Clinical trial results:
Comparative efficacy and safety of two asparaginase preparations in children with previously untreated acute lymphoblastic leukaemia

Summary

EudraCT number	2006-003180-31
Trial protocol	NL
Global end of trial date	17 February 2012

Results information

Result version number	v1 (current)
This version publication date	10 August 2016
First version publication date	10 August 2016

Trial information

Trial identification

Sponsor protocol code	MC-ASP.5/ALL

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	medac Gesellschaft für klinische Spezialpräparate mbH
Sponsor organisation address	Theaterstraße 6, Wedel, Germany, 22880
Public contact	Clinical Trial Disclosure Desk, medac Gesellschaft für klinische Spezialpräparate mbH Theaterstraße 6 22880 Wedel, 0049 04103 8006 0, eudract@medac.de
Scientific contact	Medical Expert, medac Gesellschaft für klinische Spezialpräparate mbH Theaterstraße 6 22880 Wedel, 0049 04103 8006 0, med-wiss@medac.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000013-PIP01-07
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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 October 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 February 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the rate of patients with complete asparagine (ASN) depletion in serum during induction treatment and to demonstrate non-inferiority of rASNase compared to Asparaginase medac with respect to this parameter.

Protection of trial subjects:

Only pseudonymous collection and storage of patient’s data

Background therapy:

Acute Lymphoblastic Leukaemia (ALL) type chemotherapy

Evidence for comparator:

To demonstrate non-inferiority of rASNase compared to Asparaginase medac

Actual start date of recruitment	29 October 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 199
Worldwide total number of subjects	199
EEA total number of subjects	199

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)	13
Children (2-11 years)	150
Adolescents (12-17 years)	36
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

They fulfilled the criteria to be involved in the study. Parents signed the declaration of consent.

Pre-assignment

Screening details:

Investigation, laboratory, diagnosis of ALL

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Asparaginase medac

Arm description:

Reference-Arm

Arm type	Experimental
Investigational medicinal product name	Aspraginase medac
Investigational medicinal product code	MC0904
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During induction treatment patients received eight doses of 5000 U/m² each of Asparaginase medac. In the post induction phase some high risk (HR) patients received additional infusions of 10 000 U/m² Asparaginase medac

Arm title	rASNase

Arm description:

Test-Arm

Arm type	Experimental
Investigational medicinal product name	Recombinant ASNase
Investigational medicinal product code	MC0707
Other name	rASNase
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During induction treatment patients received eight doses of 5000 U/m² each of Recombinant Asparaginase (rASNase). In the post induction phase some high risk (HR) patients received additional infusions of 10 000 U/m² Recombinant Asparaginase

Number of subjects in period 1	Asparaginase medac	rASNase
Started	101	98
Induction phase	98	94
Post-induction phase	95	92
Completed	88	84
Not completed	13	14
Adverse event, serious fatal	1	3
Consent withdrawn by subject	1	-
Physician decision	7	6
Adverse event, non-fatal	3	-
Other	1	4
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Asparaginase medac
Reporting group description:	
Reference-Arm	
Reporting group title	rASNase
Reporting group description:	
Test-Arm	

Reporting group values	Asparaginase medac	rASNase	Total
Number of subjects	101	98	199
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)	8	5	13
Children (2-11 years)	75	75	150
Adolescents (12-17 years)	18	18	36
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
median	4	5	
full range (min-max)	1 to 16	1 to 17	-
Gender categorical			
Units: Subjects			
Female	48	44	92
Male	53	54	107
Body weight			
Units: kilogram(s)			
median	18	22	
full range (min-max)	7 to 71	9 to 90	-
Body surface area			
Units: square meter			
median	0.73	0.85	
full range (min-max)	0.4 to 1.9	0.4 to 2.1	-
Body height			
Units: cm			
median	108	118.5	
full range (min-max)	72 to 191	75 to 185	-

End points

End points reporting groups

Reporting group title	Asparaginase medac
Reporting group description:	
Reference-Arm	
Reporting group title	rASNase
Reporting group description:	
Test-Arm	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients randomized for study participation	
Subject analysis set title	Per protocol set
Subject analysis set type	Per protocol
Subject analysis set description:	
Per-protocol analysis is a comparison of treatment groups that includes only those patients who completed the treatment originally allocated without major protocol deviations.	

Primary: Complete Asparagine Depletion in Serum during induction treatment

End point title	Complete Asparagine Depletion in Serum during induction treatment
End point description:	
End point type	Primary
End point timeframe:	
Induction Phase	

End point values	Asparaginase medac	rASNase	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	101	98	199	
Units: Patients				
Yes	95	93	188	
No	2	2	4	
Not Evaluable	4	3	7	

Statistical analyses

Statistical analysis title	Non-Inferiority of complete Asparagine Depletion
Comparison groups	Asparaginase medac v rASNase

Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0028
Method	REML estimates
Parameter estimate	Risk difference (RD)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.25
upper limit	8.04

Secondary: Complete Asparagine Depletion in Cerebrospinal fluid on day 33

End point title	Complete Asparagine Depletion in Cerebrospinal fluid on day 33
End point description:	

End point type	Secondary
End point timeframe:	
Induction Phase	

End point values	Asparaginase medac	rASNase	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	101	98	199	
Units: Patients				
Yes	88	82	170	
No	6	1	7	
Not Evaluable	7	15	22	

Statistical analyses

Statistical analysis title	DescriptiveAnlaysis of difference in ASN depletion
Comparison groups	Asparaginase medac v rASNase
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.67
upper limit	6.58

Secondary: Trough Levels of Asparaginase Activity in serum

End point title	Trough Levels of Asparaginase Activity in serum

End point description:

End point type	Secondary

End point timeframe:

Day 15

End point values	Asparaginase medac	rASNase	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	99	92	191	
Units: Patients				
geometric mean (full range (min-max))	146.79 (35.36 to 410.61)	159.77 (28.14 to 524.44)	152.9 (28.14 to 524.44)	

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Levels of Asparaginase Activitiy in serum

End point title	Trough Levels of Asparaginase Activitiy in serum

End point description:

End point type	Secondary

End point timeframe:

Day 21

End point values	Asparaginase medac	rASNase	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	95	94	189	
Units: Patients				
geometric mean (full range (min-max))	153.99 (1.25 to 584.69)	158.41 (3.69 to 696.33)	156.17 (1.25 to 696.33)	

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Levels of Asparaginase Activity in serum

End point title	Trough Levels of Asparaginase Activity in serum

End point description:

End point type	Secondary

End point timeframe:

Day 27

End point values	Asparaginase medac	rASNase	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	92	89	181	
Units: Patients				
geometric mean (full range (min-max))	177.45 (18.37 to 747.61)	149.58 (1.25 to 739.53)	163.15 (1.25 to 747.61)	

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Levels of Asparaginase Activity in serum

End point title	Trough Levels of Asparaginase Activity in serum

End point description:

End point type	Secondary

End point timeframe:

Day 33

End point values	Asparaginase medac	rASNase	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	95	93	188	
Units: Patients				
geometric mean (full range (min-max))	153.54 (1.25 to 1980.94)	127.26 (1.25 to 697.8)	139.92 (1.25 to 1980.94)	

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission	
End point title	Complete Remission
End point description:	

End point type	Secondary
End point timeframe:	
After induction phase	

End point values	Asparaginase medac	rASNase	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	101	98	199	
Units: Patients				
Yes	97	90	187	
No	2	2	4	
Not Evaluable	2	6	8	

Statistical analyses

Statistical analysis title	Descriptive Anlaysis of complete remission
Comparison groups	Asparaginase medac v rASNase
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.9
upper limit	2.81

Secondary: Minimal residual disease	
End point title	Minimal residual disease
End point description:	

