PROTOCOL AMENDMENT No. 02

File Ref: NGAM-08

TITLE OF TRIAL/STUDY: PROSPECTIVE, DOUBLE-BLIND, RANDOMIZED, MULTICENTER PHASE III STUDY EVALUATING EFFICACY AND SAFETY OF THREE DIFFERENT DOSAGES OF NEWGAM IN PATIENTS WITH CHRONIC INFLAMMATORY DEMYELINATING POLY(RADICULO)NEUROPATHY (ProCID Study)

EUDRACT NUMBER: 2015-005443-14
IND NUMBER: 14096

SPONSOR: Octapharma Pharmazeutika Produktionsges.m.b.H., Oberlaaer Strasse 235, A-1100 Vienna, Austria

PRODUCT: Newgam 10%
REFERENCE THERAPY: Sodium chloride 0.9% w/v solution

APPROVED BY: [redacted]
International Medical Director
Octapharma Pharmazeutika ProduktionsgmbH
Oberlaaerstr. 235, A-1100 Vienna, Austria

PROTOCOL Versions:

Version	Date	Description
Final Version 01	17-Dec-2015	Submitted to the FDA
Version 02	28-Nov-2016	Implementation of changes as requested by the FDA
Version 03	09-Mar-2017	Implementation of changes as requested by VHP
Version 04	08-Jun-2018	Implementation of recommendation of the IDMC and changes for clarification.

*The following changes have been made to the sections of the Study Protocol below: Added text is **underlined and bold** and deleted text is ~~double crossed out~~. Text not relevant for changes in the sections listed below is represented by […].*

MODIFICATON 1

Description of change:

Inclusion criteria 5 regarding age range of the patients was amended as per recommendation by the IDMC.

- ⇨ **Study Outline, Section 4.1 and 4.1.1:**

Inclusion Criteria 5 was amended as follows:

"≥ 18 **to < 80** years of age""

MODIFICATION 2

Description of change:

Exclusion criteria 10 regarding diabetic neuropathy was amended as per recommendation by the IDMC.

- ⇨ **Study Outline and Section 4.1.1:**

Exclusion Criteria 10 was amended as follows:

"10. Diabetic neuropathy~~, unless having a stable HbA1C in treated diabetic patients not exceeding the required normal values~~"

MODIFICATION 3

Description of the change:

Clarification of Exclusion Criteria 20.

- ⇨ **Study Outline and Section 4.1.1:**

Exclusion Criteria 20 was amended as follows:

"20. History of **severe** hypersensitivity, **e.g.** anaphylaxis or severe systemic response, to immuno-globulin, blood or plasma derived products, or any component of NewGam"

MODIFICATION 4

Description of the change:

Clarification regarding Patient Global Impression of Change.

- ⇨ **Section 3.2:**

The wording regarding the Patients´Global Impression of Change was amended as follows:

"*(i.e., patients ~~who decrease on~~ **whose overall status worsened according to** the Patients' Global Impression of Change[2] (PGIC).*"

MODIFICATION 5

Description of change:

The wording regarding EVA bags was amended as follows:

- **Section 5.3:**

"After transfer and pooling into ~~ethylene vinyl acetate (EVA)~~ **infusion** bags, the medication"

- **Several times in section 5.3, 5.5, 5.6 and 5.8:**

" ~~EVA~~ **infusion** bags"

MODIFICATION 6

Description of change:

The storage time of infusion bags was amended.

- **Section 5.6:**

"The ~~EVA~~ **infusion** bags can then be stored for up to ~~72~~ **24** hours at +2°C to +8°C (36°F to 46°F)."

MODIFICATION 7

Description of change:

The questionnaire Patient Global Impression of Change was listed incorrectly at Visit 1 (Screening Visit).

- **Section 6.1.1:**

The following questionnaire was listed incorrectly and was deleted:

- ~~PGIC scale~~

MODIFICATION 8

Description of change:

No time window for blood sampling is required for this study and therefore was deleted from the table.

- **Section 6.1.5:**

Time point	**Time stated**	**Tolerance**
Interval between visits	3 weeks	± 4 days
~~Blood sampling~~	~~before IMP administration~~	~~≤ 60 minutes~~
Vital signs	before IMP administration	≤ 60 minutes
Vital signs	after IMP administration	≤ 60 minutes

MODIFICATION 9

Description of change:

No time window for blood sampling is required for this study and therefore was deleted from the table.

- **Section 7.3.4:**

Viral marker samples will be taken **at screening**, before the first NewGam infusion ~~at screening~~ at Visit 2 and at the termination visit.

AGREEMENT: THESE SIGNATURES CONSTITUTE APPROVAL OF THIS PROTOCOL AMENDMENT AND PROVIDE THE NECESSARY ASSURANCE THAT THE STUDY WILL BE CONDUCTED ACCORDING TO ALL STIPULATIONS OF PROTOCOL AND AMENDMENTS.

Authorised person for signing the Study Protocol and Protocol Amendments on behalf of the Sponsor and Sponsor's Medical Expert:

[redacted] [redacted] 22.06.18

International Medical Director Signature Date
on behalf of the Sponsor
Octapharma Pharmazeutika Produktionsgesellschaft mbH
Oberlaaerstr. 235, A-1100 Vienna, Austria
Tel: [redacted], Fax: [redacted]

[redacted] [redacted] 22-JUN-2018

Manager Biometrics Signature Date
Octapharma Pharmazeutika Produktionsgesellschaft mbH
Oberlaaerstr. 235, A-1100 Vienna, Austria
Tel: [redacted], Fax: [redacted]

AGREEMENT: THESE SIGNATURES CONSTITUTE APPROVAL OF THIS PROTOCOL AMENDMENT AND PROVIDE THE NECESSARY ASSURANCE THAT THE STUDY WILL BE CONDUCTED ACCORDING TO ALL STIPULATIONS OF PROTOCOL AND AMENDMENTS.

Authorised person for signing the Study Protocol and Protocol Amendments on behalf of the Sponsor and Sponsor's Medical Expert:

Signature of the Coordinating Investigator

[redacted] (Neuro[redacted]) June 24/2018
Date

University of Toronto
Toronto General Hospital / UHN
200 Elizabeth Street, 5ES-306
Toronto, Ontario M5G 2C4

octapharma

CLINICAL STUDY PROTOCOL

"PROSPECTIVE, DOUBLE-BLIND, RANDOMIZED, MULTICENTER PHASE III STUDY EVALUATING EFFICACY AND SAFETY OF THREE DIFFERENT DOSAGES OF NEWGAM IN PATIENTS WITH CHRONIC INFLAMMATORY DEMYELINATING POLY(RADICULO)NEUROPATHY"

(ProCID study)

Investigational Product:	Immune Globulin Intravenous, Human 10% (working title "NewGam")
Indication:	Chronic Inflammatory Demyelinating Poly(radiculo)-neuropathy (CIDP)
Study Design:	Prospective, parallel group, double-blind, randomized, multicenter phase III efficacy study
Sponsor:	Octapharma Pharmazeutika Produktionsges.m.b.H. Oberlaaer Str. 235, 1100 Vienna, Austria
Study Number:	NGAM-08
EudraCT and/or IND Number:	2015-005443-14 BB-IND #14096
Development Phase:	Phase III
Planned Clinical Start:	Quarter 1 2017
Planned Clinical End:	Quarter 4 2019
Date of Protocol:	08 June 2018
Version:	04
Co-ordinating Investigator:	[redacted], University of Toronto Toronto General Hospital / UHN 200 Elizabeth Street, 5ES-306 Toronto, Ontario M5G 2C4

STUDY OUTLINE

<table>
<tr><td colspan="2">Name of Sponsor/Company:
Octapharma Pharmazeutika Produktionsges.m.b.H., 1100 Vienna, AT</td></tr>
<tr><td>Name of Investigational Product:
NewGam</td><td>Protocol Identification Code:
NGAM-08 (ProCID)</td></tr>
<tr><td>Name of Active Ingredient:
Immunoglobulin Intravenous (human) 10%</td><td>Date of Final Protocol:
08-June-2018</td></tr>
<tr><td colspan="2">Title of Study:
Prospective, Double-blind, Randomized, Multicenter Phase III Study Evaluating Efficacy and Safety of Three Different Dosages of NewGam in Patients With Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy (“ProCID trial”)</td></tr>
<tr><td colspan="2">Indication:
Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy (CIDP)</td></tr>
<tr><td colspan="2">Number of Study Centre(s):
Approximately 45 selected study sites worldwide with focus on Eastern European countries.</td></tr>
<tr><td>Study Duration: Q1 2017 to Q4 2019</td><td>Development Phase: III</td></tr>
<tr><td colspan="2">Objectives:
Primary:
• To provide confirmatory data on the effect of 1.0 g/kg NewGam every three weeks in patients with active CIDP based on the percentage of responders at Week 24, which should corroborate the existing evidence on efficacy of IGIV in CIDP as known from published literature.
Secondary:
• To assess the effect of 0.5 g/kg and 2.0 g/kg NewGam every three weeks in patients with active CIDP based on the percentage of responders at Week 24 compared to patients on 1.0 g/kg NewGam every three weeks
• To evaluate the safety of NewGam administration using various dosages in patients with CIDP
• To further evaluate the beneficial effect of three NewGam dosages in patients with CIDP by assessing different parameters/scores/scales
Exploratory:
• To assess the primary and secondary objectives at three weeks after having provided rescue medication (if applicable)
• To further evaluate the beneficial effect of NewGam administration in patients with CIDP by additional assessments/scores including quality of life (QoL) measures</td></tr>
<tr><td colspan="2">Study Design:
Prospective, parallel group, double-blind, randomized, multicenter phase III efficacy study</td></tr>
<tr><td colspan="2"></td></tr>
</table>

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H., 1100 Vienna, AT	
Name of Investigational Product: NewGam	Protocol Identification Code: NGAM-08 (ProCID)
Name of Active Ingredient: Immunoglobulin Intravenous (human) 10%	Date of Final Protocol: 08-June-2018

Number of Patients:

A minimum of 140 adult patients of both genders with definite or probable CIDP according to the EFNS/PNS Criteria are to be enrolled. Patients will be randomized 1:2:1 to receive either 0.5 g/kg or 1.0 g/kg or 2.0 g/kg NewGam for seven maintenance infusions at 3-week intervals during the Dose-evaluation Phase.

Patient Selection Criteria:

Inclusion Criteria:

1. Patients with diagnosis of definite or probable CIDP according to the EFNS/PNS Guideline 2010; including patients with Multifocal Acquired Demyelinating Sensory And Motor Neuropathy (MADSAM) or pure motor CIDP
2. Patients currently depending on treatment with immunoglobulins or corticosteroids
3. Patients with active disease, i.e. not being in remission, who are progressive or relapsing prior to trial start or during the Wash-out Phase
4. Weakness of at least 2 limbs
5. ≥ 18 to < 80 years of age
6. Adjusted INCAT disability score between 2 and 9 (with a score of 2 coming exclusively from leg disability)
7. Voluntarily given, fully informed written consent obtained from patient before any study-related procedures are conducted

Exclusion Criteria:

1. Unifocal forms of CIDP
2. Pure sensory CIDP
3. MMN with conduction block
4. Patients who previously failed immunoglobulin therapy
5. Treatment with immunomodulatory/suppressive agents (cyclosporin, methotrexate, mitoxantrone, mycophenolate mofetil or azathioprine) during the six months prior to baseline visit
6. Patients on or treated with rituximab, alemtuzumab, cyclophosphamide, or other intensive chemotherapeutic regimens, previous lymphoid irradiation or stem cell transplantation during the 12 months prior to baseline visit
7. Respiratory impairment requiring mechanical ventilation
8. Myelopathy or evidence of central nervous system demyelination or significant persisting neurological deficits from stroke, or central nervous system (CNS) trauma
9. Clinical evidence of peripheral neuropathy from another cause such as
    a. connective tissue disease or systemic lupus erythematosus (SLE)
    b. HIV infection, hepatitis, Lyme disease

c. cancer (with the exception of basal cell skin cancer)

d. IgM paraproteinemia with anti-myelin associated glycoprotein antibodies

10. Diabetic neuropathy
11. Cardiac insufficiency (New York Heart Association [NYHA] III/IV), cardiomyopathy, significant cardiac dysrhythmia requiring treatment, unstable or advanced ischemic heart disease
12. Severe liver disease (ALAT 3x > normal value)
13. Severe kidney disease (creatinine 1.5x > normal value)
14. Hepatitis B, hepatitis C or HIV infection
15. Thromboembolic events: patients with a history of deep vein thrombosis (DVT) within the last year prior to baseline visit or pulmonary embolism ever; patients with susceptibility to embolism or DVT
16. Body mass index (BMI) $\geq$40 kg/m^2
17. Patients with uncompensated hypothyroidism (abnormally high Thyroid-Stimulating Hormone [TSH] and abnormally low Thyroxine [T4]) or known vitamin B12 deficiency if they don't receive adequate substitution therapy
18. Medical conditions whose symptoms and effects could alter protein catabolism and/or IgG utilization (e.g. protein-losing enteropathies, nephrotic syndrome)
19. Known IgA deficiency with antibodies to IgA
20. History of severe hypersensitivity, e.g. anaphylaxis or severe systemic response, to immuno-globulin, blood or plasma derived products, or any component of NewGam
21. Known blood hyperviscosity, or other hypercoagulable states
22. Use of other blood or plasma-derived products within three months prior to Visit 2
23. Patients with a past or present history of drug abuse or alcohol abuse within the preceding five years prior to baseline visit
24. Patients unable or unwilling to understand or comply with the study protocol
25. Participation in another interventional clinical study with IMP treatment currently or during the three months prior to Visit 2
26. Women who are breast feeding, pregnant, or planning to become pregnant, or are unwilling to use an effective birth control method (such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomized partner) while on study

Test Product, Dose, Mode of Administration, and Batch Number(s):

NewGam is a 10% human normal immunoglobulin, solvent/detergent (S/D) treated solution for intravenous infusion. To be stored and transported light-protected at + 2°C to + 8°C

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H., 1100 Vienna, AT	
Name of Investigational Product: NewGam	Protocol Identification Code: NGAM-08 (ProCID)
Name of Active Ingredient: Immunoglobulin Intravenous (human) 10%	Date of Final Protocol: 08-June-2018

(36°F to 46°F) and brought to room or body temperature before use. NewGam must not be frozen.
During the Dose-evaluation Phase, all patients will receive a loading dose of 2.0 g/kg NewGam followed by seven times maintenance dosage of 0.5, 1.0 or 2.0 g/kg they were randomized to (given at 3-week intervals).

Duration of Treatment:

The duration of the entire study for each patient will be between >9 and up to 39 weeks and consists of the following segments: approximately 3 weeks for Screening, up to 12 weeks for the Wash-out Phase and 24 weeks for the Dose-evaluation Phase (for patients who deteriorate at the end of the 12-week Wash-out Phase and who are continued responders during the Dose-evaluation Phase). The minimal duration could be >9 weeks after Screening (for patients in the 2.0 g/kg arm deteriorating after being only a few days in the Wash-out Phase and being stable until Week 6 or deteriorating by then as they will not receive rescue treatment but drop-out). Thus, the length of the Dose-evaluation Phase can vary between 6 and 24 weeks, while the length of the Wash-out Phase can vary between >0 and 12 weeks.

Reference Therapy, Dose, Mode of Administration, and Batch Number(s):

N/A

Study Outcome Parameters (Primary, Secondary and Exploratory Endpoints):

Efficacy:

Primary

- Proportion of responders in the 1.0 g/kg NewGam arm at Week 24 (Termination Visit) relative to baseline (Week 0). A responder being defined as a patient with a decrease of at least 1 point on the adjusted INCAT disability score (a scale from 0 to 10, from healthy to unable to make any purposeful movements with arms and/or legs)

Secondary

- Proportion of responders in the 0.5 g/kg and 2.0 g/kg NewGam arms at Week 24 relative to baseline compared to the 1.0 g/kg arm, based on the adjusted INCAT disability score
- Proportion of responders in the 0.5 g/kg and 2.0 g/kg NewGam arms at Week 24 relative to baseline at Week 0 compared to the 1.0 g/kg arm, based on the grip strength (Martin Vigorimeter) using the previously published minimum clinically important difference (MCID) cut-off of 8 kPa
- Proportion of responders in the 0.5 g/kg and 2.0 g/kg NewGam arms at Week 24 relative to baseline at Week 0 compared to the 1.0 g/kg arm, based on the I-RODS scores using the MCID concept related to the varying standard errors (MCID-SE) as recently demonstrated.

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H., 1100 Vienna, AT	
Name of Investigational Product: NewGam	Protocol Identification Code: NGAM-08 (ProCID)
Name of Active Ingredient: Immunoglobulin Intravenous (human) 10%	Date of Final Protocol: 08-June-2018

- Time to first confirmed worsening on the adjusted INCAT disability scale by at least 1 point from the value at baseline (Week 0)
- Mean change from baseline (Week 0) to Termination Visit in
  - grip strength of both hands (assessed by Martin Vigorimeter)
  - Inflammatory Rasch-built overall disability sum score (I-RODS using the concept of MCID-SE as recently reported; Appendix 1) and number of improvers
  - sum of the distal evoked amplitude of 4 right sided and 4 left sided motor nerves (peroneal, tibial, ulnar and median)
  - Pain Intensity Numeric Rating Scale (PI-NRS)
- Time to first confirmed worsening on the I-RODS scale
- Time to 1 point decrease (improvement of disability) in adjusted INCAT disability score
- Time to decrease in I-RODS scores

Exploratory

- Mean change from baseline (Week 0) to Termination Visit in:
  - modified Fatigue Severity Scale (FSS; 7-item scale from 0-21 points; see Appendix 2)
  - number of improvers by at least 4 points in the MRC sum score (according to the universal rule of minimal clinical important difference)
  - SF-36 Health Survey physical composite score (PCS), mental composite score (MCS) and their 8 health domains (see Appendix 3)
  - additional NCS analyses (e.g. individual nerve analysis)
- Time to decrease in MRC sum score to or below baseline value after temporary improvement (increase)

Safety (throughout the entire Wash-out and Dose-evaluation Phases):

- Occurrence of all adverse events (AEs)
- Short term tolerance parameters including vital signs
- Physical/neurological examination
- Laboratory parameters (hematology and clinical chemistry) and tests for viral safety

Summary of Study Procedures and Statistical Analysis Plan:

Study Procedures:

Disability will be assessed by the adjusted INCAT score and the I-RODS at each visit.
Pain will be assessed by the PI-NRS at each visit.
Impairment will be assessed by the grip strength at each visit, MRC sum score and the modified FSS (Fatigue Scale) at Screening, Week 0, Week 12 and Termination Visit.
Quality of life (SF-36) will be measured at Screening, Week 0, Week 12, and at Termination Visit.

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H., 1100 Vienna, AT	
Name of Investigational Product: NewGam	Protocol Identification Code: NGAM-08 (ProCID)
Name of Active Ingredient: Immunoglobulin Intravenous (human) 10%	Date of Final Protocol: 08-June-2018

Electrophysiological measurements (nerve conduction studies) will be done at Screening, Week 0, Week 12, and at Termination Visit.
Adverse events (AEs) and serious adverse events (SAEs) temporally associated with administration of IMP or saline solution will be collected throughout the entire study (starting with the Wash-out Phase for patients on IGIV) as well as pregnancies, drug overdose, interaction, medication error, lack of efficacy, and post-study SAEs.
Laboratory safety tests (hematology and clinical chemistry) will be determined from blood samples taken at each visit. IgG level will be determined at each visit but Screening; viral markers will be determined at Screening, Week 0, and Termination Visit. Urinalysis will be performed at Screening and Termination Visit.

Statistical Analysis:

The primary endpoint will be evaluated by comparing the lower limit of the 95% Wilson-Score confidence interval for the percentage of responders on the adjusted INCAT disability scale in the 1.0 g/kg dose group with a predefined threshold of 42%.
The response rates in the alternative dose groups will be compared descriptively to the 1.0 g/kg treatment group, and the confidence intervals for the differences will be presented. In addition, an exploratory logistic regression, that includes the pre-treatment as well as the dose group as predictor variables, will be conducted. The same model will also be used for secondary response variables (based on grip strength, or I-RODS scores).
All other endpoints will be analyzed and presented in full detail by means of descriptive statistics, including summary and frequency tables, confidence intervals and graphs.
A formal statistical analysis plan describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to unblinding and the start of the statistical analysis.
The analysis of safety will be based on the safety set which includes all patients who received any study drug. The primary evaluation of efficacy endpoints will be based on the Full Analysis Set (intention-to-treat analysis).

The study assessments and scheduled time points are summarized in the Flowchart overleaf:

FLOWCHART

	Screening	Wash-out Phase[1]	Dose-evaluation Phase[2]								
	Visit 1 Week -15	**Week -12 to 0**	**Visit 2 Week 0**	**Visit 3 Week 3**	**Visit 4 Week 6**	**Visit 5 Week 9**	**Visit 6 Week 12**	**Visit 7 Week 15**	**Visit 8 Week 18**	**Visit 9 Week 21**	**Termination visit Week 24**
Informed consent	X										
Medical history	X										
In-/Exclusion criteria	X		X								
Randomization/Enrollment			X								
Concomitant medication		X[10]	X	X	X	X	X	X	X	X	X
Adverse events		X[10]	X	X	X	X	X	X	X	X	X
Physical/neurological examination	X		X				X				X
ECG	X										
Clinical chemistry[3]; Hematology[4]	X		X	X	X	X	X	X	X	X	X
Serum IgG[5]			X	X	X	X	X	X	X	X	X
Urinalysis[6]	X										X
Pregnancy test[11]	X										
Viral marker[7]	X		X								X
PGIC scale			X								
Adjusted INCAT score; I-RODS score, PI-NRS	X		X	X	X	X	X	X	X	X	X
Grip strength	X		X	X	X	X	X	X	X	X	X
MRC sum score	X		X				X				X
Modified FSS	X		X				X				X
Nerve Conduction Studies	X		X				X				X
SF-36 Health Survey	X		X				X				X
Vital signs[8]; Weight	X		X	X	X	X	X	X	X	X	
Study drug infusion			X[9]	X	X, [X[12,13]]	X, [X[12,13]]	X, [X[12]]	X, [X[12]]	X, [X[12]]	X, [X[12]]	

[1] May last up to 12 weeks (until deterioration): Selection of active patients requiring treatment after dosage reduction
[2] Infusion visits take 2 days
[3] Clinical chemistry: Na+, K+, glucose, ALAT/ALT/GPT, ASAT/AST/GOT, LDH, total bilirubin, BUN (blood urea nitrogen) or urea, creatinine, albumin, serum IgG
[4] Hematology: Hematocrit, hemoglobin, CBC with differential
[5] Serum IgG to be determined prior to infusion
[6] Urinalysis: Protein, pH, glucose, ketones, leukocytes, hemoglobin and blood
[7] Viral Markers: HIV, HBV and HCV
[8] Vital signs: Pulse, blood pressure, respiratory rate and temperature
[9] Loading dose of 2.0 g/kg NewGam
[10] Only for patients on immunoglobulin treatment visiting the site for infusions
[11] Pregnancy test should only be done in women of childbearing potential (WOCBP). Pregnancy test is mandatory at Visit 1. At Visit 2, 3, 4, 5, 6, 7, 8, 9 and Termination Visit a pregnancy test should be performed only if required by local regulations.
[12] Two consecutive 3-weekly infusions of 2.0 g/kg NewGam only for patients on 0.5 or 1.0 g/kg NewGam who deteriorate after Week 3 and until Week 18
[13] Two consecutive 3-weekly infusions of 2.0 g/kg NewGam only for patients on 0.5 or 1.0 g/kg NewGam being stable by Week 6

PROTOCOL SIGNATURES

Signature of the Sponsor's Representative

This study is intended to be conducted in compliance with the protocol, ICH-GCP E6 and the applicable regulatory requirements.

[redacted] [redacted] 15.06.2018

International Medical Director — Signature — Date
on behalf of the Sponsor
Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Str. 235
1100 Vienna
Austria

Signature of the Manager Biometrics

This study is intended to be conducted in compliance with the protocol, ICH-GCP E6 and the applicable regulatory requirements.

[redacted] [redacted] [redacted] 15-JUN-2018

Manager Biometrics | Signature | Date

Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Str. 235
1100 Vienna
Austria

Signature of the Coordinating Investigator

This study is intended to be conducted in compliance with the protocol, ICH-GCP E6 and the applicable regulatory requirements.

[redacted] [redacted] June 24/2018

[redacted] Signature Date

University of Toronto
Toronto General Hospital / UHN
200 Elizabeth Street, 5ES-306
Toronto, Ontario M5G 2C4

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADR(s)	Adverse Drug Reaction(s)
AE(s)	Adverse Event(s)
ALAT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ASAT	Aspartate Aminotransferase
CBC	Complete Blood Count
CIDP	Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy
CMAP	Compound Muscle Action Potential
CRO	Contract Research Organization
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
e-CRF(s)	electronic Case Report Form(s)
EDC	Electronic Data Capture
EFNS	European Federation of Neurological Societies
EMG	Electromyograph
EVA	Ethylene Vinyl Acetate
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSS	Fatigue Severity Scale
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgA/G/M	Immunoglobulin A/G/M
IGIV	Immunoglobulin Intravenous
IMP	Investigational Medicinal Product
INCAT	Inflammatory Neuropathy Cause and Treatment
IND	Investigational New Drug
IRB	Institutional Review Board
I-RODS	Inflammatory Rasch-built Overall Disability Scale
ITT	Intention-To-Treat
IWRS	Interactive Web Recognition System
K	Kalium (Potassium)
LDH	Lactate Dehydrogenase
MADSAM	Multifocal Acquired Demyelinating Sensory And Motor Neuropathy
MedDRA	Medical Dictionary for Regulatory Activities
MMN	Multifocal Motor Neuropathy
MRC	Medical Research Council
Na	Natrium (Sodium)
NCS	Nerve Conduction Studies
PEX	Plasma Exchange
PI-NRS	Pain Intensity Numeric Rating Scale
PNS	Peripheral Nerve Society
PP	Per-Protocol
QoL	Quality of Life
S/D	Solvent/Detergent

SAE(s)	Serious Adverse Event(s)
SF-36	Short Form 36 Items Health Status
SOP(s)	Standard Operating Procedure(s)
TEAE(s)	Treatment Emergent Adverse Event(s)
WOCBP	Women of Childbearing Potential

1 INTRODUCTION

Since more than five decades immunoglobulins have been used to provide antibodies for the prevention of viral and bacterial diseases (replacement therapy) in immunocompromised patients. Within the last 25 years IGIV has been proven to be useful in a wide variety of clinical conditions other than replacement therapy of immunocompromised patients, in which IGIV exhibits an immunomodulatory effect. These include Idiopathic Thrombocytopenic Purpura (ITP), in children and adults at high risk of bleeding or prior to surgery to correct the platelet count, Kawasaki disease and Guillain-Barré syndrome (GBS). More recently, single IGIV brands have also been licensed for Multifocal Motor Neuropathy (MMN) and Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy (CIDP). Experimental off-label use of IGIV mostly in other neurological and dermatological indications is widespread.

NewGam is a newly developed 10% human normal immunoglobulin solution ready for intravenous administration (IGIV) developed by Octapharma. It is supplied as a ready to use liquid formulation.

The NewGam manufacturing process achieves a significant viral reduction through a combination of two dedicated manufacturing process steps: solvent/detergent (S/D) treatment and nanofiltration (20 nm). Based on the combination of these two steps, NewGam complies with the latest international consensus on best practices for viral safety. The Source Q chromatography (ion-exchange chromatography) step in the NewGam process also contributes significantly to the viral safety of NewGam. The efficacy of the virus inactivation procedures has been extensively validated according to relevant international guidelines in place. Further information can be found in the current Investigator's Brochure. ADRs reported for NewGam were similar in type and intensity to those reported with other IGIV preparations. NewGam is currently under review by the FDA and EMA.

CIDP is a distinct acquired chronic progressive or relapsing and spontaneously remitting neuropathy characterized by progressive weakness, reduced or absent tendon reflexes and impaired sensation over more than a 2 months period. The weakness and sensory impairment are typically symmetrical and the weakness may be proximal or distal.[1] Approximately 4% to 17% of CIDP patients die from the disease usually as a consequence of respiratory failure or pulmonary embolism, whereas 50% require persistent treatment, and 13% are permanently disabled.[2]

CIDP is divided into typical and atypical forms [3], and into those un-associated or associated with systemic diseases. These forms can be further divided into subgroups with symmetrical (classical), asymmetrical (MADSAM or Lewis-Sumner syndrome), pure motor, pure sensory, and mixed forms (modified according to [4]).

CIDP is generally considered to be an autoimmune disease caused by the activation of autoimmune mechanisms although the triggering event(s) are unknown.[5]

CIDP can be diagnosed throughout life, from early childhood (<1 year) to old age (>80 years). Nevertheless, on average the onset of disease is around the end of the fifth decade of life.[6] CIDP seems to affect more men than women.[7] Its prevalence given in literature has a range from 1.0 to 8.9 per 100,000, thus qualifying it as orphan disease.[8]

Various criteria for diagnosing CIDP for research studies have been published [9-11] but the most established and widely used are the European Federation of Neurological Sciences and Peripheral Nerve Society (EFNS/PNS) criteria.[12] Electrodiagnostic tests are mandatory for achieving a correct diagnosis.

1.1 Rationale for Conducting the Study

In addition to its use for the treatment of primary and secondary immunodeficiencies, IGIV is increasingly used for immunomodulating therapy in the treatment of patients with a variety of autoimmune and inflammatory neurological disorders.

IGIV is currently used as a standard treatment in patients with chronic inflammatory demyelinating neuropathies, for initiation therapy as well as for long-term treatment. However, clinical studies published so far focused on a loading dose of 2.0 g/kg IGIV and/or a standard maintenance dosage of 1.0 g/kg IGIV, without investigating different dosing response options. The ProCID study thus aims to confirm the published clinical results obtained with the 1.0 g/kg standard dose, and will in addition evaluate one higher and one lower dose, with the aim to offer CIDP patients a more adequately dosed and effective treatment policy. The safety and tolerability of the various dosages will also be investigated, since many patients need lifelong treatment.

IGIV can be used for therapy of all different types of CIDP. Corticosteroids may worsen pure motor CIDP in which IGIV is recognized as the first-line treatment.[13,14]

Corticosteroids were the first treatment introduced for CIDP.[15] Several non-randomized studies and one randomized study concluded that corticosteroids have a beneficial effect in CIDP.[16] The advantages of corticosteroids are their availability and low initial costs. Unfortunately, the doses needed are often large, treatment has to be prolonged for months or years and cushingoid and various other side effects are very common.[17]

Plasma exchange (PEX) has been shown to be beneficial in two randomized trials.[18] The usefulness of PEX as a treatment for CIDP is limited by its inconvenience, requirement for hospital attendance and specially trained staff, and the occurrence of AEs. Complications, usually from the use of a central venous catheter, have been reported.[19] Therefore, PEX is now usually only considered as a third line therapy, if corticosteroids and IGIV do not prove to be effective.[20]

Some patients do not respond or become refractory or intolerant to the above described conventional treatments. Over the years, small non-randomized studies have shown possible beneficial effects of various immunosuppressive agents. A Cochrane review concluded that there is insufficient evidence at present to decide whether these immunosuppressive drugs are beneficial in CIDP or may even cause demyelinating disease. It is difficult to prove beneficial effects of these newer treatments since they only have been administered to small groups of patients who are refractory to other treatments, and often in combination with other treatments. Various treatments for CIDP are described such as azathioprine, cyclosporine, cyclophosphamide, interferons, methotrexate, mycophenolate mofetil, rituximab and etanercept.[21]

Over the last 20 years, high-dose IGIV has become an effective and safe therapeutic option for CIDP in adults and the preferred treatment in children due to the ease of its application.[22,23] The placebo-controlled ICE study in 117 CIDP patients confirmed this short-term benefit and showed for the first time sustained benefit from maintenance treatment, leading to the approval for CIDP by various authorities.[24] Other IGIV brands have meanwhile also been licensed in European countries.

The EFNS/PNS guidelines recommend that IGIV or corticosteroids should be considered for induction of treatment in CIDP in the presence of troublesome symptoms.[12] The authors recommend IGIV as an initial treatment in pure motor CIDP and PEX only in case of ineffectiveness of corticosteroids and IGIV. However, to date no study has been performed to systematically compare different IGIV dosage options in patients with CIDP.

The rationale for conducting this study is to investigate the efficacy, safety and optimal dosage of NewGam in CIDP patients, and to confirm the efficacy results that were observed in published clinical studies in order to apply for market authorization of NewGam worldwide, including the US and the EU. The study will furthermore systematically investigate different dosages of IGIV in an uncontrolled trial.

1.2 Benefit-Risk Statement

Currently, the optimal dosage of IGIV for treatment of CIDP patients is not known and has never been systematically examined. Historically, a dose of 1.0 g/kg has been used in the largest and longest placebo-controlled study that led to approval of the first IGIV for CIDP.[24] Later studies usually relied to this dosage scheme.[25] However, there may be additional benefits to individuals and society from this trial (ProCID: "**Pro**gress in **CID**P") in which the lack of dose response data in the literature will be addressed more extensively. There might be the possible benefit of a potential finding of this trial that a lower dose is beneficial for most patients resulting in less risk of adverse treatment effects for patients and lower costs for healthcare systems. On the other hand, it could also indicate that a higher dose might increase the number of patients who benefit from IGIV treatment, thus, reducing the number of non-responders.

