Clinical trial results:

A Phase III, Multicenter, Open-label, Randomized, Two-Period, Crossover Bioequivalence Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Gammaplex® 10 and Gammaplex® 5% in Primary Immunodeficiency Diseases

Summary

EudraCT number	2013-002290-21
Trial protocol	GB HU
Global end of trial date	13 April 2016

Results information

Result version number	v1 (current)
This version publication date	22 April 2017
First version publication date	22 April 2017

Trial information

Trial identification

Sponsor protocol code	GMX07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01963143
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bio Products Laboratory Limited
Sponsor organisation address	Dagger Lane, Elstree, United Kingdom, WD6 3BX
Public contact	Head of Medical Affairs, Bio Products Laboratory Limited, 44 2089572200, medinfo@bpl.co.uk
Scientific contact	Head of Medical Affairs, Bio Products Laboratory Limited, 44 2089572200, medinfo@bpl.co.uk

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	13 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 January 2016
Global end of trial reached?	Yes
Global end of trial date	13 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the bioequivalence of Gammaplex® 10 (Gammaplex® [10%] 10 g in 100 mL) intravenous immunoglobulin (IGIV) and Gammaplex® 5% (Gammaplex® [5%] 5 g in 100 mL) IGIV with respect to area under the curve within a 28-day dosing interval (AUC0-28) in a cohort of adult subjects.

Protection of trial subjects:

The number of PK samples was the minimum number required to provide an evaluable PK profile.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 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	United Kingdom: 3
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	United States: 44
Worldwide total number of subjects	48
EEA total number of subjects	4

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)	9
Adolescents (12-17 years)	8
Adults (18-64 years)	31
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects underwent screening assessments within 30 days before first dose of Gammaplex 5% or Gammaplex 10%

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Gammaplex 5% & Gammaplex 10% on a 21-day treatment schedule

Arm description:

Adult subjects aged 16+ years

Arm type	Experimental
Investigational medicinal product name	Gammaplex 5%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

All subjects were to receive a dose of 300 to 800 mg/kg/infusion. Subjects were to receive the same dose as per their prior IGIV.
Infusions were administered on either a 21-day or 28-day treatment schedule, depending on the subject's cycle of infusions during prior IGIV treatment. Subjects were randomised to receive either 5 infusions of Gammaplex 5% followed by 5 infusions of Gammaplex 10%, or 5 infusions of Gammaplex 10% followed by 5 infusions of Gammaplex 5%.

Investigational medicinal product name	Gammaplex 10%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

All subjects were to receive a dose of 300 to 800 mg/kg/infusion. Subjects were to receive the same dose as per their prior IGIV.
Infusions were administered on either a 21-day or 28-day treatment schedule, depending on the subject's cycle of infusions during prior IGIV treatment. Subjects were randomised to receive either 5 infusions of Gammaplex 5% followed by 5 infusions of Gammaplex 10%, or 5 infusions of Gammaplex 10% followed by 5 infusions of Gammaplex 5%.

Arm title	Gammaplex 5% & Gammaplex 10% on a 28-day treatment schedule

Arm description:

Adult subjects aged 16+ years

Arm type	Experimental

Investigational medicinal product name	Gammaplex 5%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

All subjects were to receive a dose of 300 to 800 mg/kg/infusion. Subjects were to receive the same dose as per their prior IGIV.
Infusions were administered on either a 21-day or 28-day treatment schedule, depending on the subject's cycle of infusions during prior IGIV treatment. Subjects were randomised to receive either 5 infusions of Gammaplex 5% followed by 5 infusions of Gammaplex 10%, or 5 infusions of Gammaplex 10% followed by 5 infusions of Gammaplex 5%.

Investigational medicinal product name	Gammaplex 10%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

All subjects were to receive a dose of 300 to 800 mg/kg/infusion. Subjects were to receive the same dose as per their prior IGIV.
Infusions were administered on either a 21-day or 28-day treatment schedule, depending on the subject's cycle of infusions during prior IGIV treatment. Subjects were randomised to receive either 5 infusions of Gammaplex 5% followed by 5 infusions of Gammaplex 10%, or 5 infusions of Gammaplex 10% followed by 5 infusions of Gammaplex 5%.

Arm title	Gammaplex 10% on a 21 or 28 day treatment schedule

Arm description:

Paediatric subjects aged <16 years

Arm type	Experimental
Investigational medicinal product name	Gammaplex 10%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

All subjects were to receive a dose of 300 to 800 mg/kg/infusion. Subjects were to receive the same dose as per their prior IGIV.
Infusions were administered on either a 21-day or 28-day treatment schedule, depending on the subject's cycle of infusions during prior IGIV treatment.

Number of subjects in period 1	Gammaplex 5% & Gammaplex 10% on a 21-day treatment schedule	Gammaplex 5% & Gammaplex 10% on a 28-day treatment schedule	Gammaplex 10% on a 21 or 28 day treatment schedule
Started	14	19	15
Completed	14	18	14
Not completed	0	1	1
Consent withdrawn by subject	-	1	-
Physician decision	-	-	1

Baseline characteristics

Reporting groups

Reporting group title	Gammaplex 5% & Gammaplex 10% on a 21-day treatment schedule
Reporting group description: Adult subjects aged 16+ years	
Reporting group title	Gammaplex 5% & Gammaplex 10% on a 28-day treatment schedule
Reporting group description: Adult subjects aged 16+ years	
Reporting group title	Gammaplex 10% on a 21 or 28 day treatment schedule
Reporting group description: Paediatric subjects aged <16 years	

Reporting group values	Gammaplex 5% & Gammaplex 10% on a 21-day treatment schedule	Gammaplex 5% & Gammaplex 10% on a 28-day treatment schedule	Gammaplex 10% on a 21 or 28 day treatment schedule
Number of subjects	14	19	15
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	9
Adolescents (12-17 years)	1	1	6
Adults (18-64 years)	13	18	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	12	9	7
Male	2	10	8

Reporting group values	Total		
Number of subjects	48		
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)	9		
Adolescents (12-17 years)	8		
Adults (18-64 years)	31		
From 65-84 years	0		

85 years and over	0		

Gender categorical Units: Subjects			
Female	28		
Male	20		

End points

End points reporting groups

Reporting group title	Gammaplex 5% & Gammaplex 10% on a 21-day treatment schedule
Reporting group description:	
Adult subjects aged 16+ years	
Reporting group title	Gammaplex 5% & Gammaplex 10% on a 28-day treatment schedule
Reporting group description:	
Adult subjects aged 16+ years	
Reporting group title	Gammaplex 10% on a 21 or 28 day treatment schedule
Reporting group description:	
Paediatric subjects aged <16 years	

Primary: Area under the curve within a 28-day dosing interval (absolute values)

End point title	Area under the curve within a 28-day dosing interval (absolute values)[1][2]
End point description:	
Absolute AUC(0-t)	
End point type	Primary
End point timeframe:	
After a minimum of 5 infusions of Gammaplex 5% and a minimum of 5 infusions of Gammaplex 10%	

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: Statistical analysis was not performed. This secondary analysis comprised a bioequivalence assessment on the PK parameters.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary endpoint was based on the bioequivalence of Gammaplex 10% and Gammaplex 5% at the 28 day dosing interval only.

End point values	Gammaplex 5% & Gammaplex 10% on a 28-day treatment schedule			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: ratio Gammaplex 10%/Gammaplex 5%				
number (confidence interval 90%)	1.01 (0.98 to 1.03)			

Statistical analyses

No statistical analyses for this end point

Primary: Area under the curve within a 28-day dosing interval (baseline-adjusted values)

End point title	Area under the curve within a 28-day dosing interval (baseline-adjusted values)[3][4]

End point description:

Baseline-adjusted AUC(0-t)

End point type	Primary

End point timeframe:

After a minimum of 5 infusions of Gammaplex 5% and a minimum of 5 infusions of Gammaplex 10%

Notes:

[3] - 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: Statistical analysis was not performed. The primary analysis comprised a bioequivalence assessment on the PK parameters.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary endpoint was based on the bioequivalence of Gammaplex 10% and Gammaplex 5% at the 28 day dosing interval only.

