

**Clinical trial results:**

**A single center, open-label, dose escalation study of the safety and pharmacokinetics of rhLAMAN (recombinant human alpha-mannosidase or Lamazym) for the treatment of patients with alpha-mannosidosis.**

**Summary**

EudraCT number	2010-022084-36
Trial protocol	DK
Global end of trial date	21 January 2011

**Results information**

Result version number	v2 (current)
This version publication date	29 July 2016
First version publication date	09 August 2015
Version creation reason	<ul style="list-style-type: none"><li>• Correction of full data set</li><li>• Correction of the Sponsor organisation name and address.</li></ul>

**Trial information****Trial identification**

Sponsor protocol code	rhLAMAN-02
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01268358
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Zymenex A/S
Sponsor organisation address	Roskildevej 12C, Hilleroed, Denmark, 3400
Public contact	Clinical Trial Transparency, Chiesi Farmaceutici Spa, clinicaltrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency, Chiesi Farmaceutici Spa, clinicaltrials_info@chiesi.com

Notes:

**Paediatric regulatory details**

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001056-PIP02-12
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?	Yes

Notes:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	21 January 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 January 2011
Global end of trial reached?	Yes
Global end of trial date	21 January 2011
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objectives of the study are:

- To evaluate the safety profile of rhLAMAN (Lamazym)
- To determine the PK profile of rhLAMAN (Lamazym) in patients with alpha-mannosidosis as measured by rhLAMAN levels in plasma

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Protection of trial subjects:

The study was conducted in accordance with the declaration of Helsinki, good clinical practice (GCP) guidelines and local law requirements. Other than routine care, no specific measures for protection of trial subjects were implemented.

Although an Independent Data Monitoring Committee was not formally established , a Safety Committee (SC) did exist for this study.

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Background therapy: -

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Evidence for comparator: -

Actual start date of recruitment	24 October 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Denmark: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

Notes:

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**Subjects enrolled per age group**

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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)	5
Adolescents (12-17 years)	5

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

All patients were recruited at Copenhagen University Hospital, Denmark. Primary recruitment centers were:

St Mary's Hospital, Manchester, UK; Children's Hospital, Mainz, DE; Hospices Civils in Lyon, FR; The Children's Memorial Health Institute, Warsaw, PL; Universitair Ziekenhuis, Brussels, BE; Hospital Universitario Reina Sofia, ES.

### Pre-assignment

Screening details:

Ten patients were screened, entered the study and subsequently stratified. No patients failed screening or withdrew from treatment or study.

### Period 1

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

Blinding implementation details:

The present study was open-labeled, as the primary objective of this study was to evaluate safety.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Lamazym 6.25 U/kg - Group 1

Arm description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

Group 1 was expected to receive a total of 5 doses, group 2, 4 doses and so on until group 5, which was expected to receive only 1 dose.

Arm type	Experimental
Investigational medicinal product name	Lamazym
Investigational medicinal product code	
Other name	recombinant human alpha-mannosidase
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients were stratified into 5 groups (1-5) before entering the treatment phase, and each group was to receive one of the fixed doses (6.25, 12.5, 25, 50 or 100 U/kg).

Treatment phase (Visit 3-12)

Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

Group 1 was expected to receive a total of 5 doses, group 2, 4 doses and so on until group 5, which was expected to receive only 1 dose.

<b>Arm title</b>	Lamazym 12.5 U/kg - Group 2
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Arm description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

Arm type	Experimental
Investigational medicinal product name	Lamazym
Investigational medicinal product code	
Other name	recombinant human alpha-mannosidase
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients were stratified into 5 groups (1-5) before entering the treatment phase, and each group was to receive one of the fixed doses (6.25, 12.5, 25, 50 or 100 U/kg).

Treatment phase (Visit 3-12)

Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

Group 1 was expected to receive a total of 5 doses, group 2, 4 doses and so on until group 5, which was expected to receive only 1 dose.

<b>Arm title</b>	Lamazym 25 U/kg - Group 3
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Arm description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

Arm type	Experimental
Investigational medicinal product name	Lamazym
Investigational medicinal product code	
Other name	recombinant human alpha-mannosidase
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients were stratified into 5 groups (1-5) before entering the treatment phase, and each group was to receive one of the fixed doses (6.25, 12.5, 25, 50 or 100 U/kg).

Treatment phase (Visit 3-12)

Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

onefusion before entering phase IIa.

Group 1 was expected to receive a total of 5 doses, group 2, 4 doses and so on until group 5, which was expected to receive only 1 dose.

<b>Arm title</b>	Lamazym 50 U/kg - Group 4
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Arm description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

Arm type	Experimental
Investigational medicinal product name	Lamazym
Investigational medicinal product code	
Other name	recombinant human alpha-mannosidase
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients were stratified into 5 groups (1-5) before entering the treatment phase, and each group was to receive one of the fixed doses (6.25, 12.5, 25, 50 or 100 U/kg).

Treatment phase (Visit 3-12)

Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only onefusion before entering phase IIa.

Group 1 was expected to receive a total of 5 doses, group 2, 4 doses and so on until group 5, which was expected to receive only 1 dose.

<b>Arm title</b>	Lamazym 100 U/kg - Group 5
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Arm description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

Arm type	Experimental
Investigational medicinal product name	Lamazym
Investigational medicinal product code	
Other name	recombinant human alpha-mannosidase
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients were stratified into 5 groups (1-5) before entering the treatment phase, and each group was to receive one of the fixed doses (6.25, 12.5, 25, 50 or 100 U/kg).

Treatment phase (Visit 3-12)

Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

Group 1 was expected to receive a total of 5 doses, group 2, 4 doses and so on until group 5, which was expected to receive only 1 dose.

<b>Number of subjects in period 1</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3
Started	2	2	2
Completed	2	2	2

<b>Number of subjects in period 1</b>	Lamazym 50 U/kg - Group 4	Lamazym 100 U/kg - Group 5
Started	2	2
Completed	2	2

## Baseline characteristics

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### Reporting groups

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Reporting group title	Lamazym 6.25 U/kg - Group 1
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Reporting group description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

Group 1 was expected to receive a total of 5 doses, group 2, 4 doses and so on until group 5, which was expected to receive only 1 dose.

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Reporting group title	Lamazym 12.5 U/kg - Group 2
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Reporting group description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

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Reporting group title	Lamazym 25 U/kg - Group 3
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Reporting group description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

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Reporting group title	Lamazym 50 U/kg - Group 4
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Reporting group description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

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Reporting group title	Lamazym 100 U/kg - Group 5
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Reporting group description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

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<b>Reporting group values</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3
Number of subjects	2	2	2
Age categorical Units: Subjects			
Children (2-11 years)	0	1	2
Adolescents (12-17 years)	2	1	0
Age continuous Units: years			
arithmetic mean	15.1	13.2	8.1
standard deviation	± 0.1	± 3.9	± 0.5
Gender categorical Units: Subjects			
Female	0	1	2
Male	2	1	0

<b>Reporting group values</b>	Lamazym 50 U/kg - Group 4	Lamazym 100 U/kg - Group 5	Total
Number of subjects	2	2	10
Age categorical Units: Subjects			
Children (2-11 years)	1	0	4
Adolescents (12-17 years)	1	2	6
Age continuous Units: years			
arithmetic mean	9.8	16.7	
standard deviation	± 3.1	± 1.2	-
Gender categorical Units: Subjects			
Female	0	0	3
Male	2	2	7

## End points

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### End points reporting groups

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Reporting group title	Lamazym 6.25 U/kg - Group 1
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Reporting group description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

Group 1 was expected to receive a total of 5 doses, group 2, 4 doses and so on until group 5, which was expected to receive only 1 dose.

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Reporting group title	Lamazym 12.5 U/kg - Group 2
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Reporting group description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

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Reporting group title	Lamazym 25 U/kg - Group 3
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Reporting group description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

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Reporting group title	Lamazym 50 U/kg - Group 4
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Reporting group description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

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Reporting group title	Lamazym 100 U/kg - Group 5
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Reporting group description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one infusion before entering phase IIa.

**Primary: rhLaman level in plasma**

End point title	rhLaman level in plasma
End point description:	The rhLaman level in plasma is measured as AUC.
End point type	Primary
End point timeframe:	At Visit 3 (first dose)

<b>End point values</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: µg*h/L				
arithmetic mean (standard deviation)	12221 (± 7388)	54684 (± 14056)	101930 (± 27336)	268538 (± 44872)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: µg*h/L				
arithmetic mean (standard deviation)	697375 (± 264080)			

**Statistical analyses**

<b>Statistical analysis title</b>	Evaluation of dose proportionality
Comparison groups	Lamazym 6.25 U/kg - Group 1 v Lamazym 12.5 U/kg - Group 2 v Lamazym 25 U/kg - Group 3 v Lamazym 50 U/kg - Group 4 v Lamazym 100 U/kg - Group 5
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
Parameter estimate	linear regression model
Point estimate	1.42
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.19
upper limit	1.64

Notes:

[1] - This is a dose finding (dose-escalation) study

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### Secondary: DBP

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End point title	DBP
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End point description:

Only descriptive statistical data of Diastolic Blood Pressure at Visit 3 - 24 Hours 30 Minutes Post Infusion Stop are reported here.

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End point type	Secondary
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End point timeframe:

At Visit 3, 4, 5, 6 and 7 (pre-infusion, multiple post infusion start and multiple post infusion stop timepoints)

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End point values	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: mmHg				
arithmetic mean (standard deviation)	81 (± 2.8)	59.5 (± 2.1)	66.5 (± 0.7)	70 (± 12.5)

End point values	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: mmHg				
arithmetic mean (standard deviation)	69 (± 1.4)			

### Statistical analyses

No statistical analyses for this end point

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### Secondary: SBP

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End point title	SBP
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End point description:

Only descriptive statistical data on Visit 3 - 24h post infusion stop are reported here.

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End point type	Secondary
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End point timeframe:

At Visit 3, 4, 5, 6 and 7 (pre-infusion, multiple post infusion start and multiple post infusion stop timepoints).

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<b>End point values</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: mmHg				
arithmetic mean (standard deviation)	142 (± 2.8)	112.5 (± 2.1)	95.5 (± 10.6)	113.5 (± 13.4)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: mmHg				
arithmetic mean (standard deviation)	135 (± 2.8)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Heart rate

End point title	Heart rate
End point description:	Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.
End point type	Secondary
End point timeframe:	At Visit 3, 4, 5, 6 and 7 (pre-infusion, multiple post infusion start and multiple post infusion stop timepoints)

<b>End point values</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: bpm				
arithmetic mean (standard deviation)	101 (± 1.4)	69 (± 22.6)	93 (± 1.4)	81 (± 18.4)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: bpm				
arithmetic mean (standard deviation)	64.5 (± 3.5)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Temperature

End point title | Temperature

End point description:

Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.

End point type | Secondary

End point timeframe:

At Visit 3, 4, 5, 6 and 7 (pre-infusion, multiple post infusion start and multiple post infusion stop timepoints).

End point values	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: Celsius degrees				
arithmetic mean (standard deviation)	36.8 (± 1)	36.9 (± 0.1)	37.6 (± 0.5)	36.8 (± 0.1)

End point values	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Celsius degrees				
arithmetic mean (standard deviation)	37.7 (± 0.4)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Respiration rate

End point title | Respiration rate

End point description:

Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.

End point type	Secondary
End point timeframe:	
At Visit 3, 4, 5, 6 and 7 (pre-infusion, multiple post infusion start and multiple post infusion stop timepoints).	

End point values	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: beats/min				
arithmetic mean (standard deviation)	27 ( $\pm$ 4.2)	21 ( $\pm$ 4.2)	21 ( $\pm$ 1.4)	21 ( $\pm$ 1.4)

End point values	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: beats/min				
arithmetic mean (standard deviation)	20 ( $\pm$ 0)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Hematology - Basophilocytes

End point title	Hematology - Basophilocytes
End point description:	
Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.	
End point type	Secondary
End point timeframe:	
At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)	

End point values	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: 10E9/L				
arithmetic mean (standard deviation)	0.05 ( $\pm$ 0.07)	0.1 ( $\pm$ 0)	0 ( $\pm$ 0)	0.05 ( $\pm$ 0.07)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: 10E9/L				
arithmetic mean (standard deviation)	0.05 (± 0.07)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Hematology - Eosinophilocytes

End point title	Hematology - Eosinophilocytes
End point description:	Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.
End point type	Secondary
End point timeframe:	At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)

<b>End point values</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: 10E9/L				
arithmetic mean (standard deviation)	0.1 (± 0)	0.05 (± 0.07)	0.15 (± 0.21)	0.05 (± 0.07)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: 10E9/L				
arithmetic mean (standard deviation)	0.8 (± 0.99)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Hematology - Haemoglobin (Fe)

End point title	Hematology - Haemoglobin (Fe)
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End point description:

Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.

End point type	Secondary
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End point timeframe:

At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)

<b>End point values</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: mmol/L				
arithmetic mean (standard deviation)	9.5 (± 0.14)	7.7 (± 0.28)	7.45 (± 0.35)	7.05 (± 0.78)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: mmol/L				
arithmetic mean (standard deviation)	9 (± 0.57)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Hematology - Mean cell haemoglobin concentration

End point title	Hematology - Mean cell haemoglobin concentration
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End point description:

Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.

End point type	Secondary
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End point timeframe:

At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)

<b>End point values</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: mmol/L				
arithmetic mean (standard deviation)	21.5 (± 0.7)	21 (± 0)	21 (± 0)	21 (± 0)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: mmol/L				
arithmetic mean (standard deviation)	21 (± 0)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Hematology - Mean cell haemoglobin

End point title	Hematology - Mean cell haemoglobin
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End point description:

Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.

End point type	Secondary
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End point timeframe:

At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)

<b>End point values</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: fmol				
arithmetic mean (standard deviation)	1.85 (± 0.07)	1.85 (± 0.21)	1.75 (± 0.07)	1.65 (± 0.07)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: fmol				
arithmetic mean (standard deviation)	1.8 (± 0.14)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Hematology - Lymphocytes

End point title Hematology - Lymphocytes

End point description:

Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.

End point type Secondary

End point timeframe:

At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)

End point values	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: 10E9/L				
arithmetic mean (standard deviation)	1.65 (± 0.49)	1.45 (± 0.21)	1.6 (± 0.57)	2.3 (± 0.42)

End point values	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: 10E9/L				
arithmetic mean (standard deviation)	3.05 (± 1.06)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Hematology - Monocytes

End point title Hematology - Monocytes

End point description:

Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.

End point type Secondary

End point timeframe:

At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion).

<b>End point values</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: 10E9/L				
arithmetic mean (standard deviation)	0.35 (± 0.07)	0.4 (± 0.14)	0.1 (± 0)	0.3 (± 0)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: 10E9/L				
arithmetic mean (standard deviation)	0.35 (± 0.21)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Hematology - Neutrophilocytes

End point title	Hematology - Neutrophilocytes
End point description:	Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.
End point type	Secondary
End point timeframe:	At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)

<b>End point values</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: 10E9/L				
arithmetic mean (standard deviation)	2.85 (± 1.63)	2.85 (± 0.64)	2.5 (± 0.92)	2.1 (± 0.28)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			

Units: 10E9/L				
arithmetic mean (standard deviation)	3.15 (± 1.34)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Hematology - Platelets

End point title	Hematology - Platelets
End point description:	Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.
End point type	Secondary
End point timeframe:	At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)

End point values	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: 10E9/L				
arithmetic mean (standard deviation)	206.5 (± 30.4)	177 (± 7.1)	223.5 (± 60.1)	167.5 (± 14.8)

End point values	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: 10E9/L				
arithmetic mean (standard deviation)	194.5 (± 12)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Hematology - Erythrocytes

End point title	Hematology - Erythrocytes
End point description:	Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.
End point type	Secondary
End point timeframe:	At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)

<b>End point values</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: 10E12/L				
arithmetic mean (standard deviation)	5.1 (± 0.14)	4.2 (± 0.42)	4.2 (± 0)	4.25 (± 0.35)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: 10E12/L				
arithmetic mean (standard deviation)	5.05 (± 0.64)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Hematology - Leucocytes

End point title	Hematology - Leucocytes
End point description:	Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.
End point type	Secondary
End point timeframe:	At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)

<b>End point values</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: 10E9/L				
arithmetic mean (standard deviation)	4.95 (± 1.06)	4.75 (± 0.21)	3.95 (± 0.07)	4.8 (± 0.14)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			

Units: 10E9/L				
arithmetic mean (standard deviation)	7.35 (± 3.61)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Blood Chemistry - S-Alat

End point title	Blood Chemistry - S-Alat
End point description:	Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.
End point type	Secondary
End point timeframe:	At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion).

End point values	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: U/L				
arithmetic mean (standard deviation)	14.5 (± 3.5)	18.5 (± 7.8)	15 (± 4.2)	25 (± 11.3)

End point values	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: U/L				
arithmetic mean (standard deviation)	14 (± 1.4)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Blood chemistry - S-Alkaline phosphatase

End point title	Blood chemistry - S-Alkaline phosphatase
End point description:	Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.
End point type	Secondary
End point timeframe:	At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion).

<b>End point values</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: U/L				
arithmetic mean (standard deviation)	121.5 (± 19.1)	183 (± 124.5)	246 (± 79.2)	248.5 (± 106.8)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: U/L				
arithmetic mean (standard deviation)	120.5 (± 13.4)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Blood chemistry - S-Amilase

End point title | Blood chemistry - S-Amilase

End point description:

Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.

End point type | Secondary

End point timeframe:

At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)

<b>End point values</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: U/L				
arithmetic mean (standard deviation)	57 (± 8.5)	52 (± 4.2)	43 (± 24)	35.5 (± 3.5)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			

Subject group type	Reporting group			
Number of subjects analysed	2			
Units: U/L				
arithmetic mean (standard deviation)	63 (± 2.8)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Blood chemistry - S-Bilirubin

End point title	Blood chemistry - S-Bilirubin
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End point description:

Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.

End point type	Secondary
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End point timeframe:

At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)

End point values	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: µmol/L				
arithmetic mean (standard deviation)	23 (± 4.2)	23.5 (± 23.3)	8.5 (± 0.7)	6 (± 2.8)

End point values	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: µmol/L				
arithmetic mean (standard deviation)	17 (± 8.5)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Blood chemistry - S-Calcium

End point title	Blood chemistry - S-Calcium
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End point description:

Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.

End point type	Secondary
End point timeframe:	
At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)	

End point values	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: mmol/L				
arithmetic mean (standard deviation)	2.36 ( $\pm$ 0.01)	2.38 ( $\pm$ 0.14)	2.36 ( $\pm$ 0.04)	2.37 ( $\pm$ 0.04)

End point values	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: mmol/L				
arithmetic mean (standard deviation)	2.4 ( $\pm$ 0.02)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Blood chemistry - S-Creatin kinase

End point title	Blood chemistry - S-Creatin kinase
End point description:	
Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.	
End point type	Secondary
End point timeframe:	
At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)	

End point values	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: U/L				
arithmetic mean (standard deviation)	74.5 ( $\pm$ 20.5)	61 ( $\pm$ 22.6)	63 ( $\pm$ 5.7)	102.5 ( $\pm$ 50.2)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: U/L				
arithmetic mean (standard deviation)	72.5 (± 23.3)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Blood chemistry - S-Creatininium substr.c.

End point title	Blood chemistry - S-Creatininium substr.c.
End point description:	Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.
End point type	Secondary
End point timeframe:	At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)

<b>End point values</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: µmol/L				
arithmetic mean (standard deviation)	88.5 (± 7.8)	67.5 (± 0.7)	61 (± 2.8)	63.5 (± 9.2)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: µmol/L				
arithmetic mean (standard deviation)	83 (± 4.2)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Blood chemistry - S-Potassium ion subst.c.

End point title	Blood chemistry - S-Potassium ion subst.c.
End point description:	Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.

End point type	Secondary
End point timeframe:	
At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)	

End point values	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: mmol/L				
arithmetic mean (standard deviation)	3.65 (± 0.21)	3.85 (± 0.07)	4 (± 0)	4.05 (± 0.07)

End point values	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: mmol/L				
arithmetic mean (standard deviation)	3.65 (± 0.07)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Blood Chemistry - S-LDH

End point title	Blood Chemistry - S-LDH
End point description:	
Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.	
End point type	Secondary
End point timeframe:	
At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion).	

End point values	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: U/L				
arithmetic mean (standard deviation)	183.5 (± 3.5)	187.5 (± 94)	214.5 (± 10.6)	232.5 (± 21.9)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: U/L				
arithmetic mean (standard deviation)	187.5 (± 4.9)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Blood Chemistry - S-Phosphate inorg.

End point title	Blood Chemistry - S-Phosphate inorg.
End point description:	Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.
End point type	Secondary
End point timeframe:	At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)

<b>End point values</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: mmol/L				
arithmetic mean (standard deviation)	1.03 (± 0.04)	1.04 (± 0.03)	1.32 (± 0.11)	1.3 (± 0.18)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: mmol/L				
arithmetic mean (standard deviation)	1.09 (± 0)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Blood Chemistry - S-Sodium ion

End point title	Blood Chemistry - S-Sodium ion
End point description:	Only descriptive statistical data at Visit 3 - 24 h post infusion stop are reported here.

End point type	Secondary
End point timeframe:	
At Visit 2 (baseline), 3 (pre infusion, 24 h post infusion stop), and 7 (pre-infusion)	

<b>End point values</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3	Lamazym 50 U/kg - Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	2	2
Units: mmol/L				
arithmetic mean (standard deviation)	140.5 ( $\pm$ 0.7)	140.5 ( $\pm$ 0.7)	139 ( $\pm$ 0)	138.5 ( $\pm$ 0.7)

<b>End point values</b>	Lamazym 100 U/kg - Group 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: mmol/L				
arithmetic mean (standard deviation)	139 ( $\pm$ 2.1)			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Visit 2 (baseline) to Visit 12

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.0
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### Reporting groups

Reporting group title	Lamazym 6.25 U/kg - Group 1
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Reporting group description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one fusion before entering phase IIa.

Group 1 was expected to receive a total of 5 doses, group 2, 4 doses and so on until group 5, which was expected to receive only 1 dose.

Reporting group title	Lamazym 12.5 U/kg - Group 2
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Reporting group description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one fusion before entering phase IIa.

Reporting group title	Lamazym 25 U/kg - Group 3
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Reporting group description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one fusion before entering phase IIa.

Reporting group title	Lamazym 50 U/kg - Group 4
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Reporting group description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one fusion before entering phase IIa.

Reporting group title	Lamazym 100 U/kg - Group 5
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Reporting group description:

A fixed dose regimen was chosen (6.25, 12.5, 25, 50 or 100 U/kg).

The dose was determined after an evaluation at baseline and on the basis of which group the patient

was stratified to (from 1-5). Each patient was to receive an infusion once a week. The number of infusions was dependant on the group number the patient was stratified to hence the onset of the first infusion for each patient.

Infusions were administered weekly commencing with group 1, where patients received their first dose at Day 0 (Visit 3). One week later (7 days  $\pm$  2 days) group 2 received their first infusion (Visit 3) whereas group 1 received their second dose (Visit 4) and so on until group 5 who would have only one fusion before entering phase IIa.

<b>Serious adverse events</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

<b>Serious adverse events</b>	Lamazym 50 U/kg - Group 4	Lamazym 100 U/kg - Group 5	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (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: 1 %

<b>Non-serious adverse events</b>	Lamazym 6.25 U/kg - Group 1	Lamazym 12.5 U/kg - Group 2	Lamazym 25 U/kg - Group 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	1 / 2 (50.00%)	1 / 2 (50.00%)
Investigations			
Urine analysis abnormal			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0

Reflux gastritis subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Infections and infestations Skin infection subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 2 (50.00%) 1	0 / 2 (0.00%) 0

<b>Non-serious adverse events</b>	Lamazym 50 U/kg - Group 4	Lamazym 100 U/kg - Group 5	
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 2 (50.00%)	1 / 2 (50.00%)	
Investigations Urine analysis abnormal subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1	1 / 2 (50.00%) 1	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)  Reflux gastritis subjects affected / exposed occurrences (all)  Vomiting subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1  1 / 2 (50.00%) 1  0 / 2 (0.00%) 0	0 / 2 (0.00%) 0  0 / 2 (0.00%) 0  0 / 2 (0.00%) 0	
Infections and infestations Skin infection subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2010	<ul style="list-style-type: none"><li>• Addition of a pregnancy test in the post-menarchal adolescents women at inclusion and throughout the study as requested by the IEC.</li><li>• Reduction of the infusion rate from 1.5 mg/min to 0.5 mg/min as requested by the SC.</li><li>• Addition of an ECG taken immediately after the infusion stop, as requested by the SC.</li></ul>

Notes:

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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.

NO limitations or caveats are applicable to this summary.

Notes: