Clinical trial results:
Controlled trail of immunoglobulin therapy for patients with idiopathic cardiomyopathy and endomyocardial parvovirus B19 persistence - - a prospective, double-blind, randomized, placebo-controlled clinical trial.

Summary

EudraCT number	2009-009463-61
Trial protocol	NL
Global end of trial date	06 June 2018

Results information

Result version number	v1 (current)
This version publication date	29 November 2021
First version publication date	29 November 2021
Summary attachment (see zip file)	Synopsis_2009-009463-61 (SynopsisCSR_2009-009463-61.pdf)

Trial information

Trial identification

Sponsor protocol code	MD2009.01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00892112
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanquin Plasma Products B.V.
Sponsor organisation address	Plesmanlaan 125, Amsterdam, Netherlands, 1066CX
Public contact	I. Kleine Budde, Clinical Operations, Prothya Biosolutions (formely Sanquin Plasma Products), ilona.kleinebudde@prothya.com
Scientific contact	S. Heymans, Maastricht University Medical Centre+ , s.heymans@maastrichtuniversity.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 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate whether high dose of intravenous immunoglobulin (IVIg) in addition to conventional heart failure therapy in patients with idiopathic cardiomyopathy and PVB19 persistence in the heart achieves improvement of cardiac function in conjunction with virus elimination.

Protection of trial subjects:

Risks are low. All patients underwent routine diagnostic work-up (including physical examination, coronary angiogram, transthoracic echocardiogram, blood studies and endomyocardial biopsies (EMB)), treatment and follow-up for their heart failure. Patients were randomized to either receive IVIg or placebo on top of their standard heart failure regimen. The incidence of undesirable side effects from IVIg is low. Side effects from placebo (Albuman/G.P.O.) are rare. All visits and investigations were part of the routine check-up, except for the second EMB. The procedure to obtain EMB is a very safe one, with a very low risk (<0,5 %) of peri-procedure complications.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 November 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 53
Worldwide total number of subjects	53
EEA total number of subjects	53

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	53

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were referred for further analyses of their unexplained cardiomyopathy by cardiologists from the Maastricht University Medical Centre and referral hospitals from the region. If they fulfill the inclusion criteria they were asked if they want to particpate in the study.

Pre-assignment

Screening details:

Patients with symptomatic idiopathic cardiomyopathy for more than 6 months despite optimal standard heart failure medication and a significant PVB19 viral load in endomyocardial biopsies.

Period 1

Period 1 title	total period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	IVIG

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Nanogam 50 mg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A total dose of 2 gr/kg bodyweight of intravenous immunoglobulin product administered as 0.5 gr/kg IV over a period of 6 hours on each of 4 consecutive days.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Albumin
Investigational medicinal product code	
Other name	Albuman 40 g/L, G.P.O.
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A total dose of 40 ml/kg bodyweight of intravenous immunoglobulin product Nanogam® administered as 10 ml/kg IV over a period of 6 hours on each of 4 consecutive days.

Number of subjects in period 1[1]	IVIG	Placebo
Started	26	24
Completed	26	24

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: Three patients were withdrawn before administration of study medication, due to patient's preference.

Baseline characteristics

Reporting groups	
Reporting group title	IVIG
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	IVIG	Placebo	Total
Number of subjects	26	24	50
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)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	53.5	54.5	
standard deviation	± 13.15	± 9.49	-
Gender categorical Units: Subjects			
Female	6	5	11
Male	20	19	39

End points

End points reporting groups	
Reporting group title	IVIG
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: absolute change in LVEF	
End point title	absolute change in LVEF
End point description:	
End point type	Primary
End point timeframe:	
Baseline versus 6 months after treatment	

End point values	IVIG	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	24		
Units: percentage				
geometric mean (standard deviation)	4.7 (± 8.78)	6.1 (± 10.33)		

Statistical analyses

Statistical analysis title	Mann-Whitney-U-Test
Comparison groups	IVIG v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.547
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	4

Secondary: presence of virus PVB19 in EMB	
End point title	presence of virus PVB19 in EMB

End point description:

End point type	Secondary

End point timeframe:

Baseline versus 6 months after treatment

End point values	IVIG	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	24		
Units: copies per µg DNA				
median (inter-quartile range (Q1-Q3))	-121 (-387 to 90)	-116 (-394 to -12.5)		

Statistical analyses

Statistical analysis title	T-test
Comparison groups	IVIG v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2582
Method	t-test, 2-sided

Secondary: Neutralizing antibodies against PVB19 antigens (anti VP1/VP2)

End point title	Neutralizing antibodies against PVB19 antigens (anti VP1/VP2)

End point description:

End point type	Secondary

End point timeframe:

Baseline and Day 4 after last infusion

End point values	IVIG	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	23		
Units: U/ml				
median (inter-quartile range (Q1-Q3))	887.35 (771.70 to 1076.70)	-50.00 (-105.80 to -24.80)		

Statistical analyses

Statistical analysis title	T-test
Comparison groups	Placebo v IVIG
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Study period of 6 months	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.1
Reporting groups	
Reporting group title	IVIG group
Reporting group description: -	
Reporting group title	Placebo group
Reporting group description: -	

Serious adverse events	IVIG group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 26 (7.69%)	1 / 24 (4.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Salivary Gland Cancer			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Vessel puncture site haematoma			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	IVIG group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 26 (42.31%)	6 / 24 (25.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 26 (42.31%)	4 / 24 (16.67%)	
occurrences (all)	12	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 26 (7.69%)	4 / 24 (16.67%)	
occurrences (all)	2	4	

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/33347677