The risks of IGIV administration are well documented. In general, the incidence of AEs associated with IGIV tends to increase with the rate of infusion, and thus the recommended dosage, infusion rates, and monitoring procedures should be adhered to. Patients naïve to IGIV are at higher risk compared to those who are well maintained and on regular therapy.

Patients with pre-existing risk factors for thrombotic events (such as advanced age, obesity, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilization, severely hypovolemic patients, patients with diseases which increase blood viscosity) may be at risk.

When medicinal products prepared from human blood or plasma are given to a patient, the transmission of infectious agents cannot be totally excluded. This applies also to hitherto unknown pathogens. However, specific virus inactivation procedures are implemented in the manufacturing process of NewGam which are described in detail in the Investigator's Brochure.

The safety profile of NewGam is well characterized. For NewGam, the same type of adverse reactions has been seen as with other IGIV products. No new or unknown safety problems are expected to emerge which are not already described in the Investigator's Brochure.

In terms of efficacy, it can reasonably be assumed that NewGam exhibits the same effectiveness as other IGIV brands.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To provide confirmatory data on the effect of 1.0 g/kg NewGam every three weeks in patients with active CIDP based on the percentage of responders at Week 24, which should corroborate the existing evidence on efficacy of IGIV in CIDP as known from published literature.

2.2 Secondary Objectives

- To assess the effect of 0.5 g/kg and 2.0 g/kg NewGam every three weeks in patients with active CIDP based on the percentage of responders at Week 24 compared to patients on 1.0 g/kg NewGam every three weeks
- To evaluate the safety of NewGam administration using various dosages in patients with CIDP
- To further evaluate the beneficial effect of three NewGam dosages in patients with CIDP by assessing different parameters/scores/scales

2.3 Exploratory Objectives

- To assess the primary and secondary objectives at three weeks after having provided rescue medication (if applicable)
- To further evaluate the beneficial effect of NewGam administration in patients with CIDP by additional assessments/scores, including quality of life (QoL) measures

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

- Proportion of responders in the 1.0 g/kg NewGam arm at Week 24 (Termination Visit) relative to baseline (Week 0). A responder being defined as a patient with a decrease of at least 1 point on the adjusted[1] INCAT disability score (a scale from 0 to 10, from healthy to unable to make any purposeful movements with arms and/or legs)

3.1.2 Secondary Endpoints

Efficacy:

- Proportion of responders in the 0.5 g/kg and 2.0 g/kg NewGam arms at Week 24 relative to baseline at Week 0 compared to the 1.0 g/kg arm, based on the adjusted INCAT disability score
- Proportion of responders in the 0.5 g/kg and 2.0 g/kg NewGam arms at Week 24 relative to baseline at Week 0 compared to the 1.0 g/kg arm, based on the grip strength (Martin Vigorimeter) using the previously published minimum clinically important difference (MCID) cut-off of 8 kPa.[26]
- Proportion of responders in the 0.5 g/kg and 2.0 g/kg NewGam arms at Week 24 relative to baseline at Week 0 compared to the 1.0 g/kg arm, based on the I-RODS scores using the MCID concept related to the varying standard errors (MCID-SE) as recently demonstrated.[27]
- Time to first confirmed worsening on the adjusted INCAT disability scale by at least 1 point from the value at Baseline
- Mean change from Baseline (Week 0) to Termination Visit in
  - grip strength of both hands (assessed by Martin Vigorimeter) Inflammatory Rasch-built Overall Disability Sum Score (I-RODS using the concept of MCID-SE as recently reported; Appendix 1) and number of improvers
  - sum of the distal evoked amplitude of 4 right sided and 4 left sided motor nerves (peroneal, tibial, ulnar and median)
  - Pain Intensity Numeric Rating Scale (PI-NRS)
- Time to first confirmed worsening on the I-RODS scale
- Time to 1 point decrease (improvement of disability) in adjusted INCAT disability score
- Time to decrease in I-RODS scores

[1] The adjusted INCAT score is identical to the original INCAT disability score with the exception that upper extremity score changes from 0 (normal) to 1 (minor symptoms) or from 1 to 0 are excluded in determining the adjusted score, given that these changes are not considered clinically meaningful.

Safety:

Throughout the entire 24-week Dose-evaluation Phase:

- Occurrence of all adverse events (AEs)
- Short term tolerance parameters including vital signs
- Physical/neurological examination
- Laboratory parameters (hematology and clinical chemistry) and tests for viral safety
- Standard ECG (only at screening visit)

3.1.3 Exploratory Endpoints

Efficacy:

Mean change from baseline (Week 0) to Termination Visit in:

- modified Fatigue Severity Scale (FSS; 7-item scale from 0-21 points; see Appendix 2)
- number of improvers by at least 4 points in the MRC sum score (according to the universal rule of MCID [28] at Week 12 or at time of rescue NewGam infusion [26]
- SF-36 Health Survey physical composite score (PCS), mental composite score (MCS) and their 8 health domains (see Appendix 3)
- additional NCS analyses (see Section 7.2.3.4)

Time to decrease in MRC sum score [29] to or below baseline value after temporary improvement (increase)

3.2 Overall Study Design and Plan

ProCID study is planned to start in Q1 2017 and be completed by Q4 2019, corresponding to a total duration of 30 months. The enrollment period is projected to last approximately 20 months.

ProCID study will be a prospective, parallel group, double-blind, randomized, multicenter, Phase 3 study in a minimum of 140 adult patients of both genders with definite or probable CIDP according to the EFNS/PNS Criteria.[12] As CIDP is a rare disease, about 45 sites are projected to participate worldwide, with emphasis on Eastern European countries, and projecting about 3-4 patients for each study site.

Data from the 1.0 g/kg arms in the ICE [24] and PRIMA [25] trials will be used as historical controls.

Patients will be screened, and if eligible for this trial, their current medication will be reduced in a predefined standard manner (immunoglobulins: 25% at each sequential infusion or corticosteroids as per the discretion of the Investigator at a rate to expect study entry within 6-12 weeks) for a maximum of 12 weeks. Only patients who deteriorated in this phase, i.e. active patients who demonstrate needing treatment (i.e., patients whose overall status worsened according to the Patients' Global Impression of Change[2] (PGIC) scale PLUS are either increasing on the INCAT by at least 1 point OR decreasing at least 8 kPa on grip strength in

[2] PGIC, a 7-point scale on which patients rate change in overall status since start of Wash-out Phase (1–3 = improved, 4 = no change, 5–7 = worsened).

one hand OR at least reaching the I-RODS MCID-SE cut-off of -1.96 or less), will be randomized 1:2:1 between three different maintenance dosages of 0.5 g/kg, 1.0 g/kg or 2.0 g/kg NewGam in the Dose-evaluation Phase.

Patients not deteriorating in the 12-week Wash-out Phase will not be enrolled into the ProCID study as they are not having active disease. Their treating physician will decide when and which treatment will be started in these patients as part of the health system's standard of care foreseen for CIDP patients.

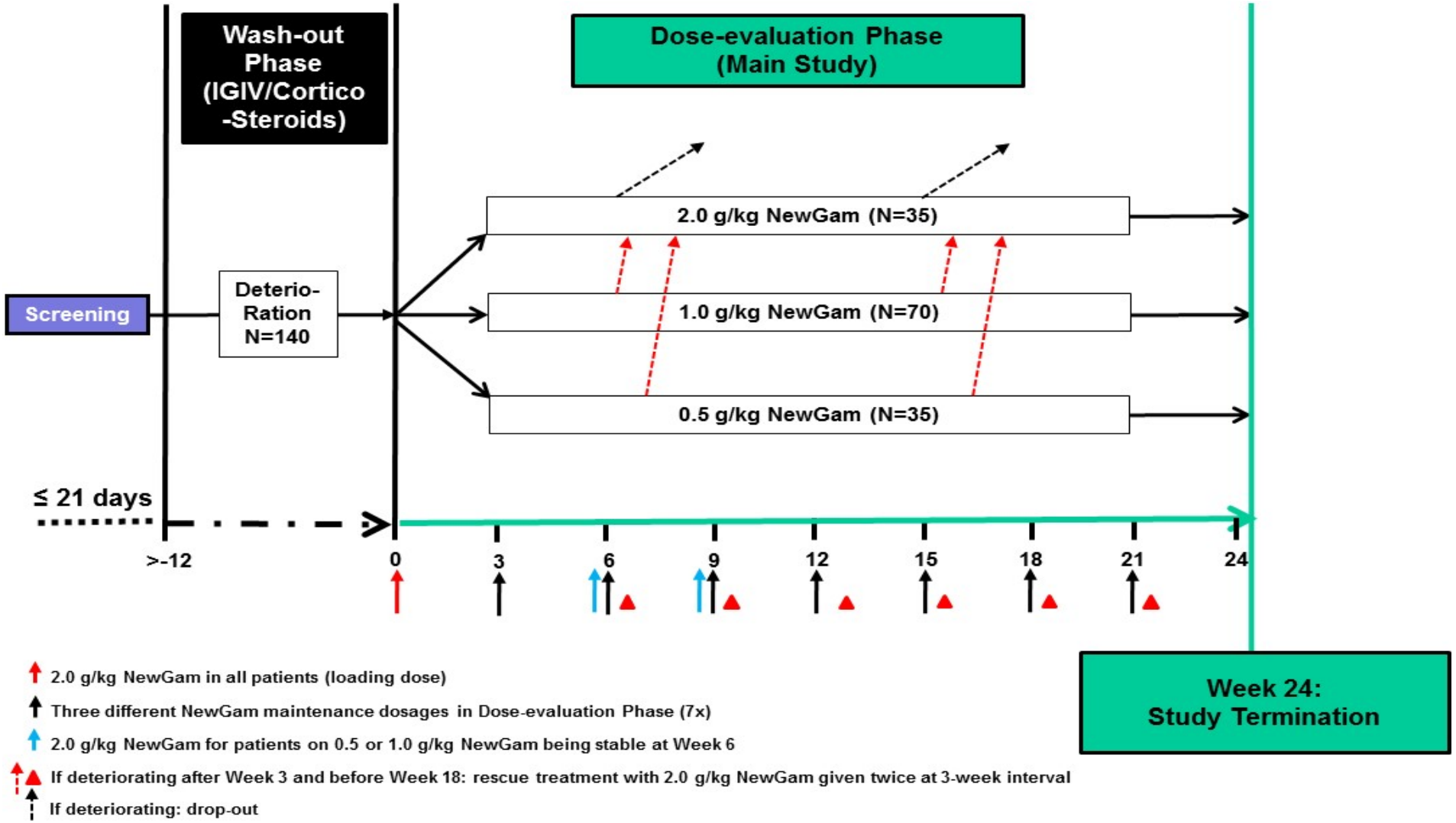
During the 24-week Dose-evaluation Phase all patients will first receive an initial loading dose of 2.0 g/kg NewGam, followed by 7 maintenance dosages of 0.5 g/kg, 1.0 g/kg or 2.0 g/kg NewGam every 3 weeks (± 4 days) as they were randomized to. Two different maintenance dosages of NewGam (a higher one of 2.0 g/kg and a lower one of 0.5 g/kg) applied in the Dose-evaluation Phase will be compared with the standard dosing scheme of 1.0 g/kg every 3 weeks regarding efficacy and safety.

Due to the opportunity to receive 2.0 g/kg NewGam twice as a rescue medication and to receive standard or higher IGIV doses, it is not expected that many patients drop out. Thus, patients dropping out will not be replaced in general, but are included in the sample size calculations.

The end of the study is defined as the last visit of the last patient participating in the study.

The graph overleaf shows the study design.

Graph 3.1: Scheme of Study Design



3.3 Discussion of Study Design and Choice of Control Group(s)

3.3.1 Study Design

The design of this prospective, parallel group, randomized, double-blind multicenter study with three maintenance dosage groups in the Dose-evaluation Phase is appropriate to verify the clinical efficacy observed in published clinical studies, and to evaluate whether different dosages of NewGam could cause an effect in patients with definite or probable CIDP and whether there will be differences in efficacy compared to CIDP patients from the ICE [24] and PRIMA [25] studies. The study design includes all major scientific, state-of-the-art interventions with respect to assessment of the safety and efficacy of IGIV administration in CIDP patients.

Previously, a meta-analysis of five double-blind randomized clinical trials with altogether 235 patients has shown that infusing 2.0 g/kg IGIV once produces a significant improvement in disability lasting 2-6 weeks.[30-34] In the ICE trial [24] it was demonstrated that a dosage of 1.0 g/kg IGIV administered at 3-week intervals (after a loading dose of 2.0 g/kg IGIV) was significantly superior to placebo also as long-term treatment. For maintenance therapy, a dosage of 0.4–1.0 g/kg IGIV is often administered at intervals varying from 2-8 weeks. Therefore, this ProCID study intends to compare three different, commonly used IGIV dosages: 0.5 g/kg (half of the standard maintenance dose), 1.0 g/kg (standard maintenance dose) or 2.0 g/kg (generally used loading dose as mentioned at the beginning of this paragraph).

To our knowledge, currently only one randomized study has been published evaluating prospectively different IGIV dosages.[35] This trial in 59 CIDP and MMN patients (2:1 ratio) was not placebo-controlled, but used 0.25 g/kg IGIV as lowest dosage. The other two arms were 1.0 g/kg and 2.0 g/kg IGIV. Patients were switched 9 weeks after first administration to the next higher dosage if they were non-responders and not already on the highest dosage.

About half of the IGIV responders show a positive development after the initial 2.0 g/kg loading dose and the other half only after one or more additional 1.0 g/kg dose(s).[36] For comparability with the ICE trial results, the primary endpoint will be the proportion of responders to treatment, where response is defined as improvement of at least 1 point on the adjusted INCAT disability scale compared to baseline for those randomized to the 1.0 g/kg arm (the adjusted INCAT score is identical to the original INCAT disability score with the exception that upper extremity score changes from 0 (normal) to 1 (minor symptoms) or from 1 to 0 are excluded in determining the adjusted score, given that these changes are not considered clinically meaningful). Hence, a newer and better scale (I-RODS, [27]) will only be applied as secondary endpoint. In conformity with ICE and PRIMA studies, the primary endpoint will be assessed at Week 24, although the maximum response in the ICE study has been published to be after 10.2 weeks on average.[36]

Patients eligible after screening will first enter a Wash-out Phase of up to 12 weeks or until deterioration (see Section 3.2), whatever comes first, in order to select active patients who are in need of treatment. Selected patients will subsequently enter the 24-week Dose-evaluation Phase.

This Wash-out Phase and the 3-week interval between infusions have been chosen to make results comparable to the ICE and PRIMA studies.[24,25] It is in line with the “EFNS guidelines for the use of IGIV in treatment of neurological diseases”.[37] Therein it is recommended to reduce the dose in IGIV responders at intervals in order to discover whether

the patient still needs IGIV and what dosage is needed. The 3-week interval [±4 days] chosen is also in line with the general treatment practice to administer IGIV every 2-6 weeks.

In the Dose-evaluation Phase, three NewGam dosages will be employed and the efficacy results of the higher (2.0 g/kg) and lower (0.5 g/kg) doses compared to the standard dose (1.0 g/kg) results to evaluate a potential linear dependency between dose and response. The responder rates under standard dose will be compared with the responder rates of the ICE and PRIMA studies.

Risk minimization is achieved due to the introduction of a potential rescue treatment option: Two consecutive infusions of 2.0 g/kg NewGam at 3-week intervals [±4 days] for all patients in the 0.5 and 1.0 g/kg NewGam arms who are either stable at Week 6 or deteriorate after Week 3 and before Week 18. The potential rescue treatment during the Dose-evaluation Phase provides the opportunity to assess if two high-dose courses of NewGam (2.0 g/kg) will convert previous non-responders (stable or deteriorating patients) in the low or medium NewGam dosage arms to responders. Patients in the 2.0 g/kg NewGam arm will drop-out if they are stable at Week 6 or deteriorating after Week 3 and before Week 21.

Measures will be taken to ensure that the sponsor, the evaluating Investigator and all parties involved in the conduct of the trial will remain blinded.

3.3.2 Control Group(s)

Since the placebo-controlled ICE study, which confirmed the beneficial results from earlier trials that were much smaller and shorter in duration, led to the licensure of the Gamunex IGIV brand in the US, it is not ethically justified to conduct additional large placebo-controlled studies with other IGIV brands. Further, with corticosteroids and plasma exchange there are also different treatment options available that have proven beneficial for this chronic disease [16,18], and Investigators and patients would be reluctant to participate. One higher (2.0 g/kg) and one lower (0.5 g/kg) dosage of NewGam serve as the study's internal control with the lower dose being putatively not sufficient for certain patients to remain stable or improve, thus mimicking a placebo arm to some extent.

