Clinical trial results:
A European, randomised, double-blind, active comparator-controlled, cross-over, efficacy and safety study of a new 10% ready-to-use liquid human intravenous immunoglobulin (I10E) versus Kiovig® in patients with Multifocal Motor Neuropathy .

Summary

EudraCT number	2012-001995-12
Trial protocol	IT GB ES FR
Global end of trial date	01 July 2016

Results information

Result version number	v1 (current)
This version publication date	03 June 2017
First version publication date	03 June 2017

Trial information

Trial identification

Sponsor protocol code	I10E-0901

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	LFB Biotechnologies
Sponsor organisation address	3, Avenue des Tropiques - BP 40305, COURTABOEUF, France, 91958
Public contact	Global Clinical Development Leader, LFB BIOTECHNOLOGIES, +33 169 82 56 56,
Scientific contact	Global Clinical Development Leader, LFB BIOTECHNOLOGIES, +33 169 82 56 56,

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	04 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 July 2016
Global end of trial reached?	Yes
Global end of trial date	01 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy of I10E compared to Kiovig® for maintenance treatment of patients with MMN in a randomised, double-blind, active comparator-controlled, cross-over design.

Protection of trial subjects:

No specific protection.

Background therapy:

None

Evidence for comparator:

The comparator was Kiovig, the only human normal immunoglobulin with an indication in Multifocal Motor Neuropathy when the study protocol was written

Actual start date of recruitment	04 September 2013
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	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Italy: 9
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)	22
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient signed a consent form on 4 September 2013
The last patient signed a consent form on 2 July 2015

Pre-assignment

Screening details:

A blood sample was drawn during the screening visit for laboratory tests, in order to rule out some exclusion criteria.

Pre-assignment period milestones

Number of subjects started	30[1]
Number of subjects completed	22

Pre-assignment subject non-completion reasons

Reason: Number of subjects	screening failure: 8

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 8 patients are on screening failure.

Period 1

Period 1 title	Before 1st administration of study drug
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Before shipment to investigational sites, each vial of IMP was covered by a masking system and was packaged in an individual box. Each vial and box was labelled with a unique identification number and all other useful information for the study except information enabling the identification of IMP. Before each course, the hospital pharmacist logged in the IWRS and obtained the vial identification numbers for vials to be administered to the subject.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence A arm

Arm description:

The patients randomized in Sequence A received Kiovig in Period 1 and I10E in period 2.

Arm type	Active comparator
Investigational medicinal product name	Kiovig
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

No administration during this period.

Arm title	Sequence B arm

Arm description:

The patients randomized in Sequence B received I10E in Period 1 and Kiovig in period 2.

Arm type	Experimental

Investigational medicinal product name	I10E
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

No administration during this period.

Number of subjects in period 1[2]	Sequence A arm	Sequence B arm
Started	12	10
Completed	12	10

Notes:

[2] - 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: 23 patients randomized (worldwide number) but one patient on screening failure after randomization.

Period 2

Period 2 title	Treatment period 1
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Before shipment to investigational sites, each vial of IMP was covered by a masking system and was packaged in an individual box. Each vial and box was labelled with a unique identification number and all other useful information for the study except information enabling the identification of IMP. Before each course, the hospital pharmacist logged in the IWRS and obtained the vial identification numbers for vials to be administered to the subject.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence A arm

Arm description:

The patients randomized in Sequence A received Kiovig in Period 1 and I10E in period 2.

Arm type	Active comparator
Investigational medicinal product name	Kiovig
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage and treatment course frequency could vary from subject to subject. The treatment schedule was to be maintained stable at the same level as before inclusion into the study. The allowed range was between 1 g/kg over 1-3 days and 2 g/kg over 2-5 days every 4 to 8 weeks.
I10E and Kiovig were administered in a double-blind manner by investigators.
Duration of treatment:
Randomized subjects were treated for between 42 and 50 weeks including two 21 to 25-week periods with Kiovig and I10E or vice versa. The exact duration of the treatment and follow-up depended on each subject’s own schedule.

Arm title	sequence B arm

Arm description:

The patients randomized in Sequence B received I10E in Period 1 and Kiovig in period 2.

Arm type	Experimental
Investigational medicinal product name	I10E
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage and treatment course frequency could vary from subject to subject. The treatment schedule was to be maintained stable at the same level as before inclusion into the study. The allowed range was between 1 g/kg over 1-3 days and 2 g/kg over 2-5 days every 4 to 8 weeks.
I10E and Kiovig were administered in a double-blind manner by investigators.
Duration of treatment:
Randomized subjects were treated for between 42 and 50 weeks including two 21 to 25-week periods with Kiovig and I10E or vice versa. The exact duration of the treatment and follow-up depended on each subject's own schedule.

Number of subjects in period 2	Sequence A arm	sequence B arm
Started	12	10
Completed	12	9
Not completed	0	1
Patient dissatisfaction with IMP	-	1

Period 3

Period 3 title	Treatment period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Before shipment to investigational sites, each vial of IMP was covered by a masking system and was packaged in an individual box. Each vial and box was labelled with a unique identification number and all other useful information for the study except information enabling the identification of IMP. Before each course, the hospital pharmacist logged in the IWRS and obtained the vial identification numbers for vials to be administered to the subject.

Arms

Are arms mutually exclusive?	Yes

Arm title	Sequence A arm

Arm description:

The patients randomized in Sequence A received I10E during Period 2.

Arm type	Experimental
Investigational medicinal product name	I10E
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage and treatment course frequency could vary from subject to subject. The treatment schedule was to be maintained stable at the same level as before inclusion into the study. The allowed range was between 1 g/kg over 1-3 days and 2 g/kg over 2-5 days every 4 to 8 weeks.
I10E and Kiovig were administered in a double-blind manner by investigators.
Duration of treatment:
Randomized subjects were treated for between 42 and 50 weeks including two 21 to 25-week periods with Kiovig and I10E or vice versa. The exact duration of the treatment and follow-up depended on each subject's own schedule.

Arm title	Sequence B arm

Arm description:

The patients randomized in Sequence B received Kiovig during period 2.

Arm type	Active comparator
Investigational medicinal product name	Kiovig
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage and treatment course frequency could vary from subject to subject. The treatment schedule was to be maintained stable at the same level as before inclusion into the study. The allowed range was between 1 g/kg over 1-3 days and 2 g/kg over 2-5 days every 4 to 8 weeks.
I10E and Kiovig were administered in a double-blind manner by investigators.
Duration of treatment:
Randomized subjects were treated for between 42 and 50 weeks including two 21 to 25-week periods with Kiovig and I10E or vice versa. The exact duration of the treatment and follow-up depended on each subject's own schedule.

Number of subjects in period 3	Sequence A arm	Sequence B arm
Started	12	9
Completed	12	9

Baseline characteristics

Reporting groups	
Reporting group title	Sequence A arm
Reporting group description:	
The patients randomized in Sequence A received Kiovig in Period 1 and I10E in period 2.	
Reporting group title	Sequence B arm
Reporting group description:	
The patients randomized in Sequence B received I10E in Period 1 and Kiovig in period 2.	

Reporting group values	Sequence A arm	Sequence B arm	Total
Number of subjects	12	10	22
Age categorical Units: Subjects			
Adults (18-79 years)	12	10	22
Age continuous Units: years			
arithmetic mean	49.8	48.3	
full range (min-max)	32 to 78	31 to 64	-
Gender categorical Units: Subjects			
Female	1	2	3
Male	11	8	19

Subject analysis sets	
Subject analysis set title	Modified Intent-To-Treat set Kiovig
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The modified intent-to-treat (mITT) population was defined as all randomized subjects who received at least one administration of IMP, with the baseline and at least one post treatment MMRC efficacy assessment available. The EOS visit assessment constituted a valid post treatment assessment for this definition.	

Subject analysis set title	Modified Intent-To-Treat set I10E
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The modified intent-to-treat (mITT) population was defined as all randomized subjects who received at least one administration of IMP, with the baseline and at least one post treatment MMRC efficacy assessment available. The EOS visit assessment constituted a valid post treatment assessment for this definition.	

Subject analysis set title	Total treated set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Total treated set is defined as all subjets who received at least one administration of IMP	

Reporting group values	Modified Intent-To-Treat set Kiovig	Modified Intent-To-Treat set I10E	Total treated set
Number of subjects	21	22	22

Age categorical Units: Subjects			
Adults (18-79 years)	21	22	22
Age continuous Units: years			
arithmetic mean	48.9	49.1	49.1
full range (min-max)	31 to 78	31 to 78	31 to 78
Gender categorical Units: Subjects			
Female	3	3	3
Male	18	19	19

End points

End points reporting groups

Reporting group title	Sequence A arm
Reporting group description:	
The patients randomized in Sequence A received Kiovig in Period 1 and I10E in period 2.	
Reporting group title	Sequence B arm
Reporting group description:	
The patients randomized in Sequence B received I10E in Period 1 and Kiovig in period 2.	
Reporting group title	Sequence A arm
Reporting group description:	
The patients randomized in Sequence A received Kiovig in Period 1 and I10E in period 2.	
Reporting group title	sequence B arm
Reporting group description:	
The patients randomized in Sequence B received I10E in Period 1 and Kiovig in period 2.	
Reporting group title	Sequence A arm
Reporting group description:	
The patients randomized in Sequence A received I10E during Period 2.	
Reporting group title	Sequence B arm
Reporting group description:	
The patients randomized in Sequence B received Kiovig during period 2.	
Subject analysis set title	Modified Intent-To-Treat set Kiovig
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The modified intent-to-treat (mITT) population was defined as all randomized subjects who received at least one administration of IMP, with the baseline and at least one post treatment MMRC efficacy assessment available. The EOS visit assessment constituted a valid post treatment assessment for this definition.	

Subject analysis set title	Modified Intent-To-Treat set I10E
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The modified intent-to-treat (mITT) population was defined as all randomized subjects who received at least one administration of IMP, with the baseline and at least one post treatment MMRC efficacy assessment available. The EOS visit assessment constituted a valid post treatment assessment for this definition.	

Subject analysis set title	Total treated set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Total treated set is defined as all subjets who received at least one administration of IMP	

Primary: Mean MMRC 10 sum score during the evaluation period

End point title	Mean MMRC 10 sum score during the evaluation period[1]
End point description:	
The MMRC 10 sum score measure muscle strength in 10 muscle groups (5 in upper limbs and 5 in lower limbs) right and left. Each muscle group is scored from 0 (paralysis) to 5 (normal strength), resulting in a global score from 0 to 100.	
End point type	Primary
End point timeframe:	
The evaluation period started 13 weeks after the initiation of each product and lasted until the end of the respective period.	

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: The linear mixed model used in this study estimated the effects of the products, periods and sequence on the mean MMRC 10 sumscore. The estimates of the effect of each of these 3 factors were adjusted based on the 2 other factors and on the baseline values. The estimated 95% confidence interval was also calculated for these 3 factors.
The non-inferiority of I10E compared to Kiovig was tested at 1-sided alfa risk of 2.5%. The non-inferiority margin was of 2 points.

End point values	Modified Intent-To-Treat set Kiovig	Modified Intent-To-Treat set I10E		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	22		
Units: score (from 0 to 100)				
arithmetic mean (standard deviation)	94.8 (± 7.3)	94.6 (± 7.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the first administration of the IMP to the end-of-study visit	
Adverse event reporting additional description:	
All the adverse events that occured in at least 5% of patients (i.e. in at least 2 patients among 22)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16

Reporting groups	
Reporting group title	Kiovig group
Reporting group description: -	
Reporting group title	I10E group
Reporting group description: -	

Serious adverse events	Kiovig group	I10E group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Kiovig group	I10E group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 21 (71.43%)	16 / 22 (72.73%)	
Vascular disorders			
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 21 (0.00%)	3 / 22 (13.64%)	
occurrences (all)	0	3	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 21 (47.62%)	8 / 22 (36.36%)	
occurrences (all)	23	22	
Sciatica			

subjects affected / exposed	2 / 21 (9.52%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 21 (9.52%)	5 / 22 (22.73%)	
occurrences (all)	2	6	
Gait disturbances			
subjects affected / exposed	1 / 21 (4.76%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	1 / 21 (4.76%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Leukopenia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 21 (4.76%)	1 / 22 (4.55%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 21 (4.76%)	2 / 22 (9.09%)	
occurrences (all)	1	4	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 21 (9.52%)	2 / 22 (9.09%)	
occurrences (all)	3	3	
Pain in extremity			
subjects affected / exposed	2 / 21 (9.52%)	2 / 22 (9.09%)	
occurrences (all)	2	2	
Arthralgia			
subjects affected / exposed	0 / 21 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Back pain			

subjects affected / exposed	0 / 21 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Infections and infestations			
nasopharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 21 (14.29%)	3 / 22 (13.64%)	
occurrences (all)	3	3	
Influenza			
subjects affected / exposed	1 / 21 (4.76%)	2 / 22 (9.09%)	
occurrences (all)	1	2	
Gastroenteritis			
subjects affected / exposed	1 / 21 (4.76%)	1 / 22 (4.55%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 September 2014	- The inclusion of subjects who received Kiovig more than 6 months before enrolment was permitted. - The definition of the PPS population was modified to be more conservative. - The limitation to 4 subjects per site was withdrawn to help enrol one or two more subjects in a few sites. - The IMP dosage reduction in obese subjects was removed because it was not appropriate during the maintenance treatment phase with IVIg. - The enrolment period was extended until the end of 3rd quarter 2016.
26 August 2015	- For the replacement of non-evaluable subjects, the new subject was to undergo a new randomization rather than having the same sequence group as the replaced subject. - Modifications on some exclusion criteria. - The potential risks related to the IMP were aligned with the European Guideline EMA/CHMP/BPWP/94038/2007 rev. 4. - The follow-up of AEs was clarified. - This amendment also incorporated rephrasing for clarification and consistencies between different clinical protocols. - This amendment also specified various administrative changes.
18 September 2015	A urine protein reagent strip test was added before IMP administration at all follow-up visits in subjects who had an abnormal (one cross or more) urine protein reagent strip test at screening and/or had GFR in the range of 60-80 mL/min/1.73 m2 measured according to the MDRD formula.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported