Clinical trial results:
Multicenter, open-label extension study to investigate the long-term safety and efficacy of IgPro20 in maintenance treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) in subjects completing study IgPro20_3003

Summary

EudraCT number	2013-004157-24
Trial protocol	GB IT DE ES FI NL CZ
Global end of trial date	10 July 2017

Results information

Result version number	v1 (current)
This version publication date	25 July 2018
First version publication date	25 July 2018

Trial information

Trial identification

Sponsor protocol code	IgPro20_3004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02027701
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring GmbH
Sponsor organisation address	Emil-von-Behring-Strasse 76, Marburg, Germany,
Public contact	Clin Trial Registration Coordinator, CSL Behring GmbH, clinicaltrials@cslbehring.com
Scientific contact	Clin Trial Registration Coordinator, CSL Behring GmbH, clinicaltrials@cslbehring.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	17 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate long-term safety and efficacy of IgPro20.

Protection of trial subjects:

This study was carried out in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and standard operating procedures for clinical research and development at CSL Behring, LLC (CSLB).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 July 2014
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	Japan: 10
Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Australia: 1
Worldwide total number of subjects	82
EEA total number of subjects	55

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)	55
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subject had completed Study 3003 (SC Week 25) or was successfully rescued from a relapse during the SC Treatment Period of Study 3003, and if treatment for CIDP was required it had to include IgGs.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	IgPro20

Arm description:

20% liquid formulation (200 mg/mL) of human normal immunoglobulin administered SC weekly at 0.2 g/kg, and subjects who experience CIDP relapse on 0.2 g/kg IgPro20 will have an increase to 0.4 g/kg IgPro20.

Arm type	Experimental
Investigational medicinal product name	IgPro20
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

20% liquid formulation (200 mg/mL) of human normal immunoglobulin for SC use administered SC weekly: 0.2 g/kg bw (low-dose IgPro20) for up to 48 weeks. Subjects who experience CIDP relapse on 0.2 g/kg IgPro20 will have an increase to 0.4 g/kg IgPro20 immediately and will continue on high-dose until they have completed a total of 48 weeks of IgPro20 treatment.

Number of subjects in period 1	IgPro20
Started	82
Completed	66
Not completed	16
Physician decision	2
Consent withdrawn by subject	3
Adverse event, non-fatal	3
Lack of efficacy	8

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	82	82	
Age categorical Units: Subjects			
Adults (18-64 years)	55	55	
From 65-84 years	27	27	
Gender categorical Units: Subjects			
Male	50	50	
Female	32	32	

End points

End points reporting groups

Reporting group title	IgPro20

Reporting group description:

20% liquid formulation (200 mg/mL) of human normal immunoglobulin administered SC weekly at 0.2 g/kg, and subjects who experience CIDP relapse on 0.2 g/kg IgPro20 will have an increase to 0.4 g/kg IgPro20.

Subject analysis set title	Safety Data Set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Data Set (SDS): all subjects who received at least 1 dose of IgPro20 in this study.

Subject analysis set title	Total Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Total Set: all subjects enrolled in the study, ie, the subject's informed consent was obtained. In the study protocol, this analysis set was referred to as the Intention-to-Treat Data Set.

Primary: Overall rate of Adverse Events (AEs) per infusion (SDS)

End point title	Overall rate of Adverse Events (AEs) per infusion (SDS)[1]

End point description:

End point type	Primary

End point timeframe:

Up to 49 weeks

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: Only descriptive statistics were given for this outcome measure.

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: Adverse events per infusion				
number (not applicable)	0.032			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CIDP Total Adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) Score (Total Set)

End point title	Change From Baseline in CIDP Total Adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) Score (Total Set)

End point description:

The INCAT score is a 10-point scale that covers the functionality of legs and arms, and has been successfully used to measure treatment effects in various CIDP studies. Scores for arm disability range from 0 ("No upper limb problems") to 5 ("Inability to use either arm for any purposeful movement"), and scores for leg disability range from 0 ("Walking not affected") to 5 ("Restricted to wheelchair, unable to stand and walk a few steps with help"). The INCAT (total) score is the sum of these 2 scores and ranges from 0 to 10. For the "adjusted" INCAT score, changes in the function of the upper limbs

from 0 (normal) to 1 (minor symptoms) or from 1 to 0 were not recorded as deterioration or improvement because these changes are not considered clinically significant.

