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.

Published: 20-03-2014
Last updated: 20-04-2024

Primary objective: To evaluate the long-term safety of IgPro20.Secondary objectives: * To evaluate the long-term safety of IgPro20 by dose. * To evaluate the efficacy of IgPro20.Exploratory objectives:* To evaluate health-related quality of life (...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immunodeficiency syndromes
Study type	Interventional

Summary

ID

NL-OMON44389

Source
ToetsingOnline

Brief title
IgPro20_3004

Condition

- Immunodeficiency syndromes
- Demyelinating disorders

Synonym
peripheral nerve damage, polyneuropathy

Research involving
Human

Sponsors and support

Primary sponsor: CSL Behring GmbH
Source(s) of monetary or material Support: CSL Behring GmbH (pharmaceutical industry)

Intervention

Keyword: CIDP, open-label, Subcutaneous Immunoglobulin

Outcome measures

Primary outcome

Primary endpoint:

* Overall rate of AEs per infusion.

Secondary outcome

Secondary endpoints:

Safety

* Overall rate of AEs per infusion (by system organ class [SOC], preferred term

[PT], severity, causality, and seriousness).

* Percentage of subjects with AEs (overall, and by SOC, PT, severity,

causality, seriousness).

* Rate of AEs per infusion (by SOC, PT, severity, causality, and seriousness)

by dose.

* Percentage of subjects with AEs (overall, and by SOC, PT, severity,

causality, seriousness) by dose.

Efficacy

* Changes from baseline in total adjusted INCAT score, MRC sum score, R-ODS,

and mean grip strength.

* Time to first relapse based on adjusted INCAT score.

Exploratory Endpoints:

Safety

* Descriptive statistics of laboratory safety parameters for hematology and serum chemistry.

* Electrocardiogram (ECG) (Japan only), and physical examination.

Efficacy

* Changes from baseline in total adjusted INCAT score, Medical Research Council (MRC) score, Rasch-built Overall Disability Scale (R-ODS), and mean grip strength, by dose.

* Time to first relapse based on adjusted INCAT score by dose.

* Changes from baseline in serum IgG levels by dose.

HRQL

Changes from baseline in:

* EuroQoL 5-Dimension Questionnaire (EQ-5D),

* Treatment Satisfaction Questionnaire for Medication (TSQM),

* Work Productivity and Activity Impairment Questionnaire for General Health (WPAI-GH),

* Subject preference for treatment.

Study description

Background summary

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired neurological, demyelinating neuropathy with an assumed autoimmune-mediated pathogenesis. The clinical course can be relapsing/remitting or chronic and progressive, the former being much more common in young adults.

The prevalence of CIDP is estimated to be about 4.7 per 100,000 adults and about 0.5 per 100,000 children.

Primary treatment modalities include IVIGs (normal human immunoglobulin for intravenous administration) and plasma exchange and corticosteroids, with the choice usually based on availability, cost, and side-effect profile.

IgPro20 is a ready-to-use formulation of human immunoglobulin G (IgG) with *98% purity for subcutaneous (SC) administration. It is approved in the United States of America (US), the European Union, Switzerland, Latin America, eastern Europe, Canada, Japan, and Australia under the brand name Hizentra® for primary immunodeficiency syndromes, and is manufactured at CSL Behring*s (CSLB*s) facility in Berne, Switzerland.

The current study is an extension study to the pivotal study IgPro20_3003. Clinical studies have demonstrated the clinical efficacy and safety of using IVIGs to treat CIDP. Study IgPro20_3003 is being conducted to provide evidence of subcutaneous immunoglobulin (SCIG) as an alternative treatment option for CIDP in demonstrating safety and efficacy of IgPro20 as maintenance therapy in subjects treated with IVIG and switched to SCIG.
The current extension study will provide further insight into the long-term safety and efficacy of treatment with IgPro20.

Study objective

Primary objective: To evaluate the long-term safety of IgPro20.

Secondary objectives:
* To evaluate the long-term safety of IgPro20 by dose.
* To evaluate the efficacy of IgPro20.

Exploratory objectives:
* To evaluate health-related quality of life (HRQL).
To evaluate serum immunoglobulin G (IgG) levels.

Study design

This is an open-label prospective, multicenter extension study for subjects who have completed subcutaneous (SC) Week 25 or were successfully rescued from a CIDP relapse during the SC Treatment Period of the preceding pivotal study IgPro20_3003. All eligible subjects must transition directly from study IgPro20_3003 to the extension study IgPro20_3004.
Eligible subjects will receive open-label IgPro20 (0.2 g/kg body weight [bw]) weekly for 48 weeks.
Subjects who relapse on IgPro20 0.2 g/kg bw will be given the option to remain in the study with an increase in the IgPro20 dose to 0.4 g/kg bw. Subjects remaining in the study on IgPro20 0.4 g/kg bw will have to successfully recover from the CIDP relapse within 4 weeks (±2 days), as confirmed by a site visit, or will otherwise be withdrawn from the study.
Successful recovery after a CIDP relapse is defined as the return of the total adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) score back to (or better than) the baseline score.
The last dose of IgPro20 is administered at Week 48; after the completion visit (Week 49) the subject is treated at the discretion of the investigator with standard of care therapy, ie, the subject will return to the CIDP treatment prescribed by the treating physician. If a subject has a CIDP relapse with less than 4 weeks remaining before the completion visit (Week 49), the subject will continue on the study and have the completion visit (Week 49) as planned followed by treatment at the discretion of the investigator with standard of care therapy.
A subject enrolled under the original protocol (09 Dec 2013) will convert to Amendment 2 procedures at Week 25 after Amendment 2 approval at the site (conversion to Amendment 2 may be later than Week 25 if the site has not yet been granted approval). An IgPro20 dose adjustment from 0.4 to 0.2 g/kg bw will be required for subjects who did not experience a CIDP relapse during the first 25 weeks. For subjects under the original protocol (09 Dec 2013) who recovered from a CIDP relapse during the first 25 weeks, their IgPro20 dose will be maintained at 0.4 g/kg bw for the remainder of the study. If they experience a second relapse after Week 25, they will be withdrawn from the study, as per this amendment.

Intervention

The study duration will be up to 49 weeks. The last dose of IgPro20 is administered at Week 48.
* 48 weeks of low dose IgPro20.
If CIDP relapse occurs, high dose IgPro20 until Week 48.

Study burden and risks

RISK-BENEFIT ASSESSMENT

Risk

In the 3 pivotal studies performed by CSLB for approval of IgPro20 in primary immunodeficiency syndromes, almost all adverse events (AEs [99%]) were mild or moderate in intensity. There was no dose-dependent increase in the overall rate of AEs, and there was no evidence in either study of severe systemic AEs.
The most frequently reported AEs in these studies were local reactions (swelling, erythema, warmth, bruising, pain, pruritis), followed by headache, diarrhea, fatigue, back pain, nausea, arthralgia, pain in extremity, cough, rash, pruritis, vomiting, upper abdominal pain, migraine, fever and pain. In addition, in the postmarketing setting, reactions such as hypersensitivity, tremor, burning sensation and infusion site ulcer were reported; as well as rare events such as anaphylaxis, aseptic meningitis syndrome (AMS) and thrombotic events. SC infusions generally result in lower rates of headache and other systemic adverse reactions than IV infusions, which is attributed to the more stable serum IgG concentrations attained with SCIG treatment (see Hizentra Investigator*s Brochure). Clinical trial and postmarketing experience with IgPro20 in pediatric and geriatric patients shows an overall similar safety profile as in adult patients.
The risk that products manufactured from plasma could transmit an infectious agent has been reduced by screening plasma donors for prior exposure to pathogens and by testing the donations for the presence of certain markers of infections. In addition, different complementary virus elimination processes used during the manufacture of IgPro20 (incubation at pH 4, virus filtration, fractionation, and depth filtration) effectively reduce the potential for viral transmission. The manufacturing process was also investigated for its capacity to eliminate hamster-adapted scrapie agent 263K, which is considered to be a model for Creutzfeldt-Jakob disease and variant Creutzfeldt-Jakob disease. The results demonstrated substantial removal of the infectious agent by the manufacturing process in all model systems. To date, no viral infection related to the infusion of IgPro20 was reported. However, the possibility of transmitting infective agents cannot be totally excluded.
At the start of this extension study, the pivotal study is still ongoing. Therefore, no final assessment of the efficacy and safety of IgPro20 in CIDP will have been performed. Depending on these results, the extension study may be modified, terminated, or continued as planned.

Justification for IgPro 20 Dose used in this extension study
The preplanned IgPro20_3003 safety interim analysis (March 2014) after 89 subjects were randomized to IgPro20 or placebo treatment revealed no safety issue. Altogether, a total of 2463 infusions were administered for the 3 treatment arms (IgPro20 0.4 g/kg bw; IgPro20 0.2 g/kg bw; and placebo). There were 4 (4.5%) subjects with serious treatment-emergent adverse events (2 subjects with arthralgias, 1 subject with acute allergic skin reaction, and 1 subject who required surgery of his ankle). In only 1 subject was the serious treatment-emergent adverse event (acute allergic skin reaction) assessed as related to the blinded study drug. All these events were of temporary duration and the subjects recovered completely by the end of the study. These results suggest that both doses of IgPro20 were well tolerated.

The low IgPro20 dose from Study IgPro20_3003 has been chosen for this study as it is suggested to be the minimum effective dose necessary to maintain CIDP. High IgPro20 dose subjects in Study IgPro20_3003 will have their dose reduced * which is in line with current guidelines to lower the dose after a period of stability. Low dose subjects in Study 3003 will continue with their low dose, and placebo subjects in Study 3003 will start with the low dose.
The low IgPro20 dose will be administered in a lower volume, unlike in Study 3003 where half of the low IgPro20 dose consisted of placebo in order to allow for blinding of the higher volume necessary for high IgPro20 dose treatment. It is therefore assumed that the low IgPro20 dose will be at least as safe in subjects participating in the extension study (minimizing local site reactions due to lower volume) while still being effective to control the CIDP.
In conclusion, the lowIgPro20 dose from Study 3003 has been chosen for this extension study as the probable minimum effective dose. The dose change does not pose a specific risk and is recommended by current treatment guidelines. Also see Section 9.1.3 *Adverse Events of Special Interest*.

Benefit
The expected benefit of the extension study for subjects is the continuation of SCIG therapy in subjects a) who have completed the pivotal study and were treated with either high dose or low dose IgPro20; or b) who have relapsed in the pivotal study on placebo
Volume up to 50 mL per infusion site
In Study 3003 up to 40 mL per infusion site is allowed. The preplanned safety interim analysis (March 2014) after 89 patients were randomized to IgPro20/placebo treatment revealed no safety issues with regards to infusion volume. The maximum infusion volume per site has therefore been increased to 50 mL in this study. This allows a syringe (50 mL) of IgPro20 to be used without changing infusion needles which is expected to increase comfort, decrease pain and decrease infusion time. The infusion method details are described in Section 6.4.1.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Written informed consent for study IgPro20_3004 before any study-specific procedures are performed.
2. Subject has completed the pivotal study IgPro20_3003 (SC Week 25), or was successfully rescued from a CIDP relapse during the SC Treatment Period of study IgPro20_3003.

Exclusion criteria

1. Subject is unable to directly transition from the pivotal study IgPro20_3003, ie, the subject is unable to have the baseline visit conducted at the same time as the completion visit for the pivotal study IgPro20_3003.
2. New medical condition and/or social behavior (ie, alcohol, drug, or medication abuse) during participation in pivotal study IgPro20_3003 that in the judgment of the investigator could increase risk to the subject, interfere with the evaluation of IMP, and/or conduct of the study. See Section 6.7 (Contraindications and Precautions for Further Dosing).
3. Pregnant or intention to become pregnant during the course of the study.
4. Female subjects of childbearing potential either not using, or not willing to continue to use, a medically reliable method of contraception for the entire duration of the study, or not sexually abstinent for the entire duration of the study, or not surgically sterile.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-03-2015
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Hizentra
Generic name:	Human normal Immunoglobulin (SCIg)
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	20-03-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	02-12-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	08-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	08-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-004157-24-NL
ClinicalTrials.gov	NCT00751621
CCMO	NL48011.018.14