Clinical trial results:
A multicentre, open, randomized, Phase 2/3 study, evaluating efficacy and safety of red blood cells (RBC) encapsulating L-Asparaginase (GRASPA®) versus reference L-asparaginase treatment in combination with standard polychemotherapy in patients with first recurrence of Philadelphia chromosome negative Acute Lymphoblastic Leukemia (ALL Ph-)

Summary

EudraCT number	2009-012584-34
Trial protocol	BE ES
Global end of trial date	06 September 2016

Results information

Result version number	v1 (current)
This version publication date	21 March 2020
First version publication date	21 March 2020

Trial information

Trial identification

Sponsor protocol code	GRASPALL2009-06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01518517
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Erytech Pharma
Sponsor organisation address	60 Avenue Rockefeller, LYON, France,
Public contact	Jean-baptiste Bertrand, ERYTECH Pharma, 33 78781586, jb.bertrand@erytech.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000341-PIP02-09
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	06 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 September 2016
Global end of trial reached?	Yes
Global end of trial date	06 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the efficacy and safety of GRASPA at a dose equivalent to 150 U/kg of L-asparaginase (ASNase) combined with standard polychemotherapy in several populations of patients with first recurrence of Ph- ALL, i.e., children from 1 to <18 years old and adults from 18 to 55 years old, with or without known hypersensitivity to ASNase.

Protection of trial subjects:

An independent DSMB reviewed the interim results from the study as well as safety and futility on a regular basis. The DSMB had the potential to stop the study for overwhelming evidence of benefit or futility.

Background therapy:

All patients were to receive the recommended standard polychemotherapy, i.e., the COOPRALL protocol, which consisted of successive blocks of chemotherapy of 14 to 21 days each (F1: Days 1-14; F2: Days 15-28; R2: Days 1-14; R1: Days 1-14; then subsequent R2 and R1 blocks every 3 weeks, alternately).

Evidence for comparator: -

Actual start date of recruitment	01 December 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	France: 82
Worldwide total number of subjects	85
EEA total number of subjects	85

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)	1
Children (2-11 years)	48
Adolescents (12-17 years)	12
Adults (18-64 years)	24
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment completed.
85 patients were enrolled and 80 received treatment and were included in the Full Analysis Set.

Pre-assignment

Screening details:

Inclusion Criteria:
•Pts from 1 to 55 years old (Children and adolescents from 1 to <18 years/ Adults from 18 to 55 years)
•Pts with 1st ALL relapse, which could be either isolated bone marrow relapse, or combined (medullary and extra-medullary) relapse, or extra-medullary isolated relapse; or lymphoblastic lymphoma (excepted Burkitt lymphoma)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	GRASPA-non allergic population

Arm description:

Each patient randomized in GRASPA® group is to receive at least 2 and up to 10 administration of GRASPA® 150IU/kg, in combination with standard chemotherapy (COOPRALL).

GRASPA® administration takes place as below:
◦for induction phase: at Day 4 and D18 (F1-F2 induction) or at D6 if Vanda induction applies (according disease severity)
◦for consolidation phase: at Day 6 of R2 / R1 blocks, each time block of chemotherapy is given (up to 8 cycles)

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

Dosage and administration details:

Each patient randomized in GRASPA® group is to receive at least 2 and up to 10 administration of GRASPA® 150 IU/kg, in combination with standard chemotherapy (COOPRALL).

GRASPA® administration takes place as below:
◦for induction phase: at Day 4 and D18 (F1-F2 induction) or at D6 if Vanda induction applies (according disease severity)
◦for consolidation phase: at Day 6 of R2 / R1 blocks, each time block of chemotherapy is given (up to 8 cycles)

Arm title	L-asparaginase-non allergic population

Arm description:

For patient randomized in control group, reference L-asparaginase 10,000 IU/m² will be administered every 3 days intravenously, in combination with standard chemotherapy (COOPRALL).

Arm type	Active comparator

Investigational medicinal product name	L-asparaginase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

For patient randomized in control group, reference L-asparaginase 10,000 IU/m² was administered every 3 days intravenously, in combination with standard chemotherapy (COOPRALL).

•for induction phase:at Day 4 , D7, D10, D13 (F1 block) then at Day 18, D21, D24, D27 (of F2 Blocks).

NB: administrations take place at D6, D9, D12 and D15 in case of F1-F2 Induction is replaced by VANDA (according disease severity)

•for consolidation phase: at D6, D9, D12 ofR2/R1 blocks, each time block of chemotherapy is given (up to 8 cycles).

Arm title	GRASPA Allergic population

Arm description:

GRASPA was administered at a dose of 150 U/kg of ASNase on Day 4 of F1 block and Day 18 of F2 block (or Day 6 of VANDA), and on Day 6 of R2 and R1 blocks.

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

Dosage and administration details:

Each patient randomized in GRASPA® group was to receive at least 2 and up to 10 administration of GRASPA® 150 IU/kg, in combination with standard chemotherapy (COOPRALL).

GRASPA® administration takes place as below:
◦for induction phase: at Day 4 and D18 (F1-F2 induction) or at D6 if Vanda induction applies (according disease severity)
◦for consolidation phase: at Day 6 of R2 / R1 blocks, each time block of chemotherapy is given (up to 8 cycles)

Number of subjects in period 1	GRASPA-non allergic population	L-asparaginase-non allergic population	GRASPA Allergic population
Started	29	30	26
Receiving study treatment	26	28	26
Completed	1	3	0
Not completed	28	27	26
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	1	2	-
other termination prior consolidation	2	-	-
Adverse event, non-fatal	1	15	1
progressive disease	-	5	2
other term prior to consolidation	-	-	3
allograft	7	3	5

Lack of efficacy	12	-	14
treatment not received	3	2	-
ASN depletion target not reached	2	-	-

Baseline characteristics

Reporting groups	
Reporting group title	GRASPA-non allergic population

Reporting group description:

Each patient randomized in GRASPA® group is to receive at least 2 and up to 10 administration of GRASPA® 150IU/kg, in combination with standard chemotherapy (COOPRALL).

GRASPA® administration takes place as below:
◦for induction phase: at Day 4 and D18 (F1-F2 induction) or at D6 if Vanda induction applies (according disease severity)
◦for consolidation phase: at Day 6 of R2 / R1 blocks, each time block of chemotherapy is given (up to 8 cycles)

Reporting group title	L-asparaginase-non allergic population

Reporting group description:

For patient randomized in control group, reference L-asparaginase 10,000 IU/m² will be administered every 3 days intravenously, in combination with standard chemotherapy (COOPRALL).

Reporting group title	GRASPA Allergic population

Reporting group description:

GRASPA was administered at a dose of 150 U/kg of ASNase on Day 4 of F1 block and Day 18 of F2 block (or Day 6 of VANDA), and on Day 6 of R2 and R1 blocks.

Reporting group values	GRASPA-non allergic population	L-asparaginase-non allergic population	GRASPA Allergic population
Number of subjects	29	30	26
Age categorical			
number of subject in the age category			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
children: from 1 to <18 years old	23	23	15
Adults from 18 to 55 years	6	7	11
Gender categorical			
Units: Subjects			
Female	11	10	8
Male	18	20	18

Reporting group values	Total		
Number of subjects	85		
Age categorical			
number of subject in the age category			
Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
children: from 1 to <18 years old	61		
Adults from 18 to 55 years	24		
Gender categorical			
Units: Subjects			
Female	29		
Male	56		

Subject analysis sets

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

Subject analysis set description:

All patients who received at least 1 dose of study medication and had at least 1 post-Baseline efficacy assessment performed

Subject analysis set title	Per Protocol analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

All patients of the full analysis set without any major protocol violations

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who received at least 1 dose of medication - coincides with the Full Analysis Set

Reporting group values	Full Analysis set	Per Protocol analysis set	Safety population
Number of subjects	80	79	80
Age categorical			
number of subject in the age category			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
children: from 1 to <18 years old	57	57	57
Adults from 18 to 55 years	23	22	23

Gender categorical Units: Subjects			
Female	28	28	28
Male	52	51	52

End points

End points reporting groups

Reporting group title	GRASPA-non allergic population

Reporting group description:

Each patient randomized in GRASPA® group is to receive at least 2 and up to 10 administration of GRASPA® 150IU/kg, in combination with standard chemotherapy (COOPRALL).

GRASPA® administration takes place as below:
◦for induction phase: at Day 4 and D18 (F1-F2 induction) or at D6 if Vanda induction applies (according disease severity)
◦for consolidation phase: at Day 6 of R2 / R1 blocks, each time block of chemotherapy is given (up to 8 cycles)

Reporting group title	L-asparaginase-non allergic population

Reporting group description:

For patient randomized in control group, reference L-asparaginase 10,000 IU/m² will be administered every 3 days intravenously, in combination with standard chemotherapy (COOPRALL).

Reporting group title	GRASPA Allergic population

Reporting group description:

GRASPA was administered at a dose of 150 U/kg of ASNase on Day 4 of F1 block and Day 18 of F2 block (or Day 6 of VANDA), and on Day 6 of R2 and R1 blocks.

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

Subject analysis set description:

All patients who received at least 1 dose of study medication and had at least 1 post-Baseline efficacy assessment performed

Subject analysis set title	Per Protocol analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

All patients of the full analysis set without any major protocol violations

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who received at least 1 dose of medication - coincides with the Full Analysis Set

Primary: Duration of asparaginase activity >100 U/L during induction

End point title	Duration of asparaginase activity >100 U/L during induction[1]

End point description:

Co-primary efficacy endpoint: duration in days of asparaginase activity >100 U/L in whole blood during the induction treatment phase: last available date/time of activity >100 UI/L before activity drops below 100 U/L – date/time of first activity >100 UI/L. Asparaginase activity is compared for GRASPA versus native ASNase to demonstrate the non-inferiority of GRASPA.

End point type	Primary

End point timeframe:

Induction treatment phase

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only non allergic population evaluated for efficacy (i.e. 2 randomized arms).

End point values	GRASPA-non allergic population	L-asparaginase-non allergic population		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	28		
Units: days				
arithmetic mean (confidence interval 95%)	18.9 (16.7 to 21.0)	8.5 (6.0 to 11.1)		

Statistical analyses

Statistical analysis title	Non-inferiority of GRASPA for duration of activity

Statistical analysis description:

Non-inferiority was evaluated using the ratio of the mean duration of ASNase activity (> 100 U/L) of eryaspase and native ASNase employing bootstrap sampling and constructing the 95% CI for the ratio of the means. Non-inferiority (at the one-sided 2.5% level of significance) was declared if the interval was above 0.80.

Comparison groups	GRASPA-non allergic population v L-asparaginase-non allergic population
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.001 [3]
Method	Bootstrap
Parameter estimate	Ratio of means
Point estimate	2.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.57
upper limit	2.97

Notes:

[2] - Non-inferiority

[3] - One-sided, highly significant supporting the non-inferiority of GRASPA. Confidence interval also excludes 1 for the ratio of the means and this provides evidence supporting the superiority of GRASPA for duration of activity

Primary: Allergic reaction during induction phase

End point title	Allergic reaction during induction phase

End point description:

Co-primary safety endpoint: allergic reaction regardless of grade during induction phase. Only those reactions that were reported in relation to the treatment to which the patient was randomised were counted.

End point type	Primary

End point timeframe:

Induction treatment period

End point values	GRASPA-non allergic population	L-asparaginase-non allergic population	GRASPA Allergic population	Full Analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	26	28	26	80
Units: binary	0	13	3	16

Statistical analyses

Statistical analysis title	Superiority of GRASPA for fewer allergic reactions

Statistical analysis description:

Evaluate superiority of GRASPA over native ASNase treatment by comparing the number of patients having at least one allergic reaction related to study treatment during the induction phase

Comparison groups	GRASPA-non allergic population v L-asparaginase-non allergic population
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [4]
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-46.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-67.3
upper limit	-20.4

Notes:

[4] - Highly statistically significant supporting the superiority of GRASPA in reducing the number of allergic reactions

Secondary: Complete Remission (CR)

End point title	Complete Remission (CR)

End point description:

CR is defined as, no physical evidence of leukemia, normal CBC, cytologic remission: normally regenerating bone marrow, with <5% leukemic blasts and the absence of detectable CNS or extramedullary disease, evaluated with physical examination and CSF findings, at the end of induction

End point type	Secondary

End point timeframe:

Induction treatment period

End point values	GRASPA-non allergic population	L-asparaginase-non allergic population	GRASPA Allergic population	Full Analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	25	28	25	78
Units: binary	19	13	15	47

Statistical analyses

Statistical analysis title	Compare CR rates between GRASPA and native ASNase
Comparison groups	GRASPA-non allergic population v L-asparaginase-non allergic population
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028 [5]
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	29.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.6
upper limit	54.5

Notes:

[5] - Statistically significant supporting a higher rate of CR in the GRASPA group

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS is defined as the time from randomisation or date of inclusion (allergic arm) until death due to any cause. Patients who did not die were censored at 36 months of follow-up or the date of the patient's last visit, whichever was earlier.