End point values	Gammaplex 5% & Gammaplex 10% on a 28-day treatment schedule			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: ratio Gammaplex 10%/Gammaplex 5%				
number (confidence interval 90%)	1.07 (0.93 to 1.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the curve within a 21-day dosing interval (absolute values)

End point title	Area under the curve within a 21-day dosing interval (absolute values)[5]

End point description:

End point type	Secondary

End point timeframe:

After a minimum of 5 infusions of Gammaplex 5% and a minimum of 5 infusions of Gammaplex 10%

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This secondary endpoint was based on the bioequivalence of Gammaplex 10% and Gammaplex 5% at the 21 day dosing interval only.

End point values	Gammaplex 5% & Gammaplex 10% on a 21-day treatment schedule			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ratio Gammaplex 10%/Gammaplex 5%				
number (confidence interval 90%)	0.99 (0.95 to 1.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the curve within a 21-day dosing interval (baseline-adjusted values)

End point title	Area under the curve within a 21-day dosing interval (baseline-adjusted values)[6]

End point description:

End point type	Secondary

End point timeframe:

After a minimum of 5 infusions of Gammaplex 5% and a minimum of 5 infusions of Gammaplex 10%

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This secondary endpoint was based on the bioequivalence of Gammaplex 10% and Gammaplex 5% at the 21 day dosing interval only.

End point values	Gammaplex 5% & Gammaplex 10% on a 21-day treatment schedule			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ratio				
number (confidence interval 90%)	1.1 (0.96 to 1.26)			

Statistical analyses

No statistical analyses for this end point

Secondary: IgG trough levels for 28-day dosing interval

End point title	IgG trough levels for 28-day dosing interval[7]

End point description:

End point type	Secondary

End point timeframe:

After a minimum of 5 infusions of Gammaplex 5% and a minimum of 5 infusions of Gammaplex 10%

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This secondary endpoint was based on the bioequivalence of Gammaplex 10% and Gammaplex 5% at the 28 day dosing interval only.

End point values	Gammaplex 5% & Gammaplex 10% on a 28-day treatment schedule			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: ratio Gammaplex 10%/Gammaplex 5%				
number (confidence interval 90%)	0.98 (0.94 to 1.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: IgG trough levels for 21-day dosing interval

End point title	IgG trough levels for 21-day dosing interval[8]

End point description:

End point type	Secondary

End point timeframe:

After a minimum of 5 infusions of Gammaplex 5% and a minimum of 5 infusions of Gammaplex 10%

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This secondary endpoint was based on the bioequivalence of Gammaplex 10% and Gammaplex 5% at the 28 day dosing interval only.

End point values	Gammaplex 5% & Gammaplex 10% on a 21-day treatment schedule			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ratio Gammaplex 10%/Gammaplex 5%				
number (confidence interval 90%)	0.95 (0.92 to 0.99)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signature of informed consent until 28 days following the last dose of Gammaplex 5% or Gammaplex 10%

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Gammaplex 5% - all subjects

Reporting group description: -

Reporting group title	Gammaplex 10% - all subjects

Reporting group description: -

Serious adverse events	Gammaplex 5% - all subjects	Gammaplex 10% - all subjects	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 33 (6.06%)	1 / 47 (2.13%)	
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)			
neuroendocrine tumour			
subjects affected / exposed	1 / 33 (3.03%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 33 (3.03%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
IIIrd nerve paralysis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Anaphylactic reaction			
subjects affected / exposed	0 / 33 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	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	Gammaplex 5% - all subjects	Gammaplex 10% - all subjects	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 33 (69.70%)	44 / 47 (93.62%)	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	2 / 33 (6.06%)	0 / 47 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 33 (18.18%)	11 / 47 (23.40%)	
occurrences (all)	16	28	
Migraine			
subjects affected / exposed	3 / 33 (9.09%)	3 / 47 (6.38%)	
occurrences (all)	4	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 33 (9.09%)	1 / 47 (2.13%)	
occurrences (all)	7	5	
Pyrexia			
subjects affected / exposed	0 / 33 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 33 (6.06%)	2 / 47 (4.26%)	
occurrences (all)	2	2	
Nausea			
subjects affected / exposed	3 / 33 (9.09%)	1 / 47 (2.13%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal			

disorders				
Cough				
subjects affected / exposed	2 / 33 (6.06%)	4 / 47 (8.51%)		
occurrences (all)	2	4		
Oropharyngeal pain				
subjects affected / exposed	3 / 33 (9.09%)	2 / 47 (4.26%)		
occurrences (all)	3	2		
Rales				
subjects affected / exposed	2 / 33 (6.06%)	0 / 47 (0.00%)		
occurrences (all)	2	0		
Skin and subcutaneous tissue disorders				
Rash				
subjects affected / exposed	0 / 33 (0.00%)	5 / 47 (10.64%)		
occurrences (all)	0	6		
Dermatitis				
subjects affected / exposed	3 / 33 (9.09%)	1 / 47 (2.13%)		
occurrences (all)	3	1		
Psychiatric disorders				
Insomnia				
subjects affected / exposed	3 / 33 (9.09%)	0 / 47 (0.00%)		
occurrences (all)	3	0		
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	1 / 33 (3.03%)	3 / 47 (6.38%)		
occurrences (all)	2	4		
Infections and infestations				
Upper respiratory tract infection				
subjects affected / exposed	2 / 33 (6.06%)	8 / 47 (17.02%)		
occurrences (all)	2	8		
Nasopharyngitis				
subjects affected / exposed	1 / 33 (3.03%)	5 / 47 (10.64%)		
occurrences (all)	2	7		
Viral upper respiratory tract infection				
subjects affected / exposed	4 / 33 (12.12%)	4 / 47 (8.51%)		
occurrences (all)	5	5		
Acute sinusitis				

subjects affected / exposed	5 / 33 (15.15%)	3 / 47 (6.38%)	
occurrences (all)	6	3	
Chronic sinusitis			
subjects affected / exposed	2 / 33 (6.06%)	4 / 47 (8.51%)	
occurrences (all)	2	4	
Sinusitis			
subjects affected / exposed	1 / 33 (3.03%)	7 / 47 (14.89%)	
occurrences (all)	1	7	
Influenza			
subjects affected / exposed	0 / 33 (0.00%)	6 / 47 (12.77%)	
occurrences (all)	0	6	
Bronchitis			
subjects affected / exposed	3 / 33 (9.09%)	0 / 47 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 May 2014	Investigational New Drug number added Abbreviations updated Exclusion criterion 18: clarified fructose intolerance Exclusion criteria 13 and 14: defined 'chronic' added recommended frequency of monitoring vital signs PK sample collection windows expanded to allow for subject compliance guidance provided for recording medical history defined who could record TEE monitoring added that results of a chest x-ray or CT scan could be used at Screening instead of only chest x-ray clarified dosing calculation formula removed reference to Table 6, Appendix I (Summary of Investigator and Sponsor Reporting Responsibilities) DMC first meeting date modified correction of DMC abbreviation Table 6 (Schedule of Study Visit Assessments): footnote d amended to include CT scan Table 7 (Schedule of Pharmacokinetic Assessments): PK sample collection windows expanded to allow for subject compliance
09 October 2014	Added text to allow for additional infusions if subjects have dosing/scheduling issues and are not at steady state prior to the scheduled PK sampling Added text to mention the role of the Home Health Agency in PK sampling Removed the requirement for the infusion bag to be made of polyvinyl chloride
16 July 2015	Added measles antibody testing to the list of specific antibody tests (to be performed on the last available reserve blood sample taken after each treatment period) Updated Sponsor contact details

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/28316003