Clinical trial results:
Protocol ALL-11: Treatment study protocol of the Dutch Childhood Oncology Group for children and adolescents (1-19 year) with newly diagnosed acute lymphoblastic leukemia

Summary

EudraCT number	2012-000067-25
Trial protocol	NL
Global end of trial date	30 May 2023

Results information

Result version number	v1 (current)
This version publication date	08 August 2024
First version publication date	08 August 2024

Trial information

Trial identification

Sponsor protocol code	ALL11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	OMON register: NL-OMON29675

Notes:

Sponsors

Sponsor organisation name	Princess Máxima Center for pediatric oncology
Sponsor organisation address	Heidelberglaan 25, Utrecht, Netherlands, 3584 CS
Public contact	Trial and Data Center, Princess Máxima Center for pediatric oncology, 0031 889727272, trialmanagement@prinsesmaximacentrum.nl
Scientific contact	Trial and Data Center, Princess Máxima Center for pediatric oncology, 0031 889727272, trialmanagement@prinsesmaximacentrum.nl

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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 November 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 May 2023
Global end of trial reached?	Yes
Global end of trial date	30 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To treat children with ALL with the best available treatment as possible, based upon the risk factors of the patient at diagnosis.

Protection of trial subjects:

Patient data are pseudonymised by applying a subject study code.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2012
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: 819
Worldwide total number of subjects	819
EEA total number of subjects	819

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)	55
Children (2-11 years)	600
Adolescents (12-17 years)	163
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:
risk classification

Period 1

Period 1 title	ASP randomisation
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:
No blinding

Arms

Are arms mutually exclusive?	Yes
Arm title	ASP continu

Arm description:
arm B

Arm type	Experimental
Investigational medicinal product name	Oncospar
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:
17 international units per day

Arm title	ASP interrupted

Arm description:
arm A

Arm type	Active comparator
Investigational medicinal product name	Oncospar
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:
17 international units per day

Number of subjects in period 1[1]	ASP continu	ASP interrupted
Started	155	157
Completed	151	155
Not completed	4	2
Adverse event, serious fatal	3	1
Lack of efficacy	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The ALL11 protocol is the standard of care therapy for children with ALL. Only the randomizations are reported here.

Period 2

Period 2 title	IVIG randomisation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	IVIG profylaxis

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Nanogam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

0,7 g/kg

Arm title	IVIG control

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2[2]	IVIG profylaxis	IVIG control
Started	130	131
Completed	91	86
Not completed	39	45
Adverse event, serious fatal	1	2
Consent withdrawn by subject	3	-
Adverse event, non-fatal	1	1
stratified to SR/HR - predefined not eligible	34	42

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The ALL11 protocol is the standard of care therapy for children with ALL. Only the randomizations are reported here.

Baseline characteristics

Reporting groups

Reporting group title	ASP randomisation

Reporting group description: -

Reporting group values	ASP randomisation	Total	
Number of subjects	312	312	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	27	27	
Children (2-11 years)	226	226	
Adolescents (12-17 years)	58	58	
Adults (18-64 years)	1	1	
Gender categorical Units: Subjects			
Female	120	120	
Male	192	192	

Subject analysis sets

Subject analysis set title	IVIG cohort
Subject analysis set type	Per protocol

Subject analysis set description:

Treatment completed for at least 1 year

Subject analysis set title	ASP cohort
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to treat according to randomization

Reporting group values	IVIG cohort	ASP cohort	
Number of subjects	177	312	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	11	27	
Children (2-11 years)	132	226	
Adolescents (12-17 years)	34	58	
Adults (18-64 years)	0	1	
Gender categorical Units: Subjects			
Female	72	120	
Male	105	192	

End points

End points reporting groups

Reporting group title	ASP continu
Reporting group description: arm B	
Reporting group title	ASP interrupted
Reporting group description: arm A	
Reporting group title	IVIG profylaxis
Reporting group description: -	
Reporting group title	IVIG control
Reporting group description: -	
Subject analysis set title	IVIG cohort
Subject analysis set type	Per protocol
Subject analysis set description: Treatment completed for at least 1 year	
Subject analysis set title	ASP cohort
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention to treat according to randomization	

Primary: Hospital admissions

End point title	Hospital admissions[1]
End point description: per protocol	
End point type	Primary
End point timeframe: 1 year	

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: Documentation has been uploaded in Section "Chart"

End point values	IVIG cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	177			
Units: admissions	463			

Attachments (see zip file)	ALL11_IVIG_stat-analysis2024/ALL11_IVIG_stat-analysis2024.

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of hypersensitivity

End point title	Incidence of hypersensitivity[2]

End point description:

End point type	Primary

End point timeframe:

1 year of treatment

Notes:

[2] - 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: Documentation has been uploaded in Section "Chart"

End point values	ASP continu	ASP interrupted	ASP cohort	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	155	157	312	
Units: reactions	4	17	21	

Attachments (see zip file)	ALL 11_Publication JCO 2024_vd Sluis et al_Aspa.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Disease free survival

End point title	Disease free survival

End point description:

End point type	Secondary

End point timeframe:

5 years

End point values	ASP continu	ASP interrupted	IVIG cohort	ASP cohort
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	155	157	177	312
Units: % of patients				
number (not applicable)	91.9	95.3	92.1	93.6

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Max 2 year	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.03
Reporting groups	
Reporting group title	IVIG cohort
Reporting group description: Patients randomized for IVIG randomisation	
Reporting group title	ASP cohort
Reporting group description: All patients randomized according to ASP randomisation	

Serious adverse events	IVIG cohort	ASP cohort	
Total subjects affected by serious adverse events			
subjects affected / exposed	71 / 177 (40.11%)	54 / 312 (17.31%)	
number of deaths (all causes)	1	4	
number of deaths resulting from adverse events	0	4	
Vascular disorders			
thrombosis	Additional description: Includes cerebral and peripheral thrombosis		
subjects affected / exposed	16 / 177 (9.04%)	12 / 312 (3.85%)	
occurrences causally related to treatment / all	0 / 16	3 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 177 (1.13%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neurotoxicity	Additional description: Includes Central neurotoxicity convulsion, Central neurotoxicity encephalopathy, Central neurotoxicity other and Peripheral neurotoxicity		
subjects affected / exposed	17 / 177 (9.60%)	19 / 312 (6.09%)	
occurrences causally related to treatment / all	0 / 22	0 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

bleeding			
subjects affected / exposed	1 / 177 (0.56%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte disorder			
subjects affected / exposed	2 / 177 (1.13%)	3 / 312 (0.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycemia			
subjects affected / exposed	3 / 177 (1.69%)	5 / 312 (1.60%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
other	Additional description: not specified		
subjects affected / exposed	5 / 177 (2.82%)	11 / 312 (3.53%)	
occurrences causally related to treatment / all	0 / 7	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction	Additional description: incl anaphylaxis		
subjects affected / exposed	3 / 177 (1.69%)	3 / 312 (0.96%)	
occurrences causally related to treatment / all	1 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
gastrointestinal disorders	Additional description: Includes GI bleeding, GI colitis, GI constipation, GI diabetes,GI pancreatitis, GI perforation and other gastrointestinal events Liver failure Veno-occlusive disease		
subjects affected / exposed	29 / 177 (16.38%)	32 / 312 (10.26%)	
occurrences causally related to treatment / all	0 / 29	8 / 37	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 177 (0.56%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
kidney failure			

subjects affected / exposed	1 / 177 (0.56%)	4 / 312 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections	Additional description: Includes bacterial, fungal, viral and pneumocystis jerovecii (carini) infections and infections of unknown origin		
subjects affected / exposed	25 / 177 (14.12%)	30 / 312 (9.62%)	
occurrences causally related to treatment / all	0 / 30	0 / 34	
deaths causally related to treatment / all	0 / 0	0 / 3	

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

Non-serious adverse events	IVIG cohort	ASP cohort	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	160 / 177 (90.40%)	286 / 312 (91.67%)	
Vascular disorders			
Thrombosis			
subjects affected / exposed	29 / 177 (16.38%)	42 / 312 (13.46%)	
occurrences (all)	62	91	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	14 / 177 (7.91%)	18 / 312 (5.77%)	
occurrences (all)	16	21	
Musculoskeletal and connective tissue disorders			
avascular necrosis			
subjects affected / exposed	2 / 177 (1.13%)	2 / 312 (0.64%)	
occurrences (all)	5	5	
Infections and infestations			
Febrile neutropenia			
subjects affected / exposed	138 / 177 (77.97%)	255 / 312 (81.73%)	
occurrences (all)	285	531	
Infection	Additional description: all types of infections		
subjects affected / exposed	107 / 177 (60.45%)	210 / 312 (67.31%)	
occurrences (all)	204	402	

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

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37459571