The responder rates (improvement in adjusted INCAT score at Week 24) from the ICE and PRIMA studies will be used to compare the rates found in ProCID. Both used the current standard dose of 1.0 g/kg IGIV every 3 weeks that is also used in ProCID for the evaluation of the primary endpoint.

3.3.3 Target Parameters

Because of the pleiotropic mechanisms of action of polyvalent immunoglobulin preparations, the exact mode(s) of action that lead(s) to the beneficial effects of IGIV in CIDP patients is/are not yet fully understood. Potential mechanisms of IGIV include blocking of antibodies, B-cells, T-cells, and macrophages at multiple sites, neutralization of activated complement, modulation of pro-inflammatory cytokines, and influence on cell migration, thus resulting in immunomodulation. The current hypothesis assumes that multiple effects of IGIV act in concert to evoke the beneficial effects seen in patients with neuro(auto)immunological diseases.

The chosen safety parameters are commonly used to obtain safety information on IGIV treatment.

4 STUDY POPULATION

4.1 Population Base

Male or female patients of ≥ 18 to < 80 years of age with documented diagnosis of CIDP by a neurologist specialized/experienced in neuromuscular diseases will be enrolled in this study. Eligible patients need to fulfill the definite or probable EFNS/PNS criteria for CIDP [12] and must have an adjusted INCAT disability score between 2 and 9.

4.1.1 Inclusion Criteria

Patients who meet all of the following criteria are eligible for the study:

1. Patients with diagnosis of definite or probable CIDP according to the EFNS/PNS Guideline 2010 [12]; including patients with Multifocal Acquired Demyelinating Sensory And Motor Neuropathy (MADSAM) or pure motor CIDP
2. Patients currently depending on treatment with immunoglobulins or corticosteroids
3. Patients with active disease, i.e. not being in remission, who are progressive or relapsing prior to trial start or during the Wash-out Phase
4. Weakness of at least 2 limbs
5. ≥ 18 to < 80 years of age
6. Adjusted INCAT disability score between 2 and 9 (with a score of 2 coming exclusively from leg disability)
7. Voluntarily given, fully informed written consent obtained from patient before any study-related procedures are conducted

4.1.2 Exclusion Criteria

Patients who do meet any of the following criteria are not eligible for the study:

1. Unifocal forms of CIDP
2. Pure sensory CIDP
3. MMN with conduction block [12]
4. Patients who previously failed immunoglobulin treatment
5. Treatment with immunomodulatory/suppressive agents (cyclosporin, methotrexate, mitoxantrone, mycophenolate mofetil or azathioprine) during the six months prior to baseline visit
6. Patients on or treated with rituximab, alemtuzumab, cyclophosphamide, or other intensive chemotherapeutic regimens, previous lymphoid irradiation or stem cell transplantation during the 12 months prior to baseline visit
7. Respiratory impairment requiring mechanical ventilation
8. Myelopathy or evidence of central nervous system demyelination or significant persisting neurological deficits from stroke, or central nervous system (CNS) trauma
9. Clinical evidence of peripheral neuropathy from another cause such as
    a. connective tissue disease or systemic lupus erythematosus (SLE)
    b. HIV infection, hepatitis, Lyme disease
    c. cancer (with the exception of basal cell skin cancer)

d. IgM paraproteinemia with anti-myelin associated glycoprotein antibodies

10. Diabetic neuropathy
11. Cardiac insufficiency (New York Heart Association [NYHA] III/IV), cardiomyopathy, significant cardiac dysrhythmia requiring treatment, unstable or advanced ischemic heart disease
12. Severe liver disease (ALAT 3x > normal value)
13. Severe kidney disease (creatinine 1.5x > normal value)
14. Hepatitis B, hepatitis C or HIV infection
15. Thromboembolic events: patients with a history of deep vein thrombosis (DVT) within the last year prior to baseline visit or pulmonary embolism ever; patients with susceptibility to embolism or DVT
16. Body mass index (BMI) ≥40 kg/m^2
17. Patients with uncompensated hypothyroidism (abnormally high Thyroid-Stimulating Hormone [TSH] and abnormally low Thyroxine [T4]) or known vitamin B12 deficiency if they don't receive adequate substitution therapy
18. Medical conditions whose symptoms and effects could alter protein catabolism and/or IgG utilization (e.g. protein-losing enteropathies, nephrotic syndrome)
19. Known IgA deficiency with antibodies to IgA
20. History of severe hypersensitivity, e.g. anaphylaxis or severe systemic response, to immuno-globulin, blood or plasma derived products, or any component of NewGam
21. Known blood hyperviscosity, or other hypercoagulable states
22. Use of other blood or plasma-derived products within three months prior to Visit 2
23. Patients with a past or present history of drug abuse or alcohol abuse within the preceding five years prior to baseline visit
24. Patients unable or unwilling to understand or comply with the study protocol
25. Participation in another interventional clinical study with IMP treatment currently or during the three months prior to Visit 2
26. Women who are breast feeding, pregnant, or planning to become pregnant, or are unwilling to use an effective birth control method (such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomized partner) while on study

4.2 Prior and Concomitant Therapy

Details of any prior (up to 12 months before screening for all CIDP related treatments; up to 3 months for all others) and concomitant medication (drug and non-drug therapy, such as physical therapy taken throughout the study) must be recorded in the source documentation and the electronic case report form (e-CRF).

4.2.1 Prior Therapy

Prior treatment with first-line CIDP therapies (IGIV or corticosteroids) is required (at least 3 months on stable dosage).

Treatment with azathioprine is permitted if patients have been taking it for ≥12 months prior to Visit 2 (Baseline) on a stable dose: such patients should continue taking the same dose during the trial.

Patients should not require the use of pre-medication for IGIV infusions to treat tolerability problems of IGIVs.

Medications not particularly permitted or forbidden have to be evaluated by the Investigator under consideration of possible interactions with the presumed mode of action of IGIV products in CIDP.

4.2.2 Permitted Concomitant Therapy

Mild forms of pain can be treated with acetaminophen, if required.

Corticosteroids (prednisolone or equivalent) ≤ 20 mg/day or equivalent (i.e., ≤ 40 mg every 2 days) on a stable dose during the Dose-Evaluation-Phase are permitted for patients with prior corticosteroid therapy.

4.2.3 Forbidden Concomitant Therapy

Corticosteroids may not be given as a pre-treatment to alleviate potential tolerability problems.

Administration of any other blood or plasma-derived product is forbidden and should only be given for emergency reasons. Patients will be withdrawn from the study if immunoglobulin preparations other than NewGam are administered.

- Corticosteroids (prednisolone or equivalent) > 20 mg/day or equivalent (i.e., > 40 mg every 2 days)
- PEX
- Cyclosporin, methotrexate, mitoxantrone, mycophenolate mofetil and interferon or other immunosuppressive or immunomodulatory drugs
- Rituximab, alemtuzumab, cyclophosphamide or other chemotherapeutic regimens
- Any experimental treatment
- Regulatory Authorities discourage the use of pre-medication in clinical trials designed to evaluate the safety of biologic products, except in cases where such pre-medication is important to the safety of the trial patients. Therefore any routine pre-medication to alleviate potential tolerability problems is disallowed. However, patients who experience 2 consecutive infusion-related AEs that are likely to be prevented by pre-medication are permitted to receive antipyretics, antihistamines, or antiemetic drugs. Non-steroidal anti-inflammatory drugs (NSAIDs) can affect renal function and should be avoided.

NewGam must not be mixed with other medicinal products; a separate intravenous line should be used in such cases.

4.3 Assignment of Patients to Treatment Groups

For each patient screened, the Investigator or designee will enter the center number and the month and year of birth into an interactive web response system (IWRS) or another comparable electronic system. The IWRS will allocate the next available screening ID, ensuring that

screening IDs are assigned sequentially per center. The screening ID will be a 6-digit number with the first two digits being the country code (e.g. "49" for Germany), the next two digits identifying the center (01, 02, …) and the last two digits the sequence number assigned by the IWRS (01, 02, …) for each site continuously. Leading zeros will be used for center and patient numbers below 10. The second patient screened at center 4 in Germany would e.g. be identified as 490402.

The Investigator will enter the information – month and year of birth and the associated screening ID – into the confidential patient identification list.

If the patient qualifies, randomization will be done centrally through the IWRS after deterioration, i.e., at start of the Dose-evaluation Phase, after all inclusion and exclusion criteria have been checked again and the patient is still found eligible. The IWRS will ensure balance of allocation by means of a stratified block design, using the treatment before enrollment (immunoglobulin or corticosteroids treatment) as strata. The fact that a patient has been randomized will be reported immediately and automatically by the system to the Investigator, the contract research organization (CRO) and the sponsor. The result of randomization, i.e. the treatment group assignment, will however only be reported to the hospital pharmacist or designee by a dedicated email that no other trial personnel will have access to.

The patient will be identified by the previously assigned screening ID throughout the trial, no additional patient or randomization number will be used.

No randomization results will be transmitted to the sponsor to comply with the double-blind character of this study. The responsible monitor will be informed of new patients enrolled automatically by the IWRS system via email.

Under no circumstances are patients who enroll in the study permitted to re-enroll.

4.4 Withdrawal and Replacement of Patients

4.4.1 Premature Patient Withdrawal

For any discontinuation after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation in the CRF. If the reason for withdrawal of a patient is an AE, the main specific event or laboratory test will be recorded in the CRF, and the Investigator will make thorough efforts to clearly document the outcome.

Patients have the right to withdraw from the study at any time for any reason, without the need to justify their decision. The Investigator also has the right to withdraw patients from the study in case of AEs, poor compliance, or other reasons. Since an excessive rate of withdrawal can render the study non-interpretable, the unnecessary withdrawal of patients must be avoided. Should a patient decide to withdraw, the Investigator will make the best efforts to complete and report the observations. The Investigator will document the reason(s) for withdrawal of each patient in the electronic Case Report Form (eCRF).

Patients who terminate the study prematurely are drop-outs. The Investigator has to organize the pre-termination visit.

Reasons for premature termination of patients may be:

- Withdrawal of patient's consent (e.g. due to ineffective therapy in case of deterioration)
- Pregnant patients will be immediately excluded from the study

- Investigator's opinion that the patient may be severely harmed if he/she continues trial participation, namely by the treatment and procedures according to the study protocol
- Occurrence of a disease which interferes with the study treatment or represents an exclusion criterion
- Administration of IGIV other than NewGam.

4.4.2 Patient Replacement Policy

Only in case of a withdrawal portion in excess of 10%, patients will be replaced, unless the planned number of patients in the respective dose group has been achieved already. A replacement patient will be assigned to the same treatment group as the withdrawn patient.

Patients withdrawn from the study because of safety reasons will not be replaced.

5 INVESTIGATIONAL MEDICINAL PRODUCT(S)

5.1 Treatment Compliance

5.1.1 Drug Dispensing and Accountability

Any IMP provided to the site will be accounted for. This includes IMP received at the site and IMP dispensed to patients.

NewGam will be delivered to the participating centers/pharmacists by the Sponsor or designee.

A Drug Inventory and Dispensing Log will be kept current by the Investigator/pharmacist, detailing the dates and quantities of IMP received and dispensed to each patient and the remaining quantity.

The inventory and dispensing log will be available to the unblinded monitor to verify drug accountability during the study.

Unused IMP can be destroyed at the study site or returned to the Sponsor for destruction.

Destruction can be initiated only after accountability has been verified and fully reconciled by the monitor and after the Sponsor has granted written approval of destruction. Empty or partially used bottles should be destroyed at the study site following local policies after the peel-off label has been removed and stuck to the drug accountability form.

When saline has been used for patients on low or medium IGIV dosage, the product name and batch number have to be recorded on the drug accountability form in addition to the tear-off label of the NewGam bottle.

5.1.2 Assessment of Treatment Compliance

All patients will be infused at the study site under the surveillance of authorized study personnel. Infusion details will be documented together with the batch number(s) on the drug accountability form kept by the pharmacist or designee, which will be checked regularly by the unblinded monitor.

5.2 Characterization of Investigational Product(s)

NewGam is a 10% IGIV ready for intravenous administration. NewGam is made from a pool of at least 1000 donations of human fresh-frozen plasma per batch. During the manufacturing process of NewGam, significant viral reduction is obtained via a combination of S/D treatment and 20 nm nanofiltration. In addition, the Source Q chromatography (ion-exchange chromatography) step in the NewGam manufacturing process contributes significantly to the viral safety of NewGam. The S/D method is highly effective against enveloped viruses, while the 20 nm nanofiltration is effective against both, enveloped and non-enveloped viruses. A further phenomenon which contributes to the viral safety of NewGam is neutralization by the present antibodies. The efficacy of the virus inactivation procedures has been extensively validated according to relevant international guidelines in place. The composition with the most important ingredients and the biochemical characteristics are summarized in the Investigators' Brochure.

5.3 Packaging and Labeling

NewGam is delivered as ready-to-use solution in glass bottles.

Each NewGam bottle will be labeled as follows:

EU Master Label – NewGam:

FOR CLINICAL TRIAL USE ONLY
NewGam

Study: **NGAM-08**
Unit size: _____ **mL**

1 mL contains: 100 mg protein of which ≥ 95% is human normal immunoglobulin.
Infusion solution for intravenous administration.
To be stored at +2°C to +8°C and protected from light. Must not be frozen.
Must be inspected visually for particulate matter and discoloration prior to administration. Do not use non-homogenous solutions or those that have a deposit.

To be warmed up to room or body temperature before use.

Dosage: see study protocol Section 5.5

EudraCT number: 2015-005443-14

Investigator: _____

Sponsor: OCTAPHARMA PPG, Oberlaaer Str. 235, 1100 Vienna, Austria, Tel: [redacted]

CRO: _____

Batch no.: _____ Expiration date: _____

Final labeling will be in compliance with the national requirements of each country where the study will be conducted.

After transfer and pooling into infusion bags, the medication (NewGam or 0.9% saline solution) will be blinded with an overpouch and re-labelled. The following labels will be used for sending the medication from the pharmacy/clinic to the ward:

EU Master Label – Overpouch for infusion bags:

FOR CLINICAL TRIAL USE ONLY Study: **NGAM-08**

NewGam OR Sodium Chloride 0.9% w/v solution Volume: _____ **mL**

1 mL contains: 100 mg protein of which ≥ 95% is human normal immunoglobulin OR sodium chloride 0.9% w/v solution.

Infusion solution for intravenous administration.

To be stored at +2°C to +8°C (see study protocol Section 5.4). Must not be frozen.

To be warmed up to room temperature before use.

Dosage: see study protocol Section 5.5

Pat. number: |__|__|__|__|__| Infusion week: |____| Bag number: |__| of |__|

Date and time of preparation: _____

Use by (date and time): _____

Any unused solution residues or waste material to be disposed according to local requirements at the study site.

EudraCT number: 2015-005443-14

Investigator: _____

Sponsor: OCTAPHARMA PPG, Oberlaaer Str. 235, 1100 Vienna, Austria, Tel: [redacted]

CRO: _____

Final labeling will be in compliance with the national requirements of each country where the study is to be conducted.

5.4 Conditions for Storage and Use

NewGam should be stored and transported light-protected at +2°C to +8°C (36°F to 46°F) and must not be frozen.

NewGam must not be used after its expiration date.

Authorized personnel at the individual study centers/pharmacies will ensure that the IMPs are stored under appropriate conditions with restricted access and in compliance with national regulations.

5.5 Dose and Dosing Schedule

NewGam is available in glass bottles with different volumes of human immunoglobulin. Glass bottles of different content should be combined in order to reach the required amount of IgG (split into infusions of 0.5 g/kg and 1.0 g/kg to maintain blinding). The total amount per patient should be dosed exactly. Partially used bottles must be discarded.

All patients should be clinically assessed for being adequately hydrated prior to infusion.

In the Dose-evaluation Phase, all patients will receive a loading dose of 2.0 g/kg Newgam (administered over two consecutive days), followed by seven infusions of the maintenance dose the patient has been randomized to (0.5, 1.0 or 2.0 g/kg NewGam), also administered over two consecutive days every 3 weeks (±4 days). If a patient is randomized to receive the low or medium NewGam dose, the same volume with the same infusion rate as would have been applied in case the patient would have been randomized to 2.0 g/kg NewGam will be used, thus

supplemented with an authorized 0.9% w/v isotonic sodium chloride solution as appropriate and detailed in the following infusion bag split to maintain the blinding:

Treatment Arms	Infusion Bag Content	
	Day 1	**Day 2***
0.5 g/kg NewGam	0.5 g/kg NewGam + 0.5 g/kg *saline*	1.0 g/kg *saline*
1.0 g/kg NewGam	0.5 g/kg NewGam + 0.5 g/kg NewGam	1.0 g/kg *saline*
2.0 g/kg NewGam	0.5 g/kg NewGam + 0.5 g/kg NewGam	1.0 g/kg NewGam

* Volume of Day 2 may be split up using 2 bags

The following infusion schedule must be adhered to in the Dose-evaluation Phase [all doses per kg body weight; rescue treatment only for patients who had been on 0.5 or 1.0 g/kg NewGam before, patients on 2.0 g/kg before will drop-out]:

1. Patients deteriorating* after Week 3 and before Week 6 <u>or</u> being stable at Week 6**

Week 0	Week 3	Week 6	Week 9	Week 12
2.0 g (**LD**)	0.5g 1.0 g	2.0 g (**RT**)	2.0 g (**RT**)	**EOS**
	2.0 g	**EOS**		

2. Patients deteriorating* after Week 6 and before Week 9

Week 0	Week 3	Week 6	Week 9	Week 12	Week 15
2.0 g (**LD**)	0.5g 1.0 g	0.5g 1.0 g	2.0 g (**RT**)	2.0 g (**RT**)	**EOS**
	2.0 g	2.0 g	**EOS**		

3. Patients deteriorating* after Week 9 and before Week 12

Week 0	Week 3	Week 6	Week 9	Week 12	Week 15	Week 18
2.0 g (**LD**)	0.5g 1.0 g	0.5g 1.0 g	0.5g 1.0 g	2.0 g (**RT**)	2.0 g (**RT**)	**EOS**
	2.0 g	2.0 g	2.0 g	**EOS**		

4. Patients deteriorating* after Week 12 and before Week 15

Week 0	Week 3	Week 6	Week 9	Week 12	Week 15	Week 18	Week 21
2.0 g (**LD**)	0.5g 1.0 g	0.5g 1.0 g	0.5g 1.0 g	0.5g 1.0 g	2.0 g (**RT**)	2.0 g (**RT**)	**EOS**
	2.0 g	2.0 g	2.0 g	2.0 g	**EOS**		

5. Patients deteriorating* after Week 15 and before Week 18

Week 0	Week 3	Week 6	Week 9	Week 12	Week 15	Week 18	Week 21	Week 24
2.0 g (**LD**)	0.5g 1.0 g	0.5g 1.0 g	0.5g 1.0 g	0.5g 1.0 g	0.5g 1.0 g	2.0 g (**RT**)	2.0 g (**RT**)	**EOS**
	2.0 g	2.0 g	2.0 g	2.0 g	2.0 g	**EOS**		

LD – Loading Dose, **RT** – Rescue Treatment, **EOS** – End-of-Study-Visit
* = adjusted INCAT disability score increase of at least 1 point
** = adjusted INCAT disability score remains unchanged

5.6 Preparation and Method of Administration

All NewGam or saline vials/bottles necessary to achieve the calculated amount according to the body weight of the patient must be pooled by the hospital pharmacist or designee in three separate infusion bags to be administered at 2 consecutive days. **NewGam must not be mixed with other medicinal products or saline** - the saline solution may be administered after NewGam in the same intravenous line. For other IV products a separate IV line must be used.

The preparation should be performed under aseptic conditions using a sterile bench, as described in the manual handed out to the hospital pharmacist or designee. The infusion bags can then be stored for up to 24 hours at +2°C to +8°C (36°F to 46°F). IMP prepared without the use of a laminar air flow must be administered within 3-4 hours after preparation.

Each bottle of NewGam must be examined visually by the pharmacist or designee for particulate matter and discoloration prior to pooling. Non-homogenous solutions or those that have a deposit must not be pooled. The same procedures should be performed also for saline. The infusion bags must be allowed to warm to room or body temperature prior to infusion. The same holds true for saline for patients on the low and medium (standard) NewGam dosages.

Patients must be monitored and carefully observed for any symptoms throughout the infusion period and at least 1 hour thereafter.

The special warnings and precautions for use (see Investigator's Brochure) of NewGam must be respected.

The initial infusion rate will be 0.01 mL/kg/min (60 mg/kg/hr) for the first 30 minutes; if tolerated, advanced to 0.02 mL/kg/min (120 mg/kg/hr) for the next 30 minutes; if tolerated, advanced to 0.04 mL/kg/min (240 mg/kg/hr) for the next 30 minutes; if tolerated, advanced to 0.08 mL/kg/min (480 mg/kg/hr) for the next 30 minutes and, if tolerated, advanced to 0.12 mL/kg/min (720 mg/kg/hr) for the remainder of the infusion. From the third infusion on, the 30 minutes interval for the 0.02 to 0.08 mL/kg/min infusion rates may be shortened to 15 minutes as per the discretion of the investigator.

If AEs occur during infusion, the rate is to be reduced to half the rate at which the event occurred, or the infusion interrupted until symptoms subside. The infusion may then be resumed at a rate tolerated by the patient.

5.7 Treatment Duration

In the Dose-evaluation Phase, all patients will receive a loading dose of 2.0 g/kg NewGam followed by seven times the dosage they were randomized to (0.5, 1.0 or 2.0 g/kg NewGam). Patients in the 0.5 and 1.0 g/kg NewGam arms being clinically stable until Week 6 (i.e. with unchanged adjusted INCAT disability score compared to baseline) will receive further infusions of 2.0 g/kg NewGam at Week 6 and 9, still keeping the blind. Patients who deteriorate (i.e. with increase in adjusted INCAT disability score of at least 1 point) after Week 3 and before Week 18 will receive two infusions of 2.0 g/kg NewGam at the next two consecutive 3-week intervals (earliest at Week 6 and latest at Week 21). Afterwards they will continue with the regular termination visit. Patients deteriorating after Week 18 will drop-out and have their Termination Visit at Week 21; patients deteriorating after Week 21 will drop-out and have their Termination Visit at Week 24.

5.8 Blinding, Emergency Unblinding and Breaking the Study Blind

The Investigators will be provided with an unblinding procedure to disclose the actual treatment of a particular patient in case of medical emergency. Blinding in individual patients should not be broken only in case of a serious adverse event or unexpected ADR, when knowledge of the type of the administered IMP is required for therapeutic decisions regarding this event. However the decision and the responsibility to break the treatment code in emergency situations resides solely with the investigator. In the event of medical emergency to keep subject safety, the investigator is able to unblind a patient immediately by accessing the IWRS system without needing a PIN code and without needing to contact any third party.

To maintain blinding in the Dose-evaluation Phase, infusions will be given in three infusion bags (corresponding to a volume of 0.5 g/kg, 0.5 g/kg and 1.0 g/kg NewGam or saline). Thus, the old label will be discarded together with the vial/bottle, and a new label will be fixed onto an opaque overpouch by the hospital pharmacist or designee. The order of the infusion bags will be added on the label: on Day 1 of an infusion visit the NewGam infusion bag (corresponding to 0.5 g/kg NewGam) comes first, then the second infusion bag (corresponding to 0.5 g/kg NewGam or matching saline) and last, at the following Day 2, the large infusion bag (corresponding to 1.0 g/kg NewGam or matching saline). Volume of Day 2 may be split up using two infusion bags instead of one.

An overpouch (normally used for light protection) will be put over each infusion bag to maintain blinding. The new labels will be identical for both, NewGam and saline, so that the content of the bags is only known to the unblinded hospital pharmacist or designee. An example of this label can be found above in Section 5.3.

The hospital pharmacist or designee will send the 3 infusion bags per patient (potentially already fixed to the opaque infusion line) to the ward on the corresponding days. At the ward, the infusions will be given according to the order stated on the label (“1 of 3”, “2 of 3”, on Day 1 and “3 of 3” on Day 2). To further assure the double-blind character of this study, the physician or designee who applies the medication to the patient will not be involved in any other evaluations other than drawing blood samples or checking for vital signs, i.e. will not be involved in any patient ratings (e.g. INCAT, I-RODS, NCS, grip strength). In parallel, all Investigators for the electrophysiological or neurological evaluations will not be involved in the application of the medication.

Blinding of the patient: The patient will be blinded to the medication throughout the entire study. Because of the opaque (non-transparent) infusion line and overpouches, the patient will not be able to see the medication he/she is treated with.

Therefore, patients deteriorating (increase in adjusted INCAT disability score of at least 1 point) in the 0.5 and 1.0 g/kg NewGam arms after Week 3 and before Week 18 or remaining stable (unchanged adjusted INCAT disability score from baseline) by Week 6, and thus receiving 2 additional treatments with 2.0 g/kg NewGam, will continue with all study procedures as described in this protocol and will remain blinded as no serious safety issues are expected related to these procedures for patients continuing with NewGam treatment, while patients on 2.0 g/kg NewGam will drop-out if they deteriorate or are stable at Week 6.

The local study file will contain code break envelopes (or detailed instructions for the electronic equivalent thereof). If paper envelopes are used, the monitor will check the envelopes at each visit. Any breaking of the blind has to be documented with date, time, person, and reason.

The Investigator has to notify the Sponsor as soon as possible about the unblinding of a patient.

5.9 Subsequent Therapy

In case a patient decides to withdraw from the study or is withdrawn by the Investigator, he/she may continue with the treatment he/she has received before study participation or with another standard of care.

5.10 Relevant Protocol Deviations

Deviations from the protocol should not occur. If deviations occur, the Investigator should promptly inform the Monitor and the implication of the deviation must be reviewed and discussed. Any deviation must be documented, stating the reason and date, the action taken, and the impact for the patient and/or the trial. The documentation must be kept in the Investigator's Trial File and the Sponsor's file.

Examples of relevant protocol deviations that will be addressed are:

- Patients who entered the study even though they did not satisfy the entry criteria
- Patients who developed withdrawal criteria during the study
- Patients who received the wrong treatment or incorrect dose
- Patients who received an excluded concomitant treatment (e.g. IGIV other than NewGam).

In case of any major protocol deviations or violations the Investigator and Octapharma will decide on the further participation of the patient in this study, after having discussed all relevant aspects.

A list of all included patients with all deviations from the intended study procedures and other criteria that may affect the patient's validity for statistical analysis will be prepared upon clinical completion of the study. This will then be discussed by a panel consisting of the clinical project manager, a medical expert of the Sponsor, the data manager, the study biometrician and the Steering Committee. This panel will decide upon the membership of the patient in the ITT and PP efficacy and safety populations for statistical analysis.

6 STUDY CONDUCT

A signed informed consent form must be available before the start of screening activities.

The schedule of all visits is applicable for all patients of all treatment arms.

6.1 Observations by Visit

6.1.1 Screening (Visit 1; duration up to 21 days, i.e. Week -15 to -12)

Patients have to be informed about the study details and have to give their written informed consent. Prior to treatment initiation, patients will have to be screened for eligibility (inclusion and exclusion criteria). This includes general physical/neurological examination, vital signs and medical history assessment. Also, electrophysiological recordings (NCS of 4 right sided and 4 left-sided motor nerves) to confirm the diagnosis of definite or probable CIDP will be done as part of the in-/exclusion criteria evaluation. Women of childbearing potential (WOCBP) must have a negative pregnancy test to be eligible for the study. At Visit 2, 3, 4, 5, 6, 7, 8, 9 and Termination Visit a pregnancy test should be performed only if required by local requirements.

If feasible, screening should be completed within three weeks. However, screening results should be available as soon as possible but might take up slightly longer until also the results of the centrally evaluated NCS (by [redacted]) become available. Based on the screening results, the patients' eligibility for the study is determined, and a patient could proceed with the Wash-out Phase, if he/she is eligible.

Screening failures will be entered into the eCRF.

The following assessments will be performed during screening:

- Obtaining voluntarily given, written (signed and dated) informed consent
- Medical history and prior/concomitant medication
- Physical/neurological examination
- Vital signs (including body weight and height)
- Inclusion and exclusion criteria
- Standard ECG
- Urinalysis
- Blood sample (5 mL) for viral markers
- Blood samples (10 mL) for safety laboratory (hematology and clinical chemistry)
- Pregnancy test
- Grip strength
- Adjusted INCAT disability score
- I-RODS
- MRC sum score
- Modified FSS
- PI-NRS
- NCS
- SF-36

6.1.2 Procedures During the Wash-out Phase of the Study

Eligible patients will have to enter a Wash-out Phase of up to 12 weeks, i.e., they have to decrease their current medication (immunoglobulins or corticosteroids; see Section 3.2). In this Phase the medication will successively be reduced until the patient deteriorates.

For patients on corticosteroids, no scheduled or required study evaluations/visits will take place during the Wash-out Phase. However the patients must inform the investigator whenever they notice any symptom of disease worsening at any time during the Wash-out Phase and must come to the site for assessment of deterioration. If deterioration cannot be confirmed, the Wash-out Phase will continue.

Patients on immunoglobulin treatment will have to visit the study site (e.g. IGIV every three weeks) for their infusions. Thus, from these patients concomitant medications and AEs will be recorded.

6.1.3 Procedures During the Dose-evaluation Phase of the Study

Only patients who deteriorate during the Wash-out Phase (active patients) will visit the study site and enter the Dose-evaluation Phase after randomization. All other patients who do not have active disease will not be eligible for enrollment into ProCID and will discuss their further treatment possibilities with their treating physician.

Visit 2 (Week 0; up to 12 weeks after Screening end; Baseline for Dose-evaluation Phase)

All patients who deteriorate during the Wash-out Phase will be rechecked for eligibility and, if positive, will be treated with 2.0 g/kg NewGam. At this time they will also be randomized to one of three NewGam dosages employed. The following assessments will be performed:

Before infusion:

- Physical/neurological examination
- Confirm eligibility (in-/exclusion criteria)
- Randomization and enrollment
- Blood sample (5 mL) for viral markers
- Blood samples (15 mL) for safety laboratory (serum IgG, hematology and clinical chemistry)
- Grip strength
- Adjusted INCAT disability score
- I-RODS
- MRC sum score
- Modified FSS
- PI-NRS
- NCS
- PGIC scale

During and after infusion:

- Administration/Infusion of IMP (2.0 g/kg NewGam)
- SF-36 (during infusion)

- Vital signs (including body weight) before, at least once during and after infusion
- Monitoring of adverse events (AEs)
- Documentation of concomitant medication

Visits 3, 4, and 5 (Week 3, 6, and 9)

The following assessments will be performed:

Before infusion:

- Blood sample(s) (15 mL) for safety laboratory (serum IgG, hematology and clinical chemistry)
- Grip strength
- Adjusted INCAT disability score
- I-RODS
- PI-NRS

During and after infusion:

- Administration/Infusion of IMP (0.5, 1.0 or 2.0 g/kg NewGam)
- Vital signs before, at least once during and after infusion
- Monitoring of adverse events (AEs)
- Documentation of concomitant medication

Visit 6 (Week 12)

The following assessments will be performed:

Before infusion:

- Physical/neurological examination
- Blood samples (15 mL) for safety laboratory (serum IgG, hematology and clinical chemistry)
- Grip strength
- Adjusted INCAT disability score
- I-RODS
- MRC sum score
- Modified FSS
- PI-NRS
- NCS

During and after infusion:

- Administration/Infusion of IMP (0.5, 1.0 or 2.0 g/kg NewGam)
- SF-36 (during infusion)
- Vital signs (including body weight) before, at least once during and after infusion
- Monitoring of adverse events (AEs)
- Documentation of concomitant medication

Visits 7, 8 and 9 (Week 15, 18 and 21)

The following assessments will be performed:

Before infusion:

- Blood sample(s) (15 mL) for safety laboratory (serum IgG, hematology and clinical chemistry)
- Grip strength
- Adjusted INCAT disability score
- I-RODS
- PI-NRS

During and after infusion:

- Administration/Infusion of IMP (0.5, 1.0 or 2.0 g/kg NewGam)
- Vital signs before, at least once during and after infusion
- Monitoring of adverse events (AEs)
- Documentation of concomitant medication

End of Study (Final) Examination

The final examination is performed three weeks after the last IMP administration (regularly at Visit 10 scheduled for Week 24 for responders), which can be either the last dose as randomized, or the last rescue dose.

The following investigations will be performed:

- Physical/neurological examination
- Blood sample (5 mL) for viral markers
- Blood samples (15 mL) for safety laboratory (serum IgG, hematology and clinical chemistry)
- Urinalysis
- Grip strength
- Adjusted INCAT disability score
- I-RODS
- MRC sum score
- Modified FSS
- PI-NRS
- NCS
- SF-36
- Monitoring of adverse events (AEs)
- Documentation of concomitant medication

After the Final Examination, the clinical study is considered completed for the patient. No further study-related assessments will be performed, unless safety concerns (e.g., ongoing AEs) require follow-up.

6.1.4 Procedures during the Rescue Treatment

This section is only applicable for patients in the 0.5 and 1.0 g/kg NewGam arms, namely

a) for patients deteriorating after Week 3 and before Week 18 or

b) for patients being stable until Week 6

Depending on the time point when deterioration is detected or at Week 6 for patients remaining stable, the Rescue Treatment is initiated.

During the Rescue Treatment patients receive two doses of 2.0 g/kg NewGam in a 3-week interval; first dose at the visit when the deterioration is detected, or at the visit in Week 6 for patients remaining stable, the second dose three weeks later.

Please refer to Section 5.5 for an overview on dosing if a Rescue Treatment is required.

Visit procedures at the Rescue Treatment follow essentially the same process as described for corresponding visits.

Three weeks after the second rescue dose the study termination visit is performed.

6.1.5 Interpretation of Time Windows in this Study

For this study the following time windows apply:

Time point	Time stated	Tolerance
Interval between visits	3 weeks	± 4 days
Vital signs	before IMP administration	≤ 60 minutes
Vital signs	after IMP administration	≤ 60 minutes

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The duration of the entire study for each patient will be between >9 and up to 39 weeks and consists of the following: approximately 3 weeks for Screening, up to 12 weeks for the Wash-out Phase and 24 weeks for the Dose-evaluation Phase (for patients who deteriorate at the end of the 12-week Wash-out Phase and who are continued responders during the Dose-evaluation Phase). The minimal duration could be >9 weeks after Screening (for patients in the 2.0 g/kg arm deteriorating after being only a few days in the Wash-out Phase and being stable until Week 6 or deteriorating by then as they will not receive rescue treatment but drop-out). Thus, the length of the Dose-evaluation Phase can vary between 6 and 24 weeks, while the length of the Wash-out Phase can vary between >0 and 12 weeks.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed, when all patients have completed the study termination visit.

The study as a whole should be completed within 30 months. The estimated start of the study (enrollment of first patient) is Q1 2017 with the estimated end of the study (last visit of last patient) being Q4 2019. The enrollment period is projected to last approximately 20 months.

6.2.3 Premature Termination of the Study

Both the Investigator and the Sponsor reserve the right to terminate the study at any time. Should this be necessary, the procedures will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

Regulatory authorities and IECs/IRBs should be informed according to national regulations.

Early termination of the study as a whole or center-wise may apply for the following reasons:

Clinical Study:

At any time the study as a whole will be terminated prematurely if:

- New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk-assessment.

Study Centre:

At any time the study can be terminated at an individual center if:

- The center cannot comply with the requirements of the protocol.
- The center cannot comply with ICH-GCP E6 standards.
- The center’s first patient is not recruited by 24 weeks after initiation of the center.
- The required recruitment rate is not met.

Should the study be prematurely terminated, all study materials (including IMP etc.) must be returned to the Sponsor.

7 ASSESSMENTS AND METHODS

7.1 Background / Baseline Information

The following information will be captured at Screening and upon enrollment:

Demographics: including gender, age, weight and height (calculated Body Mass Index [BMI]), and ethnic origin.

Relevant medical and neurological history: obtained by interviewing the patient and by performing a physical examination.

Previous and concomitant medication: obtained by interviewing the patient and retrieving the Patients Global Impression of Change (PGIC)

Disease status: obtained by adjusted INCAT disability score, I-RODS (disability score), grip strength (measured by Martin Vigorimeter), MRC sum score (impairment scale), modified FSS (fatigue scale), PI-NRS (pain score), NCS (electrophysiological recordings)

Quality of Life: assessed by SF-36

7.2 Efficacy Assessments

All participating centers will be trained by a third party in the assessment of the following efficacy endpoints:

- Nerve Conduction Studies (NCS) by [redacted]
- Adjusted INCAT disability scale, I-RODS, modified FSS, PI-NRS, MRC sum score and grip strength by [redacted].

7.2.1 Assessments for Primary Efficacy Endpoints

7.2.1.1 Adjusted INCAT Score (Disability Score)

Functional disability will be assessed by an adjusted INCAT disability score at each visit. The adjusted score is identical to the INCAT disability score with a range from 0 (no disability) to 10 (maximum disability), except for the exclusion of changes in upper limb function from 0 (normal) to 1 (minor symptoms) or from 1 to 0, because these changes were judged by the regulatory authorities as not being clinically significant in the patients in the recently published ICE trial. However, all other 1-point steps in either the arm or the leg scale represented clinically meaningful changes in disability. The original INCAT disability score has an arm and a leg grade, both with a score range from 0 to 5.[38]

7.2.2 Assessments for Secondary Efficacy Endpoints

7.2.2.1 I-RODS (Disability Scale)

A great variety of disability scales have been applied as primary outcome measures in immune-mediated neuropathy trials. The recently developed patient-reported Inflammatory Rasch-built Overall Disability Sum Score (I-RODS) using the concept of minimum clinically important differences using the individually obtained standard errors (MCID-SE) as reported very recently [27,39], which is the first outcome measure that captures activity and participation limitations in patients with immune-mediated neuropathies, will be employed in this study. The

I-RODS fulfils all modern clinimetric requirements and its use is therefore suggested in future clinical trials in these conditions.[27] Patients' dynamics will be captured using the MCID-SE concept as previously described.

7.2.2.2 Grip Strength (Muscle Strength)

Grip strength of both hands (assessed by the best of 3 attempts with a Martin Vigorimeter, a hand-held dynamometer to measure grip strength) will be determined at each visit. This tool has demonstrated to be more sensitive than the INCAT score in detecting significant improvement or deterioration.[40]

7.2.3 Assessments of Exploratory Efficacy Endpoints

All the exploratory parameters are commonly used in studies of this kind and also in daily clinical practice.

7.2.3.1 MRC Sum Score (Impairment Scale)

The MRC sum score is an impairment scale that assesses motor impairment and is widely used in patients suffering from peripheral neuropathies.

The MRC sum score is a summation of the MRC grades (range 0–5) given in full numbers of the following muscle pairs: upper arm abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and foot dorsal flexors.[41] The MRC sum score ranges from 0 ("total paralysis") to 60 ("normal strength"). The individual MRC grades range from 0 = no movement, 1 = flicker, 2 = movement in the absence of gravity, 3 = movement against gravity, 4 = movement against gravity and resistance and 5 = full movement. Recently, the ability of physicians to differentiate between the various MRC has been examined and a proposed Rasch-built 4-grades modified version has been proposed, since physicians demonstrated having great difficulty differentiating between the various grades. However, as part of the current study, extensive training will be given providing > 100 illustrative pictures standardizing the assessment of MRC grades. [29] Both, the traditional and newly proposed grades will be assessed as part of the current study.

7.2.3.2 Modified FSS Scale (Fatigue Scale)

Fatigue is a major disabling complaint in patients with immune-mediated neuropathies like CIDP.[42] The 9-item Fatigue Severity Scale (FSS) has been used to assess fatigue in these conditions, despite having limitations due to its classic test theory construct. The authors were able to construct a 7-item linearly weighted Rasch-built modified FSS scale for proper assessment of fatigue in future studies in patients with immune-mediated neuropathies. The use of its sum score (ranging from 0 [no fatigue] to 21 [most severe fatigue]) is suggested, since the data also fit the rating scale model.[43]

A research manual will be provided to all participating centers presenting elegantly the various parts of the selected measures.

7.2.3.3 Pain Intensity Numeric Rating Scale (Assessment of Pain)

The Pain Intensity Numeric Rating Scale (PI-NRS, a numeric scale where 0 = no pain and 10 = worst possible pain) is an 11–point scale for patient self-reporting of pain.

7.2.3.4 Nerve Conduction Studies (Electrophysiological Measurements)

A pre-specified secondary endpoint in the study will be the change from baseline to the last measurement in the sum of the distal evoked amplitude of 4 right sided and 4 left sided motor nerves (peroneal, tibial, ulnar and median). All additional NCS analyses are considered exploratory (e.g. individual nerve analysis).

Electromyograph (EMG) will not be performed.

The NCS will be conducted in a standardized fashion, and a central neurology core laboratory will monitor the NCS for quality control.

The electrophysiological core lab has developed a standard electrophysiological operations manual (SOM) for each study site. All methodological details such as filter settings, rules for supramaximal stimulation, gain and sweep speed settings for tracing measurement, etc. are outlined comprehensively in the SOM.

Motor nerve studies: The median motor nerve will be tested using stimulation at the wrist and elbow; the ulnar motor nerve will be tested using stimulation at the wrist and below the elbow; the peroneal motor nerve will be tested using stimulation at the ankle and below the fibular head; and the tibial motor nerve will be tested using stimulation at the ankle. F-wave latencies will be tested in all nerves with a minimum of 10 stimulations.

Parameters measured for the motor responses will include distal and proximal onset latency, amplitude (baseline-to-peak), velocity, duration (from the onset of the waveform to the return to baseline), area (calculated by the computer), and F-wave latency.

All original nerve conduction tracings will be reviewed in a blinded fashion by the core electrophysiology laboratory for all pertinent information and for adherence to the standardized measures set out in the study protocol and in the study operations manual provided to each study site. Prior to enrolling patients with CIDP, each study site will perform nerve conduction testing on two healthy controls (one man and one woman). All nerves will be tested on each control subject during two separate visits to ensure technical reliability. Commercially available EMG equipment will be employed as long as required functions were part of the equipment (e.g., hard copy tracings and averaging capabilities). Motor calibrations will be performed at the beginning of each set of NCS for each patient. Limb temperatures will be recorded on the original tracings before and after the study, and temperature control equipment (warming water bath, heating pads, heating blanket, or radiant lamp) will be used for NCS to ensure a minimum temperature of 32°C over digit 2 and 31°C on the toe. Careful attention to distance measurements is mandated, and standardized stimulation sites for each nerve are employed by all Investigators. Approval of each site's reference (control) NCS will be in place prior to testing of any patient with CIDP in the study.

7.2.3.5 SF-36 Health Survey (Quality of Life Assessment)

The SF-36 Health Survey generic health survey will be used for assessing quality of life (www.sf-36.org/; www.qualitymetric.com). The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. The SF-36 is the most widely evaluated generic patient assessed health outcome measure being used in more than 200 diseases and conditions. It has been validated in multiple diseases and languages and has been used successfully in more than

600 randomized clinical trials reported in over 240 scientific and medical journals. The SF-36 has been proven responsive in 44 disease conditions and is accepted by the FDA as proof of benefit for improved functioning and other patient-reported outcomes. The SF-36 is available in 103 language translations.

The SF-36 has mental (4) and physical (4) component subscales. All 8 individual subscales will be measured but the principal analysis will be on the physical component summary score which is expected to be the most relevant for this patient population.

7.3 Safety Assessments

Any of the following drug safety information shall be collected:

Adverse events (AEs) and serious adverse events (SAEs) temporally associated with administration of IMP or saline solution (definitions and reporting requirements see Sections 7.3.1 and 7.3.2)

Pregnancies, drug overdose, interaction, medication error, lack of efficacy, post-study SAEs (see Section 7.3.6)

7.3.1 Adverse Events

7.3.1.1 Definitions

Adverse event (AE): An AE is any untoward medical occurrence in a study patient receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

Adverse drug reaction (ADR): An ADR is any noxious and unintended response to an IMP related to any dose. The phrase “response to an IMP” means that a causal relationship between the IMP and an AE carries at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Other significant AEs: Any marked laboratory abnormalities or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction or significant additional concomitant therapy.

Withdrawal due to AE/ADR: AE/ADR leading to discontinuation of treatment with IMP. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the patient is stable. All follow-up information collected will be made available to the Sponsor.

7.3.1.2 Collection

The condition of the patient will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard non-leading question such as “How have you been since the last visit / during the previous study period?” In addition, the patient diaries (if applicable) will be checked by the Investigator for any documented event.

Any AE or ADR which occurs during the study will be noted in detail on the appropriate pages of the eCRF. If the patient reports several signs or symptoms, which represent a single

syndrome or diagnosis, the latter should be recorded in the eCRF. The Investigator responsible will grade the severity of all AEs or ADRs (mild, moderate or severe), the seriousness (non-serious or serious) and causality, as defined below (Sections 7.3.1.3, 7.3.1.4 and 7.3.2). The Sponsor is responsible to assess the expectedness of each ADR (expected or unexpected), as defined below (Section 7.3.1.4).

In the event of clinically significant abnormal laboratory findings, the tests will be repeated and followed-up until they have returned to normal and/or an adequate explanation is available.

Diseases, signs and symptoms and/or laboratory abnormalities already existing before the first administration of IMP are not considered as AEs when observed at a later stage unless they represent an exacerbation in intensity or frequency (worsening).

The Investigator responsible should always provide detailed information concerning any abnormalities and the nature of, and reasons for any necessary action(s), as well as any other observations or comments, which are useful for the interpretation and understanding of the patients' AEs or ADRs.

7.3.1.3 Severity

The intensity/severity of all AEs will be graded as follows:

- mild: an AE, usually transient, which causes discomfort but does not interfere with the patient's routine activities;
- moderate: an AE which is sufficiently discomforting to interfere with the patient's routine activities;
- severe: an AE which is incapacitating and prevents the pursuit of the patient's routine activities.

Grading of an AE is up to the medical judgment of the Investigator and will be decided on a case by case basis.

7.3.1.4 Causality

The relationship of AEs to the administered IMP will be assessed by the Investigator:

- probable: reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the patient's clinical state.
- possible: reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.
- unlikely: reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the patient's clinical state or by environmental factors or other therapies administered.

- not related (unrelated): events for which sufficient information exists to conclude that the etiology is unrelated to the IMP.
- unclassified: reports which for one reason or another are not yet assessable, e.g. because of outstanding information (can only be a temporary assessment).

Classification of ADRs:

ADRs will be classified by the Sponsor as either expected or unexpected:

- expected: an ADR that is listed in the current edition of the Investigator's Brochure (or other reference safety information).
- unexpected: an ADR that is not listed in the current edition of the Investigator's Brochure or other reference safety information, or that differs because of greater severity or greater specificity.

7.3.1.5 Outcome

The outcome of all reported AEs has to be documented as follows:

1. recovered, resolved
2. recovering, resolving
3. not recovered, not resolved
4. recovered, resolved with sequelae
5. fatal
6. unknown

NOTE: A patient's **death** per se is not an event, but an outcome. The event which resulted in patient's death must be fully documented and reported, even in case the death occurs within 4 weeks after IMP treatment end, and without respect of being considered treatment-related or not.

7.3.1.6 Action(s) taken

AEs requiring action or therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment in an emergency situation.

The action taken by the Investigator must be documented:

a) in general

- none
- medication (other than IMP) or other (e.g., physical) therapy started
- test performed
- other (to be specified)

b) on IMP

- none
- product withdrawn
- dose reduced
- dose increased

The Investigator will follow-up each AE until it is resolved or until the medical condition of the patient is stable, and all relevant follow-up information will be reported to the Sponsor.

7.3.2 Serious Adverse Events

A **serious** AE (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is another important medical event.

NOTE: The term "life-threatening" refers to an event in which the patient was — in the view of either the reporting Investigator or the Sponsor — at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical judgment should be exercised in deciding whether an adverse event/reaction is serious in other situations: Important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definitions above, should also be considered serious.

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent should be reported as SAE. A suspected virus transmission means that virus antigen has been detected in the patient. A passive transmission of antibodies alone does not constitute a suspected virus transmission.

SAE reporting timelines

All SAEs, whether suspected to be related to study treatment or not, are to be reported by telephone, fax or e-mail immediately to the Clinical Project Manager or designee.

Contact details will be communicated at the study initiation visit.

An Octapharma "Serious Adverse Event Report" must be completed and submitted within 24 hours after recognition of the event.

All SAEs should additionally be reported to

Octapharma's Central Drug Safety Unit:
OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235, 1100 Vienna, Austria
Fax: [redacted]
E-mail: [redacted]

24 hours emergency telephone number:

Europe: [redacted]

USA: [redacted]

Waiver from SAE reporting requirement:

These exceptions/waivers include surgeries that are elective or planned before study entry, hospitalization because of study-related procedures or prolongation of the existing hospitalizations due to economic or social reasons, but not medical reasons. These should not be considered as SAEs.

7.3.3 Laboratory Safety Tests

Laboratory determinations will be done at a central laboratory.

