Clinical trial results:
Efficacy and safety of recombinant asparaginase in infants (< 1 year) with previously untreated acute lymphoblastic leukaemia - Phase II Clinical Trial -

Summary

EudraCT number	2008-006300-27
Trial protocol	NL DE
Global end of trial date	14 September 2010

Results information

Result version number	v1 (current)
This version publication date	23 September 2016
First version publication date	23 September 2016

Trial information

Trial identification

Sponsor protocol code	MC-ASP.6/INF

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 GmbH Theaterstraße 6 22880 Wedel Germany, 0049 04103 8006 0, eudract@medac.de
Scientific contact	Medical Expert, medac GmbH Theaterstraße 6 22880 Wedel Germany, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 October 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 September 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the number of patients with hypersensitivity reactions to rASNase.

Protection of trial subjects:

Only pseudonymous collection and storage of patient`s data

Background therapy:

ALL type chemotherapy

Evidence for comparator:

Not applicable

Actual start date of recruitment	12 August 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Germany: 8
Worldwide total number of subjects	12
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	1
Infants and toddlers (28 days-23 months)	11
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Included in the study only if "Inclusion Criteria" applied and "Exclusion criteria" did not applied
Included in Interfant 06 Protocol

Pre-assignment

Screening details:

Demographic data, Laboratory, Results of bone marrow biopsy and/or Peripheral blood sample, Risk group stratification

Period 1

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

Arms

Arm title	rASNase

Arm description:

(Days 15, 18, 22, 25, 29, 33 of the INTERFANT-06 induction phase)
Infusion (depend on BSA) on these days; blood samples immediately before ASNase infusions; controlling of allergic reactions; day 33 assessment of complete remission and MRD status

Arm type	Experimental
Investigational medicinal product name	r-L-asparaginase
Investigational medicinal product code	CAS number: 9015-68-3 (MC0707)
Other name	recombinant L-Asparaginase, L-Asparaginase aminohydrolase,
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10,000 U/m² ; adjusted to the current age of the patient at the time of administration; over 1+- 0.5 hours, on day 15, 18, 22, 25, 29 and 33 (6 doses).

Number of subjects in period 1	rASNase
Started	12
Completed	8
Not completed	4
Relapse	4

Baseline characteristics

Reporting groups	
Reporting group title	Induction phase
Reporting group description:	
We have only 12 Subjects in this study. See listed before.	

Reporting group values	Induction phase	Total	
Number of subjects	12	12	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	1	1	
Infants and toddlers (28 days-23 months)	11	11	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: months			
median	6		
full range (min-max)	0.5 to 12.2	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	7	7	
Immunophenotype Units: Subjects			
Pro-B-ALL	9	9	
Common ALL	1	1	
Pre-B-ALL	2	2	
Genetics Units: Subjects			
MLL-AF4	5	5	
MLL-AF9	1	1	
MLL-ENL	2	2	
t(1,14)	1	1	
No aberration	3	3	
Risk group stratification Units: Subjects			
Low Risk	4	4	
Medium Risk	4	4	
High Risk	4	4	

Height Units: cm median full range (min-max)	 65.5 46 to 79	 -	
Weight Units: Gramm median full range (min-max)	 6982.5 3100 to 9870	 -	
BodySurfaceArea Units: m² median full range (min-max)	 0.36 0.19 to 0.45	 -	

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who received all six rASNase infusions and for whom ASN-levels were available from at least 2 of the 3 sceduled time points (measured directly before rASNase infusion 2, 4 and 6)

Reporting group values	Full Analysis Set		
Number of subjects	12		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	1		
Infants and toddlers (28 days-23 months)	11		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: months			
median	6		
full range (min-max)	0.5 to 12.2		
Gender categorical Units: Subjects			
Female	5		
Male	7		
Immunophenotype Units: Subjects			
Pro-B-ALL	9		
Common ALL	1		
Pre-B-ALL	2		
Genetics Units: Subjects			
MLL-AF4	5		

MLL-AF9	1		
MLL-ENL	2		
t(1,14)	1		
No aberration	3		
Risk group stratification Units: Subjects			
Low Risk	4		
Medium Risk	4		
High Risk	4		
Height Units: cm			
median	65.5		
full range (min-max)	46 to 79		
Weight Units: Gramm			
median	6982.5		
full range (min-max)	3100 to 9870		
BodySurfaceArea Units: m²			
median	0.36		
full range (min-max)	0.19 to 0.45		

End points

End points reporting groups

Reporting group title	rASNase

Reporting group description:

(Days 15, 18, 22, 25, 29, 33 of the INTERFANT-06 induction phase)
Infusion (depend on BSA) on these days; blood samples immediately before ASNase infusions; controlling of allergic reactions; day 33 assessment of complete remission and MRD status

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who received all six rASNase infusions and for whom ASN-levels were available from at least 2 of the 3 sceduled time points (measured directly before rASNase infusion 2, 4 and 6)

Primary: Hypersensitivity Reactions

End point title	Hypersensitivity Reactions[1]

End point description:

Hypersensitivity reactions were defined as:
- Any allergic reaction occurring during or up to 12 hours after rASNase infusion (e.g. rash, urticaria, oedema/angiooedema, symptomatic bronchospasm, anaphylaxis)
- Silent inactivation of ASNase activity, defined as ASNase trough serum activity < 20 U/L (directly before rASNase administration numbers 2, 4, and 6).

End point type	Primary

End point timeframe:

- allergic reaction occurring during or up to 12 hours after rASNase infusion
- silent inactivation directly before rASNase administration numbers 2, 4, 6

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis for comparison has been performed because this trial consists only of one treatment arm.

End point values	rASNase	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	12	12		
Units: Number				
Patients with hypersensitivity reactions	4	4		

Statistical analyses

No statistical analyses for this end point

Secondary: ASNase activity in serum Day 15

End point title	ASNase activity in serum Day 15

End point description:

ASNase activity in serum directly before ASNase infusion 1 during induction treatment

End point type	Secondary

End point timeframe:

Day 15

End point values	rASNase	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	12	12		
Units: U/L				
geometric mean (standard deviation)	1 (± 1)	1 (± 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: ASNase activity in serum Day 18

End point title	ASNase activity in serum Day 18
End point description:	
ASNase activity in serum directly before ASNase infusion 2 during induction treatment	
End point type	Secondary
End point timeframe:	
Day 18	

End point values	rASNase	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: U/L				
geometric mean (standard deviation)	177.122 (± 2.007)	177.122 (± 2.007)		

Statistical analyses

No statistical analyses for this end point

Secondary: ASNase activity in serum Day 25

End point title	ASNase activity in serum Day 25
End point description:	
ASNase activity in serum directly before ASNase infusion 4 during induction treatment	
End point type	Secondary
End point timeframe:	
Day 25	

End point values	rASNase			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: U/L				
geometric mean (standard deviation)	102.034 (± 3.562)			

Statistical analyses

No statistical analyses for this end point

Secondary: ASNase activity in serum Day 33

End point title	ASNase activity in serum Day 33
End point description:	
ASNase activity in serum directly before rASNase infusion 6 during induction treatment	
End point type	Secondary
End point timeframe:	
Day 33	

End point values	rASNase			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: U/L				
geometric mean (standard deviation)	31.444 (± 2.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: CR Rate

End point title	CR Rate
End point description:	
Complete remission rate after induction	
End point type	Secondary
End point timeframe:	
Day 33	

End point values	rASNase			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Number				
number (not applicable)	12			

Statistical analyses

No statistical analyses for this end point

Secondary: MRD Status

End point title	MRD Status
End point description:	
Minimal Residual Disease Status after induction	
End point type	Secondary
End point timeframe:	
Day 33	

End point values	rASNase			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Number				
number (not applicable)				
negative	1			
positiv	9			
ND	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Level of ASN in serum Day 15

End point title	Level of ASN in serum Day 15
End point description:	
Concentration of ASN in serum directly before rASNase infusion 1 during treatment	
End point type	Secondary
End point timeframe:	
Day 15	

End point values	rASNase			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: µmol/L				
geometric mean (standard deviation)	45.452 (± 1.397)			

Statistical analyses

No statistical analyses for this end point

Secondary: Level of ASN in serum Day 18

End point title	Level of ASN in serum Day 18
End point description:	
Concentration of ASN in serum directly before rASNase infusion 2 during treatment	
End point type	Secondary
End point timeframe:	
Day 18	

End point values	rASNase			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: µmol/L				
geometric mean (standard deviation)	0.25 (± 1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Level of ASN in serum Day 25

End point title	Level of ASN in serum Day 25
End point description:	
Concentration of ASN in serum directly before rASNase infusion 4 during treatment	
End point type	Secondary
End point timeframe:	
Day 25	

End point values	rASNase			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: µmol/L				
geometric mean (standard deviation)	0.25 (± 1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Level of ASN in serum Day 33

End point title	Level of ASN in serum Day 33

End point description:

Concentration of ASN in serum directly before rASNase infusion 6 during treatment

End point type	Secondary

End point timeframe:

Day 33

End point values	rASNase			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: µmol/L				
geometric mean (standard deviation)	0.324 (± 2.464)			

Statistical analyses

No statistical analyses for this end point

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 directly before rASNase infusion 1

End point type	Secondary

End point timeframe:

Day 15

End point values	rASNase			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: µmol/L				
geometric mean (standard deviation)	78.086 (± 1.698)			

Statistical analyses

No statistical analyses for this end point

Secondary: Level of glutamic acid in serum Day 18

End point title	Level of glutamic acid in serum Day 18
End point description:	
Concentration of glutamic acid in serum directly before rASNase infusion 2	
End point type	Secondary
End point timeframe:	
Day 18	

End point values	rASNase			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: µmol/L				
geometric mean (standard deviation)	98.407 (± 1.668)			

Statistical analyses

No statistical analyses for this end point

Secondary: Level of glutamic acid in serum Day 25

End point title	Level of glutamic acid in serum Day 25
End point description:	
Concentration of glutamic acid in serum directly before rASNase infusion 4	
End point type	Secondary
End point timeframe:	
Day 25	

End point values	rASNase			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: µmol/L				
geometric mean (standard deviation)	89.268 (± 1.77)			

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 directly before rASNase infusion 6

End point type	Secondary

End point timeframe:

Day 33

End point values	rASNase			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: µmol/L				
geometric mean (standard deviation)	75.888 (± 1.667)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs had to be documented and followed from Day 15 up to Day 39. Thereafter, up to Day 64, only AEs with suspected relationship to the investigational drug were reported. All SAEs were followed until resolved or stabilised.

Adverse event reporting additional description:

Please refer to the 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	Study subjects

Reporting group description:

All 12 study subjects

Serious adverse events	Study subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 12 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Thrombosis/thrombus/embolism			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Edema larynx			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Infection (documented clinically)			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Study subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Vascular disorders			
Hematoma			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Thrombosis/thrombus/embolism			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Edema: head and neck			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Edema limb			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Constitutional Symptoms - other			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Edema: trunk/genital			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Fever			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Immune system disorders			
Allergic reaction			

subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Respiratory, thoracic and mediastinal disorders Hemorrhage pulmonary subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		
Investigations Weight loss subjects affected / exposed occurrences (all)	 3 / 12 (25.00%) 3		
Blood and lymphatic system disorders Febrile neutropenia subjects affected / exposed occurrences (all)	 3 / 12 (25.00%) 3		
Gastrointestinal disorders Diarrhea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Mucositis (clinical exam) subjects affected / exposed occurrences (all) Pain [Abdomen NOS] subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 5 / 12 (41.67%) 5 3 / 12 (25.00%) 3 2 / 12 (16.67%) 2 2 / 12 (16.67%) 2 2 / 12 (16.67%) 2		
Skin and subcutaneous tissue disorders			

Dermatology - other subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Decubitus subjects affected / exposed occurrences (all)	 2 / 12 (16.67%) 2 2 / 12 (16.67%) 2 1 / 12 (8.33%) 1		
Endocrine disorders Cushingoid subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		
Musculoskeletal and connective tissue disorders Musculoskeletal - other subjects affected / exposed occurrences (all) Pain [Bone] subjects affected / exposed occurrences (all) Pain [Extremity-limb] subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Infections and infestations Infection (documented clinically) subjects affected / exposed occurrences (all) Infection - other subjects affected / exposed occurrences (all)	 4 / 12 (33.33%) 6 1 / 12 (8.33%) 1		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

none

Notes: