Clinical trial results:
Pharmacokinetics and safety of the intravenous human immunoglobulin product Nanogam 100 mg/ml

Summary

EudraCT number	2012-005727-32
Trial protocol	NL
Global end of trial date	09 March 2015

Results information

Result version number	v1 (current)
This version publication date	05 December 2021
First version publication date	05 December 2021

Trial information

Trial identification

Sponsor protocol code	MD2012.02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01985373
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Prothya Biosolutions Netherlands B.V. (previously Sanquin Plasma Products B.V.)
Sponsor organisation address	Plesmanlaan 125, Amsterdam, Netherlands, 1066CX
Public contact	Clinical Operations, Prothya Biosolutions, +31 205123537, ilona.kleinebudde@prothya.com
Scientific contact	Clinical Operations, Prothya Biosolutions, +31 205123537, ilona.kleinebudde@prothya.com

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	14 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Objective of the study is to show bioequivalency between Nanogam® 50 mg/ml and Nanogam 100 mg/ml by comparing the pharmacokinetics.

Protection of trial subjects:

Risk minimal. Patients are already stabilised on treatment with Nanogam 50 mg/ml.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 January 2014
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: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	18
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment from 08-01-2014 till 07-11-2014. Four clinical sites in the Netherlands.

Pre-assignment

Screening details:

Primary a- or hypogammaglobulinemia, particularly patients with XLA or CVID, stabilised on treatment with Nanogam 50 mg/ml . A stable clinical situation.

Period 1

Period 1 title	Nanogam 50 mg/ml
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Nanogam 50 mg/ml

Arm description:

One infusion Nanogam 50 mg/ml

Arm type	Active comparator
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:

Advised dose for Nanogam 50 mg/ml: 0.2-0.8 g/kg every 3-4 weeks. Patients included in current study received one infusion Nanogam 50 mg/ml following their current treatment regimen.

Number of subjects in period 1	Nanogam 50 mg/ml
Started	23
Completed	23

Period 2

Period 2 title	Nanogam 100 mg/ml
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Nanogam 100 mg/ml

Arm description:

Four infusions Nanogam 100 mg/ml

Arm type	Experimental
Investigational medicinal product name	Nanogam 100 mg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Advised dose for Nanogam: 0.2-0.8 g/kg every 3-4 weeks. Patients in current study continued treatment with Nanogam 100 mg/ml at the same dose (in grams) and interval as their regular treatment with Nanogam 50 mg/ml.

Number of subjects in period 2	Nanogam 100 mg/ml
Started	23
Completed	23

Baseline characteristics

Reporting groups	
Reporting group title	Nanogam 50 mg/ml
Reporting group description: Cross-over	

Reporting group values	Nanogam 50 mg/ml	Total	
Number of subjects	23	23	
Age categorical Units: Subjects			
Adults (18-64 years)	18	18	
From 65-84 years	5	5	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	51		
full range (min-max)	20 to 72	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	10	10	

End points

End points reporting groups

Reporting group title	Nanogam 50 mg/ml
Reporting group description: One infusion Nanogam 50 mg/ml	
Reporting group title	Nanogam 100 mg/ml
Reporting group description: Four infusions Nanogam 100 mg/ml	

Primary: C trough

End point title	C trough[1]
End point description: predose plasma concentration	
End point type	Primary
End point timeframe: PK profiles of total IgG on Visit 1 (Nanogam 5%) and Visit 5 (Nanogam 10%): directly after infusion (within 5 min) and 1 hour, 2 hours, 1, 2, 3, 7, 14 and 21 days after infusion	

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: Descriptive statistics were performed.

End point values	Nanogam 50 mg/ml	Nanogam 100 mg/ml		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: g/L				
arithmetic mean (standard deviation)	8.9 (± 1.85)	8.7 (± 1.9)		

Statistical analyses

No statistical analyses for this end point

Primary: t1/2 term

End point title	t1/2 term[2]
End point description:	
End point type	Primary
End point timeframe: PK profiles of total IgG on Visit 1 (Nanogam 5%) and Visit 5 (Nanogam 10%): directly after infusion (within 5 min) and 1 hour, 2 hours, 1, 2, 3, 7, 14 and 21 days after infusion	

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: Descriptive statistics were performed.

End point values	Nanogam 50 mg/ml	Nanogam 100 mg/ml		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	17		
Units: hours				
arithmetic mean (standard deviation)	672.2 (± 226.6)	630.6 (± 129.0)		

Statistical analyses

No statistical analyses for this end point

Primary: C min

End point title	C min

End point description:

minimum plasma concentration during the dosing interval

End point type	Primary

End point timeframe:

PK profiles of total IgG on Visit 1 (Nanogam 5%) and Visit 5 (Nanogam 10%): directly after infusion (within 5 min) and 1 hour, 2 hours, 1, 2, 3, 7, 14 and 21 days after infusion)

End point values	Nanogam 50 mg/ml	Nanogam 100 mg/ml		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: g/L				
arithmetic mean (standard deviation)	8.65 (± 1.88)	8.53 (± 1.88)		

Statistical analyses

Statistical analysis title	Bioequivalence C min

Statistical analysis description:

Cmin logarithmic scale. All paired observations for test and reference were included in the statistical analysis. The LSmeans and intrasubject variance of the parameters for each treatment group were estimated with a linear mixed effects model, controlling for treatment, sequence and period as fixed effects, and subject as a random effect. A 90% CI were constructed around the difference between the LS means of test and reference. Difference LSmeans/CI were retransformed to the original scale.

Comparison groups	Nanogam 50 mg/ml v Nanogam 100 mg/ml
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence[3]
Parameter estimate	LS means ratio
Point estimate	98.58

Confidence interval	
level	90 %
sides	2-sided
lower limit	96.43
upper limit	100.77

Notes:

[3] - Nanogam 100 mg/ml was bioequivalent to Nanogam 50 mg/ml Nanogam if the 90% confidence intervals for IgG Cmin (Test vs Reference) were within 80.00% to 125.00%.

Primary: C max

End point title	C max[4]

End point description:

Maximum plasma concentration. Cmax is dependent on the rate of infusion, which varied between subjects. Therefore Cmax needs to be interpreted with caution.

End point type	Primary

End point timeframe:

PK profiles of total IgG on Visit 1 (Nanogam 5%) and Visit 5 (Nanogam 10%): directly after infusion (within 5 min) and 1 hour, 2 hours, 1, 2, 3, 7, 14 and 21 days after infusion

Notes:

[4] - 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: Descriptive statistics were performed.

End point values	Nanogam 50 mg/ml	Nanogam 100 mg/ml		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: g/L				
arithmetic mean (standard deviation)	17.8 (± 4.14)	17.6 (± 4.58)		

Statistical analyses

No statistical analyses for this end point

Primary: t max

End point title	t max[5]

End point description:

time to reach maximum plasma concentration. tmax is dependent on the rate of infusion and infusion duration which varied between subjects. Therefore tmax needs to be interpreted with caution.

End point type	Primary

End point timeframe:

PK profiles of total IgG on Visit 1 (Nanogam 5%) and Visit 5 (Nanogam 10%): directly after infusion (within 5 min) and 1 hour, 2 hours, 1, 2, 3, 7, 14 and 21 days after infusion

Notes:

[5] - 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: Descriptive statistics were performed.

End point values	Nanogam 50 mg/ml	Nanogam 100 mg/ml		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: hour				
median (full range (min-max))	2.58 (1.23 to 6.92)	2.08 (0.62 to 3.75)		

Statistical analyses

No statistical analyses for this end point

Primary: AUC lctp

End point title	AUC lctp

End point description:

Area under the plasma concentration time curve from start of infusion up to the last common time point between treatments within one subject; calculated by linear-linear trapezoidal summation.

End point type	Primary

End point timeframe:

PK profiles of total IgG on Visit 1 (Nanogam 5%) and Visit 5 (Nanogam 10%): directly after infusion (within 5 min) and 1 hour, 2 hours, 1, 2, 3, 7, 14 and 21 days after infusion

End point values	Nanogam 50 mg/ml	Nanogam 100 mg/ml		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: h*g/L				
arithmetic mean (standard deviation)	5612 (± 1265)	5462 (± 1189)		

Statistical analyses

Statistical analysis title	Bioequivalence AUClctp

Statistical analysis description:

AUClctp logarithmic scale. All paired observations for test and reference were included in the statistical analysis. The LSmeans and intrasubject variance of the parameters for each treatment group were estimated with a linear mixed effects model, controlling for treatment, sequence and period as fixed effects, and subject as a random effect. A 90% CI were constructed around the difference between the LS means of test and reference. Difference LSmeans/CI were retransformed to the original scale

Comparison groups	Nanogam 50 mg/ml v Nanogam 100 mg/ml
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence[6]
Parameter estimate	LS means ratio
Point estimate	97.6

Confidence interval	
level	90 %
sides	2-sided
lower limit	95.02
upper limit	100.25

Notes:

[6] - Nanogam 100 mg/ml was bioequivalent to Nanogam 50 mg/ml if the 90% confidence intervals for IgG AUClctp (Test vs Reference) were within 80.00% to 125.00%.

Primary: C avg

End point title	C avg[7]

End point description:

Average plasma concentration at steady-state over the dosing interval (τ) calculated by AUCτ/τ at steady-state.

End point type	Primary

End point timeframe:

PK profiles of total IgG on Visit 1 (Nanogam 5%) and Visit 5 (Nanogam 10%): directly after infusion (within 5 min) and 1 hour, 2 hours, 1, 2, 3, 7, 14 and 21 days after infusion

Notes:

[7] - 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: Descriptive statistics were performed.

End point values	Nanogam 50 mg/ml	Nanogam 100 mg/ml		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: g/L				
arithmetic mean (standard deviation)	11.9 (± 2.63)	11.6 (± 2.55)		

Statistical analyses

No statistical analyses for this end point

Primary: Fluctuation (FI)

End point title	Fluctuation (FI)[8]

End point description:

Fluctuation between the maximum and minimum analyte concentration (FI)

End point type	Primary

End point timeframe:

PK profiles of total IgG on Visit 1 (Nanogam 5%) and Visit 5 (Nanogam 10%): directly after infusion (within 5 min) and 1 hour, 2 hours, 1, 2, 3, 7, 14 and 21 days after infusion

Notes:

[8] - 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: Descriptive statistics were performed.

End point values	Nanogam 50 mg/ml	Nanogam 100 mg/ml		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: percentage				
arithmetic mean (standard deviation)	76.6 (± 17.8)	77.9 (± 22.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Apparent terminal elimination rate constant (λz)

End point title	Apparent terminal elimination rate constant (λz)[9]

End point description:

Apparent terminal elimination rate constant, determined by linear regression of the terminal points of the ln-linear plasma concentration-time curve

End point type	Primary

End point timeframe:

PK profiles of total IgG on Visit 1 (Nanogam 5%) and Visit 5 (Nanogam 10%): directly after infusion (within 5 min) and 1 hour, 2 hours, 1, 2, 3, 7, 14 and 21 days after infusion

Notes:

[9] - 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: Descriptive statistics were performed.

End point values	Nanogam 50 mg/ml	Nanogam 100 mg/ml		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	17		
Units: 1/hour				
arithmetic mean (standard deviation)	0.00115 (± 0.00039)	0.00115 (± 0.000280)		

Statistical analyses

No statistical analyses for this end point

Primary: Vss

End point title	Vss[10]

End point description:

Volume of distribution. Calculations of Vss are reported as approximations, as extrapolations of more than 20.00% of the total AUC and/or R2adj < 0.80 were used for the calculation of AUC∞ (needed for the calculation of Vss).

End point type	Primary

End point timeframe:

PK profiles of total IgG on Visit 1 (Nanogam 5%) and Visit 5 (Nanogam 10%): directly after infusion (within 5 min) and 1 hour, 2 hours, 1, 2, 3, 7, 14 and 21 days after infusion

Notes:

[10] - 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: Descriptive statistics were performed.

End point values	Nanogam 50 mg/ml	Nanogam 100 mg/ml		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	17		
Units: litre(s)				
arithmetic mean (standard deviation)	4.25 (± 1.06)	4.43 (± 0.747)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period of observation for adverse events extended from the time the patient gave informed consent till the end of the observation period.

Adverse event reporting additional description:

Safety was monitored by measuring vital signs (blood pressure, heart rate, temperature) and recording all adverse events during and after the infusions with Nanogam.
NB All SAEs occured in same patient, who met the exclusion criterion: 'had a known insufficiency of coronary or cerebral circulation', which was considered a major protocol deviation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Nanogam 50 mg/ml (1 infusion)

Reporting group description:

Period between study start and first infusion Nanogam 100 mg/ml. Dosing interval ranged between 13 and 35 days.

Reporting group title	Nanogam 100 mg/ml (4 infusions)

Reporting group description:

Period between first dose Nanogam 100 mg/ml and End of Observation (=first regular infusion). Four dosing periods; dosing interval ranged between 13 and 43 days.

Serious adverse events	Nanogam 50 mg/ml (1 infusion)	Nanogam 100 mg/ml (4 infusions)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Cardiac disorders			
Cardiac Arrest	Additional description: After end of obervation period (29 days after the last infusion). Reported because of seriousness.		
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
COPD exacerbation			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Pneumonia			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflamed Salivary Gland			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
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: 4.5 %

Non-serious adverse events	Nanogam 50 mg/ml (1 infusion)	Nanogam 100 mg/ml (4 infusions)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)	5 / 23 (21.74%)	
Blood and lymphatic system disorders			
Leukopenia	Additional description: Without clinical symptoms. No lab performed after Nanogam 5%.		
subjects affected / exposed	0 / 23 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	4	
General disorders and administration site conditions			
Flu-like illness			
subjects affected / exposed	1 / 23 (4.35%)	2 / 23 (8.70%)	
occurrences (all)	1	2	
Infections and infestations			
Sinusitis			
subjects affected / exposed	0 / 23 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	

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