The following parameters will be investigated during the study period as specified in Section 6.1 "Observations by visit":

Clinical chemistry: Na+ (sodium), K+ (potassium), glucose, ALAT/ALT/GPT (alanine aminotransferase), ASAT/AST/GOT (aspartate aminotransferase), LDH, total bilirubin, BUN (blood urea nitrogen), creatinine, albumin

Hematology: hematocrit, hemoglobin, complete blood count (CBC) with differential (erythrocytes/RBC, leukocytes/WBC, neutrophils, eosinophils, basophils, lymphocytes, monocytes, platelets)

Serum IgG

Urinalysis: protein, pH, glucose, ketones, leukocytes, hemoglobin and blood will be tested in urine by dipstick test (middle stream urine will be used)

Pregnancy test: Urine pregnancy test; if positive, a serum pregnancy test will be performed at central laboratory.

Blood sampling will take place prior to infusion of NewGam. The methods used for each parameter and the normal ranges of each determination will be provided in the Clinical Study Report.

7.3.4 Viral Safety Tests

Viral marker samples will be taken at screening, before the first NewGam infusion at Visit 2 and at the termination visit. Viral safety will be determined by serology tests for HIV, HBV and HCV at the central laboratory.

A screening and termination visit retention sample will be collected and stored frozen at ≤-70°C at the central laboratory for possible future testing.

7.3.5 Vital Signs and Physical Examination

To evaluate short-term tolerance, close monitoring of vital signs including pulse and respiratory rate, blood pressure and body temperature will be performed at time points specified in Section 6.1. Measurements will be carried out before the start of each infusion, at least once during each infusion, and up to 1 hour after end of infusion. Hemodynamic changes may occur during IGIV infusion and minor changes in pulse and blood pressure are frequent. For this reason, only changes in vital signs considered clinically significant by the Investigator are to be reported as AEs. In case fever occurs, temperature will be measured every morning until the body temperature is normalized. Fever will be defined as a body temperature >37.8 °C orally, >38.2 °C rectally, >38 °C axillary, >38.2 °C tympanic, and has to be documented as an AE.

Weight will be recorded at each infusion visit and reported to the pharmacist or designee as it is needed for the preparation of the next study medication dosage by the unblinded pharmacist or designee 3 weeks later. Height will be measured at baseline.

7.3.6 Other Relevant Safety Information

Post study related safety reports:

Any SAE which occurs up to four weeks after the last IMP administration should be reported by the Investigator to the Sponsor if the Investigator becomes aware of it. Proactive monitoring for post study SAEs is not required.

If a post study SAE is identified, the Investigator should complete an SAE form. Relation to the clinical study should be stated on the report.

If a patient dies within 4 weeks after the last IMP administration, this should be reported as well, regardless of being considered treatment-related or not.

Pregnancies:

Every effort will be made to avoid a pregnancy during the use of an IMP. WOCBP using an acceptable effective contraceptive method during the study will be enrolled.

WOCBP is defined as fertile woman, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Acceptable effective contraceptive measures include the following:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomised partner

- sexual abstinence
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide

Pregnancies occurring during the study (fetal exposure to the IMP) need to be reported.

In case of pregnancy during the study the Investigator is asked to complete the pregnancy notification form and to send it (by fax) to the CPM or designee.

Follow-up information on the outcome of both mother and fetus will be requested by a Sponsor representative.

Overdose, interaction, misuse, medication error and lack of efficacy:

The following safety relevant information should be reported as an AE or, if the reaction fulfils one of the criteria for seriousness, as a SAE.

Drug overdose:

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than that specified in the protocol, and higher than the known therapeutic dose and of clinical relevance. The reaction must be clearly identified as an overdose.

Interaction:

A drug interaction is a situation in which a substance/medicinal product affects the activity of an IMP, i.e., the effects are increased or decreased, or they produce an effect that none of the products exhibits on its own. The reaction must be clearly identified as drug interaction.

Misuse:

Misuse is the deliberate administration or use of the medicinal product outside its described indication or outside the current state of the art medical practice (off-label-use). The reaction must be clearly identified as misuse.

Medication error:

Medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, instructions for use/labelling. The reaction must be clearly identified as a medication error.

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all the information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (e.g., case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the Investigator will indicate in the source records that the patient participates in this study.

All data entered into the eCRF must be supported by source data in the patient records with the exceptions listed in Section 8.1.2.

The Investigator will permit study-related monitoring, audit(s), IEC/IRB review(s) and regulatory inspection(s), by providing direct access to source data/records.

The Investigator may authorize site staff (e.g., sub-Investigators, nurses) to enter study data into the eCRF. This must be documented in the „Delegation of Authority Log“, signed by the Investigator.

8.1.2 Electronic Case Report Forms

For each patient enrolled, an electronic CRF (eCRF) will be completed within the Electronic Data Capture (EDC) system and approved by the Investigator or an authorized sub-Investigator.

Study site staff (e.g. research nurse) will be responsible for entering patient data into the validated EDC system. All site personnel will be trained on the EDC system and study specific eCRFs prior to receiving access to the live database for data entry. The site is also provided with the approved eCRF Completion Guidelines which will assist in data entry and data issues/questions. The site will be notified once the database is active to begin data entry. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or change eCRF data must appear on the delegation of authority log.

8.1.3 Changes to Case Report Form Data

Monitors will perform source data verification (SDV) as defined for the study.

If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated programmatically within the EDC system, and ‘manual’ queries will be generated by either a monitor or Data Management.

Discrepancies and queries can only be corrected by the Investigator(s) or other authorized site personnel. An audit trail documents all changes to the data over the entire study period. If the reason for a change is not obvious, a comment must be supplied within the query’s response, stating the reason for the change, prior to closing. The study monitor should provide guidance to Investigator(s) and the Investigator(s)’ designated representatives on making such corrections.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks are performed and programs are run throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the Investigator prior to database lock.

8.2 Information of Investigators

An Investigator's Brochure will be handed out to the Investigator before the start of the study. This Brochure contains all information in the Sponsor's possession necessary for the Investigator to be fully and accurately informed about the safety of the IMP under evaluation and the respective benefit-risk ratio.

The Investigator's Brochure will be updated by the Sponsor at regular intervals and in case new information concerning the IMP becomes available.

The Investigators will be informed about the methods for rating relevant study outcomes and for completing CRFs in order to reduce discrepancies between participating Investigators and study sites.

The Investigator will be kept informed of important data that relate to the safe use of the IMP as the study proceeds.

8.3 Responsibilities

The Sponsor provides the study medication (NewGam). In this role, the Sponsor can be contacted in case of medical issues and is responsible for the assessment of the reported SAEs as well as for the further distribution to the relevant regulatory authorities.

The Co-ordinating Investigator of this study is [redacted]

The Principal Investigator is accountable for the conduct of the clinical study. Responsibilities may be delegated to appropriately qualified persons.

A „Delegation of Authority Log" will be filled in and signed by the Principal Investigator. In accordance with this authority log, study site staff (e.g., sub-Investigators, nurses) is authorized to perform tasks relating to the study.

Monitoring will either be done by the Sponsor or by a subcontractor (to be appointed later).

Study data management and statistics and EDC system will be delegated under an agreement of transfer of responsibilities to an external CRO and/or third party vendor. All Octapharma procedures and policies have to be met by this CRO/third party vendor, discrepancies or exceptions are to be approved by Octapharma's Manager of Biometrics.

An Independent Data Monitoring Committee (IDMC) will be installed to observe the safety throughout the trial. The detailed obligations and procedures will be laid down in a written procedure provided by the Sponsor.

All laboratory tests (hematology, clinical chemistry, virology and urinalysis) will be done centrally.

NCS will be centrally reviewed by [redacted].

All parties involved in the study are responsible to comply with local and international obligations, regulatory requirements and duties in accordance with local laws, ICH-GCP E6 and GLP guidelines, SOPs and other applicable regulations.

8.4 Investigator's Site File

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by ICH-GCP E6 guidelines and regulations (e.g., copies of the protocol, study approval letters, all original informed consent forms, a blank print-out of the e-CRF, drug dispensing and accountability logs, correspondence pertaining to the study, etc.) should be filed accurately and kept by the Investigator for the maximum period of time required by local regulations.

The Investigator is responsible for maintaining a confidential patient identification code list, which provides the unique link between named source records and eCRF data for the Sponsor. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.5 Provision of Additional Information

On request, the Investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records, ensuring that the patient's confidentiality is maintained. This is particularly important when errors in data transcription are encountered. In case of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the patient's confidentiality is protected in accordance with applicable regulations.

8.6 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established by the Sponsor. The IDMC will be composed of recognized experts in the field of peripheral neuropathy who are not actively recruiting patients.

The IDMC will review relevant data periodically during the study and will give advice on the continuation, modification or termination of the study. A written study specific procedure will define in detail the composition, responsibilities and procedures of the IDMC.

8.7 Steering Committee

A Steering Committee will be established to medically/scientifically advice and guide the Sponsor during the study progress. The Steering Committee will be responsible for overall study overview, may give recommendations for protocol amendments after discussion with the Sponsor and may be involved in publication writing together with the DMC members and Co-

ordinating Investigator. It will consist of at least three national coordinating investigators and/or internationally well-known CIDP experts with experience in conducting clinical trials.

9 STATISTICAL METHODS AND SAMPLE SIZE

The statistical analysis will be delegated under an agreement of transfer of responsibilities to an external CRO. All Octapharma procedures and policies have to be met by this CRO. Discrepancies or exceptions are to be approved by the Sponsor's Manager of Biometrics.

9.1 Determination of Sample Size

The sample size calculation is based on the proportion of responders in the 1.0 g/kg dose group. This dose regimen is the currently most commonly used for maintenance IGIV doses in CIDP. Recent experiences with this dosing regimen are available from the ICE study [24] and the PRIMA trial.[25] In both of these studies, the lower confidence limit of the 95% Wilson-Score confidence interval for the proportion of responders (R) was 42% if rounded to the nearest integer, and thus we have also chosen 42% as the threshold for the following pair of hypotheses for evaluation of the primary endpoint:

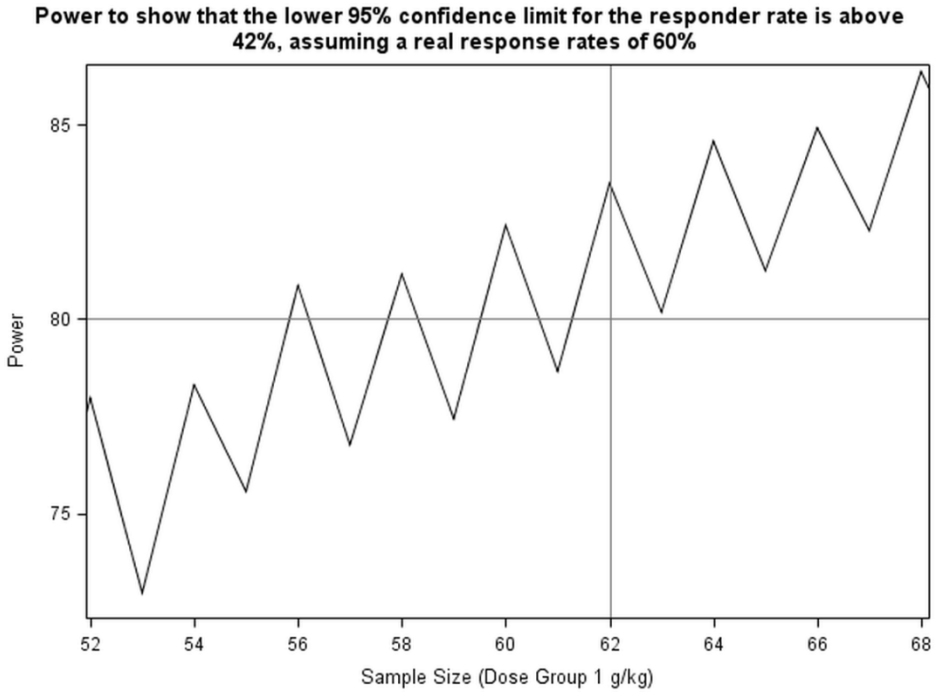
$$H_0: R < 0.42$$

$$H_1: R \geq 0.42$$

This will be tested by comparing the lower limit of the 95% Wilson-Score confidence interval for the observed proportion of responders with the pre-defined threshold of 0.42.

We estimate the true percentage of responders in CIDP patients treated with NewGam as 60%. This corresponds to the 60.7% of responders observed in the PRIMA study, but is higher than the outcome in the ICE (54.2%), that in the opinion of many experts underestimates the true percentage of responders.

We applied these parameters to a computer simulation realized in SAS to determine the statistical power associated with various group sizes:



To achieve a power of at least 80%, a minimum of 62 evaluable patients in the 1.0 g/kg dose group will be needed; to account for possible dropouts we plan to enroll 70 patients into this group.

In order to allow for the comparison between dose groups, ProCID will enroll half of the eligible patients in the standard dose arm (1.0 g/kg NewGam) and the other half into the lower and higher dose arms (0.5 g/kg and 2.0 g/kg NewGam), resulting in a total of 124 evaluable patients, and an enrollment target of 140 patients overall (ratio: 1:2:1 for 0.5 g/kg, 1.0 g/kg, and 2.0 g/kg, respectively).

9.2 Statistical Analysis

A formal statistical analysis plan describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to unblinding and the start of the statistical analysis.

Data tabulations will comprise the results for the different dose groups and for the whole analysis set whenever appropriate. Evaluation of primary and secondary endpoints will be presented for each randomization stratum (prior treatment with Immunoglubulins or Corticosteroids) separately to facilitate the identification of noteworthy differences in the clinical responses between these two groups. No further subgroup analyses are pre-specified for this study, but the different CIDP variants eligible for enrollment, such as Multifocal Acquired Demyelinating Sensory And Motor Neuropathy (MADSAM) or pure motor CIDP, will be compared with respect to dose group, INCAT score and proportion of response as well. If indicated by the data, further comparisons between these CIDP variants will be added post-hoc.

9.2.1 Population for Analysis

The following populations will be considered for the statistical analysis:

The safety set (SAF) will include all randomized patients who received at least part of one infusion of IMP.

The full analysis set (FAS) is defined according to the intention-to-treat principle, and will include all patients of the SAF who satisfy all major entry criteria – in particular the diagnosis of CIDP – and for whom any data was collected post infusion of IMP. Every treated subject will be considered in the analysis according to his randomized treatment/dose assignment.

The per-protocol set (PPS) – being a subset of the FAS — will exclude patients with significant protocol deviations, which may have an impact on the evaluation of the primary study outcome parameter(s). This is the set of patients who participated in the study as intended and for whom the primary efficacy endpoint can be evaluated as planned.

All protocol deviations documented during the conduct of the study or identified at the data review process prior to DB lock will be reviewed and classified with respect to its effect on the planned analysis. Only protocol violations with the potential to significantly affect the study results or to invalidate the interpretation of the data obtained will lead to exclusion of patients from the PPS. This classification of protocol violations is the joint responsibility of the clinical study manager, the study statistician, and Octapharma's responsible medical expert, and will be performed and documented before the database is locked, the data is unblinded, and the statistical analyses are performed.

Protocol deviations to be considered will include (but are not limited to):

- Deviations of the study entry criteria
- Administration of any other blood or plasma-derived product or of any other immunoglobulin preparations
- Any prohibited concomitant medication
- Failure to attend two scheduled consecutive visits OR three or more scheduled visits during the study for reasons other than clinical reasons

The analysis of safety will be based on the safety set.

The evaluation of primary objective(s) will be performed for the FAS (intention-to-treat analysis) and for the PPS (per-protocol analysis). The ITT analysis is considered to be the most relevant, and will be presented first in the statistical report.

The evaluation of secondary objectives will be performed for the FAS, and in addition for the PPS in case the two populations differ by more than 5%

9.2.2 Efficacy Analysis Plan

Efficacy will be evaluated by a variety of commonly used parameters to assess the severity and progression of CIDP, with the adjusted INCAT disability score being the most important parameter. The primary efficacy endpoint will thus be the proportion of responders in the 1.0 g/kg NewGam arm, where a responder is defined as a patient with a decrease of at least 1.0 point on the adjusted INCAT disability score at Week 24 relative to Baseline.

Confirmatory statistical testing of the primary endpoint will be done by constructing the 95% Wilson-Score confidence interval for the proportion of responders, and comparing the lower confidence limit with the predefined threshold of 0.42. This corresponds to a one-sided test of the following pair of hypotheses at the α=0.025 confidence level.

$$H_0: R < 0.42$$

$$H_1: R \geq 0.42$$

Where R is the proportion of responders i.e. the number of patients in the FAS who are responders according to the abovementioned definition, divided by the total number of patients in the FAS.

This evaluation will also be presented for the PPS to assess the robustness of the primary study endpoint with respect to protocol violations.

To assess and compare the effectiveness of the different dose groups, these will be presented side-by-side in descriptive statistics, including the 95% confidence intervals for the proportion of responders. In addition the response rates in the alternative dose groups will be compared descriptively to the 1.0 g/kg treatment group by presenting the confidence intervals for the differences; furthermore an exploratory logistic regression, that includes the pre-treatment as well as the dose group as predictor variables, will be conducted.

All efficacy endpoints detailed in Sections 3.1.2 and 3.1.3 will be summarized by means of descriptive statistics, presented graphically as appropriate, and listed in full detail. Tables and graphs will allow for direct comparison of the different dose groups whenever feasible. A similar logistic regression as for the primary endpoint will also be used for the secondary response variables (based on grip strength or I-RODS scores).

9.2.3 Safety Analysis Plan

The safety analysis will comprise descriptive statistics, tabulations and listings of all treatment emergent adverse events (TEAEs), safety laboratory results, viral markers, vital signs, physical examination findings, and any other relevant safety information as detailed in Section 7.3.

9.2.3.1 Adverse Events

All reported AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA).

An AE is defined as treatment-emergent, if first onset or worsening is after start of the first IMP administration. Only TEAEs are accounted for in the analysis.

A TEAE will be considered to be temporally associated with the infusion (or 'infusional') if it starts during or within 72 hours of the end of the infusion.

Incidences of TEAEs will be given as numbers and percentages of patients and infusions with:

- Any TEAE
- Any serious TEAE
- Any TEAE probably or possibly related to the trial drug
- Any severe TEAE
- Number of infusional TEAEs
- Number and percentage of infusions temporally associated with one or more TEAE
- Any withdrawal due to TEAE
- Any significant TEAE (see Section 7.3.1.1)
- Any TEAE by MedDRA Preferred Term (PT)
- Any TEAE by MedDRA System Organ Class (SOC)

Summary tables for TEAEs will be given by System Organ Class (SOC) and Preferred Term (PT). Additionally, TEAEs will be summarized by severity and relationship to study treatment.

All TEAEs for each patient, including multiple occurrences of the same event, will be listed in full detail, including reported term, MedDRA PT and SOC, onset, duration, time to the AE occurrence from last dose, causality, dosage, severity, seriousness and actions taken.

Narratives will be prepared describing each death, other SAEs, and other significant TEAEs that are judged to be of special interest because of clinical importance.

9.2.3.2 Laboratory Safety Tests

The safety laboratory data (Clinical chemistry, hematology, and urinalysis) will be converted to standard units during the data management process. The laboratory data will be listed with suitable flags indicating abnormal values (L=Lower than reference range, H=Higher than reference range) and clinical significance as judged by the investigator whenever available. Summary statistics for the laboratory values as well as their changes from baseline at each time point will be tabulated.

9.2.3.3 Viral Safety tests

All viral marker results will be listed, and shift tables will be used to identify any possible seroconversion during the course of the study.

9.2.3.4 Vital Signs

Vital signs parameters will be summarized by visit, using the standard set of summary statistics for both, absolute values and changes from baseline.

9.2.3.5 Physical Examination

Shift tables will be used to identify changes in the assessments between visits. New or worsened symptoms/findings will be listed individually.

9.2.3.6 Other Relevant Safety Information

All additional safety information collected in the study will be listed and reviewed. If judged to be of relevance, narratives will be prepared to describe any such results in full detail.

9.2.4 Handling of Missing Data

In general, missing data will not be imputed, and all data derivations will be based on observed values only. Only in case of missing body weight, the last available weight measurement will be used for calculating the dose per kg bodyweight (last observation carried forward).

If missing values occur in the confirmatory analysis of the primary endpoint in the FAS, they will be imputed by worst observed values, i.e. the patient concerned will be analyzed as non-responder.

9.3 Randomization / Stratification / Code Release

All patients still qualified to participate in the study at Visit 2 will be randomized to one of the three treatment arms by an electronic IWRS tool. The randomization will apply a randomization ratio of 1:2:1 with respect to the dosage groups of 0.5, 1.0, and 2.0 g/kg of NewGam by means of a stratified block design, using the treatment before enrollment (immunoglobulin or corticosteroids treatment) as strata and a fixed block size. This will ensure the desired overall randomization ratio and avoid random differences between the dosage groups with respect to the CIDP treatment used prior to enrollment into the ProCID study.

The randomization scheme will only be available to the statisticians responsible for creating it, and the programmer implementing the scheme into the IWRS system. No information on treatment assignment will be communicated to the sponsor or any CRO personnel responsible for the conduct of the study or the analysis of data.

The result of randomization, i.e. the treatment group assignment of individual patients will only be reported to the hospital pharmacist or designee by a dedicated email that no other trial personnel will have access to.

Blinding will not be broken while the study is ongoing, unless in case of medical emergencies as described in Section 5.8. Only after completion of all procedures related to data cleaning, the medical review of the data, the finalization of the statistical analysis plan, the agreement on the final patient disposition, and the formal database lock the blind will be broken and the individual treatment assignment will be added to the clinical database for analysis.

9.4 Interim Analysis

No interim analysis is planned.

10 ETHICAL / REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical / Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an Independent Ethics Committee (IEC) / Institutional Review Board (IRB) and to the Regulatory Authority. The study will be conducted in compliance with the protocol, ICH-GCP E6 regulations and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (e.g. CRO) as required by national law and in accordance with FDA/Regulatory Authority regulations.

10.2 Approval of Study Documents

The study protocol, a sample of the patient information and informed consent form, any other materials provided to the patients, and further requested information will be submitted by the Sponsor or the Investigator to the appropriate IEC/IRB and the Regulatory Authority. The study approval letter must be available before any patient is exposed to a study-related procedure.

The Sponsor, the Investigator and any third party (e.g., CRO) involved in obtaining approval, must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

10.3 Patient Information Sheet and Informed Consent Form

The Investigator will obtain freely given written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards and any other aspect of the study which is relevant to the patient's decision to participate. An English master version of the patient information sheet and the informed consent form will be translated into local languages. The informed consent form must be signed, with name and date and time noted by the patient, before the patient is exposed to any study-related procedure, including screening tests for eligibility.

The Investigator will explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify. The Investigator will complete the informed consent section of the CRF for each patient enrolled.

Each patient will be informed that his/her medical (source) records may be reviewed by the study monitor, a quality assurance auditor or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Investigator (Co-ordinating Investigator in multicenter studies) and the Sponsor prior to its implementation. Any such amendments will be submitted to the IEC/IRB(s) and/or competent authority responsible as required by applicable regulations. IEC/IRB(s) approval will at a minimum be requested for any change to this protocol which could affect the safety of the patients, the objective/design of

the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Patients' Data

The Investigator will ensure that the patient's confidentiality is preserved. In eCRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient number. Documents not for submission to the Sponsor, i.e., the confidential patient identification code list, original consent forms and source records will be maintained by the Investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries compared to source data. The Investigator will co-operate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take place shortly after the inclusion of the first patient. Thereafter, monitoring frequency will depend on study progress, but is expected to be every 10 to 12 weeks depending on the sites' performance and recruitment rate.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyze, verify and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the eCRFs, including all laboratory results.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IEC/IRB/regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and effectiveness of the IMP have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (CSR; in accordance with relevant guidelines and Sponsor's SOPs) will be prepared by the Sponsor or designee after the completion of the study. The Co-ordinating Investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is envisaged by an Investigator, the Investigator agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor prior to submission to an editorial board or scientific review committee. This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multicenter studies only in their entirety and not as individual center data. Authorship will be determined by mutual agreement.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a patient in association with the IMP or the participation in the study, the Sponsor will contract insurance in accordance with local regulations.

The Investigator is responsible for dispensing the IMP according to this protocol, and for its secure storage and safe handling throughout the study.

14 REFERENCES

1. Hughes RA, Allen D, Makowska A, Gregson NA. Pathogenesis of chronic inflammatory demyelinating polyradiculoneuropathy. JPeripherNervSyst. 2006;11(1):30-46.
2. Hughes RA. Management of chronic inflammatory demyelinating polyradiculoneuropathy. Drugs. 2003;63(3):275-87.
3. Dyck PJ, Lais AC, Ohta M, Bastron JA, Okazaki H, Groover RV. Chronic inflammatory polyradiculoneuropathy. Mayo Clin Proc. 1975;50(11):621-37.
4. Finsterer J. Treatment of immune-mediated, dysimmune neuropathies. Acta neurologica Scandinavica. 2005;112(2):115-25.
5. Hughes RA, Hadden RD, Gregson NA, Smith KJ. Pathogenesis of Guillain-Barre syndrome. JNeuroimmunol. 1999;100(1-2):74-97.
6. McLeod JG, Pollard JD, Macaskill P, Mohamed A, Spring P, Khurana V. Prevalence of chronic inflammatory demyelinating polyneuropathy in New South Wales, Australia. AnnNeurol. 1999;46(6):910-3.
7. Rentzos M, Anyfanti C, Kaponi A, Pandis D, Ioannou M, Vassilopoulos D. Chronic inflammatory demyelinating polyneuropathy: A 6-year retrospective clinical study of a hospital-based population. JClinNeurosci. 2007;14(3):229-35.
8. Dalakas MC. Advances in the diagnosis, pathogenesis and treatment of CIDP. Nature reviewsNeurology. 2011;7:507-17.
9. Taskforce AHSotAAoNA. Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Report from an Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. Neurology. 1991;41(5):617-8.
10. Nicolas G, Maisonobe T, Le FN, Leger JM, Bouche P. Proposed revised electrophysiological criteria for chronic inflammatory demyelinating polyradiculoneuropathy. Muscle Nerve. 2002;25(1):26-30.
11. Koski CL, Baumgarten M, Magder LS, Barohn RJ, Goldstein J, Graves M, et al. Derivation and validation of diagnostic criteria for chronic inflammatory demyelinating polyneuropathy. JNeurolSci. 2009;277(1-2):1-8.
12. van den Bergh PYK, Hadden RDM, Bouche P, Cornblath DR, Hahn A, Illa I, et al. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society - First Revision. Eur J Neurol. 2010;17:356-63.
13. Donaghy M, Mills KR, Boniface SJ, Simmons J, Wright I, Gregson N, et al. Pure motor demyelinating neuropathy: deterioration after steroid treatment and improvement with intravenous immunoglobulin. JNeurolNeurosurgPsychiatry. 1994;57(7):778-83.
14. Busby M, Donaghy M. Chronic dysimmune neuropathy. A subclassification based upon the clinical features of 102 patients. JNeurol. 2003;250(6):714-24.
15. Austin JH. Recurrent polyneuropathies and their corticosteroid treatment; with five-year observations of a placebo-controlled case treated with corticotrophin, cortisone, and prednisone. Brain. 1958;81(2):157-92.
16. Hughes RA, Mehndiratta MM. Corticosteroids for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev. 2015;1:CD002062.
17. Van den Bergh PY. Intravenous immunoglobulin (IVIG) in the treatment of chronic demyelinating polyradiculoneuropathy 1. Acta NeurolBelg. 2001;101(3):147-51.
18. Mehndiratta MM, Hughes RAC, Pritchard J. Plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy (Review). Cochrane Database of Systematic Reviews. 2015(Issue 8):Art. No.: CD003906. DOI: 10.1002/14651858.CD003906.pub4.
19. Couriel D, Weinstein R. Complications of therapeutic plasma exchange: a recent assessment. JClinApher. 1994;9(1):1-5.

20. Koller H, Kieseier BC, Jander S, Hartung HP. Chronic inflammatory demyelinating polyneuropathy. New England Journal of Medicine. 2005;352(13):1343-56.
21. Kuitwaard K, van Doorn PA. Newer therapeutic options for chronic inflammatory demyelinating polyradiculoneuropathy. Drugs. 2009;69(8):987-1001.
22. Simmons Z, Wald JJ, Albers JW. Chronic inflammatory demyelinating polyradiculoneuropathy in children: I. Presentation, electrodiagnostic studies, and initial clinical course, with comparison to adults. Muscle Nerve. 1997;20(8):1008-15.
23. Simmons Z, Wald JJ, Albers JW. Chronic inflammatory demyelinating polyradiculoneuropathy in children: II. Long-term follow-up, with comparison to adults. Muscle Nerve. 1997;20(12):1569-75.
24. Hughes RA, Donofrio P, Bril V, Dalakas MC, Deng C, Hanna K, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. Lancet Neurol. 2008;7(2):136-44.
25. Leger JM, De Bleecker JL, Sommer C, Robberecht W, Saarela M, Kamienowski J, et al. Efficacy and safety of Privigen((R)) in patients with chronic inflammatory demyelinating polyneuropathy: results of a prospective, single-arm, open-label Phase III study (the PRIMA study). J PeripherNervSyst. 2013;18(2):130-40.
26. Merkies IS, van Nes SI, Hanna K, Hughes RA, Deng C. Confirming the efficacy of intravenous immunoglobulin in CIDP through minimum clinically important differences: shifting from statistical significance to clinical relevance. J Neurol Neurosurg Psychiatry. 2010;81(11):1194-9.
27. Draak THP, Vanhoutte EK, van Nes SI, Gorson KC, van der Pol WL, Notermans NC, et al. Changing outcome in inflammatory neuropathies: Rasch-comparative responsiveness. Neurology. 2014;83(23):2124-32.
28. Sloan JA. Assessing the minimally clinically significant difference: scientific considerations, challenges and solutions. COPD. 2005;2(1):57-62.
29. Vanhoutte EK, Faber CG, van Nes SI, Jacobs BC, van Doorn PA, van KR, et al. Modifying the Medical Research Council grading system through Rasch analyses. Brain. 2012;135(Pt 5):1639-49.
30. Eftimov F, Winer JB, Vermeulen M, de HR, van S, I. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. The Cochrane database of systematic reviews. 2013;12:CD001797.
31. van Doorn PA, Brand A, Strengers PF, Meulstee J, Vermeulen M. High-dose intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy: a double-blind, placebo-controlled, crossover study. Neurology. 1990;40(2):209-12.
32. Vermeulen M, van Doorn PA, Brand A, Strengers PF, Jennekens FG, Busch HF. Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy: a double blind, placebo controlled study. JNeurolNeurosurgPsychiatry. 1993;56(1):36-9.
33. Hahn AF, Bolton CF, Zochodne D, Feasby TE. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy. A double-blind, placebo-controlled, cross-over study. Brain. 1996;119 (Pt 4):1067-77.
34. Mendell JR, Barohn RJ, Freimer ML, Kissel JT, King W, Nagaraja HN, et al. Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating polyradiculoneuropathy. Neurology. 2001;56(4):445-9.
35. Kubori T, Mezaki T, Kaji R, Kimura J, Hamaguchi K, Hirayama K, et al. [The clinical usefulness of high-dose intravenous immunoglobulin therapy for chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy]. No To Shinkei. 1999;51(2):127-35.
36. Latov N, Deng C, Dalakas MC, Bril V, Donofrio P, Hanna K, et al. Timing and Course of Clinical Response to Intravenous Immunoglobulin in Chronic Inflammatory Demyelinating Polyradiculoneuropathy. Arch Neurol. 2010;67(7):E1-E6.

37. Elovaara I, Apostolski S, Van DP, Gilhus NE, Hietaharju A, Honkaniemi J, et al. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases: EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases. European Journal of Neurology. 2008;15(9):893-908.
38. Hughes R, Bensa S, Willison H, Van den BP, Comi G, Illa I, et al. Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. AnnNeurol. 2001;50(2):195-201.
39. Vanhoutte EK, Faber CG, van Nes SI, Cats EA, van der Pol WL, Gorson KC, et al. Rasch-built Overall Disability Scale for Multifocal motor neuropathy (MMN-RODS(©)). Journal of the peripheral nervous system : JPNS. 2015;20(3):296-305.
40. Vanhoutte EK, Latov N, Deng C, Hanna K, Hughes RA, Bril V, et al. Vigorimeter grip strength in CIDP: a responsive tool that rapidly measures the effect of IVIG - the ICE study. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2012:doi:10.1111/j.468-331.2012.03851.x.
41. Kleyweg RP, van der Meche FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barre syndrome. Muscle Nerve. 1991;14(11):1103-9.
42. Merkies IS, Schmitz PI, Samijn JP, van der Meche FG, van Doorn PA. Fatigue in immune-mediated polyneuropathies. European Inflammatory Neuropathy Cause and Treatment (INCAT) Group. Neurology. 1999;53(8):1648-54.
43. van Nes SI, Vanhoutte EK, Faber CG, Garssen M, van Doorn PA, Merkies ISJ, et al. Improved fatigue assessment in immune-mediated neuropathies: the modified Rasch-built fatigue severity scale. J Peripheral Nervous System. 2009;14:268-78.

15 APPENDICES

Appendix 1: Inflammatory Rasch-built overall disability sum score (I-RODS)

Appendix 2: Modified Fatigue Severity Scale (FSS)

Appendix 3: SF-36 Health Survey