23 June 2011

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kiovig

human normal immunoglobulin (ivig)

Procedure No.: EMEA/H/C/000628/II/0037

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Scientific discussion

Introduction

About the product

KIOVIG is a plasma-derived product consisting of a highly purified preparation of human IgG. It is supplied as a ready-to-use liquid formulation with a pH of 4.6 to 5.1. 98% of the protein is gamma globulin with a normal subclass distribution. The manufacturing process results in an intact IgG molecule with complete functional activity. The final product contains only trace amounts of IgA and IgM. Glycine is used as a stabiliser. KIOVIG is supplied in single-dose vials that nominally contain 1g, 2.5g, 5g, 10g, 20g and 30g protein per vial.

In the EU, KIOVIG is currently licensed for replacement therapy in a number of primary immunodeficiency disorders (PID), for immune modulation in idiopathic thrombocytopenic purpura (ITP), Guillain Barré syndrome and Kawasaki disease, and for allogeneic bone marrow transplantation according to the current Core SmPC for human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/094038/2007).

About the disease

Multifocal motor neuropathy (MMN) is a rare, probably immune-mediated disorder characterized by slowly progressive, asymmetric, distal weakness of one or more limbs, most commonly the arms, with no objective loss of sensation. Multifocal motor neuropathy was described in detail in 1988 for the first time (Parry GJ, Clarke S. Multifocal acquired demyelinating neuropathy masquerading as motor neuron disease. Muscle Nerve 1988;11:103-7). This weakness may be accompanied by muscle atrophy in later stages of the disease, and cramps and fasciculation are reported to occur in approximately 50% of patients with MMN. Tendon reflexes are often decreased or absent in the affected limb. The hallmark of the disease is the presence of multifocal conduction block on electrophysiological testing outside the usual sides of nerve compression.

Almost 80% of people with MMN are between 20 and 50 years of age at onset of the disease, and men are more frequently affected than women (2.6:1). The prevalence is estimated to be 1 to 2 per 100,000.

MMN seems to be an immune mediated disorder. Serum IgM GM1 antibodies are detectable in 30% to 80% of the patients, furthermore increased signal intensities on T2-weighted MR images of the brachial plexus have been observed suggesting an inflammatory process.

Treatment options for MMN patients are sparse. Patients with MMN do not respond to steroids or plasma exchange, and may even worsen with these treatments.

Cyclophosphamide and interferon-beta 1a have been suggested beneficial in several uncontrolled studies, but cyclophosphamide has serious long-term side effects and interferon-beta 1a has only been tested in a very limited number of patients.

Previous studies on the use of IVIg in patients with MMN suggest variable effects on disability or muscle impairment, which is partly due to the small patient populations studied. In addition, the disability scales and scores for muscle weakness used have their limitation in that they are not adapted specifically for MMN resulting in changes in overall strength and disability parameter are comparably small.

Limitations regarding the available data on the efficacy of IVIg treatment in patients with MMN are essentially related to the rare nature of the condition, and the interindividual variability in response

rates. Furthermore, the use of different disability scales in the studies, for instance the modified Norris scale by Azulay (Intravenous immunoglobulin treatment in patients with motor neuron syndromes associated with anti-GM1 antibodies. Neurol. 1994; 44:429-432), modified Rankin scale by van den Berg (Improvement of multifocal motor neuropathy during long-term weekly treatment with human immunoglobulin. Neurology.1995; 45:987-988.) and a self-evaluation scale score from 0 to 5 by Léger (Intravenous immunoglobulin therapy in multifocal motor neuropathy. Brain.2001;124:145-153) contribute to impression of divergent results.

An analysis (Cochrane Review) across all randomized controlled-trials on IVIg treatment in MMN demonstrated a non-significant trend towards improvement in disability after intravenous immunoglobulin compared with placebo, and a significant improvement in muscle strength (van Schaik IN, van den Berg LH, de Haan R, Vermeulen M. Intravenous immunoglobulin for multifocal motor neuropathy. Cochrane Database Syst.Rev. 2005, CD004429).

Treatment guidelines / recommendations

The treatment of multifocal motor neuropathy (MMN) with IVIg is recommended by the Guideline on Management of Multifocal Motor Neuropathy and the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) Guideline for the Use of IVIg in the Treatment of Neurological Diseases. The EFNS/PNS Guideline recommends IVIg dosage regimens of 1 g/kg every 2-4 weeks or 2 g/kg every 4-8 weeks. Treatment strategies that aim to detect the lowest effective dose and the longest tolerated interval may lead to insufficient dosing in the long-term in many patients.

The use of IVIg in the treatment of MMN is supported by the 2009 assessment of off-label-use expert panel convened by the German Ministry of Health. The expert panel concluded that IVIg therapy in patients with MMN was recommended despite recognized weaknesses of published studies, since a positive safety profile and a response rate to IVIg of approximately 80% have been established and alternative therapies are lacking.

Distinct IVIgs have been approved for the treatment of MMN in a few European Countries on a national basis (France, the Netherlands, and Belgium).

The present variation application has been submitted to add the treatment of MMN to the approved indications for Kiovig in 4.1 of the SmPC. It considers the CHMP guideline on the clinical investigation of human normal immunoglobulin for the intravenous administration (IVIg) (EMA/CHMP/BPWP/94033/2007 rev.2).

The Applicant did not seek scientific advice from CHMP for the development in this indication. The applicantion included a summary of published literature and the results of two completed clinical studies in patients with MMN.

Information on Paediatric requirements

This variation did not fall under Article 8 of Regulation (EC) N° 1901/2006, as amended (“Paediatric Regulation”).

The Applicant has provided a statement confirming the absence of EU patent coverage for the product which was recognised by EMA as the reason for being exempt from the formal PIP requirements posed by the Article 8 of the regulation.

Clinical aspects

Introduction

- Tabular overview of clinical studies

The application is based on the data from the following trials:

Table 1.

Study ID	No. of study sites/ location	Design	Study Objective	Subjs by arm entered/ completed	Duration	Gender M/F	Diagnosis Inclusion criteria	Primary Endpoint
MMN Conver-sion/ **Study I**	1/ NL.	Prospective, open-label, single-arm and Follow-up	maintenance therapy: efficacy, safety, and tolerability	20/20 Follow-up: 19/19	12 mo., thereof 9 mo. on KIOVIG Follow up: 2 y.	16/4	definite, or probable MMN	Change in MRC score
Initial treatment of MMN/ **Study II**	1/ NL	Prospective, open-label, single-arm	Initiation and maintenance therapy: efficacy, safety, and tolerability	8/8 Follow-up: 7/8	1 loading dose of KIOVIG Follow up: 1-3 y	7/1	definite, or probable MMN	Change in MRC score

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Literature review

The Applicant provided a comprehensive literature review on MMN treatments.

Placebo-controlled Studies on IVIg Products in MMN

The use of IVIg for MMN was the subject of an extensive review by the Cochrane Collaboration. The Cochrane search retrieved 285 studies including a total of 484 MMN patients, 383 of whom were treated with IVIg. Four controlled, double-blind studies were identified, in which a total of 46 patients with MMN received treatment with IVIg (Table 2). In a meta-analysis of these studies conducted by van Schaik et al. (2005), an improvement in strength was reported in 78% of patients following IVIg treatment compared to 4% following a placebo. Improvement in disability was observed in 39% and 11% of patients following IVIg therapy and placebo, respectively.

Table 2.

Placebo-controlled Studies on Efficacy of IVIG Products in Patients with MMN						
Author	**Design**	**Wash-out phase**	**IVIG dose**	**Target criterion**	**Number of patients with MMN**	**Outcome**
Leger 2001 [14] (Baxter study IMAG-089)	Double-blind, partial cross-over design	No	0.5 g/kg/day for 5 days (Endobulin 5%, Baxter) once per month for 3 months	MRC score, self-evaluation scale	19 (18 completed study)	11/18 patients responded to IGIV, 2/18 responded to placebo
Van den Berg 1995 [33]	Double-blind cross-over design	Yes, variable	Two courses of 0.4 g/kg/day for 5 days, interval variable IVIG (CLB Amsterdam)	Muscle strength determined by dynamometric measurements	6	5/6 patients responded to IGIV, none responded to placebo
Azulay 1994 [34]	Double-blind cross-over design	Yes, 8 weeks	One course of 0.4 g/kg/day for 5 days IVIG (CNTS France)	Isometric muscle strength	5	Muscle strength increased ≥50% in all patients following IGIV and none following the placebo
Federico 2000 [35]	Double-blind cross-over design	Yes, variable	One course of 0.4 g/kg/day for 5 days IVIG (Bayer Inc, Canada)	Subjective strength assessment, grip strength, neurologic disability scale	16	Subjective strength ratings improved in 11/16 patients after IGIV and in no patients after placebo. Grip strength and neurologic disability scale scores improved significantly following IGIV treatment but not placebo.

Long-term Treatment of MMN with IVIg products

Several studies, involving a total of 89 patients, have assessed the long-term efficacy (up to 12 years) of treatment of MMN with IVIg (Table 3). The beneficial effects of treatment appeared within days or 1-4 weeks, and declined within 4 to 8 weeks, requiring repeat dosing at variable intervals. Maintenance treatment, guided by the functional disability of the individual patient, is therefore necessary to maintain the beneficial effect on muscle strength in most cases.

The response to IVIg treatment decreased in some subjects over time, which is likely to be a result of progressive axonal loss. However, increasing monthly doses appeared to restore treatment response. Notably, despite general disease progression and increases in muscle weakness over time, MMN patients on long-term maintenance treatment with IVIg had improved strength scores at the end of observation period compared to baseline.

Nonetheless, disease progression is inherent in the natural course of MMN, and cannot be completely halted by IVIg treatment. For example, in a long-term observational study in 11 patients receiving IVIg (GAMMAGARD SD, Baxter) over 4-8 years, the average slope of the MRC sum scores was -0.2 (standard deviation [SD] 0.2). With respect to Guy's disability scores, the average slopes were -0.1 (SD 0.8) for upper limbs, and -0.4 (SD 0.7) for lower limbs. Statistically, the declines were not different from zero, and reflected intra-, and inter-individual variation. Overall, muscle strength tended to be slightly lower at the end of the observation period, compared to the initial response, but was still higher than before IVIg initiation. These findings are similar to other long-term observational studies.

Table 3.

Efficacy of Long-term Treatment of MMN with IVIG products					
Author	**Patients**	**Follow-up duration**	**IVIG treatments**	**Clinical Parameters**	**Main outcomes**
Azulay 1997 [42]	18 (15 male, 3 female)	9-48 months (mean 25.3)	0.4 g/kg daily over 3-5 days, at intervals determined individually. Mean of 6.3 infusions per patient.	Maximum voluntary isometric contraction (MVIC), Modified Rankin scale	12/18 patients improved MVIC score by ≥30%, the mean increase was 54%. Responders improved ≥1 grade on Rankin scale. The mean duration of IVIG effect was 53 days. 1/12 responders deteriorated after 3 courses, 2/12 went into remission, and 3/12 required cyclophosphamide after 3 IVIG courses due to decrease in response.
Léger 2008 [40]	40 (23 male, 17 female), 22/40 IGIV-naïve.	Mean 7.1 months for IGIV-naive patients; 2.2±2.0 years for all	2g/kg within 3-5 days monthly for 6 months, then maintenance doses as required.	MRC score	14/20 evaluable IGIV-naive patients responded after 6 months (MRC score increased ≥1 point in ≥2 of 8 most affected muscles). After long-term treatment, 8/37 patients with available data were in remission, 4/37 were non-responders. 25/37 patients were clinically stable dependent on ongoing IVIG treatment. In 6 naive patients for whom data were available at >12 months, MRC scores at final follow up were lower than after 1st infusion in 4 patients, and higher in 2 patients.
Terenghi 2004 [37]	10 (6 male, 4 female)	5-12 years, (mean 8.2)	Initially 2g/kg over 4-5 days, followed by 1-1.2g/kg over 3-4 days, as needed.	MRC score Rankin disability scale functional disability	All patients showed increased MRC sum scores after initial treatment but only 2/10 maintained maximum strength scores until final follow up. Mean MRC, Rankin and functional scores at final follow-up were all improved compared to baseline. Dosage was progressively increased in all patients in the second year of follow-up to maintain improvement but did not prevent deterioration in 4 patients.
Van den Berg-Vos 2002 [36]	11 (10 male, 1 female)	4-8 years	Initially 0.4g/kg over 5 days, then 0.4g/kg weekly for 12 months. Subsequently, dosages adjusted depending on functional disability.	Muscle strength (dynamometry) MRC score Guy's Neurological Disability score	Mean MRC scores were 92±7 SD at baseline and 95±6 SD after the initial course of IVIG ($p<0.001$). MRC scores remained significantly higher than before treatment at final examination (mean 94±7 SD, $p<0.001$). Mean disease progression during the follow period compared to after initial IGIV course was significant for MRC scores (mean -0.2) but not for disability scores.
Vucic 2004 [38]	10 (4 male, 6 female)	3.5-12 years (mean 7.25)	Initially 2g/kg over 5 days monthly for 3 months, followed by monthly treatment at dosages adjusted depending on functional disability (mean 1.63g/kg).	MRC score Modified Rankin disability scale	Mean MRC scores increased significantly after initial treatment (75.2) compared to baseline (69.3) and did not decline during the follow up period (mean 75.2). This trend was also observed for functional disability scores. One patient went into remission but clinical stability was dependent on IGIV in the remaining patients.

Uncontrolled Studies

Many open and uncontrolled studies on the efficacy of IVIg therapy in patients with MMN have been published. An analysis conducted by van Schaik (2005) showed that 383 of the 487 MMN patients described were treated with IVIg. Improvement in muscle strength was reported in 303/373 patients (81.2%), an improvement in disability was reported in 91/23 IVIg treated patients (74.0%).

In a national MMN database in the Netherlands described by van den Berg, 90/94 (96%) of MMN patients received an initial IVIg course at a cumulative dose of 2g/kg. Seventy-four (79%) patients responded to initial treatment and received IVIg maintenance treatment. This clinical response to initial treatment with IVIg is comparable to that reported in placebo-controlled studies.

The available data on the efficacy of IVIg treatment in patients with MMN have limitations from a biometrical perspective with respect to patient number, cross-over design and duration of the post-observation periods. These limitations are essentially related to the rare nature of the condition and the inter-individual variability in response rates. The use of different disability scales in the studies (for instance the modified Norris scale by Azulay 1994, modified Rankin scale by van den Berg 1995 and a self-evaluation scale score from 0 to 5 by Léger 2001 contribute to impression of divergent results, but an analysis across all studies on IVIg treatment in MMN demonstrated maintained muscle strength and functionality.

Comparability of different IVIg products

Human normal immunoglobulins are produced from a pool of donations from 1,000 to more than 50,000 healthy donors (depending on the manufacturer) and hence contain principally IgG, with a subclass distribution that largely reflects that of IgG in normal subjects. The large number of pooled

donations provides a large array of antibodies that cover specificities for infectious agents to provide replacement therapy for immune deficiencies. The large array of antibodies from multiple donors also provides naturally occurring antibodies that are cross-reactive to self antigens or pathologic antibodies.

Some investigators consider the latter to be the basis of immune effects of IVIg therapy in autoimmune disease. Although all IVIgs have to adhere to the European Pharmacopoeia monograph 0918, some differences in the pharmaceutical composition between products, but also between batches of one product do exist. These differences may impact IVIg tolerability and safety. The extent of the impact on therapeutic efficacy is not known exactly. However, it can be expected to be small, given the similarity in the active ingredients composition, namely in IgG content and half-life (Cherin et al. 2010).

To assess if different IVIg brands, or different lots of the same brand, may affect efficacy, Zhang et al examined the protective efficacy of 8 different brands of IVIg and different lots of two brands: GAMMAGARD S/D (Baxter), Iveegam EN / Endobulin (Baxter), Flebogamma (Grifols) (3 different batches), Panglobulin NF (American Red Cross), Carimune NF (ZLB Bioplasma), Octagam (Octapharma), Gamunex (Bayer Healthcare) and Gammar-PLV (ZLB Behring) (4 different batches).

The efficacy model used by Zhang et al. is an anti-ganglioside antibody-mediated, complement-dependent neurotoxicity assay considered to be relevant notably for MMN. In this cell culture model of autoimmune nerve injury, the results showed that a) the eight different commercial brands of IVIg have similar protective efficacy and b) for 2 IVIg products (Endobulin and Gammar-PLV) there is no lot-to-lot variability. These results suggest that efficacy of different IVIg products is comparable in a standardized model.

Clinical pharmacology

Pharmacokinetics

Baxter has not performed pharmacokinetic studies in MMN, but has submitted pharmacokinetic data on KIOVIG in 22 patients with PID in the course of the centralized licensing procedure in Europe. There is no evidence suggesting that the pharmacokinetic characteristics of KIOVIG in patients with MMN are different to those in patients treated for approved indications. The pharmacokinetic characteristics of IVIg products are also well described in the literature.

Pharmacodynamics

The mechanism of action of KIOVIG in indications other than replacement therapy has not been elucidated, but may include a variety of immunomodulatory effects. MMN seems to be an immune mediated disorder. Serum IgM GM1 antibodies are detectable in 30% to 80% of the patients, furthermore increased signal intensities on T2-weighted MR images of the brachial plexus have been observed suggesting an inflammatory process. There are no conclusive data on the specific mode of action of IVIg in patients with MMN.

Clinical efficacy

Introduction

The evaluation of the efficacy is based on two investigator-initiated, open-label clinical studies evaluating the efficacy of KIOVIG treatment in patients with MMN:

1. **MMN Conversion study (Study I)**: a prospective open-label, non-controlled study over 12 months in 20 MMN patients, in order to demonstrate clinical equivalence in two IVIg preparations (KIOVIG vs. GAMMAGARD S/D) in maintenance treatment. 19 of the 20 patients entered a two-year follow-up period to document long-term efficacy and adverse effects of KIOVIG.

   GAMMAGARD S/D is a freeze-dried 5% (50 g/l) IVIg preparation for reconstitution prior to infusion; it is approved for use in the indication MMN in the Netherlands. KIOVIG is a liquid concentrated (10%, 100 g/l) ready-to-use IVIg preparation for infusion.

2. A prospective, open-label, non-controlled study was conducted in 2007-2010 to investigate the efficacy of KIOVIG for **initial treatment** in 8 patients with newly diagnosed MMN (**Study II**). Seven of the eight patients were administered long-term treatment following completion of the initial 5-day course.

A randomized, double-blind, placebo controlled, cross-over study (Baxter clinical study 160604) is currently being conducted to investigate the efficacy of KIOVIG in the treatment of subjects with MMN. A total of 40 subjects are planned to be enrolled in this study. Efficacy data were not yet available at the time of assessment of this application.

Dose response study

No formal dose-finding studies have been conducted with KIOVIG. As recommended by the EFNS guideline for the Use of IVIg in Treatment of Neurological Diseases and the EFNS/PNS Guideline on Management of MMN, the doses for the two MMN studies described above were 2g/kg (given over 2-5 days) as fist line treatment and individual dosing for subsequent infusions (guided by responses, e.g. 0.4g/kg every 1-2 weeks or 2g/kg every 4-8 weeks).

Main studies

Methods

- **Study Participants**

MMN Conversion Study (Study I)

The study was to included 20 adult subjects with a diagnosis of “definitive MMN” or “probable MMN” according to published criteria (Van den Berg, 2000; Asseldonk et al., 2005) that were responsive to IVIg treatment and had received maintenance treatment with freeze-dried 5% IVIg (GAMMAGARD S/D) for a period of at least one year prior to inclusion. Patients had to have normal sensory nerve conduction in segments with motor conduction block (CB) and normal distal sensory nerve action potential amplitudes at the first nerve conduction study. Exclusion criteria included treatment with immunosuppressive drugs in the three preceding months, a history of severe adverse reactions to immunoglobulin treatment, IgA deficiency, chronic heart failure or renal dysfunction; pregnant or breast-feeding women were also excluded.

Initial treatment of MMN (Study II)

8 adult (1 female, 7 male) subjects who had been newly diagnosed with MMN were enrolled in the study. The duration from first onset of clinical symptoms of MMN (reported muscle weakness) and start of treatment varied from 1 to 12 years.

Table 4.

Patient	1	2	3	4	5	6	7	8
Sex	M	M	M	M	M	F	M	M
Age of onset (y)	26	35	53	49	42	44	31	48
Site of onset	UR	LR	UR	UR	UR	UR	UR	UR
Disease duration at onset of treatment (y)	1	7	6	6	3	12	7	10

- **Treatments**

MMN Conversion Study (Study I)

After enrolment, patients were treated with their regular maintenance dose of GAMMAGARD S/D for 3 months. During this time, patients visited the outpatient clinic three times: at baseline (t = -2), after 6 (t=-1) and after 12 weeks (t=0), at which time treatment with KIOVIG was initiated. Patients were then treated for a further 9 months with KIOVIG at an equivalent dose (Figure 1).

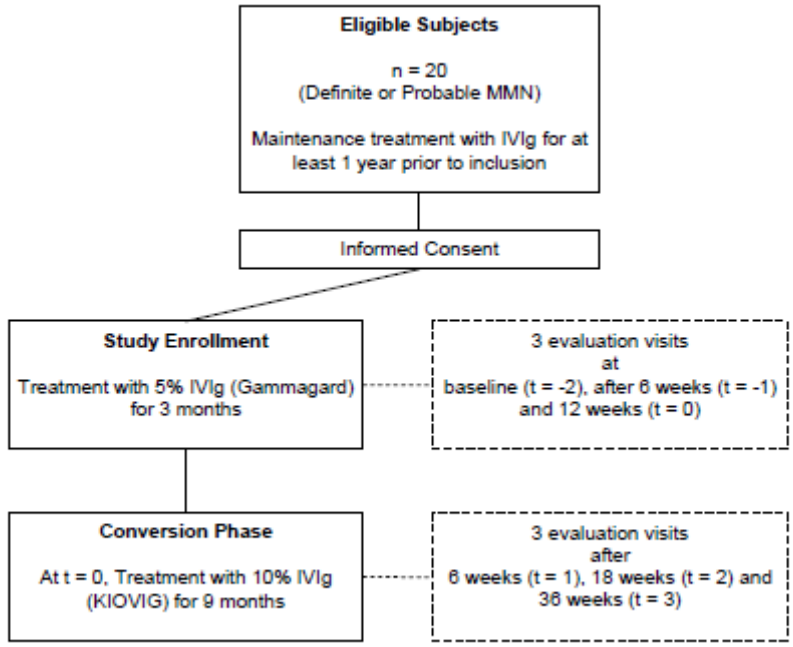

Figure 1 Study design of MMN Conversion study (Study I)

After 9 months of treatment with KIOVIG, patients could be continued on maintenance treatment with KIOVIG. A **two year follow-up study** was conducted in these patients to document the long-term efficacy and tolerability of KIOVIG. During this follow-up period, efficacy was evaluated by measuring the same parameters of impairment and disability as those monitored during the main phase of the study.

The treatment doses per patient are indicated in the table below.

Table 5.

Patient no.	Treatment dose	Infusion time GAMMAGARD (h)	Infusion time KIOVIG (h)
1	30 g/2 wks	3	2
2	35 g/1 wk	1.5	1.5
3	40 g/4 wks	6	1.5

Patient no.	Treatment dose	Infusion time GAMMAGARD (h)	Infusion time KIOVIG (h)
4	35 g/3 wks	5	2.5
5	45 g/3 wks	6	3
6	40 g/2 wks	2.5	1.5
7	40 g/2 wks	4	2
8	30 g/2 wks	3	3
9	35 g/3 wks	1.5	1
10	40 g/3 wks	5	5
11	4 5g/2 wks	2,5	1.5
12	50 g/4 wks	5	2.5
13	50 g/2.5wks	5	2
14	30 g/3 wks	7.5	4
15	40 g/3 wks	6	2.5
16	45 g/1 wks	6	4
17	30 g/1 wk	3	1.5
18	45 g/2 wks	7.5	4
19	45 g/3 wks	7.5	2.5
20	40 g/2 wks	4.5	2

In comparison with infusion times for the GAMMAGARD S/D treatment, infusion time for KIOVIG remained the same in 3 patients (15%), was reduced up to two-fold in 12 patients (60%) and was reduced more than two-fold in 5 patients (25%). As it would be expected of a 10% solution, mean infusion time with KIOVIG was significantly shorter than with GAMMAGARD S/D (2.5 hours compared to 4.5 hours).

Initial treatment of MMN (Study II)

Patients received a first five-day course of KIOVIG at a cumulative dose of 2 g/kg body weight (0.4 g/kg for 5 consecutive days). To document the extent and duration of the effect of this first IVIg treatment course, the patients were followed until muscle strength returned to pre-treatment levels. At that time, a second full course of IVIg treatment (0.4 g/kg for 5 consecutive days) was given and IVIg maintenance treatment was then initiated (0.4 g/kg every 2-4 weeks).

Table 6.

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Sex	M	M	M	M	M	F	M	M
Follow-up maintenance IVIg (y)	3	3	3	2	2	1	2	n.a.
IVIg dose per week (g/kg body weight) during follow-up	0.13	0.10	0.10	0.07	0.10	0.07	0.25	n.a.

- **Objectives**

MMN Conversion Study (Study I)

This study aimed to switch MMN patients who were successfully treated with GAMMAGRAD S/D to treatment with KIOVIG.

The primary objective was to demonstrate that KIOVIG was clinically equivalent to GAMMAGARD S/D in the maintenance treatment of MMN. This was evaluated by muscle strength, which was documented using a modified Medical Research Council (MRC) scale.

Additionally, functional impairment was assessed using Guy's Neurological Disability Scale (GNDS) and Self Evaluation Scales and long-term efficacy and adverse effects were evaluated.

Initial treatment of MMN (Study II)

The primary objective was to evaluate whether KIOVIG was effective in the initial treatment of MMN. Efficacy was evaluated using MRC sum scores.

Secondary objectives of this study were the evaluation of long-term efficacy (up to 3 years).

- **Outcomes/endpoints**

Efficacy in both studies was evaluated using two primary endpoints:

(a) **Muscle strength**: A modified Medical Research Council (MRC) sum score of ten muscle groups (shoulder abduction, elbow flexion, elbow extension, wrist flexion, wrist extension, hip flexion, knee flexion, knee extension, foot dorsiflexion, foot plantar flexion, on both sides) to measure impairment. MRC scores range from 0 (no contraction) to 5 (normal power) and the total score (max. 100) was calculated by summing up the individual scores. Subjects are defined as responders if the MRC sum scores remain stable.

(b) **Disability** ("functional impairment") as monitored using the Guy's Neurologic Disability Scale (GNDS) and a Self-Evaluation Scale.

MRC scores were tested 10 days after IVIg administration. For patients in the treatment initiation study, a second full course of IVIg was administered when muscle strength returned to pre-treatment levels and initiation of maintenance treatment is provided.

Clinical efficacy was evaluated by using the definitions of clinical improvement, decline and stability in the patient's condition listed in following table. Endpoints were evaluated by the same investigator at all visits.

Table 7. Definition of Assessment Criteria

Improvement	1. either the upper or lower limb score of the GNDS, OR the score of two or more motor activities on the self evaluation scale decreases by 1 point AND 2. if muscle strength increases ≥ 1 MRC grade in at least two muscle groups without a decrease in other muscle groups.
Decline	1. either the upper or lower limb score of the GDNS, OR the score of two or more motor activities on the self evaluation scale increases by 1 point AND 2. if muscle strength worsens one grade on the MRC scale in at least two affected muscles or muscle groups.
Stable	Patient demonstrates neither decline nor improvement

A patient was considered as a responder if muscle strength remained unchanged when switching from Gammagard SD to KIOVIG (Conversion study I) or if IVIg could not be stopped without worsening of muscle strength (Study I and II).

MMN Conversion Study (Study I)

MRC sum scores as measured with GAMMAGARD at baseline (t=-2), after 6 (t=-1) and after 12 (t=0) weeks were compared with scores at 6 (t=1), 18 (t=2) and 36 weeks (t=3) after initiation of KIOVIG treatment as well as at the end of the 2 year maintenance phase in a descriptive manner.

Initial treatment of MMN (Study II)

MRC sum scores were provided for five time points:

- at baseline (before the 1st course of treatment)
- 4-6 weeks after the 1st course of treatment (when the maximal effect on muscle strength was observed)
- Before the 2nd treatment course (return of muscle strength to pre-treatment level)
- After the 2nd course of treatment
- At last follow-up examination (after 1-3 years of maintenance treatment)

Additionally, a descriptive analysis of the response to KIOVIG on functional impairment (regarding daily life activities) was presented for each of the eight subjects.

Dynamometry

In addition to the MRC sum score, the isometric strength of muscles was also evaluated by hand-held dynamometry (HHD). HHD measurements were obtained on a selection of those muscles with an MRC score >3 and <5 at any time. This range was chosen because muscles with an MRC of 5 (normal strength) are unlikely to demonstrate improvement, and those with an MRC of ≤3 are too weak to adequately measure using a hand-held dynamometer.

As with MRC scores, an average of 3 measurements after treatment with GAMMAGARD S/D (and before treatment with KIOVIG) was compared to the average of 3 measurements post-treatment with KIOVIG.

- **Sample size**

There was no formal sample size calculation.

- **Randomisation**

Not applicable as both studies were uncontrolled single-arm trials.

- **Blinding (masking)**

Not applicable as both studies were open-label.

- **Statistical methods**

Only a descriptive analysis was presented for both clinical studies.

For statistical analysis the mean of 3 MRC sum scores was calculated. The rationale was to test the hypothesis that the mean MRC sum score was similar during GAMMAGARD and KIOVIG treatment periods. Because of non-normality of the data distribution and the relatively small sample size, a conservative approach using the Wilcoxon signed rank test was chosen. The Wilcoxon signed rank test

was used because distributional assumptions of parametric tests, including the t-test, could not be satisfied.

Results

- **Conduct of the study**

No major amendments were made to the protocol.

The MMN Conversion study (Study I) was conducted between 2007–2008 (follow-up study: 2007-2010) at the University Medical Centre in Utrecht, The Netherlands. The study protocol received IEC approval in March 2006. The Initial Treatment of MMN study (Study II) was conducted at the same site between 2007-2010.

- **Baseline data**

MMN Conversion Study (Study I)

The study population consisted of 20 adults (4 female, 16 male) with definite or probable MMN who were in a stable clinical condition and had been receiving maintenance therapy with GAMMAGARD S/D for at least 12 months. The mean age of the patients included was 53 (range: 37-67) and there was a male to female ratio of 4:1. MRC sum scores as assessed prior to KIOVIG treatment ranged from 81.06 to 98.38. Dosing of GAMMAGARD varied from 0.10 g/kg/week to 0.49 g/kg/week.

Table 8. Patient population in the Conversion study (Study I)

Patient no.	Age at disease onset	anti-GM1 antibody titre	Age 2007	Years without treatment	MMN classification	Home treatment	by
1	25	1600	38	2	definite	Yes	Home care nurse
2	26	200	50	16	definite	Yes	family physician
3	38	800	51	5	definite	Yes	Home care nurse
4	36	0	46	1	definite	Yes	Home care nurse
5	47	100	64	9	definite	Yes	Home care nurse
6	34	800	45	5	definite	Yes	Home care nurse
7	40	0	54	10	probable	Yes	self
8	22	0	41	8	definite	Yes	self
9	49	0	64	6	definite	Yes	Home care nurse
10	47	200	67	5	definite	Yes	Home care nurse
11	33	800	37	1	definite	Yes	Home care nurse
12	36	100	44	1	definite	Yes	Home care nurse
13	35	100	61	15	definite	Yes	Home care nurse
14	54	6400	59	2	probable	Yes	Home care nurse
15	47	400	61	12	definite	Yes	Home care nurse
16	35	400	46	5	definite	Yes	self
17	30	12800	43	5	probable	Yes	Home care nurse
18	33	6400	60	20	definite	Yes	Home care nurse
19	42	0	59	9	probable	Yes	Home care nurse
20	47	0	67	11	definite	Yes	Home care nurse

Other immunosuppressive treatment prior to use of GAMMAGARD/KIOVIG is presented in the following table. There was no treatment effect observed with interferon B, mycophenolate or prednisolone.

Table 9. Concomitant medication by patient (Study I)

Patient	Other immunosuppressive treatment for MMN	Duration, effect	Other drugs
1	mycophenolate	1 year in 2005, no effect	No
2	No		No
3	Interferon B	Interferon B 2000 to 2002, no long-term effect	No
4	Mycophenolate / interferon B	mycophenolate 1 year 2005, no effect /interferon B 1999, no effect	No
5	mycophenolate	1 year in 2005, no effect	chloortalidon and zocor
6	mycophenolate	1 year in 2005, no effect	No
7	mycophenolate	1 year in 2005, no effect	Ventolin
8	Interferon B	4 months in 1999, no effect	No
9	No		No
10	mycophenolate	1 year in 2005, no effect	No
11	No		No
12	Interferon B	Interferon B 2000-2001, no long-term effect	No
13	No		No
14	No		No
15	No		No
16	No		No
17	mycophenolate	1 year in 2005, no effect	No
18	No		No
19	mycophenolate	1 year in 2005, no effect	No
20	prednisone	1999, no effect	No

Initial treatment of MMN (Study II)

Eight patients with newly diagnosed MMN and functional impairment due to muscle weakness were enrolled. Functional features were presented in a descriptive manner for each individual with the majority of patients suffering from upper limb weakness.

Table 10. Patient population in the Initial treatment of MMN (Study II)

Patient no.	Age at disease onset	anti-GM1 antibody titre	Age 2007	Years without treatment	MMN classification	Home treatment	by
1	26	800	27	1	definite	No	Hospital
2	35	800	42	7	definite	No	Hospital
3	53	100	59	6	definite	Yes	Home care nurse
4	49	0	55	6	definite	Yes	Home care nurse
5	42	0	44	2	definite	Yes	Home care nurse
6	44	100	55	12	definite	Yes	Home care nurse
7	31	0	37	7	probable	Yes	Home care nurse
8	48	400	58	10	definite	n.a.	n.a.

Table 11. Concomitant medication by patient (Study II)

Patient	Other immunosuppressive treatment for MMN	Duration, effect	Other drugs
1	No		
2	Interferon B	2000 (6 months), 2002 (6 months), 2006 (6 months), no long-term effect	No
3	No		No
4	No		No
5	No		No
6	Interferon B	2005 (6 months), no long-term effect	No
7	No		No
8	No		No

- **Numbers analysed**

MMN Conversion study (Study I)

The data of all 20 patients were analysed throughout the 12 month maintenance study (intent-to-treat population, ITT). Nineteen (19) of them continued on KIOVIG with the two-year follow up period. One patient (pt number 10) decided to switch back to GAMMAGARD S/D due to dizziness that he experienced on KIOVIG.

Initial treatment of MMN (Study II)

Data of 8 patients were analysed regarding efficacy after a first full course of KIOVIG (cumulative dose 2 g/kg). Seven of those continued KIOVIG treatment for the subsequent follow-up period. One patient remained stable after an initial loading dose and did not start on maintenance treatment. Therefore he was not further assessed during the follow-up phase.

- **Outcomes and estimation**

MMN Conversion study (Study I)

Results were presented as a tabular listing and a descriptive comparison of the MRC sum scores as measured with GAMMAGARD at baseline (t=-2), after 6 (t=-1) and after 12 (t=0) weeks and 6 (t=1), 18 (t=2) and 36 weeks (t=3) after KIOVIG was initiated (2007).

Table 12. Muscle strength and functional impairment

Patient no.	Average MRC Sum Score before KIOVIG treatment (t=-2, -1, 0)	Average MRC Sum Score after KIOVIG treatment (t=1, 2, 3)	Guy arm t=0/t=3	Guy leg t=0/t=3	SES t=0/t=3
1	87.55	88.67	2/2	3/3	9/9
2	82.78	86.85	2/2	3/3	11/11
3	97.62	98.01	2/2	0/0	9/8
4	94.89	96.23	2/2	0/0	9/9
5	94.72	97.23	2/2	1/1	11/12
6	90.84	93.39	2/2	2/2	15/15
7	96.17	96.12	2/2	0/0	7/7
8	92.12	92.90	2/2	2/2	11/10
9	83.05	84.48	2/2	4/4	15/15

Patient no.	Average MRC Sum Score before KIOVIG treatment (t=-2, -1, 0)	Average MRC Sum Score after KIOVIG treatment (t=1, 2, 3)	Guy arm t=0/t=3	Guy leg t=0/t=3	SES t=0/t=3
10	85.56	84.67	3/3	0/0	12/12
11	98.38	99.45	1/1	1/1	6/6
12	97.45	97.67	2/2	1/1	14/14
13	91.24	91.79	2/2	2/2	11/11
14	87.15	86.22	2/2	1/1	13/13
15	97.45	97.89	1/1	0/0	2/2
16	88.23	88.07	3/3	1/1	19/19
17	81.06	79.56	3/3	4/4	15/15
18	86.17	83.46	3/3	2/2	15/15
19	95.78	94.84	1/1	0/0	9/9
20	92.11	94.50	2/2	1/2	10/10

Guy arm = Guy's Neurological Disability score arms; *Guy leg* = Guy's Neurological Disability score legs; SES = Self-Evaluation Scale

In the conversion study (Study I), GAMMAGARD maintenance treatment could be converted successfully to long-term KIOVIG maintenance treatment in 19 out of 20 (95% (95% CI 85.5 - 100%)) MMN patients. The MAH concluded that results of this study show that muscle strength and disability ("functional impairment") were comparable between the treatment period with GAMMAGARD S/D and KIOVIG (Wilcoxon signed-rank test for MRC sum score analysis, p=0.126) (Cats et al 2008). There is no data documenting on- and off-treatment with KIOVIG since the study was not designed to assess such fluctuations. Nevertheless, the results from another clinical MMN trial have been submitted as supportive data (see below).

The presented results indicate that the majority of patients remained relatively stable after switching from GAMMAGARD to KIOVIG, with an identical number of patients either worsening or improving slightly within the observation period.

Long-term effect of KIOVIG (MMN conversion study):

Nineteen out of 20 MMN patients participated in the long-term follow up part of the study. The results after 2 additional years of KIOVIG treatment (2010) are presented in the table below.

Table 13. Long-term effect on muscle strength and disability

Table 4. Long-term effect of KIOVIG on muscle strength and disability						
Pt	MRC Sum GAMMAGARD S/D 2007	MRC Sum KIOVIG 2007	MRC Sum KIOVIG 2010	Guy's disability score GAMMAGARD S/D 2007/ KIOVIG 2007/ KIOVIG 2010	Guy's disability score GAMMAGARD S/D 2007/ KIOVIG 2007/ KIOVIG 2010	Self Evaluation Scale GAMMAGARD S/D 2007/ KIOVIG 2007/ KIOVIG 2010
1	87.55	88.67	87.34	2/2/2	3/3/3	9/9/9
2	82.78	86.85	82.78	2/2/2	3/3/3	11/11/11
3	97.62	98.01	97.68	2/2/2	0/0/0	9/8/8
4	94.98	96.23	98.68	2/2/2	0/0/0	9/9/9
5	94.72	97.23	96.51	2/2/2	1/1/1	11/12/12
6	90.84	93.39	93.34	2/2/2	2/2/2	15/15/15
7	96.17	96.12	96.12	2/2/2	0/0/0	7/7/7
8	92.12	92.90	92.84	2/2/2	2/2/2	11/10/10
9	83.05	84.48	83.65	2/2/3	4/4/4	15/15/16
10*	85.56	84.67	NA: pt on GGSD*	NA: Pt on GGSD*	NA: Pt on GGSD*	NA: Pt on GGSD*
11	98.38	99.45	98.58	1/1/1	1/1/1	6/6/6
12	97.45	97.67	97.67	2/2/2	1/1/1	14/14/14
13	91.24	91.79	92.01	2/2/2	2/2/2	11/11/11
14	87.15	86.22	86.31	2/2/2	1/1/1	13/13/13
15	97.45	97.89	98.00	1/1/1	0/0/0	2/2/2
16	88.23	88.07	88.07	3/3/3	1/1/1	19/19/19
17	81.06	79.56	79.34	3/3/4	4/4/4	15/15/16
18	86.17	83.46	83.46	3/3/3	2/2/2	15/15/16
19	95.78	94.84	97.34	1/1/1	0/0/0	9/9/9
20	92.11	94.50	92.11	2/2/2	1/2/3	10/10/10

LEGEND: MRC Sum= Medical Research Council sum score of 10 muscle groups (shoulder abduction, elbow flexion, elbow extension, wrist flexion and wrist extension, hip flexion, knee flexion, knee extension, foot dorsiflexion and foot plantar flexion, both sides, max score 100); GGDS: Gammagard SD; *Patient wanted to switch back to GAMMAGARD S/D because this patient experienced dizziness on KIOVIG, even at a low infusion rate.

One patient (pt number 10) did not enter the long-term follow-up phase because he experienced dizziness on KIOVIG, even at a low infusion rate. This patient was switched back to GAMMAGARD S/D. Twenty percent of subjects required slightly higher doses of KIOVIG compared with GAMMAGARD. One patient was clinically stable while using a slightly lower dose.

The MAH concluded that three patients worsened >1 MRC grade on their MRC sum score (pt number 1, 2, 20) on KIOVIG in 2010 compared to 2007. Three patients improved >1 MRC grade on their MRC sum score (pt number 4, 14, 19) on KIOVIG in 2010 compared to 2007. Three patients worsened 1 point on the Guy's disability score on KIOVIG in 2010 compared to 2007 (pt number 9, 17, 20) and three patients worsened one point on the Self Evaluation Scale on KIOVIG in 2010 compared to 2007 (pt number 9, 17,18). Four patients with MMN used a slightly higher dose (5 g per 1 to 3 weeks) of KIOVIG in 2010 compared to 2007 (pt number 1, 2, 4, 20). One patient used a slightly lower dose of KIOVIG in 2010 compared to 2007 (pt number 11).

The MAH pointed out that disease progression cannot be completely halted by IVIg treatment and response to IVIg treatment mildly decreases over time, which is likely to be a result of progressive axonal loss. Additionally, the MAH clarified that in the GAMMAGARD to KIOVIG conversion study the dose of IVIg remained the same without worsening of muscle strength over a nine months follow-up of

KIOVIG treatment. After another two years of KIOVIG treatment the dose had to be increased slightly (5 gram per 1-3 weeks) in 4 patients (patient 1: from 0.18 in 2007 to 0.21 g/kg/wk in 2010; patient 2: from 0.49 in 2007 to 0.56 g/kg/wk in 2010; patient 4: from 0.15 in 2007 to 0.17 g/kg/wk in 2010; and patient 20: from 0.27 in 2007 to 0.30 g/kg/wk in 2010). Taken together, a slight increase of IVIg dose was not specific for a liquid formulation such as KIOVIG, but due to the natural course of the disease.

Dynamometry data

Supplemental post-hoc analysis of data was provided by the applicant during the procedure. The MAH stated that in all but one of the 20 patients monitored, pooled dynamometry measurements for all muscle groups tested indicated improved muscle strength when switching from GAMMAGARD S/D to KIOVIG. The average improvement in muscle strength for all 20 patients was ~36% in proximal muscles (shoulder abductors; elbow flexors and extensors; hip flexors; knee extensors and flexors and ~18% in distal muscles (wrist flexors and extensors; foot dorsiflexors and plantar flexors).

Initial treatment of MMN (Study II)

The MRC sum scores for each patient are presented in the table below.