End point type	Secondary

End point timeframe:

Overall trial period to 36 months

End point values	GRASPA-non allergic population	L-asparaginase-non allergic population	GRASPA Allergic population	Full Analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	26[6]	28	26	80
Units: count	9	12	14	35

Notes:

[6] - Entries given below are number of patients dying in each group

Statistical analyses

Statistical analysis title	Compare OS Kaplan-Meier curves
Statistical analysis description:	
Hazard ratio estimated using Cox regression with logrank p-value	
Comparison groups	GRASPA-non allergic population v L-asparaginase-non allergic population
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.468 [7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	1.73

Notes:

[7] - Not statistically significant. There is no evidence to support a treatment difference for overall survival

Secondary: Event free survival (EFS)

End point title	Event free survival (EFS)

End point description:

EFS is defined as the time from randomisation until the first documented sign of disease relapse or death due to any cause.
In line with CHMP guidance (CHMP, 2016), patients who did not achieve CR at the end of the induction period were considered to have had an event at time 0.
For the patients enrolled in the GRASPA allergic arm, EFS is defined from the date of inclusion in the study.
Patients who achieved CR at the end of induction and who did not have a documented relapse or death due to any cause were censored at 36 months of follow-up or the date of the patient's last visit, whichever was earlier.

End point type	Secondary

End point timeframe:

Overall trial period to 36 months

End point values	GRASPA-non allergic population	L-asparaginase-non allergic population	GRASPA Allergic population	Full Analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	26[8]	28	26	80
Units: count	15	17	19	51

Notes:

[8] - Entries below are the numbers of patients with events in each treatment group

Statistical analyses

Statistical analysis title	Comparison of Kaplan-Meier EFS curves

Statistical analysis description:

Hazard ratio obtained using the Cox model with logrank p-value

Comparison groups	GRASPA-non allergic population v L-asparaginase-non allergic population
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.574 [9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.69

Notes:

[9] - Not statistically significant. No evidence for treatment differences for EFS

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From randomization until 4 months after last dose of study drug	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1
Reporting groups	
Reporting group title	GRASPA-non allergic population
Reporting group description: -	
Reporting group title	GRASPA-allergic population
Reporting group description: -	
Reporting group title	L-asparaginase-non allergic population
Reporting group description: -	

Serious adverse events	GRASPA-non allergic population	GRASPA-allergic population	L-asparaginase-non allergic population
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 26 (88.46%)	23 / 26 (88.46%)	26 / 28 (92.86%)
number of deaths (all causes)	6	13	9
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia recurrent			
subjects affected / exposed	8 / 26 (30.77%)	7 / 26 (26.92%)	9 / 28 (32.14%)
occurrences causally related to treatment / all	0 / 9	0 / 8	0 / 9
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 4
metabolism and nutient disorder			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	3 / 28 (10.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Blood and lymphatic system disorders			

Febrile bone marrow aplasia			
subjects affected / exposed	11 / 26 (42.31%)	5 / 26 (19.23%)	7 / 28 (25.00%)
occurrences causally related to treatment / all	1 / 23	1 / 7	1 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 26 (0.00%)	3 / 26 (11.54%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	4 / 26 (15.38%)	4 / 26 (15.38%)	5 / 28 (17.86%)
occurrences causally related to treatment / all	0 / 4	0 / 7	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	15 / 26 (57.69%)	6 / 26 (23.08%)	8 / 28 (28.57%)
occurrences causally related to treatment / all	0 / 15	1 / 6	2 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	3 / 26 (11.54%)	3 / 26 (11.54%)	7 / 28 (25.00%)
occurrences causally related to treatment / all	1 / 3	0 / 3	4 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 26 (3.85%)	1 / 26 (3.85%)	3 / 28 (10.71%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Mucosal inflammation			

subjects affected / exposed	3 / 26 (11.54%)	5 / 26 (19.23%)	4 / 28 (14.29%)
occurrences causally related to treatment / all	0 / 3	1 / 5	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	2 / 28 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infections and infestations			
Sepsis			
subjects affected / exposed	4 / 26 (15.38%)	0 / 26 (0.00%)	2 / 28 (7.14%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	2 / 28 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	3 / 26 (11.54%)	1 / 26 (3.85%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Staphylococcal sepsis			
subjects affected / exposed	3 / 26 (11.54%)	0 / 26 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fusarium infection			

subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Human herpesvirus 6 infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

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

Non-serious adverse events	GRASPA-non allergic population	GRASPA-allergic population	L-asparaginase-non allergic population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 26 (100.00%)	26 / 26 (100.00%)	28 / 28 (100.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 26 (7.69%)	4 / 26 (15.38%)	0 / 28 (0.00%)
occurrences (all)	3	4	0
Asthenia			
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	7 / 26 (26.92%)	17 / 26 (65.38%)	18 / 28 (64.29%)
occurrences (all)	8	21	21
Graft versus host disease			
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)	2 / 28 (7.14%)
occurrences (all)	2	0	2
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	2 / 28 (7.14%)
occurrences (all)	0	1	2
Investigations			

Transaminases increased			
subjects affected / exposed	16 / 26 (61.54%)	15 / 26 (57.69%)	16 / 28 (57.14%)
occurrences (all)	40	21	33
Hypokalaemia			
subjects affected / exposed	13 / 26 (50.00%)	9 / 26 (34.62%)	11 / 28 (39.29%)
occurrences (all)	13	12	12
Antithrombin III decreased			
subjects affected / exposed	4 / 26 (15.38%)	9 / 26 (34.62%)	20 / 28 (71.43%)
occurrences (all)	7	11	44
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 26 (30.77%)	7 / 26 (26.92%)	14 / 28 (50.00%)
occurrences (all)	20	16	15
Blood albumin decreased			
subjects affected / exposed	5 / 26 (19.23%)	6 / 26 (23.08%)	11 / 28 (39.29%)
occurrences (all)	5	7	15
Hyponatraemia			
subjects affected / exposed	6 / 26 (23.08%)	7 / 26 (26.92%)	10 / 28 (35.71%)
occurrences (all)	6	8	19
Blood bilirubin increased			
subjects affected / exposed	4 / 26 (15.38%)	7 / 26 (26.92%)	9 / 28 (32.14%)
occurrences (all)	6	8	11
Hyperglycaemia			
subjects affected / exposed	5 / 26 (19.23%)	6 / 26 (23.08%)	7 / 28 (25.00%)
occurrences (all)	6	12	12
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 26 (3.85%)	5 / 26 (19.23%)	4 / 28 (14.29%)
occurrences (all)	2	5	7
Hypocalcaemia			
subjects affected / exposed	3 / 26 (11.54%)	1 / 26 (3.85%)	4 / 28 (14.29%)
occurrences (all)	3	3	4
Blood triglycerides increased			
subjects affected / exposed	2 / 26 (7.69%)	3 / 26 (11.54%)	3 / 28 (10.71%)
occurrences (all)	4	3	4
Prothrombin level decreased			

subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	3 / 28 (10.71%)
occurrences (all)	0	0	5
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	2 / 28 (7.14%)
occurrences (all)	0	1	2
Blood potassium increased			
subjects affected / exposed	3 / 26 (11.54%)	0 / 26 (0.00%)	2 / 28 (7.14%)
occurrences (all)	3	0	2
C-reactive protein increased			
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)	0 / 28 (0.00%)
occurrences (all)	3	0	0
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	2 / 26 (7.69%)	2 / 26 (7.69%)	2 / 28 (7.14%)
occurrences (all)	2	2	2
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	25 / 26 (96.15%)	26 / 26 (100.00%)	27 / 28 (96.43%)
occurrences (all)	76	74	81
Thrombocytopenia			
subjects affected / exposed	24 / 26 (92.31%)	22 / 26 (84.62%)	26 / 28 (92.86%)
occurrences (all)	69	71	71
Neutropenia			
subjects affected / exposed	24 / 26 (92.31%)	25 / 26 (96.15%)	25 / 28 (89.29%)
occurrences (all)	89	81	93
Lymphopenia			
subjects affected / exposed	21 / 26 (80.77%)	20 / 26 (76.92%)	23 / 28 (82.14%)
occurrences (all)	43	49	43
Febrile bone marrow aplasia			
subjects affected / exposed	5 / 26 (19.23%)	8 / 26 (30.77%)	7 / 28 (25.00%)
occurrences (all)	17	13	17
Hypofibrinogenaemia			
subjects affected / exposed	9 / 26 (34.62%)	11 / 26 (42.31%)	19 / 28 (67.86%)
occurrences (all)	11	12	37
Febrile neutropenia			

subjects affected / exposed	1 / 26 (3.85%)	3 / 26 (11.54%)	5 / 28 (17.86%)
occurrences (all)	4	6	9
Anaemia			
subjects affected / exposed	7 / 26 (26.92%)	6 / 26 (23.08%)	9 / 28 (32.14%)
occurrences (all)	9	6	14
Bone marrow failure			
subjects affected / exposed	2 / 26 (7.69%)	1 / 26 (3.85%)	3 / 28 (10.71%)
occurrences (all)	2	1	4
Blood phosphorus decreased			
subjects affected / exposed	4 / 26 (15.38%)	3 / 26 (11.54%)	3 / 28 (10.71%)
occurrences (all)	5	3	3
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	2 / 28 (7.14%)
occurrences (all)	1	0	2
Abdominal pain			
subjects affected / exposed	1 / 26 (3.85%)	2 / 26 (7.69%)	2 / 28 (7.14%)
occurrences (all)	2	2	2
Diarrhoea			
subjects affected / exposed	3 / 26 (11.54%)	2 / 26 (7.69%)	2 / 28 (7.14%)
occurrences (all)	3	2	3
Rectal haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Vomiting			
subjects affected / exposed	4 / 26 (15.38%)	1 / 26 (3.85%)	1 / 28 (3.57%)
occurrences (all)	4	1	1
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	2 / 26 (7.69%)	8 / 26 (30.77%)	6 / 28 (21.43%)
occurrences (all)	2	9	12
Cholestasis			
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			

Drug hypersensitivity			
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)	1 / 28 (3.57%)
occurrences (all)	0	2	1
Renal and urinary disorders			
renal failure acute			
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Sepsis			
subjects affected / exposed	3 / 26 (11.54%)	1 / 26 (3.85%)	1 / 28 (3.57%)
occurrences (all)	3	1	1
Bronchopulmonary aspergillosis			
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	1
Infection			
subjects affected / exposed	1 / 26 (3.85%)	1 / 26 (3.85%)	2 / 28 (7.14%)
occurrences (all)	2	1	3
Bacteraemia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	1 / 28 (3.57%)
occurrences (all)	1	0	2
Candida infection			
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)	1 / 28 (3.57%)
occurrences (all)	3	0	1
Staphylococcal infection			
subjects affected / exposed	3 / 26 (11.54%)	4 / 26 (15.38%)	1 / 28 (3.57%)
occurrences (all)	7	4	1
Staphylococcal sepsis			
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)	0 / 28 (0.00%)
occurrences (all)	0	3	0
Folliculitis			
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Streptococcal infection			
subjects affected / exposed	3 / 26 (11.54%)	1 / 26 (3.85%)	0 / 28 (0.00%)
occurrences (all)	3	1	0
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 26 (0.00%) 0	2 / 28 (7.14%) 3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2009	Answer ANSM questions
28 April 2010	-change of inclusion criteria, to include isolated extramedullary relapse -changes for compliance to medicinal product status (regarding vigilance and traceability)
24 April 2013	- Change of the duration of the follow up and contraception (request from authorities) - Collection of survival status at 24 months (M24) and 36 months M36 (PDCO PaeDiatric COmmittee request) - French Investigators / subinvestigators list update
02 July 2014	Requested by PDCO, in accordance to CHMP (Committee for Medicinal Products for Human Use) advice, to clarify and revised one of the primary endpoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported