

**Clinical trial results:****NOR-GRASPALL 2016: SINGLE-ARM****PHARMACOKINETIC/PHARMACODYNAMIC AND SAFETY STUDY OF ERYASPASE (GRASPA®) FOR PATIENTS WITH HYPERSENSITIVITY TO PEG-ASPARAGINASE, DIAGNOSED WITH PH(-) ACUTE LYMPHOBLASTIC LEUKEMIA****Summary**

EudraCT number	2016-004451-70
Trial protocol	DK NO FI SE EE LT
Global end of trial date	22 November 2020

**Results information**

Result version number	v1 (current)
This version publication date	13 March 2022
First version publication date	13 March 2022

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

Sponsor protocol code	NOR-GRASPALL-2016
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03267030
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Boulevard 99, Aarhus N, Denmark, 8200
Public contact	Birgitte Klug Albertsen, Department of Paediatrics and Adolescent Medicine, Aarhus University Hospital, 0045 20224643, biralber@rm.dk
Scientific contact	Birgitte Klug Albertsen, Department of Paediatrics and Adolescent Medicine, Aarhus University Hospital, 0045 20224643, biralber@rm.dk

Notes:

**Paediatric regulatory details**

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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## Results analysis stage

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Analysis stage	Final
Date of interim/final analysis	23 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 November 2020
Global end of trial reached?	Yes
Global end of trial date	22 November 2020
Was the trial ended prematurely?	No

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Notes:

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## General information about the trial

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Main objective of the trial:

Main objectives of this study are to evaluate the pharmacokinetic and pharmacodynamic profile of eryaspase administered to patients who experience a PEG-asparaginase hypersensitivity event during treatment with the multi-agent NOPHO ALL 2008 or ALLTogether chemotherapy for the treatment of children and adult patients with ALL

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Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements related to safety of trial subjects were also followed during the conduct of the trial.

Written informed consent was obtained from all participants, for children both parents or legal guardians signed the informed consent. Children aged 15 to 17 years were allowed to give written informed consent for themselves, in close collaboration with their parents or legal guardians.

Data was registered, saved and managed using REDCap (Research Electronic Data Capture), hosted at the Department of Clinical Medicine, Aarhus University. REDCap is a secure, web-based software platform designed to support data capture for research studies.

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Background therapy:

All patients received backbone therapy according to the NOPHO ALL2008 protocol or the ALLTogether Pilot protocol.

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Evidence for comparator: -

Actual start date of recruitment	02 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

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Notes:

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## Population of trial subjects

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### Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	Denmark: 10
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	Lithuania: 14
Worldwide total number of subjects	55
EEA total number of subjects	55

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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)	2
Children (2-11 years)	40
Adolescents (12-17 years)	11
Adults (18-64 years)	2
From 65 to 84 years	0
85 years and over	0

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## Subject disposition

### Recruitment

Recruitment details:

Study participants were recruited on the site when a participant developed clinical allergy or if inactivation of asparaginase enzyme activity was identified using therapeutic drug monitoring.

### Pre-assignment

Screening details:

Medical assessment and therapeutic drug monitoring

### Period 1

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

### Arms

<b>Arm title</b>	Intervention
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Arm description:

Single-arm study.

All patients with hypersensitivity to PEG-asparaginase received 1–7 doses of eryaspase (150 IU/kg) with two-week or six-week intervals. The number of doses depended on number of PEG-asparaginase doses administered before inclusion and the number of dose scheduled in the backbone treatment protocol (NOPHO ALL2008 protocol 8 doses with 2- and 6-weeks intervals for all patients. ALLTogether Pilot protocol 1-4 doses scheduled with 2-weeks interval stratified by ALL risk group)

Arm type	Experimental
Investigational medicinal product name	GRASPA
Investigational medicinal product code	
Other name	Eryaspase
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous drip use

Dosage and administration details:

All patients with hypersensitivity to PEG-asparaginase received 1–7 doses of eryaspase (150 IU/kg) with two-week or six-week intervals. The number of doses depended on number of PEG-asparaginase doses administered before inclusion and the number of dose scheduled in the backbone treatment protocol (NOPHO ALL2008 protocol 8 doses with 2- and 6-weeks intervals for all patients. ALLTogether Pilot protocol 1-4 doses scheduled with 2-weeks interval stratified by ALL risk group)

<b>Number of subjects in period 1</b>	Intervention
Started	55
Completed	50
Not completed	5
Adverse event, serious fatal	1
Consent withdrawn by subject	1
Adverse event, non-fatal	2
Protocol deviation	1



## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
Reporting group description:	
Total study population	

Reporting group values	Overall trial	Total	
Number of subjects	55	55	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	2	2	
Children (2-11 years)	43	43	
Adolescents (12-17 years)	8	8	
Adults (18-64 years)	2	2	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	6.1		
inter-quartile range (Q1-Q3)	3.5 to 10.6	-	
Gender categorical			
Units: Subjects			
Female	17	17	
Male	38	38	

## End points

### End points reporting groups

Reporting group title	Intervention
Reporting group description: Single-arm study. All patients with hypersensitivity to PEG-asparaginase received 1–7 doses of eryaspase (150 IU/kg) with two-week or six-week intervals. The number of doses depended on number of PEG-asparaginase doses administered before inclusion and the number of doses scheduled in the backbone treatment protocol (NOPHO ALL2008 protocol 8 doses with 2- and 6-weeks intervals for all patients. ALLTogether Pilot protocol 1-4 doses scheduled with 2-weeks interval stratified by ALL risk group)	

### Primary: Primary Pharmacokinetic Parameters

End point title	Primary Pharmacokinetic Parameters <sup>[1]</sup>
End point description: The primary endpoint was patients with ASNase activity >100 U/L at 14 days following the first infusion (nadir). The primary Evaluable Patients Population was used for the analysis of the primary and key secondary endpoints, defined as all patients recruited into the study who provided data on ASNase level on Day 14 ( $\pm 2$ days) following the first administration of eryaspase.	
End point type	Primary
End point timeframe: 6 months	

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 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 have been performed for the end points due to few included patients and only one study group. The manuscript (containing some statistics information) will be uploaded as soon as it is published.

End point values	Intervention			
Subject group type	Reporting group			
Number of subjects analysed	53 <sup>[2]</sup>			
Units: 53	49			

Notes:

[2] - Two patients were not included in the primary evaluable patients population due to missing sampling

### Statistical analyses

No statistical analyses for this end point

### Secondary: Secondary Pharmacokinetic Parameters

End point title	Secondary Pharmacokinetic Parameters
End point description: Patients with ASNase activity >100 U/L at 14 days following the fourth infusion of the 2-week dosing intervals. The Evaluable Patients Population for this outcome was defined as all patients recruited into the study who provided data on ASNase level on Day 14 ( $\pm 2$ days) following the fourth administration of eryaspase of 2-week dosing intervals.	
End point type	Secondary

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End point timeframe:

1 months

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<b>End point values</b>	Intervention			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: subjects	6			

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

1 month

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
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Dictionary version	5.0
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### Reporting groups

Reporting group title	Total study population
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Reporting group description: -

Serious adverse events	Total study population		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 55 (10.91%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Nervous system disorders			
Leukoencephalopathy			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Hypersensitivity			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatotoxicity			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Infections and infestations</b>			
Device related infection			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Total study population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 55 (32.73%)		
<b>General disorders and administration site conditions</b>			
pyrexia			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	9		
Hyperthermia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
<b>Immune system disorders</b>			
Febrile neutropenia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Hypersensitivity			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
<b>Gastrointestinal disorders</b>			
Constipation			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Stomatitis			

subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Hepatobiliary disorders Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Infections and infestations Device related infection subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Herpes zoster subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Pneumonia subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Infection subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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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.

Few patients included in the subgroups due to different number of doses and different intervals.

Notes: