



Clinical trial results:

Development of chronic disease in newly diagnosed Idiopathic Thrombocytopenic Purpura of Childhood. A randomized controlled study on the influence of treatment with intravenous gammaglobulin on the course of the disease.

Summary

EudraCT number	2008-001597-33
Trial protocol	NL
Global end of trial date	12 July 2016

Results information

Result version number	v1 (current)
This version publication date	15 January 2020
First version publication date	15 January 2020

Trial information

Trial identification

Sponsor protocol code	20081203
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	UMC Utrecht
Sponsor organisation address	Heidelberglaan 100, Utrecht, Netherlands, 3584 CX
Public contact	KMJ Heitink-Polle, UMC Utrecht, +31 887555555, k.m.j.heitink-polle@umcutrecht.nl
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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	19 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 July 2016
Global end of trial reached?	Yes
Global end of trial date	12 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to investigate the hypothesis that early IVIG treatment in children with newly diagnosed acute ITP reduces the risk of development of chronic disease.

Protection of trial subjects:

Standard Operation Procedures were created to cope with bleeding complications.

Background therapy:

Childhood immune thrombocytopenia (ITP) is an immune-mediated disease characterized by an isolated low platelet count (peripheral blood platelet count $< 100 \times 10^9/L$) in the absence of other causes that are associated with thrombocytopenia. Most children recover within 6-12 months and chronic ITP, until 2009 defined as a platelet count $< 150 \times 10^9/L$ at 6 months after diagnosis, occurs in about 20-25%. Since 2009, chronic ITP is defined as a platelet count $< 100 \times 10^9/L$ at 12 months after diagnosis and the rate of occurrence is not yet determined.

Observational studies have suggested a lower incidence of chronic ITP in children that were treated with intravenous immunoglobulin (IVIg), but randomized studies are lacking. Since chronic ITP has a huge impact on children and their families, being able to prevent a chronic course of the disease would be of major importance.

To address the question whether IVIg treatment can prevent a chronic course of the disease in children with ITP, the multicenter randomized 'Treatment with or without IVIg for Kids with ITP' (TIKI) trial was performed.

Evidence for comparator: -

Actual start date of recruitment	27 May 2009
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: 200
Worldwide total number of subjects	200
EEA total number of subjects	200

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)	36
Children (2-11 years)	143
Adolescents (12-17 years)	21
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From May 2009 through April 2015, 206 patients from 48 different sites were registered on the Web site. Two were ineligible and 4 declined participation. Twelve sites did not enroll patients. Two hundred patients were included in the intention-to-treat analysis: 100 patients were allocated to receive IVIg and 100 to receive careful observation.

Pre-assignment

Screening details:

Children aged 3 months to 16 years with newly diagnosed ITP, a platelet count of $20 \times 10^9/L$ or less and with mild to moderate bleeding (grade 1-3 on the adapted Buchanan bleeding score) were screened by participating pediatricians. If they met inclusion criteria and did not meet exclusion criteria they could be enrolled within 72 hours.

Period 1

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

Blinding implementation details:

Since there was no placebo, patients and physicians were aware of the allocated treatment. However, since the primary outcome parameter, namely platelet count, was not influenced by this knowledge, we did not consider this as a problem.

Arms

Are arms mutually exclusive?	Yes
Arm title	IVIg

Arm description:

All patients randomized to the intervention arm of the study received a single dose of IVIg (Nanogam®) of 0.8 gram/kg bodyweight once of Nanogam.

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

Dosage and administration details:

Name: Nanogam®, manufactured by Sanquin.
Substance: liquid human normal immunoglobulin for intravenous use
Product presentation: 50 ml= 2.5 g human protein of which is at least 95% IgG
200 ml= 10 g human protein of which is at least 95% IgG

Dose: 0.8 gram per kilogram bodyweight

Infusion rate: 0-20 min: 0.5 ml/kg/hr
if well tolerated : next 20 ml gradually increase to 1.0 ml/kg/hr
if well tolerated : increase to a maximum of 3.0 ml/kg/hr

Since Nanogam® is registered for use in children with ITP, Nanogam® could be prescribed from the regular stock. The local investigators have noted the batch number that was given to the patient on the CRF's.

Arm title	observation
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Arm description:

Patients randomized to the observational arm of the study received careful observation and immune-modulating treatment only in case of severe bleeding (grade 4-5).

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	IVIg	observation
Started	100	100
Completed	99	97
Not completed	1	3
Physician decision	1	-
Adverse event, non-fatal	-	3

Baseline characteristics

Reporting groups

Reporting group title	IVIg
Reporting group description:	
All patients randomized to the intervention arm of the study received a single dose of IVIg (Nanogam ®) of 0.8 gram/kg bodyweight once of Nanogam.	
Reporting group title	observation
Reporting group description:	
Patients randomized to the observational arm of the study received careful observation and immune-modulating treatment only in case of severe bleeding (grade 4-5).	

Reporting group values	IVIg	observation	Total
Number of subjects	100	100	200
Age categorical			
Units: Subjects			
Infants and toddlers (28 days-23 months)	16	20	36
Children (2-11 years)	76	67	143
Adolescents (12-17 years)	8	13	21
Age continuous			
age in years			
Units: years			
median	3.6	4.5	
full range (min-max)	0.3 to 16.1	0.5 to 16.6	-
Gender categorical			
Units: Subjects			
Female	46	45	91
Male	54	55	109
preceding infection			
infection within 1 month before diagnosis of ITP			
Units: Subjects			
preceding infection	56	51	107
not recorded	1	2	3
no preceding infection	43	47	90
preceding vaccination			
vaccination in month before diagnosis			
Units: Subjects			
vaccination	3	5	8
no vaccination	97	93	190
not recorded	0	2	2
grade 3 bleeding			
mucosal bleeding at diagnosis			
Units: Subjects			
grade 3 bleeding	38	42	80
grade 0-2 bleeding	61	57	118
not recorded	1	1	2

duration of symptoms			
durations of symptoms before diagnosis			
Units: days			
median	3	3	
full range (min-max)	1 to 60	0 to 60	-
platelet count			
platelet count at diagnosis			
Units: platelet count x 10E9/L			
median	6	5	
full range (min-max)	0 to 20	0 to 20	-

End points

End points reporting groups

Reporting group title	IVIg
Reporting group description: All patients randomized to the intervention arm of the study received a single dose of IVIg (Nanogam®) of 0.8 gram/kg bodyweight once of Nanogam.	
Reporting group title	observation
Reporting group description: Patients randomized to the observational arm of the study received careful observation and immune-modulating treatment only in case of severe bleeding (grade 4-5).	

Primary: Development of chronic ITP

End point title	Development of chronic ITP
End point description: Chronic ITP was defined as a platelet count < 150 x 10E9/L at 6 months after diagnosis.	
End point type	Primary
End point timeframe: 6 months	

End point values	IVIg	observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97 ^[1]	97 ^[2]		
Units: platelet count				
number (not applicable)				
Platelet count < 150 x 10E9/L at 6 months	18	28		
Platelet count > 150 x 10E9/L at 6 months	79	69		

Notes:

[1] - intention to treat analysis; 3 subjects no available platelet count at 6 months

[2] - intention to treat analysis; 3 subjects no available platelet count at 6 months

Statistical analyses

Statistical analysis title	risk ratio with 95% confidence interval
Statistical analysis description: risk ratio with 95% confidence interval	
Comparison groups	IVIg v observation
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.09
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.64

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.08
Variability estimate	Standard deviation

Notes:

[3] - no comment

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

1 year

Adverse event reporting additional description:

Since this was a phase 3 study for an already registered treatment and indication, we did not collect adverse effect data, but only severe adverse events. There was a standard operating procedure developed about reporting severe adverse events. Local investigators were asked to fill out SAE forms within 24 hours after the SAE occurred.

Assessment type	Systematic
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Dictionary used

Dictionary name	not applicable
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Dictionary version	0
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Reporting groups

Reporting group title	IVIg
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Reporting group description:

Group that was randomized to IVIg

Reporting group title	observation
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Reporting group description:

group randomized to observation

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: Since this was a phase 3 study for an already registered treatment and indication, we did not collect adverse effect data, but only severe adverse events.

Serious adverse events	IVIg	observation	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 100 (10.00%)	19 / 100 (19.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
mild traumatic head injury	Additional description: mild traumatic head injury		
subjects affected / exposed	3 / 100 (3.00%)	4 / 100 (4.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
bleeding	Additional description: Bleeding that necessitates intervention		
subjects affected / exposed	1 / 100 (1.00%)	13 / 100 (13.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
allergic reaction	Additional description: allergic reaction IVIg		

subjects affected / exposed	1 / 100 (1.00%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
nausea, vomiting or headache	Additional description: nausea vomiting or headache leading to admission to hospital		
subjects affected / exposed	4 / 100 (4.00%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
infections	Additional description: infections leading to hospital admission		
subjects affected / exposed	1 / 100 (1.00%)	2 / 100 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	IVIg	observation	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 100 (0.00%)	0 / 100 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2010	- exclusion criteria are more extensively explained - the infusion rate of Nanogam is adjusted to the guidelines in the IB-1 text - paragraph 11.3 regarding Quality Assurance has been changed according to the monitoring plan of the study.
06 August 2012	- Paragraph 4.4: due to a too stringent alpha (0.01 instead of 0.05) sample size was miscalculated. This has been corrected and sample size now is 100 subjects in each group. - Paragraphs 5.3, 7.4 and 7.5: patients that receive rescue medication for severe bleeding or immunomodulating therapy for other conditions will NOT be withdrawn from the study, since they are included in the intention to treat analysis. This has been corrected in the abovementioned paragraphs.

Notes:

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/29945954>