Table 14. MRC sum scores in MMN patients (Study II)

Patient / **MRC sum score**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Baseline (before first course of treatment	96	96	98	98	95	95	95	95
Maximal effect after the first full course (at 4-6 weeks)	99	98	99	100	99	97	98	96
Before second treatment course (muscle strength return to baseline value)	96	97	97	n.a.	96	95	95	n.a.
Maximal effect after the second treatment course	99	98	99	n.a.	99	97	98	n.a.
At last follow-up examination (after 1-3 years of maintenance of treatment)	99	98	100	100	99	97	98	n.a.
Duration effect of the 1st course (weeks)	6	8	8	8	9	12	5	12
Follow-up maintenance IVIg treatment (years)	3	3	3	2	2	1	2	n.a.
IVIg dose per week (g/kg body weight) during follow-up	0.13	0.10	0.10	0.07	0.10	0.07	0.25	n.a.

n.a.: Not available

- Patient 8 remained stable after the initial full course treatment and did not start maintenance treatment. He decided to return to the local neurologist for follow-up care and therefore no follow-up data are available.
-For patient 4, efficacy data are not available for 2 timepoints because the patient was followed-up in another hospital.

The maximal effect of IVIg treatment was reported at 4-6 weeks after the first full course of IVIg treatment. Before the second treatment course (5-12 weeks after the first full course), the MRC sum score returned to the pretreatment levels in all patients; the MRC sum scores were inferior to the MRC sum score measured at baseline in 6 patients (data not available for patients 4 and 8). The maximal effect of IVIg treatment after the 1st and the 2nd full course of IVIg treatment were identical for 6 patients (data not available for patients 4 and 8).

After one to three years of maintenance treatment, the MRC sum score was equal (n=6 patients) or superior (n=1 patient) to the score measured at the maximal effect (4-6 weeks after the 1st full course) (data not available for patient 8). According to the MAH, these individual results demonstrate that muscle strength decreased when IVIg infusions were withheld and therefore that fluctuations were related to phases on-treatment and off-treatment.

Guy's Neurological Disability score in MMN patients (Study II)

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Guy's Neurological Disability Score								
Upper limb data								
Before first treatment	2	3	3	2	2	2	2	2
Maximal effect after the first treatment (at 4-6 weeks)	1	2	2	1	1	1	1	2
Before second treatment	2	3	3	n.a.	2	2	2	n.a.
Maximal effect after the second treatment course	1	2	2	n.a.	1	1	1	n.a.
At the last follow-up examination	1	2	2	1	1	1	1	n.a.
Lower limb data								
Before first treatment	1	2	0	0	0	0	0	0
Maximal effect after the first treatment (at 4-6 weeks)	1	1	0	0	0	0	0	0
Before second treatment	1	2	0	0	0	0	0	n.a.
Maximal effect after the second treatment course	1	1	0	0	0	0	0	n.a.
At the last follow-up examination	1	1	0	0	0	0	0	n.a.

n.a.: Not available

As seen with the MRC sum score, there was an improvement in disability for the upper limbs (Guy's score decreased) after the first full IVIg course in 7 out of the 8 patients, which then deteriorated to the pretreatment levels before the second treatment (for patient 8, the score remained the same). The maximal effect of IVIg treatment for the upper limb Guy's score after the 1st and the 2nd full course of IVIg treatment were identical for 6 patients (data not available for patients 4 and 8). After one to three years of maintenance treatment, the upper limb Guy's score was equal (n= 7 patients) to the score measured after the maximal effect (4-6 weeks after the 1st full course) (data not available for patient 8).

The lower limb disability score at baseline was low (0 or 1) in 7 out of 8 patients and remained unchanged throughout the study. In patient 2 (the only patient who had onset of the disease in the

lower limbs), the Guy's score was 2 at baseline, decreased to 1 after the 1st full IVIg treatment, returned to the pretreatment levels before the 2nd treatment and responded to the 2nd IVIg full course with a score of 1, a score which was maintained throughout the long-term follow-up period.

In summary, the MAH concluded that the response rate in the treatment initiation study (Study II) was 100%. The response to KIOVIG was similar to experience with GAMMAGARD and consistent with published literature on other products.

Regarding the overall efficacy of KIOVIG in MMN, the Applicant argued that the efficacy results from Study I and Study II are consistent with the published results from other studies that document efficacy fluctuation related to IVIg infusion (Van den Berg et al., 1995; Van den Berg et al. 1998, Harbo et al., 2009).

One of the four placebo-controlled studies submitted as supportive evidence for the efficacy of KIOVIG in MMN evaluated the effect of an IVIg from the Central Laboratory Blood Transfusion, Amsterdam, in six patients with MMN (Van den Berg et al., 1995). Although this study was not performed with KIOVIG, 5 out of 6 patients in this study continued in a "maintenance study", in which they received regular IV infusions of GAMMAGARD (Baxter). The MAH argued that the efficacy results with GAMMAGARD can be extrapolated to KIOVIG for the following reasons:

- The results of the MMN Conversion study (Study I) had shown that clinical efficacy of Kiovig and Gammagard was comparable, and that changes in muscle strength observed were reflective of normal fluctuations for MMN patients treated with IVIg.
- Gammagard is similar to Kiovig in their IgG subclass distribution and in their efficacy (pre-clinical)

Furthermore, a randomised single-blinded cross-over study conducted on 10 MMN IVIg pre-treated patients reported efficacy of 2 IVIg products from Baxter: Subcuvia, administered subcutaneously and Endobulin (Harbo et al., 2009). During pre-study phase, a prolonged treatment free-IVIg interval (maximal 10 weeks) was initiated in order to confirm responsiveness to IVIg for all patients (defined as at least 10% dynamometric decline of strength of one or more muscle groups as compared to a baseline value assessed half way between the two previous regular doses of IVIg). During this period, a significant decrease in muscle strength of 14% ± 11% ($P<0.005$) was observed, which subsequently improved during the randomised part of the study (with IVIg responsive patients).

- **Ancillary analyses**

In response to the CHMP's request to further justify the robustness of the clinical data provided, the MAH provided the results of a post-hoc analysis comparing the efficacy results from Study II against a historical placebo control.

Data from the randomized, placebo-controlled trial in MMN patients published by Léger et al (2001) were used to provide a historical placebo group. In this placebo-controlled study 18 treatment-naïve patients were included (9 were treated with Endobulin and 9 received placebo). Treatment response was evaluated after an initial 3 months of placebo/IVIg treatment and "responders" were defined as patients with an improvement of at least one point on the MRC score in at least two muscles together with a reduction of at least 1 point in two activities of daily life compared to baseline. This definition is identical to the definition of "improvement" in the two Baxter studies submitted. According to the results from the study by Léger et al 78% (95% CI= 44-93%) of IVIg-treated patients (7/9) and 22% (95% CI= 7-55%) of placebo-treated patients (2/9) were responders. The results from Study II show that all 8 patients (100%, 95% CI=66-100%) experienced improvement in muscle strength and disability following an initial course of treatment with KIOVIG (2g/kg). This improvement rate,

expressed as mean with 95% confidence intervals (CIs), was compared with the historical placebo responder rate. The 66% lower CI for treatment improvement in Study II was significantly greater than the 22% responder rate in the historical placebo group ($p<0.0001$), indicating that KIOVIG was more effective than the historical placebo control in the treatment of MMN. In addition, the percentage of responders in BAXTER's Study II and the IVIg-treated group from Léger et al (2001) were comparable: 100% (95% CI=66-100%) for KIOVIG vs. 78% (95% CI= 44-93%) for Endobulin.

Summary of Main Efficacy Results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy – MMN Conversion study

Title: MMN Conversion study			
Design	Prospective, open-label, non-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months not applicable 2 years
Hypothesis	Equivalence of KIOVIG vs. GAMMAGARD		
Treatments groups	Clinically stable patients with MMN who previously have been treated with GAMMAGARD (at least one year)		Treatment: KIOVIG, individual dosing Duration: 12 months (2 years) Number: 20 (19)
Endpoints and definitions	Primary endpoint	MRC sum score	MRC scores were analyzed three times during the 9 months treatment phase and again at the end of the follow-up period
	other:	- Guy's disability score - Self evaluation scale	Additional information on functional impairment
Database lock	2010		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	MRC sum scores at baseline and after 36 weeks		
Descriptive statistics and estimate variability	Treatment group	MMN patients who have received maintenance treatment with GAMMAGARD	MMN patients who completed MMN Conversion study and were enrolled in follow-up phase
	Number of subjects	20	19
	endpoint	Tabular listing of MRC sum scores c.f. Table 12	Tabular listing of MRC sum scores c.f. Table 13
	variability statistic	n.a.	n.a.
Analysis description	Only descriptive reporting and tabular listing of the changes in MRC scores		

Summary of Efficacy – Treatment initiation study

Title: Initial treatment of MMN			
Design	Prospective, open-label, non-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Initial treatment phase (first full course of IVIg) not applicable 1-3 years
Hypothesis	Efficacy of KIOVIG in treatment initiation and maintenance therapy		
Treatments groups	Patients newly diagnosed with MMN		Treatment: KIOVIG, cumulative 2g/kg over a five day period for treatment initiation, maintenance phase: individual dosing Duration: 12 months (up to 3 years) Number: 8 (7)
Endpoints and definitions	Primary endpoint	MRC sum score	MRC scores were analyzed at baseline, after a first full IVIg course and at the last follow-up visit
Database lock	2010		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	MRC sum scores at baseline, after a first full IVIg course, and at the last follow-up visit		
Descriptive statistics and estimate variability	Treatment group	Newly diagnosed MMN patients	MMN patients who completed the trial and were enrolled in the follow-up phase
	Number of subjects	8	7
	endpoint	Tabular listing of MRC sum scores c.f. Table 14	Tabular listing of MRC sum scores c.f. Table 14
	variability statistic	n.a.	n.a.
Analysis description	Descriptive reporting and tabular listing of the changes in MRC scores, description of changes in daily life activities.		

Supportive studies

Feasibility of KIOVIG home treatment

Thirty-six (36) MMN patients who receive KIOVIG maintenance treatment at home filled out a questionnaire regarding time, dose, adverse events, and practicality of home treatment. Advantages indicated by these patients were: time gain (72%) and convenience (94%) or other (autonomy, presence of next of kin, less time off from work, no hospital atmosphere) (19%). Reported disadvantages were: absence of medical staff in case of an adverse event (28%), problems with IV access or the infusion system (6%) or other (different nurses, logistic problems) (11 %). Six patients reported mild adverse events following IVIg infusions: headache (three patients), chills (two patients) and mild skin rash (one patient). No serious adverse events occurred during KIOVIG home-therapy over a 3 year period.

Discussion of clinical efficacy

A formal dose-finding study has not been conducted with KIOVIG in this indication, and the mechanism of IVIg in autoimmune disorders has not been fully elucidated. However, the doses chosen for the submitted clinical trials are in line with available recommendations and treatment guidelines and therefore are considered acceptable by CHMP.

CHMP noted that MMN is a chronic condition and patients may worsen long term, hereby requiring continuous therapy. Therefore, the concept of the presented clinical study reports to demonstrate that KIOVIG is efficacious in both treatment initiation and maintenance therapy was endorsed by the CHMP. However, the MAH chose an open-label design with a single treatment arm, arguing that the lack of active comparator was dictated by EU clinical practices. The CHMP commented that generally, in order to obtain an unbiased estimate of the size of the treatment effect, randomization to placebo or an active control group would be considered necessary; however, the difficulties in conducting placebo-controlled MMN trials in the EU were acknowledged. Given the open-label study design of the submitted studies with KIOVIG in MMN, the CHMP emphasized the need for a reliable endpoint in such a setting. Furthermore, the MAH was requested to further demonstrate how the potential risks of bias have been minimized. CHMP also requested the MAH to further justify the robustness of the clinical data provided (see below).

GCP compliance of the submitted study data was initially questioned by the CHMP. During the procedure, the MAH has provided further data to clarify the Committee's questions, and a separate declaration has been provided by the MAH confirming that the KIOVIG studies in MMN submitted with this application have been conducted in compliance with GCP principles.

CHMP acknowledged that, given the rareness of the condition, a sample size smaller than usually expected for confirmatory clinical trials might be acceptable.

With regard to the chosen outcome measures, the MAH clarified that the two primary endpoints were muscle strength (MRC sum score) and functional impairment (Guy's Neurological Disability Scale, Self Evaluation Scale) that were evaluated by the same investigator at all visits in order to reduce possible bias. The CHMP concurred that muscle strength is the only driver of disability in MMN condition, therefore an evaluation by MRC sum score is an acceptable primary outcome measure. MRC sum scores are in widespread use in the published literature and routine clinical practice, although different numbers of muscle groups have been used in previous studies and a modified MRC scale (assessing only ten pairs of muscles) was chosen for the two presented clinical trials.

The MRC sum score was originally reported by Kleyweg et al. in 1991 (using 6 bilateral muscle groups) and has since been used in modified forms with up to 28 muscles in various other clinical studies in MMN. However, the CHMP expressed concerns that the MRC score assessing only 20 muscles as used by the MAH fails to take into account several distal motor functions which are considered important for impairment due to MMN, such as fist closure, and thumb abduction. This might cause difficulties with ensuring a comprehensive and clinically meaningful assessment of the treatment effect.

In their initial response, the MAH argued that additional testing of intrinsic hand muscles would not add any value, since these muscles were most likely to have suffered axonal damage and would be the least likely to respond to treatment. Neck muscles were not affected in MMN, therefore assessing these would be unessential. In the second response, the applicant submitted data showing that grip strength had improved in response to Kiovig administration. The CHMP considered the response on grip strength acceptable.

Addressing an initial concern from CHMP, the MAH confirmed during the procedure that the efficacy data for KIOVIG submitted with this application was collected from prospectively-designed studies. In addition, the MAH detailed a number of precautionary measures which were undertaken in order to minimize bias and to improve quality of data (e.g. assessments by same investigator at all visits, analysis of ITT population, evaluation of 10 pre-defined muscle pairs). Furthermore, dynamometry was performed in selected muscle groups and the results provided during the procedure; the data is considered supportive for clinical improvement in the opinion of the CHMP.

Regarding the results of the MMN Conversion study, the CHMP had questioned whether the observation that patients remained stable after switching from GAMMAGARD to KIOVIG could be considered sufficient evidence, since efficacy in MMN treatment has not been established with GAMMAGARD so far. Therefore, the MAH was requested to provide longitudinal data from both studies which could demonstrate that muscle strength decreased when IVIg infusions were withheld.

Additional longitudinal data has subsequently been provided by the MAH for Study II in the treatment initiation setting (see below). There was no data documenting on- and off-treatment with KIOVIG from Study I since the study was not designed to assess such fluctuations. However, the MAH argued that considering that the treatment effect with IVIg lasts 5-12 weeks after an infusion (as shown in Study II), in case of loss of treatment effect, KIOVIG would have been shown to be ineffective, especially in the 2 year follow-up period, a result that was not observed in this study.

The efficacy of KIOVIG in treatment initiation was determined in 8 patients with MMN, whose treatment was started after the year 2007. All 8 patients experienced improvement in muscle strength and functionality following initial course of treatment with KIOVIG (2 g/kg). A single individual did not require continued treatment, while the remaining 7 patients receive continued KIOVIG treatment. The data obtained from those 8 patients were compared with a historical control, i.e. patients who had received their initial courses with GAMMGARD S/D. None of these patients were non-responders to KIOVIG. Based on the experience with IVIg in general, a response rate of approx. 80% to initial IVIg treatment is expected. The literature review provided by the company is supportive of the IVIg efficacy in MMN patients.

The lack of long-term follow-up data for patient no. 8 was noted. This data would have been helpful to better understand the “natural course of the disease” without a continuous maintenance treatment, especially as this is a single-arm study and no patients have been randomized to a control-group.

However, taken altogether, the Applicant provided sufficient longitudinal data to demonstrate a decline in muscle strength after cessation of both KIOVIG and GAMMAGARD infusions. This effect has also been observed with another IVIg preparation (Subcuvia). These data are considered supportive and the Applicant’s argumentation is considered acceptable.

Given the available published literature on IVIg use in MMN, the MAH was asked to justify to which extent the efficacy data from other IVIg products could be extrapolated. The MAH provided a summary of published evidence and guidelines from various learned bodies that advocate IVIg as first-line therapy for the treatment of MMN and concluded that different IVIg preparations – despite pharmaceutical differences such as osmolality, product concentration and composition – can be considered therapeutically equivalent, but may differ in safety profiles. Indeed, recommendations for off-label use of intravenous immunoglobulin products are also not product-specific, and therefore suggest product interchangeability and therapeutic equivalence.

The CHMP concurred with the Applicant’s argumentation that the extrapolation of efficacy data generated with different IVIg products could be supportive for the approval of KIOVIG in addition to the efficacy data specifically generated with KIOVIG.

The applicant presented data on use of IVIg in CIDP as supportive for the current application. The presented CIDP study is considered by the CHMP as useful for a comparison of the safety of both IVIg preparations, but it is not considered adequate for making a conclusion on the efficacy of KIOVIG in MMN patients.

The Applicant provided during the assessment data from the Dutch national MMN database demonstrate that IVIg already are widespread used in MMN therapy. The data are considered supportive for the high acceptance of this treatment by both patients and treating physicians. However, CHMP did not consider them adequate to draw conclusions on the efficacy of IVIg in MMN, especially when taking the remarkable number of clinically stable patients without IVIg treatment into account.

Based on the available data from the studies with KIOVIG and the supportive data published for other IVIg preparations, it can be accepted that sufficient evidence has been generated to show that KIOVIG is effective in the treatment of MMN. Overall, the available data is considered limited. The Committee noted that another clinical study is currently being conducted by the applicant (study 160604). This is a randomized placebo-controlled study using grip strength as primary endpoint. As of January 2011, 32 patients have completed the study of 44 that were able to participate; a final study report is expected in September 2012. The Committee considered it important to review these data once available as it would further substantiate the available data from prospective clinical trials in this indication. The MAH was therefore asked to provide this study report and also to commit to providing detailed safety and efficacy data from study 160604 in KIOVIG PSURs.

Conclusion on the clinical efficacy

Overall, results for KIOVIG from 2 prospective studies with this product and supportive data from randomized, placebo-controlled MMN trials with other IVIg products provide evidence indicating that KIOVIG is effective in the treatment of MMN.

In summary, CHMP considers that the MAH has provided data obtained from prospectively planned clinical trials, that the data comply with relevant EMA guidelines and that the data are of a standard that would support the current application. Acknowledging the limitations of the available efficacy data for KIOVIG in MMN the CHMP considers the results of the randomized, placebo-controlled trial (Study 160604) currently ongoing in the US as critical to corroborate the efficacy and safety of KIOVIG in the treatment of patients with MMN.

The CHMP considers the following measures necessary to address issues related to efficacy:

In order to further substantiate the efficacy and safety of KIOVIG in the treatment of Multifocal motor neuropathy (MMN), the MAH shall submit the final Clinical Study Report of the ongoing randomized placebo-controlled study in MMN patients (Study 160604) by 30 September 2012.

Clinical safety

Patient exposure

In the EU, KIOVIG (ready to use solution for infusion) was approved for the indications of the Core SmPC on 19 January 2006. The safety and tolerability of KIOVIG in the currently approved indications is well established and are similar to those of other marketed IVIg products.

The estimated patient exposure from completed studies with KIOVIG in MMN (Study I + II) is summarized in the table below.

Estimated patient exposure for MMN (Study I and II)

Patient	Age	Gender	Monthly exposure (g/kg/m)	Number of months exposed	Total Exposure (g/kg)
van den Berg's Conversion Study (Study I)					
1	38	M	0,78	42	32.8
2	50	M	2.1	42	88.2
3	51	M	0.56	42	23.5
4	46	M	0.64	42	26.9
5	64	F	0.92	42	38.64
6	45	M	1.08	42	45.46
7	54	M	0.96	42	40.32
8	41	M	0.76	42	31.9
9	64	M	0.4	42	16.8
10	67	M	NA	NA	NA
11	37	M	0.72	42	30.24
12	44	M	0.48	42	20.16
13	61	M	0.92	42	38.64
14	59	F	0.3	42	12.6
15	61	F	0.72	42	30.24
16	46	M	1.64	42	68.9
17	43	M	1.6	42	67.2
18	60	M	1.2	42	50.4
19	59	F	0.96	42	40.32
20	67	M	0.28	42	11.76
van den Berg's IVIg-naïve study					
1	26	M	0.52	36	18
2	42	M	0.4	36	14.4
3	59	M	0.4	42	16.8
4	55	M	0.28	42	11.76

Patient	Age	Gender	Monthly exposure (g/kg/m)	Number of months exposed	Total Exposure (g/kg)
5	45	M	0.4	30	12
6	57	F	0.28	30	8.4
7	38	M	1.0	30	38
8	58	M	2	1	2

In addition, patients with MMN are being treated with KIOVIG in the ongoing Study 160604. The cumulative exposure across all three trials, stratified by duration, is indicated in the following table:

INDICATION: MMN (Study I, II, and 160604) Study I, II Complete; 160604 ongoing
Exposure stratified BY DURATION

Duration of exposure	Persons	Person time (months)*
Cumulative Up to 1 m	8	8
Cumulative Up to 3 m	13	22
Cumulative Up to 6 m	15	33
Cumulative Up to 12 m	37	256
Cumulative Up to 4 years	70	1393

*Person time is total number of months subjects have been exposed (i.e. # persons X # months)

Adverse events

In the MMN Conversion study 7 out of 19 patients (35%) reported side effects with 10% liquid IVIg. All events were classified as non-serious and included skin reactions, fatigue and – most commonly – headache. One patient switched back to GAMMAGARD due to dizziness even with low infusion rates.

Data on Safety as reported in the Cochrane Database review on IVIg in MMN:

Adverse events reported following IGIV treatment in patients with MMN generally reflect safety data listed in the Core SmPC for IVIg as well as in the SmPC for KIOVIG that has been approved in Europe. The most common reactions are headache, rash, fever and shivering. Only 2 serious adverse events have been reported in literature (1 case of transient ischemic attack and 1 case of aseptic meningitis.)

Three randomized, controlled studies have examined the safety of IVIg products for short-term treatment of patients with MMN. With respect to long-term use of IVIg products in patients with MMN, safety data are available from four placebo-controlled clinical studies.

Safety of IVI product for short-term treatment of patients with MMN	
Azulay et al 1994	Cutaneous rash and transient fever were in 2/5 patients treated with IVIg
Federico et al 2000	Minor adverse effects in 13/16 patients: headache (5), headache and rash (3), rash alone (2), headache and malaise (1), anorexia, chills and fever (1), transient hypertension (1). Adverse effects were observed in 1 patient after placebo treatment: headache, fever, chills
Leger et al 2001 (Baxter study IMAG-089)	Headache (3), flushing (1), shivering (2), fever (1), visual blur (2) and eczema (1). One patient experienced cold feet on placebo.

Safety of IVI product for long-term treatment of patients with MMN	
Azulay et al 1997	Eight patients experienced minor adverse events, such as headache, fever, or rash. Aseptic meningitis occurred in 1 patient.
Leger 2008	One hundred and fifty minor adverse events were reported in 32/40 patients. All were events that have previously been associated with IGIV treatment.
Van den Berg-Vos 2002	Headache, rash, fatigue
Vucic 2004	One patient experienced right middle cerebral artery territory transient ischemic attack 2.8 years after beginning treatment. No permanent sequelae ensued.

Serious adverse events and deaths

Only two SAEs in MMN patients have been reported in literature (one case of transient ischemic attack, and one case of aseptic meningitis). No deaths were reported.

Discussion of clinical safety

The safety and tolerability of KIOVIG for the currently approved indications are well studied and accompanied with substantial post-marketing safety database.

An analysis of controlled studies on IVIg therapy in MMN 10 estimated a pooled relative risk of adverse events for IVIg therapy compared to placebo of 10.33 (95% CI interval: 2.15-49.77).

Only limited data on safety for KIOVIG in MMN are available. The safety data reported in patients with MMN in published studies included all AEs listed in the current SmPC. Main reported AEs were skin rash, headache, dizziness, fever, shivering and fatigue. It is not expected that the AE profile for KIOVIG in MMN will significantly differ from that already known for immunoglobulin treatment from literature and what was seen with KIOVIG in clinical studies. Although the AE profile of IVIg also depends on dosage and infusion rates, neither more AE nor more severe AE have been seen with KIOVIG compared with GAMMAGARD in the MMN Conversion study. Equivalent safety profiles for KIOVIG and GAMMAGARD for maintenance treatment have even been reported in CIDP patients.

The applicant is currently conducting another clinical study in MMN patients (study 160604). This is a randomized placebo-controlled study therefore providing additional safety data for this patient population. The Committee considered it important to review these data once available as it would further substantiate the available safety data.

CHMP is of the opinion that adverse events reported following IVIg treatment in patients with MMN generally reflect the safety data listed in the Core SmPC for IVIg as well as in the SmPC for KIOVIG that is currently approved in Europe.

Conclusion on clinical safety

The nature and frequency of adverse events reported by the applicant for KIOVIG when administered to subjects with multifocal motor neuropathy is in accordance with the pattern of adverse events described in the literature for other IVIg products. All adverse events are already included in the SPC.

Additional data on safety will be submitted by the applicant as part of the final Clinical Study Report that results from the ongoing randomised placebo-controlled study (study 160604) on use of KIOVIG in subjects with multifocal motor neuropathy. Study 160604 is expected to be completed in September 2012.

Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAH submitted a risk management plan (RMP).

This was the first version of the KIOVIG RMP; no RMP had been agreed prior to this variation.

Summary of the Risk Management Plan (version 5.0)

Safety Concerns	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Identified Risks		
Allergic / hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency and IgA antibodies	**Routine Pharmacovigilance**	**Routine Risk Minimization** **Contraindication in SmPC Section 4.3** "Hypersensitivity to the active substance or to any of the excipients." "Hypersensitivity to human immunoglobulins, especially in very rare cases of IgA deficiency when the patient has antibodies against IgA." **Special warnings and precautions for use in SmPC Section 4.4** "True hypersensitivity reactions are rare. They can occur in the very seldom cases of IgA deficiency with anti-IgA antibodies. KIOVIG is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern." "Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin." "Potential complications can often be avoided by ensuring: – that patients are not sensitive to human normal immunoglobulin by first infusing the product slowly (0.01 ml/kg BW/min); – that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human normal immunoglobulin, patients switched from an alternative IVIg product or when there has been a long interval since the previous infusion should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration."
Altered response to live attenuated vaccines, and implications for laboratory testing – Reduced efficacy of live attenuated virus vaccines such as measles, rubella, mumps, and varicella – Dilution with 5% glucose may lead to an increase in blood glucose levels – Interference with serological testing after infusion of immunoglobulin	**Routine Pharmacovigilance**	**Routine Risk Minimization** **Interactions with other medicinal products and other forms of interactions in SmPC Section 4.5** <u>Live attenuated virus vaccines</u> "Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year.

Safety Concerns	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
– Passive transfer of antibodies		Therefore patients receiving measles vaccine should have their antibody status checked." "In case of dilution with a 5% glucose solution, the KIOVIG administration may interfere with determination of blood glucose levels." **Special warnings and precautions for use in SmPC Section 4.5** Interference with serological testing "After infusion of immunoglobulin the transitory rise of the various passively transferred antibodies in the patients' blood may result in misleading positive results in serological testing." "Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D, may interfere with some serological tests for red cell antibodies, for example the antiglobulin test (Coombs test)."
Haemolysis	**Routine Pharmacovigilance**	**Routine Risk Minimization** **Special warning and precautions for use in SmPC Section 4.4** "Haemolytic anaemia can develop subsequent to IVIg (including KIOVIG) therapy. IVIg products can contain blood group antibodies that may act as haemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, haemolysis." **Undesirable effects in SmPC Section 4.8** "Cases of reversible aseptic meningitis, isolated cases of reversible haemolytic anaemia/haemolysis, and rare cases of transient cutaneous reactions have been observed with human normal immunoglobulin."
Transfusion related acute lung injury (TRALI)	**Routine Pharmacovigilance**	**Routine Risk Minimization** **Special warning and precautions for use in SmPC Section 4.4** "There have been reports of noncardiogenic pulmonary edema (Transfusion Related Acute Lung Injury, TRALI) in patients administered IVIg (including KIOVIG)."
Aseptic Meningitis Syndrome	**Routine Pharmacovigilance**	**Routine Risk Minimization** **Special Warnings and precautions for use in SmPC Section 4.4** "An aseptic meningitis syndrome (AMS) has been reported to occur in association with IVIg (including KIOVIG) treatment. Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to 2 days following IVIg treatment. – Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm^3, predominantly from the

Safety Concerns	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		granulocytic series, and elevated protein levels up to several hundred mg/dL. – AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment." **Undesirable effects in SmPC Section 4.8** "Cases of reversible aseptic meningitis, isolated cases of reversible haemolytic anaemia / haemolysis, and rare cases of transient cutaneous reactions have been observed with human normal immunoglobulin"
Thrombotic and Thromboembolic Events – myocardial infarction – stroke – pulmonary embolism – deep vein thrombosis	**Routine Pharmacovigilance**	**Routine Risk Minimization** **Special warnings and precautions for use in SmPC Section 4.4** "There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thrombosis which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin. Caution should be exercised in prescribing and infusion of IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events such as a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, hypercoagulable disorders, patients with prolonged periods of immobilisation, severely hypovolemic patients, patients with diseases which increase blood viscosity." "In patients at risk for acute renal failure or thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable."
Renal Failure	**Routine Pharmacovigilance**	**Routine Risk Minimization** **Special warnings and precautions for use in SmPC Section 4.4** "Severe renal adverse reactions have been reported in patients receiving IVIg therapy. These include acute renal failure, acute tubular necrosis, proximal tubular nephropathy and osmotic nephrosis. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medicinal products, age over 65, sepsis or paraproteinemia." "In case of renal impairment, IVIg discontinuation should be considered." "While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain sucrose may be considered."

Safety Concerns	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		"In patients at risk for acute renal failure or thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable."
Medication Error - Improper rate of infusion	**Routine Pharmacovigilance**	**Routine Risk Minimization** **Special warnings and precautions for use SmPC Section 4.4** "Certain adverse reactions such as headache and flushing may be related to the rate of infusion (see SmPC section 4.8). The recommended infusion rate given under "4.2 Method of administration" must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period." "Certain adverse reactions may occur more frequently – in case of high rate of infusion – in patients with hypo- or agammaglobulinemia with or without IgA deficiency – in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion. "
Potential Risks		
Viral Transmission	**Routine Pharmacovigilance**	**Routine Risk Minimization** **Special warnings and precautions for use in SmPC Section 4.4** "KIOVIG is made from human plasma. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infectious agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens." "The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses HAV and parvovirus B19." "There is reassuring clinical experience regarding the lack of hepatitis A or Parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety." "It is strongly recommended that every time that KIOVIG is administered to a patient, the name and batch number of the product is recorded in

Safety Concerns	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		order to maintain a link between the patient and the batch of the product."
Overdose leading to fluid overload and hyperviscosity	**Routine Pharmacovigilance**	**Routine Risk Minimization** **Overdose in SmPC Section 4.9** "Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with cardiac or renal impairment."
Important Missing Information		
Lack of information in pregnant and lactating women	**Routine Pharmacovigilance**	**Routine Risk Minimization** **Fertility, Pregnancy and lactation in SmPC Section 4.6** Pregnancy "The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore it should only be given with caution to pregnant women and breast-feeding mothers. Maternally administered IVIg products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected." Breast-feeding "Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate." Fertility Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.
Limited clinical data in paediatric patients below 16 years of age	**Routine Pharmacovigilance**	**Routine Risk Minimization** "The posology in children and adolescents (0-18 years) is not different to that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome of the above mentioned conditions."
Limited information in Geriatric patients over age 65	**Routine Pharmacovigilance** Alzheimer's Study 160701 is ongoing - 48% of subjects in this study are 72 years of age or older	**Routine Risk Minimization** **Special warnings and precautions for use in SmPC Section 4.4** "Caution should be exercised in prescribing and infusion of IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events such as a history of atherosclerosis, multiple cardiovascular risk factors, advanced age." **Overdose in SmPC Section 4.9** "Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with cardiac or renal impairment."

Safety Concerns	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Limited clinical data regarding treatment in patients with MMN	**Routine Pharmacovigilance** Study 160604 ongoing	**None**
Limited clinical data regarding treatment in patients of different ethnic origins	**Routine Pharmacovigilance**	**None**
Limited information in patients with organ impairment (eg kidney, liver, or cardiac)	**Routine Pharmacovigilance**	**Routine Risk Minimization** **Special warnings and precautions for use in SmPC Section 4.4** "Severe renal adverse events have been reported in patients receiving IVIg therapy. These include acute renal failure, acute tubular necrosis, proximal tubular nephropathy and osmotic nephrosis. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic medicinal products, age over 65, sepsis or paraproteinemia." "In case of renal impairment, IVIg discontinuation should be considered. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products containing various excipients such as sucrose, glucose and maltose, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain these excipients may be considered." "In patients at risk for acute renal failure or thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable." **Overdose in SmPC Section 4.9** "Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with cardiac or renal impairment." **Special warnings and precautions for use in SmPC Section 4.4** "There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thrombosis which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin. Caution should be exercised in prescribing and infusion of IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events such as a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output,

Safety Concerns	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, hypercoagulable disorders, patients with prolonged periods of immobilisation, severely hypovolemic patients, patients with diseases which increase blood viscosity."

The CHMP, having considered the data submitted in the application, is of the opinion that additional pharmacovigilance activities are needed in addition to the use of routine pharmacovigilance (cf section 4 and FUM in section 5).

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

PSUR

The Marketing Authorisation Holder will submit PSURs at 6-monthly intervals due to the limited available safety data in MMN patients.

Overall conclusion and Benefit-risk assessment

Benefits

Beneficial effects

Multifocal motor neuropathy is a recently-described motor neuropathy with an incidence of (about) 6 per million people and that affects adults in the age range 20 to 55yrs. Men are more commonly affected than women. There are not any known pre-disposing factors and the underlying aetiology is uncertain. Motor nerves are affected in a piece-meal fashion leading to an asymmetric weakness that (in about 70% of cases) presents with weakness of the intrinsic muscles of a hand. Symptoms are more evident than signs in the initial stages of the illness. The natural history of the disease is for slowly progressive weakness and atrophy of affected muscles with associated impaired quality of life.

Diagnosis of multifocal motor neuropathy is by a combination of a typical clinical history supplemented by nerve conduction studies and assessment of muscle strength. The presence of anti-GM antibodies may supplement the diagnosis.

Acceptable outcome measures of treatment of multifocal motor neuropathy would be increased muscle strength (of those muscles affected) and less functional disability associated with improved quality of life.

Evidence of benefit of treatment with IVIg is thus far limited. For this reason, all applications for IVIg in the indication for multifocal motor neuropathy required to be accompanied by persuasive data on increased muscle strength in response to treatment.

In the present application, the results from two, prospective, uncontrolled, open-label, investigator-initiated trials were submitted showing that intermittent intravenous infusion of KIOVIG in (i) the initiation and (ii) maintenance of treatment of patients with multifocal motor neuropathy resulted in

increased muscle strength (assessed by MRC scores, dynamometry and grip strength) and a reduction in reported disability (as assessed by the Guy's scale of disability and self-assessment).

The initiation trial involved 8 subjects who were naïve to treatment with IVIg. Patients received a five-day course of KIOVIG at a cumulative dose of 2g/kg body weight. Maintenance doses for the 7 subjects entering the long-term follow-up phase of the study were chosen by individual response. MRC sum scores were measured at baseline, after the first full course of IVIg (cumulative dose 2g/kg) and after the last follow-up examination of the long-term treatment phase. Additionally, a descriptive analysis of the response to KIOVIG on functional impairment (regarding daily life activities) was presented for each of the eight subjects. Subjects achieved up to 4 points increase in MRC score in response to Kiovig treatment: response was persistent for the duration of the trial (12 months).

The maintenance trial involved 20 subjects who were transferred from GAMMAGARD s/d (an alternate IVIg preparation licensed for use in MMN in the Netherlands) to KIOVIG at an equivalent dose. Treatment with KIOVIG was shown to maintain muscle strength for the duration of the conversion (9 months).

The MAH also submitted a review of published literature on the use of IVIg in the management of multifocal motor neuropathy.

The numbers of subjects enrolled into the two studies submitted were too small to consider sub-group analysis. The applicant justified not doing a comparator study on the grounds that cyclophosphamide (the only recognised comparator with reported efficacy) would be easy for investigator and subject to tell apart from KIOVIG on the basis of side-effects.

Overall, the data package provided was considered sufficient to demonstrate the efficacy and safety of KIOVIG in MMN, and in line with the requirements of the EMA guideline on clinical investigation of IVIgs.

It was considered that additional data submitted by the applicant on the efficacy of KIOVIG use in CIDP and on the Dutch national database of subjects with multifocal motor neuropathy did not support the current application.

Furthermore, the MAH provided information showing that home-infusion of KIOVIG was widely accepted by patients and that although only a minority self-infused, patients welcomed advantages of home-treatment such as time gain and convenience. Occurrence, frequency and severity of adverse events in home treated patients were comparable to those in the hospital setting.

As home IVIg administration has been in existence since the 1980s, and guidance material already exists, no additional risks associated with KIOVIG for MMN or any other indication foreseen, and risk minimisation activities are therefore not required. However, the available safety information on home infusion and criteria for patient selection should be included in the next RMP update.

Uncertainty in the knowledge about the beneficial effects

The mechanism of action of IVIgs in MMN has not been elucidated, leaving an uncertainty as to the pharmacodynamics. This is true for all "immunomodulatory" indications and therefore more basic research would be of essence. Nevertheless, the use of IVIg in MMN is recommended in relevant treatment guidelines, and some efficacy data has been obtained for different formulations.

The data on the efficacy of KIOVIG for the treatment of patients with MMN was derived from two open-label, single arm clinical trials. There was no dose finding study; however, dose and dosing intervals in the chronic immunomodulatory setting are generally tailored to the patient's needs. The open-label,

uncontrolled nature of the two studies inherently did raise concerns regarding the robustness of the efficacy data submitted. Also there were uncertainties regarding the MRC score system used by the applicant and the clinical relevance of the results obtained. However, the applicant has provided supplemental data on (i) dynamometry of large muscle groups and (ii) grip strength in response to treatment. These data did mitigate these uncertainties leading to the conclusion that the limited data are reasonable re-assuring.

There is lack of knowledge of the long-term use of KIOVIG in the management of multifocal motor neuropathy (beyond the timescale of the currently submitted trials) and whether or not muscle weakness may remain improved or continue to weaken in spite of treatment. There is lack of knowledge on whether or not use of KIOVIG would prevent involvement of motor nerves not yet affected. Furthermore, there is lack of knowledge on the overall impact of KIOVIG on the long-term quality of life and long-term survival. However, it may be expected that knowledge of the consequences of long-term use of KIOVIG may be gathered through surveillance during market exposure.

Overall, it is considered the available data for KIOVIG in MMN that is specifically generated for this product is limited; the data is supported by data from other IVIg preparations which was deemed acceptable. Overall, the available data is considered sufficient for granting the indication but this limitation has been reflected in the RMP as important missing information. Consequently, the CHMP considers the results of the randomized, placebo-controlled trial (Study 160604) currently ongoing in the US as relevant to corroborate the efficacy and safety of KIOVIG in the treatment of patients with MMN. The provision of the final CSR of this study is therefore requested as a condition to the marketing authorisation.

Risks

Unfavourable effects

The AE reported with KIOVIG in patients with MMN reflect what has been reported with KIOVIG in other indications. Side effects were reported in 35% of patients and included skin reactions, fatigue and – most commonly- headache. All events were classified as non-serious and were reversible. All AE reported with KIOVIG in MMN patients are already listed in the SmPC.

Therefore it is not expected that the use of KIOVIG for the treatment of MMN will have an altered safety profile.

Uncertainty in the knowledge about the unfavourable effects

The safety database from completed clinical trials with KIOVIG in MMN only covers 20 patients and is therefore relatively small. However, the data as provided with this application as well as what is known from other IVIgs in the treatment of MMN does not indicate a relevant change in the safety profile.

The limited clinical data regarding treatment in patients with MMN has been identified as important missing information in the RMP. Additional safety and efficacy data will be provided in the KIOVIG PSURs (reverted to 6 monthly cycle) as well as in the final CSR of the randomized, placebo-controlled study currently ongoing (Study 160604).

Balance

Importance of favourable and unfavourable effects

MMN is a rare, progressive debilitating disease that most commonly affects distal upper limb muscles. Though rarely fatal, the disease causes significant functional disability that interferes with daily activity such as independent eating, grooming, writing, opening and locking doors and holding objects. Any therapy to increase muscle strength and allow the patient to regain independence and resume a normal daily life is therefore essential.

In the last 10 years literature studies and case reports have repeatedly shown a benefit for the use of IVIgs in this condition. Generally, the response rate seen is around 75%; over time an increase in IVIg dose may become necessary to maintain the desired effect. This has now been confirmed by a "patchwork" approach of the company who submitted data with two forerunner products (Endobulin, GAMMAGARD) and their current product (KIOVIG) in initiation and maintenance settings, a comprehensive analysis of the literature, and of the feasibility of extrapolation between products.

Alternative treatment options are limited. Patients with MMN rarely respond to treatment with steroids and plasma exchange and may even worsen. Mycophenolate mofetil is ineffective. Very limited data are available showing a weak positive effect of interferon and natalizumab, and a more positive effect with rituximab. Cyclophosphamide appears to be the most effective treatment apart from IVIg. However, long-term treatment with cyclophosphamide is restricted due to its safety profile and high toxicity.

Given that this is a chronic, progressive disease that affects young adults and that there is not any suitable, alternate treatment then the increased muscle strength and lessened disability with associated improved quality of life in response to KIOVIG is considered to be important from the clinical perspective. Moreover, since there is not at present an IVIg that is licensed across Europe for management of multifocal motor neuropathy then this would be considered to be a product that addresses an unmet medical need.

There are no high toxicity risks related to the use of IVIgs. In general they are well tolerated even if given life-long as e.g. in replacement therapy. Risks such as hypersensitivity reactions, aseptic meningitis, thromboembolic events, or renal failure are grave but rare and risk minimisation efforts are undertaken by the company to address these side-effects. The unfavourable effects of skin reaction, fatigue and headache have been well described and documented for KIOVIG in its use for other indications and would not be considered to detract from the favourable effects.

Benefit-risk balance

It is considered that the increased muscle strength in response to KIOVIG treatment of multifocal motor neuropathy and the potential for this increase to persist over time with associated improved quality of life outweigh both the negative impact of adverse effects, as described, and the inconvenience of needing to administer an intravenous preparation.

Discussion on the benefit-risk assessment

There remain uncertainties in the full impact of treatment muscle weakness of multifocal motor neuropathy with KIOVIG: it is anticipated that these uncertainties may be addressed by the ongoing randomised, controlled study being conducted in the USA.

There is uncertainty in the ability of KIOVIG to maintain increased muscle strength over time. Progressive weakness in any one subject would lead to a shift in the benefit-risk balance for that subject with further treatment being considered to be futile. Since subjects receiving KIOVIG for management of multifocal motor neuropathy will be under continuing physician management and review then it may be expected that the development of lack of response in any one subject to KIOVIG will be addressed promptly.
Overall, however, it is considered that the MAH has provided acceptable data to support the application for the use of KIOVIG in the indication for multifocal motor neuropathy. Against this background, the CHMP considered that the benefit-risk-profile for KIOVIG is positive for the treatment of multifocal motor neuropathy and that the current variation application is approvable.