement was done on day 1 and at steady state.

Reporting group title	Control

Reporting group description:

Caspofungin pharmacokinetics was assessed in 27 critically ill patients, including 13 patients not requiring continuous renal replacement therapy (CRRT).
Sampling was performed on day 1 of caspofungin treatment (single dose) and at steady state on day 4 or later. Twelve patients were already on caspofungin when admitted to the ICU, and thus, sampling after the first dose was missed. Four patients received only a single dose and for three subjects measurement was done on day 1 and at steady state.

Serious adverse events	CVVH patients	CVVHD patients	Control
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	CVVH patients	CVVHD patients	Control
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)

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 AEs were observed in this trial.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 April 2010	Caspofungin in plasma and ultrafiltrate samples will be quantified by LCMS/MS at the Central Institute for Medical and Chemical Laboratory Diagnostics (ZIMCL). The instrumental setup is identical to equipment used for the routine immunosuppressant TDM of the ZIMCL (Seger et al. 2009). Briefly, a sample aliquot is pre-treated (protein precipitation) prior to transfer to the LC system. A online SPE purification is preceding the chromatographic separation on a RP-C18 column. The tandem MS (MS/MS) based analyte detection is performed in the selected reaction mode. Analyte quantification is relying on the added internal standard and on external calibration with Caspofungin. The method is linear in the range from 200 – 15000 ng/ml and a inter-day CV of <10 can be achieved.
15 July 2010	The aim of this research project is to determine caspofungin pharmacokinetics in critically ill patients requiring continuous veno-venous hemofiltration (CVVH) and continuous veno-venous hemodialysis (CVVHD) and to provide dose recommendation for these groups of patients. 10 patients undergoing CVVHD will be enrolled.
18 August 2011	To assess the effect of CVVH on caspofungin pharmacokinetics, 15 patients undergoing CVVH, 15 patients undergoing CVVHD will be enrolled. Another 15 patients on caspofungin therapy, who are not treated with CVVH, are included as a control group. Patient enrolment is estimated to be completed at the end of 2013 (31.12.2013).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23733471