End point type	Secondary

End point timeframe:

Baseline and up to 49 weeks

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Units on a scale				
median (full range (min-max))	0.0 (-3 to 6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Medical Research Council (MRC) Score (Total Set)

End point title	Change From Baseline in Medical Research Council (MRC) Score (Total Set)

End point description:

An adapted version of the MRC sum score as published by Kleyweg and the RMC trial group was used. With the MRC sum score, the following 8 bilateral muscle pairs were assessed, and individual muscle scores as well as the sum score documented: Shoulder abduction; Elbow flexion; Wrist extension; Index finger abduction; Hip flexion; Knee extension; Foot dorsiflexion; Great toe dorsiflexion. The MRC sum score ranges from 0 (paralysis) to 80 (normal strength) points.

End point type	Secondary

End point timeframe:

Baseline and up to 49 weeks

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: Units on a scale				
median (full range (min-max))	0.0 (-23 to 18)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Rasch-built Overall Disability Scale (R-ODS) (Total Set)

End point title	Change From Baseline in Rasch-built Overall Disability Scale (R-ODS) (Total Set)

End point description:

The R-ODS is a recently published outcome measure that captures activity and social participation in subjects with Guillain-Barré Syndrome, CIDP, and monoclonal gammopathy of uncertain significance. The 24-item questionnaire covers a wide range of tasks of daily life that are each to be rated as "impossible to perform", "able to perform with difficulty", or "easy to perform" (scale of 0 - 2 points respectively). Items are sorted in order of increasing difficulty to perform, based on data from subjects with peripheral neuropathies (chronic inflammatory demyelinating polyneuropathy, Guillain-Barré Syndrome, or monoclonal gammopathy of uncertain significance) and subjects recruited at the university outpatient clinics of Rotterdam and Maastricht.

End point type	Secondary

End point timeframe:

Baseline and up to 49 weeks

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Units on a scale				
median (full range (min-max))	0.0 (-76 to 33)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Grip Strength (Total Set)

End point title	Change From Baseline in Mean Grip Strength (Total Set)

End point description:

The hand-held Vigorimeter from Martin (Tuttlingen, Germany) is a device that measures the strength of small muscles in the hand, ie, grip strength. The subject squeezes a rubber bulb lying between the palm of the hand and the thumb and index fingers. The pressure is recorded via a rubber tube on a nanometer and expressed in kilopascal (kPa). At each assessment, the subject squeezes 3 times with each hand.

End point type	Secondary

End point timeframe:

Baseline and up to 49 weeks

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Units on a scale				
median (full range (min-max))	-0.7 (-80 to 27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of AEs by Severity Per Infusion (SDS)

End point title	Rate of AEs by Severity Per Infusion (SDS)

End point description:

End point type	Secondary

End point timeframe:

Up to 49 weeks

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: Adverse events per infusion				
number (not applicable)				
Mild	0.024			
Moderate	0.006			
Severe	0.002			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Causally Related AEs Per Infusion (SDS)

End point title	Rate of Causally Related AEs Per Infusion (SDS)

End point description:

End point type	Secondary

End point timeframe:

Up to 49 weeks

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: Adverse Events per infusion				
number (not applicable)	0.011			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Serious AEs Per Infusion (SDS)

End point title	Rate of Serious AEs Per Infusion (SDS)

End point description:

End point type	Secondary

End point timeframe:
Up to 49 weeks

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: Adverse events per infusion				
number (not applicable)	0.001			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Adverse Events (AEs) (SDS)

End point title	Percentage of Subjects with Adverse Events (AEs) (SDS)

End point description:

End point type	Secondary

End point timeframe:
Up to 49 weeks

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: percentage of subjects				
number (not applicable)	75.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with AEs by Severity (SDS)

End point title	Percentage of Subjects with AEs by Severity (SDS)

End point description:

End point type	Secondary

End point timeframe:
Up to 49 weeks

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: Percentage of subjects				
number (not applicable)				
Mild	62.2			
Moderate	29.3			
Severe	9.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Causally Related AEs (SDS)

End point title	Percentage of Subjects with Causally Related AEs (SDS)

End point description:

End point type	Secondary

End point timeframe:
Up to 49 weeks

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: Percentage of subjects				
number (not applicable)	25.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with AEs by Seriousness (SDS)

End point title	Percentage of Subjects with AEs by Seriousness (SDS)

End point description:

End point type	Secondary

End point timeframe:

Up to 49 weeks

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: Percentage of subjects				
number (not applicable)	8.5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 49 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups	
Reporting group title	IgPro20

Reporting group description: -

Serious adverse events	IgPro20		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 82 (4.88%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	2 / 82 (2.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Nerve compression			
subjects affected / exposed	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Chronic inflammatory demyelinating polyradiculoneuropathy			
subjects affected / exposed	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Faecaloma			

subjects affected / exposed	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Gallbladder perforation			
subjects affected / exposed	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary Sepsis			
subjects affected / exposed	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	IgPro20		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 82 (30.49%)		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 82 (4.88%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			

Infusion site erythema (local) subjects affected / exposed occurrences (all) Infusion site erythema (general) subjects affected / exposed occurrences (all) Infusion site swelling (local) subjects affected / exposed occurrences (all) Infusion site swelling (general) subjects affected / exposed occurrences (all)	7 / 82 (8.54%) 9 7 / 82 (8.54%) 9 9 / 82 (10.98%) 11 9 / 82 (10.98%) 11		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	11 / 82 (13.41%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2014	•Study design modified to require direct transition from the completion visit of study IgPro20_3003 to the Week 1 (baseline) visit of this study. •Inclusion criteria modified to define the study population (subjects who completed the SC Period or successfully recovered from CIDP relapse during the SC Period of the IgPro20_3003 study). •Exclusion criteria modified because of study design change, ie, direct transition from study IgPro20_3003. •IgPro20 dose reduced to 0.2 g/kg bw; if CIDP relapse occurs, subject will have the dose adjusted up to 0.4 g/kg bw; subject must successfully recover within 4 weeks (±2 days) in order to continue in the study. Dose justification and maximum volume per infusion site increased to 50 mL, as tolerated. •Subjects enrolled under the original protocol will be re-consented for Amendment 1 and started on Amendment 1 dose requirements and procedures at Week 25. If a subject enrolled under the original protocol, relapses and successfully recovers from the relapse prior to Week 25, the subject will remain on 0.4 g/kg bw for the remainder of the study. If the subject relapses again, they will be discontinued. •Week 17 and Week 41 visits converted to dispensing and inventory only visits. •Viral safety testing deleted, only retention sample collected for possible future testing if a suspected treatment-emergent viral infection occurs. •Biomarker text modified to delete anonymization of samples. This should not have been required in the original protocol, because no genetics will be tested. Biomarker results will need to be correlated with the subject's treatment in both studies and other test results in order to benefit understanding of CIDP disease progression and how to treat it. Biomarker sample collection is optional for Japan. •Missing efficacy (R-ODS) and HRQL (EQ-5D) instruments added to Section 8 and the Appendix, respectively. •Statement added that IgG levels will not be disclosed to the site or CSLB until the IgP
22 June 2015	•Number of subjects increased to approximately 80 subjects. •IVRS language updated to more closely align with the IgPro20_3003 protocol. •Biomarker language modified to confirm that a biomarker sample is required to be collected upon a CIDP relapse, either at a scheduled visit, or an unscheduled visit whichever is more timely. An unscheduled laboratory kit should be used for biomarker sample collection for both scheduled and unscheduled visits.
08 December 2015	•Adverse reactions were updated per current safety information. •IVRS language updated to clarify volume needed for each infusion session.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

For the "Endpoint Time to First CIDP Relapse (Total Set)", the subjects analyzed is 82, subjects started is 82, median is 266.0, 95%CI is 225.0 to NA (not evaluable).

Notes: