



## Clinical trial results:

### Reducing vincristine-induced peripheral neuropathy in children with acute lymphoblastic leukemia (ALL): comparing one-hour infusions with bolus injections (the VINCA trial)

#### Summary

EudraCT number	2014-001561-27
Trial protocol	NL BE
Global end of trial date	01 February 2022

#### Results information

Result version number	v1 (current)
This version publication date	23 November 2023
First version publication date	23 November 2023
Summary attachment (see zip file)	Van de Velde ME 2020 (2) (Van de Velde ME 2020 (2).pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	2000790
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Netherlands Trial Register: NTR4262, Dutch trial Register: NL4019

Notes:

##### Sponsors

Sponsor organisation name	Amsterdam UMC
Sponsor organisation address	De Boelelaan 1117, Amsterdam, Netherlands, 1081 HV
Public contact	Department of Pediatric Oncology, VU university medical center, 0031 2044444444, Mh.vandenberg@amsterdamumc.nl
Scientific contact	Department of Pediatric Oncology, VU university medical center, 0031 2044444444, Mh.vandenberg@amsterdamumc.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	01 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 February 2022
Global end of trial reached?	Yes
Global end of trial date	01 February 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate whether the administration of vincristine (VCR) in children with acute lymphoblastic leukemia, neuroblastoma, medulloblastoma, low-grade glioma, Hodgkin lymphoma or rhabdomyosarcoma by one-hour infusions leads to less peripheral neuropathy (PNP) compared to the administration by short-term (1-5 minutes) infusions or injections.

Protection of trial subjects:

Safety Committee

Background therapy:

No

Evidence for comparator:

No

Actual start date of recruitment	01 September 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 57
Country: Number of subjects enrolled	Belgium: 33
Worldwide total number of subjects	90
EEA total number of subjects	90

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)	0
Children (2-11 years)	58
Adolescents (12-17 years)	32

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patients diagnosed with ALL

### Pre-assignment

Screening details:

Patients diagnosed with ALL, who received vincristine treatment. Baseline peripheral neuropathy scores were reported

### Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Recruitment period within one week

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	One-hour administration

Arm description:

Vincristine administered via one hour infusion

Arm type	Active comparator
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage according to individual treatment schedule 1.5-2mg/m<sup>2</sup> with a maximum of 2 mg, IV infusion

<b>Arm title</b>	Push Injection
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Arm description:

Vincristine administered via push injection

Arm type	Experimental
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Dosage according to individual treatment schedule 1.5-2 mg/m<sup>2</sup> with a maximum of 2 mg, IV infusion

Number of subjects in period 1	One-hour administration	Push Injection
Started	45	45
Completed	45	45

## Period 2

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

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	One-hour administration

Arm description:

Vincristine administered via one hour infusion

Arm type	Active comparator
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage according to individual treatment schedule 1.5-2mg/m<sup>2</sup> with a maximum of 2 mg, IV infusion

<b>Arm title</b>	Push Injection
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Arm description:

Vincristine administered via push injection

Arm type	Experimental
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Dosage according to individual treatment schedule 1.5-2 mg/m<sup>2</sup> with a maximum of 2 mg, IV infusion

<b>Number of subjects in period 2</b>	One-hour administration	Push Injection
Started	45	45
Completed	44	38
Not completed	1	7
Physician decision	1	3
Consent withdrawn by subject	-	2
Adverse event, non-fatal	-	2

## Baseline characteristics

### Reporting groups

Reporting group title	Baseline
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Reporting group description: entire cohort
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Reporting group values	Baseline	Total	
Number of subjects	90	90	
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)	0	0	
Children (2-11 years)	57	57	
Adolescents (12-17 years)	33	33	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	40	40	
Male	50	50	

### Subject analysis sets

Subject analysis set title	Entire cohort
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Subject analysis set type	Intention-to-treat
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Subject analysis set description: all participants
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Subject analysis set title	VCR push
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:
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Subjects receiving vincristine by a push
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Subject analysis set title	VCR one-hour infusion
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:
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Subject receiving vincristine during a one hour infusion
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Reporting group values	Entire cohort	VCR push	VCR one-hour infusion
Number of subjects	90	45	45
Age categorical			
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)	57		
Adolescents (12-17 years)	33		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Gender categorical			
Units: Subjects			
Female	40		
Male	50		

## End points

### End points reporting groups

Reporting group title	One-hour administration
Reporting group description: Vincristine administered via one hour infusion	
Reporting group title	Push Injection
Reporting group description: Vincristine administered via push injection	
Reporting group title	One-hour administration
Reporting group description: Vincristine administered via one hour infusion	
Reporting group title	Push Injection
Reporting group description: Vincristine administered via push injection	
Subject analysis set title	Entire cohort
Subject analysis set type	Intention-to-treat
Subject analysis set description: all participants	
Subject analysis set title	VCR push
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects receiving vincristine by a push	
Subject analysis set title	VCR one-hour infusion
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subject receiving vincristine during a one hour infusion	

### Primary: Vincristine induced peripheral neuropathy (VIPN)

End point title	Vincristine induced peripheral neuropathy (VIPN)
End point description:	
End point type	Primary
End point timeframe: One year after treatment initiation or at the last vincristine administration (whichever came first)	

End point values	One-hour administration	Push Injection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	45		
Units: number of patients	21	23		

## Statistical analyses

<b>Statistical analysis title</b>	Mixed effect modelling
Comparison groups	One-hour administration v Push Injection
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	$\geq 0.34$
Method	Mixed models analysis
Parameter estimate	Slope
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	0.31
Variability estimate	Standard deviation

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Duration of the trial

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.03
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### Reporting groups

Reporting group title	One-hour infusion
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Reporting group description: -

Reporting group title	push
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Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Adverse events and Serious adverse events for this study were derived from the treatment protocols according to which these children were being treated. The adverse events were not collected separately for this study

Serious adverse events	One-hour infusion	push	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 45 (20.00%)	3 / 45 (6.67%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia recurrent			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure	Additional description: Caused by CNS infection		
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction to excipient	Additional description: Allergic reaction to IVIG		
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction	Additional description: Anaphylactic reaction to Asparaginase		

subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	3 / 45 (6.67%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis management			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
other			
Additional description: cholestatic icterus			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
Additional description: sepsis and gastro-intestinal bleeding			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
Additional description: MTX intoxication and acute renal failure			
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteonecrosis			

subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Fungal infection	Additional description: Invasive aspergillosis		
subjects affected / exposed	4 / 45 (8.89%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 45 (4.44%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella	Additional description: Infection with febrile neutropenia		
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	One-hour infusion	push	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 July 2015	Inclusion of other diseases
21 March 2016	Addition of other sites
26 July 2017	Change of SAE reporting

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33322788>

<http://www.ncbi.nlm.nih.gov/pubmed/36900422>