End point type	Secondary
End point timeframe:	
After induction phase	

End point values	Asparaginase medac	rASNase	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	101	98	199	
Units: Patients				
Negative	32	29	61	
Positive	60	63	123	
Not Evaluable	9	6	15	

Statistical analyses

Statistical analysis title	Descriptive Anlaysis of minimal residual disease
Comparison groups	Asparaginase medac v rASNase
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.97
upper limit	10.84

Secondary: Level of glutamic acid in serum Day 15

End point title	Level of glutamic acid in serum Day 15
End point description:	
Concentration of glutamic acid in serum on Day 15 of the induction phase	
End point type	Secondary
End point timeframe:	
Day 15	

End point values	Asparaginase medac	rASNase	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	99	94	193	
Units: µmol/L				
median (full range (min-max))	50.83 (5.36 to 145.8)	51.93 (5.36 to 182.23)	51.54 (5.36 to 182.23)	

Statistical analyses

No statistical analyses for this end point

Secondary: Level of glutamic acid in serum Day 21

End point title	Level of glutamic acid in serum Day 21

End point description:

Concentration of glutamic acid in serum on Day 21 of the induction phase

End point type	Secondary

End point timeframe:

Day 21

End point values	Asparaginase medac	rASNase	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	95	95	190	
Units: µmol/L				
median (full range (min-max))	49.85 (5.36 to 431.42)	53.77 (12.82 to 247.77)	51.06 (5.36 to 431.42)	

Statistical analyses

No statistical analyses for this end point

Secondary: Level of glutamic acid in serum Day 27

End point title	Level of glutamic acid in serum Day 27

End point description:

Concentration of glutamic acid in serum on Day 27 of the induction phase

End point type	Secondary

End point timeframe:

Day 27

End point values	Asparaginase medac	rASNase	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	93	89	182	
Units: µmol/L				
median (full range (min-max))	58.83 (5.36 to 197.25)	53.14 (24.25 to 405.92)	57.22 (5.36 to 405.92)	

Statistical analyses

No statistical analyses for this end point

Secondary: Level of glutamic acid in serum Day 33

End point title	Level of glutamic acid in serum Day 33
End point description:	
Concentration of glutamic acid in serum on Day 33 of the induction phase	
End point type	Secondary
End point timeframe:	
Day 33	

End point values	Asparaginase medac	rASNase	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	95	93	188	
Units: µmol/L				
median (full range (min-max))	63 (5.36 to 303.29)	61.26 (5.36 to 161.42)	62.47 (5.36 to 303.29)	

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-ASNase antibodies in serum

End point title	Anti-ASNase antibodies in serum
End point description:	
Anti-ASNase antibodies in serum during repeated administration of ASNase	
End point type	Secondary
End point timeframe:	
Determined at all time points during induction and post-induction treatment where blood sample collection was performed	

End point values	Asparaginase medac	rASNase	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	101	97	198	
Units: Patients				
Positive	55	58	113	
Negative	46	38	84	
NK	0	1	1	

Statistical analyses

Statistical analysis title	Anti-ASNase antibodies
Comparison groups	Asparaginase medac v rASNase

Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	CI based on Chan & Zhung
Point estimate	6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.52
upper limit	20.43

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Please refer to protocol.	
Adverse event reporting additional description:	
Please refer to protocol. Events coded by CTCAE V3.0, System Organ Classes mapped to CTCAE V4.0.	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups	
Reporting group title	ASNase medac
Reporting group description: -	
Reporting group title	rASNase
Reporting group description: -	

Serious adverse events	ASNase medac	rASNase	
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 101 (36.63%)	33 / 97 (34.02%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	0	3	
Investigations			
Weight loss			
subjects affected / exposed	1 / 101 (0.99%)	3 / 97 (3.09%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholesterol			
subjects affected / exposed	0 / 101 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GGT			
subjects affected / exposed	0 / 101 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular - Other			

subjects affected / exposed	4 / 101 (3.96%)	5 / 97 (5.15%)	
occurrences causally related to treatment / all	4 / 4	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis/thrombus/embolism			
subjects affected / exposed	1 / 101 (0.99%)	2 / 97 (2.06%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CNS hemorrhage			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Involuntary movement			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy-motor			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain [Head/headache]			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	7 / 101 (6.93%)	9 / 97 (9.28%)	
occurrences causally related to treatment / all	3 / 7	5 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Fever			
subjects affected / exposed	3 / 101 (2.97%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 101 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain [Chest/thorax NOS]			
subjects affected / exposed	0 / 101 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syndromes - Other			
subjects affected / exposed	0 / 101 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	2 / 101 (1.98%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis (clinical exam) [Oral cavity]			
subjects affected / exposed	2 / 101 (1.98%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 101 (0.99%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GI - Other			
subjects affected / exposed	2 / 101 (1.98%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain [Abdomen NOS]			
subjects affected / exposed	0 / 101 (0.00%)	2 / 97 (2.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophagitis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis (clinical exam) [Anus]			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis (clinical exam) [Small bowel]			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatits			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Liver dysfunction			
subjects affected / exposed	3 / 101 (2.97%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary - Other			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Airway obstruction [Larynx]			
subjects affected / exposed	0 / 101 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis (clinical exam) [Pharynx]			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonray - Other			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Obstruction, GU [Ureter]			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection (documented clinically) [Blood]			

subjects affected / exposed	2 / 101 (1.98%)	2 / 97 (2.06%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection - Other			
subjects affected / exposed	3 / 101 (2.97%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Opportunistic infection			
subjects affected / exposed	1 / 101 (0.99%)	2 / 97 (2.06%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Infection (documented clinically) [Lung (pneumonia)]			
subjects affected / exposed	2 / 101 (1.98%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC [Brain+Spinal cord (encephalomyelitis)]			
subjects affected / exposed	0 / 101 (0.00%)	2 / 97 (2.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Infection (documented clinically) [Skin (cellulitis)]			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC [Brain (encephalitis, infectious)]			
subjects affected / exposed	0 / 101 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC [Liver]			
subjects affected / exposed	0 / 101 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infection with normal ANC [Meninges (meningitis)]			
subjects affected / exposed	0 / 101 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes			
subjects affected / exposed	2 / 101 (1.98%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertriglyceridemia			
subjects affected / exposed	1 / 101 (0.99%)	2 / 97 (2.06%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 101 (0.00%)	2 / 97 (2.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorexia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ASNase medac	rASNase	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 101 (92.08%)	90 / 97 (92.78%)	
Investigations			
Weight loss			
subjects affected / exposed	3 / 101 (2.97%)	9 / 97 (9.28%)	
occurrences (all)	4	10	
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 101 (8.91%)	8 / 97 (8.25%)	
occurrences (all)	11	9	

Hematoma			
subjects affected / exposed	4 / 101 (3.96%)	5 / 97 (5.15%)	
occurrences (all)	5	5	
Nervous system disorders			
Pain [Head/headache]			
subjects affected / exposed	13 / 101 (12.87%)	17 / 97 (17.53%)	
occurrences (all)	14	17	
Neuropathy-motor			
subjects affected / exposed	15 / 101 (14.85%)	14 / 97 (14.43%)	
occurrences (all)	15	14	
Neuropathy-sensory			
subjects affected / exposed	11 / 101 (10.89%)	13 / 97 (13.40%)	
occurrences (all)	12	14	
Dizziness			
subjects affected / exposed	2 / 101 (1.98%)	6 / 97 (6.19%)	
occurrences (all)	2	8	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	36 / 101 (35.64%)	34 / 97 (35.05%)	
occurrences (all)	39	39	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	21 / 101 (20.79%)	20 / 97 (20.62%)	
occurrences (all)	21	23	
Pain [Abdomen NOS]			
subjects affected / exposed	20 / 101 (19.80%)	21 / 97 (21.65%)	
occurrences (all)	24	23	
Vomiting			
subjects affected / exposed	17 / 101 (16.83%)	16 / 97 (16.49%)	
occurrences (all)	21	20	
Constipation			
subjects affected / exposed	13 / 101 (12.87%)	13 / 97 (13.40%)	
occurrences (all)	15	13	
Nausea			
subjects affected / exposed	11 / 101 (10.89%)	14 / 97 (14.43%)	
occurrences (all)	12	17	

Mucositis (clinical exam) [Oral cavity]			
subjects affected / exposed	9 / 101 (8.91%)	12 / 97 (12.37%)	
occurrences (all)	11	12	
Pain [Stomach]			
subjects affected / exposed	4 / 101 (3.96%)	8 / 97 (8.25%)	
occurrences (all)	4	8	
Respiratory, thoracic and mediastinal disorders			
Pain [Throat/pharynx/larynx]			
subjects affected / exposed	6 / 101 (5.94%)	6 / 97 (6.19%)	
occurrences (all)	6	6	
Hemorrhage pulmonary [Nose]			
subjects affected / exposed	3 / 101 (2.97%)	6 / 97 (6.19%)	
occurrences (all)	3	9	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	9 / 101 (8.91%)	8 / 97 (8.25%)	
occurrences (all)	10	10	
Dermatology - Other			
subjects affected / exposed	7 / 101 (6.93%)	7 / 97 (7.22%)	
occurrences (all)	7	7	
Petechiae			
subjects affected / exposed	3 / 101 (2.97%)	6 / 97 (6.19%)	
occurrences (all)	3	7	
Psychiatric disorders			
Mood alteration [Agitation]			
subjects affected / exposed	14 / 101 (13.86%)	17 / 97 (17.53%)	
occurrences (all)	14	17	
Insomnia			
subjects affected / exposed	5 / 101 (4.95%)	11 / 97 (11.34%)	
occurrences (all)	5	11	
Musculoskeletal and connective tissue disorders			
Pain [Extremity-limb]			
subjects affected / exposed	21 / 101 (20.79%)	11 / 97 (11.34%)	
occurrences (all)	22	13	
Muscle weakness [Extremity-lower]			

subjects affected / exposed	12 / 101 (11.88%)	10 / 97 (10.31%)	
occurrences (all)	12	10	
Pain [Back]			
subjects affected / exposed	8 / 101 (7.92%)	13 / 97 (13.40%)	
occurrences (all)	9	13	
Pain [Bone]			
subjects affected / exposed	7 / 101 (6.93%)	11 / 97 (11.34%)	
occurrences (all)	7	13	
Pain [Joint]			
subjects affected / exposed	1 / 101 (0.99%)	5 / 97 (5.15%)	
occurrences (all)	1	5	
Infections and infestations			
Infection (documented clinically) [Oral cavity-gums (gingivitis)]			
subjects affected / exposed	6 / 101 (5.94%)	8 / 97 (8.25%)	
occurrences (all)	6	8	
Infection with normal ANC [Oral cavity-gums (gingivitis)]			
subjects affected / exposed	4 / 101 (3.96%)	6 / 97 (6.19%)	
occurrences (all)	4	6	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	7 / 101 (6.93%)	5 / 97 (5.15%)	
occurrences (all)	8	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2009	Relevant changes were: • Secondary endpoint was defined more precisely • Study medication: time of infusion was changed to 0.5 to 2.0 hours • Specification statistical data analysis • Specification on timing of blood drawings • Change of sample size and power calculation according to modified PIP • Deletion of the interim analysis • Administrative changes
14 December 2010	Relevant changes were: • Update of timelines • Update of information according to SPC Asparaginase medac • Minimal Residual Disease (MRD) status to be evaluated centrally in Rotterdam within the DOOG ALL 10 protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported