Clinical trial results:
Targeting matrix metalloproteinases with intravenous doxycycline in severe sepsis_ A randomised placebo-controller pilot trial

Summary

EudraCT number	2012-000748-81
Trial protocol	FI
Global end of trial date	01 January 2015

Results information

Result version number	v1 (current)
This version publication date	14 November 2021
First version publication date	14 November 2021
Summary attachment (see zip file)	Main results of the analyses (Results MMP-doxi 1.pptx) Laboratory analyses of MMP8 and MMP9 in individual subjects in different time points and TIMP-1 (Results MMP-doxi 2.xlsx) Published jouirnal article (Results MMP-doxi 3.pdf) Individual MMP-levels in each group (Doksi-Yksilölliset MMP-8-tasot eri hoitoryhmissä-18072014.docx)

Trial information

Trial identification

Sponsor protocol code	MMP-Doxi-1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Helsinki University Hospital
Sponsor organisation address	Haartmaninkatu 4, Helsinki, Finland,
Public contact	Dr Johanna Hästbacka, University of Helsinki, +358 504286701, johanna.hastbacka@hus.fi
Scientific contact	Dr Johanna Hästbacka, University of Helsinki, +358 504286701, johanna.hastbacka@hus.fi

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	01 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 January 2015
Global end of trial reached?	Yes
Global end of trial date	01 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The feasibility and safety of intravenbous administration of doxycycline in patients with severe sepsis
Determining a dosing regimen that achieve sub-antimicrobial plasma concentrations of doxycycline

Protection of trial subjects:

The patients received routine intensive care treatment and were treated according to written standard operating procedures in the intensive care unit.

Background therapy:

The patients received routine intensive care treatment and were treated according to written standard operating procedures in the intensive care unit.

Evidence for comparator:

Comparator was an equivalent volume of placebo (sodium chloride 0.9%)

Actual start date of recruitment	14 May 2012
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	Finland: 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)	17
From 65 to 84 years	7

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Please see Figure 1 and methods in attachment

Pre-assignment

Screening details:

Please see methods and Fig 1 in attached published article

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Blinding implementation details:

Allocation sheets provided by an external person were saved in a different department in sealed envelopes. A nurse or pharmacist from an unincluded department prepared the study drug and delivered it to the participating department blinded nurse in an opaque syringe labeled with study code.

Arms

Are arms mutually exclusive?	Yes
Arm title	Doxycycline high dose

Arm description:

Doxyxycline 200mg on first and 100mg on second and third study day, intravenously

Arm type	Experimental
Investigational medicinal product name	Doxycycline hyclate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use, Solution for infusion

Dosage and administration details:

Intravenously administrated : arm 1: 200mgx1 day 1, 100mgx1 day 2 and 100mgx1 day 3
arm 2 100mg day 1, 50mgx1 day 2 and 50mg x1 day 3
arm 3 placebo NaCl 09% equivalent volume x1 intravenously on days 1, 2, and 3

Arm title	Doxyxcycline low dose

Arm description:

Doxycycline 100mg on first , and 50mg on second and third study day , once daily, intravenously

Arm type	Active comparator
Investigational medicinal product name	Doxycycline hyclate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Solution for infusion , Intravenous use

Dosage and administration details:

Intravenously administrated : arm 1: 200mgx1 day 1, 100mgx1 day 2 and 100mgx1 day 3
arm 2 100mg day 1, 50mgx1 day 2 and 50mg x1 day 3
arm 3 placebo NaCl 09% equivalent volume x1 intravenously on days 1, 2, and 3

Investigational medicinal product name	Doxycycline hyclate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion

Routes of administration	Intravenous use, Solution for infusion

Dosage and administration details:

arm 2 100mg day 1, 50mgx1 day 2 and 50mg x1 day 3

Arm title	Placebo arm

Arm description:
Sodium chloride 0.9%

Arm type	Placebo
Investigational medicinal product name	Natriumchloride Baxter Viaflo 9mg/ml
Investigational medicinal product code	
Other name	Saline
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:
50ml infused once daily for three days

Number of subjects in period 1	Doxycycline high dose	Doxyxcycline low dose	Placebo arm
Started	8	8	8
Completed	8	7	8
Not completed	0	1	0
Consent withdrawn by subject	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Doxycycline high dose
Reporting group description:	
Doxyxycline 200mg on first and 100mg on second and third study day, intravenously	
Reporting group title	Doxyxcycline low dose
Reporting group description:	
Doxycycline 100mg on first , and 50mg on second and third study day , once daily, intravenously	
Reporting group title	Placebo arm
Reporting group description:	
Sodium chloride 0.9%	

Reporting group values	Doxycycline high dose	Doxyxcycline low dose	Placebo arm
Number of subjects	8	8	8
Age categorical			
All patients were adults, of them 65-84 years of 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)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	5	6
From 65-84 years	3	3	2
85 years and over	0	0	0
Age continuous			
Units: years			
median	57	58	58
inter-quartile range (Q1-Q3)	53 to 65	52 to 72	49 to 70
Gender categorical			
Units: Subjects			
Female	3	2	7
Male	5	6	1

Reporting group values	Total		
Number of subjects	24		
Age categorical			
All patients were adults, of them 65-84 years of age			
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)	16		
From 65-84 years	8		
85 years and over	0		
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical			
Units: Subjects			
Female	12		
Male	12		

Subject analysis sets

Subject analysis set title	MMP-8-concenbtrations
Subject analysis set type	Full analysis
Subject analysis set description:	
Please see attachment file	
Subject analysis set title	Doxycycline concentrations
Subject analysis set type	Full analysis
Subject analysis set description:	
Please see attached file 4	
Subject analysis set title	Safety and feasibility
Subject analysis set type	Safety analysis
Subject analysis set description:	
Please see published article, no adverse events were detected during study	

Reporting group values	MMP-8-concenbtrations	Doxycycline concentrations	Safety and feasibility
Number of subjects	23	23	24
Age categorical			
All patients were adults, of them 65-84 years of 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)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	5	6
From 65-84 years	3	3	2
85 years and over	0	0	0
Age continuous			
Units: years			
median	58	57	58
inter-quartile range (Q1-Q3)	52 to 72	53 to 65	49 to 70
Gender categorical			
Units: Subjects			
Female	1	3	7
Male	6	5	1

End points

End points reporting groups

Reporting group title	Doxycycline high dose
Reporting group description: Doxyxycline 200mg on first and 100mg on second and third study day, intravenously	
Reporting group title	Doxyxcycline low dose
Reporting group description: Doxycycline 100mg on first , and 50mg on second and third study day , once daily, intravenously	
Reporting group title	Placebo arm
Reporting group description: Sodium chloride 0.9%	
Subject analysis set title	MMP-8-concenbtrations
Subject analysis set type	Full analysis
Subject analysis set description: Please see attachment file	
Subject analysis set title	Doxycycline concentrations
Subject analysis set type	Full analysis
Subject analysis set description: Please see attached file 4	
Subject analysis set title	Safety and feasibility
Subject analysis set type	Safety analysis
Subject analysis set description: Please see published article, no adverse events were detected during study	

Primary: Doxycycline concentrations after dosing

End point title	Doxycycline concentrations after dosing[1][2]
End point description: Plasma doxycycline levels	
End point type	Primary
End point timeframe: 24 hours from first dosing	

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 statistics are provided in the attached documents

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistics are provided in the attached documents

End point values	Doxycycline high dose	Doxyxcycline low dose	Doxycycline concentrations	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	8	7	23	
Units: mg/L				
median (inter-quartile range (Q1-Q3))	2.1 (1.6 to 2.7)	0.72 (0.48 to 1.18)	0.72 (0 to 2)	

Statistical analyses

No statistical analyses for this end point

Primary: MMP 8 levels at 24 hours

End point title	MMP 8 levels at 24 hours[3]

End point description:

End point type	Primary

End point timeframe:

24 hours from dosing

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 statistics are provided in the attached documents

End point values	Doxycycline high dose	Doxyxcycline low dose	Placebo arm	MMP-8-concenbtrations
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	7	8	23
Units: ng/L				
median (inter-quartile range (Q1-Q3))	75.3 (24.9 to 345.7)	206.1 (78.5 to 295.6)	369.3 (71.3 to 488.0)	125.5 (56.2 to 410.1)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: Up to 28 days from astudy admissio	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	none
Dictionary version	x

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

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: There were no serious adverse events in the study

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported