Clinical trial results:
Pharmacokinetics of trimethoprim-sulfametrole in critically ill patients on continuous veno-venous haemofiltration

Summary

EudraCT number	2014-003403-29
Trial protocol	AT
Global end of trial date	11 June 2019

Results information

Result version number	v1 (current)
This version publication date	31 January 2021
First version publication date	31 January 2021

Trial information

Trial identification

Sponsor protocol code	TMP-SMT-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
Public contact	Ao. Univ.Prof. Dr. Romuald Bellmann, Medical University Innsbruck, University Hospital for Internal Medicine I, 0043 51250481389, romuald.bellmann@i-med.ac.at
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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	11 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 June 2019
Global end of trial reached?	Yes
Global end of trial date	11 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Potential effects of continuous veno-venous haemofiltration on single and multiple dose pharmacokinetics of sulfametrole and trimethoprim were assessed.

Protection of trial subjects:

Blood samples were drawn from an arterial or a venous line that had been inserted for diagnostics as part of routine management at the ICU. The blood volume needed for the study amounted 42 mL per study day, which is easily tolerated by adult patients. The risk of blood sampling from an arterial or a venous line by members of the ICU staff is very low. There is no risk by taking blood samples from the haemofilter inlet and outlet or from sampling ultrafiltrate. ICU monitoring was performed in all study patients.

Background therapy:

Subjects received treatment of an intensive care unit due to their medical history. SMT-TMP was part of routine treatment according to clinical indication.

Evidence for comparator:

There was no evidence for a comparator.

Actual start date of recruitment	01 September 2014
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: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	14
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was performed at the Medical Emergency and Intensive Care Unit (Medical ICU) and at the Transplant ICU, Department of Anaesthesia and Critical Care, Centre of Operative Medicine, Innsbruck General Hospital.
Adult critically ill patients (female and male) treated with TMP-SMT according to clinical indication were enrolled.

Pre-assignment

Screening details:

Patients at the participating ICUs on SMT-TMP treatment were screened. Patients on CRRT and patients not on CRRT with plasma creatinine < 1.5 mg/dl were eligible.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	CRRT group

Arm description:

Adult critically ill patients treated with TMP-SMT (trimethoprim and sulfametrole) according to clinical indication were enrolled. The CRRT group comprised twelve consecutive patients with renal failure undergoing CVVH. Patients obtained TMP-SMT at standard doses recommended for the respective indications, since relevant elimination of both components by CVVH is anticipated. Plasma pharmacokinetics was determined after the first administration and at steady state.

Arm type	Experimental
Investigational medicinal product name	Rokiprim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

TMP-SMT was provided as a 250-ml infusion bottle containing 160 mg of TMP and 800 mg of SMT. TMP-SMT was applied intravenously at standard doses recommended for the respective indications (250 ml b.i.d. or t.i.d.). For treatment of Pneumocystis jirovecii pneumonia higher doses were required (15-20 mg/kg body weight of TMP per day divided in 3-4 doses which equals about 7 bottles of Rokiprim®). The infusion time Tinf was set to 30 minutes using an electronic infusion pump.

Arm title	Control group

Arm description:

Adult critically ill patients treated with TMP-SMT (trimethoprim and sulfametrole) according to clinical indication were enrolled. Twelve critically ill patients on TMP-SMT treatment with approximately normal renal function were included in the control group. Patients obtained TMP-SMT at standard doses recommended for the respective indications. Plasma pharmacokinetics was determined after the first administration and at steady state.

Arm type	Control
Investigational medicinal product name	Rokiprim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

TMP-SMT was provided as a 250-ml infusion bottle containing 160 mg of TMP and 800 mg of SMT. TMP-SMT was applied intravenously at standard doses recommended for the respective indications (250 ml b.i.d. or t.i.d.). For treatment of Pneumocystis jirovecii pneumonia higher doses were required (15-20 mg/kg body weight of TMP per day divided in 3-4 doses which equals about 7 bottles of Rokiprim®). The infusion time Tinf was set to 30 minutes using an electronic infusion pump.

Number of subjects in period 1	CRRT group	Control group
Started	12	11
Completed	11	12
Not completed	1	0
Transferred to other arm/group	1	-
Joined	0	1
Transferred in from other group/arm	-	1

Baseline characteristics

Reporting groups	
Reporting group title	CRRT group
Reporting group description:	
Adult critically ill patients treated with TMP-SMT (trimethoprim and sulfametrole) according to clinical indication were enrolled. The CRRT group comprised twelve consecutive patients with renal failure undergoing CVVH. Patients obtained TMP-SMT at standard doses recommended for the respective indications, since relevant elimination of both components by CVVH is anticipated. Plasma pharmacokinetics was determined after the first administration and at steady state.	
Reporting group title	Control group
Reporting group description:	
Adult critically ill patients treated with TMP-SMT (trimethoprim and sulfametrole) according to clinical indication were enrolled. Twelve critically ill patients on TMP-SMT treatment with approximately normal renal function were included in the control group. Patients obtained TMP-SMT at standard doses recommended for the respective indications. Plasma pharmacokinetics was determined after the first administration and at steady state.	

Reporting group values	CRRT group	Control group	Total
Number of subjects	12	12	24
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)	9	5	14
From 65-84 years	3	7	10
85 years and over	0	0	0
Age continuous Units: years			
median	61	67	
full range (min-max)	25 to 79	42 to 76	-
Gender categorical Units: Subjects			
Female	6	2	8
Male	6	10	16

End points

End points reporting groups

Reporting group title	CRRT group
Reporting group description:	
Adult critically ill patients treated with TMP-SMT (trimethoprim and sulfametrole) according to clinical indication were enrolled. The CRRT group comprised twelve consecutive patients with renal failure undergoing CVVH. Patients obtained TMP-SMT at standard doses recommended for the respective indications, since relevant elimination of both components by CVVH is anticipated. Plasma pharmacokinetics was determined after the first administration and at steady state.	
Reporting group title	Control group
Reporting group description:	
Adult critically ill patients treated with TMP-SMT (trimethoprim and sulfametrole) according to clinical indication were enrolled. Twelve critically ill patients on TMP-SMT treatment with approximately normal renal function were included in the control group. Patients obtained TMP-SMT at standard doses recommended for the respective indications. Plasma pharmacokinetics was determined after the first administration and at steady state.	

Primary: AUC 0-n TMP

End point title	AUC 0-n TMP
End point description:	
AUC 0–n is defined as AUC 0–n from t=0 to t last, which was maximum 12h.	
End point type	Primary
End point timeframe:	
Maximum 12 hours	

End point values	CRRT group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: mg.h/L				
median (full range (min-max))	32 (8 to 114)	35 (7 to 92)		

Statistical analyses

Statistical analysis title	AUC 0-n TMP
Comparison groups	CRRT group v Control group
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.77
Method	Mann-Whitney-U-test

Primary: AUC 0-n SMT	
End point title	AUC 0-n SMT
End point description: AUC 0–n is defined as AUC 0–n from t=0 to t last, which was maximum 12h.	
End point type	Primary
End point timeframe: Maximum 12 hours	

End point values	CRRT group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: mg.h/L				
median (full range (min-max))	408 (163 to 1175)	546 (208 to 1547)		

Statistical analyses

Statistical analysis title	AUC 0-n SMT
Comparison groups	CRRT group v Control group
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.18
Method	Mann-Whitney-U-test

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Day 0- day 3 or later, when approximate steady state conditions were assumed

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	CRRT group

Reporting group description:

Adult critically ill patients treated with TMP-SMT (trimethoprim and sulfametrole) according to clinical indication were enrolled. The CRRT group comprised twelve consecutive patients with renal failure undergoing CVVH. Patients obtained TMP-SMT at standard doses recommended for the respective indications, since relevant elimination of both components by CVVH is anticipated. Plasma pharmacokinetics was determined after the first administration and at steady state.

Reporting group title	Control group

Reporting group description:

Adult critically ill patients treated with TMP-SMT (trimethoprim and sulfametrole) according to clinical indication were enrolled. Twelve critically ill patients on TMP-SMT treatment with approximately normal renal function were included in the control group. Patients obtained TMP-SMT at standard doses recommended for the respective indications. Plasma pharmacokinetics was determined after the first administration and at steady state.

Serious adverse events	CRRT group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	CRRT group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (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 or SAEs were observed in this trial.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 March 2015	new ICF Versions
16 October 2015	Two additional Departments at Innsbruck Medical University take part in this trial (Department of General and Surgical Intensive Care Medicine, Center of Operative Medicine and Department of Internal Medicine III). Urine samples (10 mL) will be taken from all patients presenting with diuresis via urinary catheter.
14 April 2016	another sub investigator

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/31990343