22 May 2014
EMA/339024/2014 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Plegridy

International non-proprietary name: peginterferon beta-1a

Procedure No. EMEA/H/C/002827/0000

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

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List of abbreviations

ADA	Antidrug antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine transaminase
AS	Active substance
AST	Aspartate aminotransferase
AUC_x	Area under the curve up to x hours after dosing
BAbs	Binding antibodies
BIIB017	The company code name for peginterferon beta-1a in which the α-amino group of the N-terminal amino acid residue is modified with a single, linear 20 kDa molecular mass methoxy poly(ethyleneglycol)-O-2-methylpropionaldehyde moiety
BIIB017-A	Internal product code for the process used to manufacture peginterferon beta-1a drug substance for phase 1 clinical studies
BIIB017-B	Internal product code for the process used to manufacture peginterferon beta-1a DS for the phase 3 clinical study 105MS301 (ADVANCE), the phase 3 extension study 105MS302 (ATTAIN), and for proposed commercial supply
BMI	Body Mass Index
cHAP	hydroxyapatite chromatography
CHO	Chinese Hamster Ovary
C_{max}	Peak plasma concentration of a drug after administration
CL	Clearance
CNS	Central Nervous System
CPE	Cytopathic effect
CQAs	Critical quality attributes
CYP	Cytochrome P450
DHFR	Dihydrofolate reductase
DNA	Deoxyribonucleic acid
DoE	Design of experiments
DP	Drug product
DS	Drug substance
EAE	Experimental autoimmune encephalomyelitis
ECD	Extracellular domain
EDSS	Expanded Disease Severity Scale
EEPCB	Extended End of Production Cell Bank
EMCV	Encephalomyocarditis virus

EPAR	European Public Assessment Report
ESRD	End-stage renal disease
EU	European Union
FLS	Flu-like symptoms
FP	Finished product
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HMW	High molecular weight
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INEC	Independent Neurology Evaluation Committee
IFN	Interferon
IFN ß-1a	Interferon beta-1a
IFNAR	Interferon alpha/beta receptor
IM	Intramuscular
IPC	In-process control
ISRs	Injection Site Reactions
ITT	Intent to treat
IV	Intravenous
JP	Japanese Pharmacopoeia
LIVCA	Limit of *in vitro* cell age
LMW	Low molecular weight
MAA	Marketing authorisation application
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MIU	Million international units
mPEG	Methoxy poly(ethyleneglycol)-O-2 methylpropionaldehyde
MCB	Master Cell Bank
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
MTR	Magnetization transfer ratio
MTX	Methotrexate
MxA	Myxovirus resistance protein A
Mw	Molecular weight
Nabs	Neutralising antibodies
NORs	Normal operating ranges
2′,5′-OAS	2′,5′-Oligoadenylate s synthetase
PCR	polymerase chain reaction
PD	Pharmacodynamic
PEC	Predicted Environmental Concentration

PEG	Poly(ethyleneglycol)
pegINF	Peginterferon
PFP	Pre-filled pen
PFS	Pre-filled syringe
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PP	Per protocol
ppm	Parts per million
PPMS	Primary progressive Multiple Sclerosis
PT	Preferred Term
RBC	Red Blood Cells
RNS	Rigid needle shield
RRMS	Relapsing-remitting Multiple Sclerosis
SAE	Severe adverse reaction
SC	Subcutaneous
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPMS	Secondary Progressive Multiple Sclerosis
SD	Standard Deviation
SE	Standard Error
STAT	Signal Transducers and Activators of Transcription
q2W	Every two weeks dosing
q4W	Every four weeks dosing
UF	Ultrafiltration step
ULN	Upper limits of normal
USP	United States Pharmacopoeia
WBC	White Blood Cells
WCB	Working Cell Bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Biogen Idec Ltd submitted on 30 May 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Plegridy, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004 .

The applicant applied for the following indication: treatment of relapsing multiple sclerosis in adult patients to slow the progression of disability and decrease the frequency of relapses.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that peginterferon beta 1-a was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on the applicant's own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0182/2012 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP EMEA-001129-PIP01-11 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance peginterferon beta-1a contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

A new application was filed in the following countries: United States (U.S.).

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer of the active substance

Biogen Idec, Inc.
14 Cambridge Center
Cambridge, MA 02142
USA

Manufacturer responsible for batch release

Biogen Idec Denmark Manufacturing ApS
Biogen Idec Allé 1
DK-3400 Hillerød
Denmark

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Johann Lodewijk Hillege

Co-Rapporteur: Martina Weise

- The application was received by the EMA on 30 May 2013.
- The procedure started on 26 June 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 September 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 September 2013.
- During the meeting on 10 October 2014, the PRAC adopted the PRAC Rapporteur RMP Assessment Report.
- During the meeting on 24 October 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 28 October 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 January 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 March 2014.
- During the meeting on 6 March 2014, the PRAC adopted a PRAC RMP Advice and assessment overview.
- During the CHMP meeting on 20 March 2014, the CHMP agreed on a list of outstanding

issues to be addressed in writing by the applicant.

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 April 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 30 April 2014
- During the meeting on 8 May 2014, the PRAC adopted the PRAC Rapporteur RMP Assessment Report.
- During the meeting on 22 May 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Plegridy.

2. Scientific discussion

2.1. Introduction

Multiple Sclerosis (MS) is a chronic, progressive, autoimmune, debilitating neurodegenerative disorder with multifocal demyelination affecting the brain, optic nerves and spinal cord. This process leads to dysfunctions of the Central Nervous System (CNS) manifesting in various symptoms and frequently leading to severe disability. Its prevalence rate varies between races and geographical latitude, ranging from more than 100 per 100,000 in Northern and Central Europe to 50 per 100,000 in Southern Europe.

The pathogenesis of MS remains unknown. It is generally assumed that MS is mediated by an autoimmune process possibly triggered by infection based on a genetic predisposition.

MS may manifest in relapsing and progressive forms. Relapsing-remitting MS (RRMS) accounts for about 85% of MS cases. RRMS is characterised by unpredictable acute episodes of neurological dysfunction, followed by variable recovery and periods of clinical stability. Within 10 years of disease onset more than 50% of patients develop sustained deterioration with or without relapses i.e. secondary progressive variety of MS (SPMS). However, about 10-15% of patients develop a sustained deterioration of their neurological function from the beginning i.e. primary progressive MS (PPMS). The course of MS can also be benign i.e. RRMS with few relapses and no significant disability after several years or malignant i.e. leading to significant disability in a few years after the onset.

Relapses are considered the clinical expression of acute inflammatory focal lesions in e.g. spinal cord, optic nerve or brainstem, whereas progression is considered to reflect an increasing degree of demyelination, axonal loss and gliosis. RRMS and SPMS are probably different stages of the same disease where the relative contribution of the active immunological aspect and a degenerative aspect changes.

Current therapeutic approaches include symptomatic treatment, treatment of acute relapses with corticosteroids, disease modifying treatment with immunomodulators e.g. glatiramer acetate, beta-interferons, natalizumab, fingolimod, dimethyl fumarate, alemtuzumab, teriflunomide or immunosuppressant/cytotoxic agents.

Plegridy contains the active substance peginterferon beta-1a, which is a polyethylene glycol (PEG)-conjugated form of glycosylated, recombinant interferon beta-1a modified with a single, linear molecule of 20 kDa mPEG-O-2-methylpropionaldehyde (mPEG). The proposed product is a pre-filled syringe or a pre-filled pen containing up to 125 µg of peginterferon beta-1a. After an initial titration with 63 and 94 µg/ml solutions, the maintenance dose is 125 µg to be administered subcutaneously every other week.

Interferon betas are cytokines with immunomodulatory activity and represent established first line therapies in multiple sclerosis. The biological effects of interferon betas include up-regulation of anti-inflammatory cytokines [e.g. Interleukin-4 (IL-4), IL-10, IL-27], down-regulation of pro-inflammatory cytokines (e.g. IL-2, IL-12, IFN-γ, TNF-α) and inhibiting the migration of activated T cells across the blood brain barrier. Whether these effects mediate the mechanism of action of interferon beta is unclear as the pathogenesis of MS remains unclear.

Several products containing interferon beta were already approved in the European Union (EU) for MS treatment at the time of this report, including two interferon beta-1a products (Avonex and Rebif) and two products containing interferon beta-1b (Extavia and Betaferon). The currently available interferon beta therapies require either intramuscular (IM) or subcutaneous (SC) injections, administered once a week (interferon beta-1a IM), to as many as 3 to 4 times a week (interferon beta-1a SC, interferon beta-1b SC). In Plegridy, pegylation at the N-terminal alpha amino group of the interferon beta-1a protein was performed, as pegylation protects against enzymatic degradation and other clearance mechanisms and therefore prolongs the half-life compared to unmodified substances.

Pegylation can be considered a well-established modification to reduce the frequency of dosing while maintaining safety and efficacy of an active substance. It has been used in a number of protein products centrally approved across the EU including two interferon alpha products (Pegasys and PegIntron) approved for the treatment of hepatitis.

2.2. Quality aspects

2.2.1. Introduction

Peginterferon beta-1a (pegIFN ß-1a) is a pegylated form of interferon beta-1a (IFN β-1a). Peginterferon beta-1a is presented as a solution for subcutaneous injection, supplied either as pre-filled syringe (PFS) or pre-filled pen (PFP). For both PFS and PFP, three strengths are available: two titration doses (63 and 94 microgram) and one administration dose of 125 microgram, per 0.5 mL of solution. The dose indicates the quantity of the interferon beta-1a moiety of peginterferon beta-1a without consideration of the PEG moiety attached.

2.2.2. Active Substance

General information

Peginterferon beta-1a is a glycosylated recombinant interferon beta-1a (IFN β-1a) that is pegylated with a single 20kDa methoxypoly (ethyleneglycol)-O-2 methylpropionaldehyde (mPEG) moiety at the N-terminus. IFN-β-1a is a 166 amino acid glycoprotein. The Mw of mPEGIFN-β-1a is approximately 44 ± 2 kDa as predicted from the amino acid sequence, and the masses of the attached poly(ethyleneglycol) and carbohydrate chains.

Manufacture

The peginterferon beta-1a active substance is manufactured by Biogen Idec Inc. in Cambridge, Massachusetts, US.

Origin, source, and history of the cells, characterisation and testing

A two-tiered cell bank system consisting of a Master Cell Bank (MCB) and a Working Cell Bank (WCB) was established.

In addition, an Extended End of Production Cell Bank (EEPCB) was prepared to establish the limit of *in vitro* cell age for cell line identity, safety, and purity testing. The cell banks were tested and released accordingly to the specifications demonstrating identity, purity and suitability of all the three cell banks.

The MCB and WCB were tested for adventitious agents and identity by isoenzyme analysis. Additionally, genetic characterisation was performed. MCB and WCB are stored in the vapour phase of liquid nitrogen. The genetic characterisation of the MCB and EEPCB demonstrates that the cells are genetically stable up to the proposed limit of *in vitro* cell age (LIVCA).

Manufacturing process

The manufacturing process is comprised of cell culture expansion, a production bioreactor, clarification of the cell culture fluid, and purification resulting in highly purified interferon beta-1a. The purified interferon beta-1a is then pegylated by reaction with 20 kDa mPEG-O-2-methylpropionaldehyde and further purified resulting in the peginterferon beta-1a active substance.

All process steps and material controls are well described. The process control strategy is presented in detail and key and critical controlled parameters, in-process controls and in-process tests have been provided.

Control of Materials

All raw materials are approved for use on the basis of specified testing and a manufacturer's certificate of analysis and origin, as applicable. Non-compendial materials are also qualified with testing requirements developed by Biogen Idec. No raw materials of direct animal origin are used in either the working cell bank or the pegIFN β-1a manufacturing processes.

A comprehensive risk management plan and control strategy has been implemented in line with the requirements for starting materials (ICH Q11).

Control of critical steps and intermediates

The control strategy is based on comprehensive risk assessments to identify critical quality attributes (CQAs), raw materials and process parameters impacting on CQAs of the active substance process performance. The applicant proposes a three-tiered approach including critical, key and non-key controlled process parameters. The classification of the parameters is performed based on the impact of process parameters at each step on CQAs (=> critical) and process performance (=> key). Non-key parameters are assumed to impact neither CQAs nor process performance.

Process validation

The validation runs were well within the pre-defined acceptance criteria. Besides the in-process controls and critical in-process controls, in-process measurements were conducted demonstrating that the process performs consistently. The hold times of media, buffer and intermediates as well as shipping conditions have been provided. The lifetime of chromatography columns is prospectively set based on small scale studies and a protocol to further confirm these on full scale manufacturing conditions is set.

The information on the analytical methods used for the depletion/clearance process validation studies is considered acceptable. Input variables that control the process were initially tested during screening studies and those variables shown to control the process (greatest effect on critical quality attributes and/or process consistency) were later taken into modelling studies. These process characterisation studies were designed to evaluate the highest risk input parameters using a multifactorial design of experiments (DoE) approach. The deduced normal operating ranges (NOR) are well within the ranges tested.

Characterisation

The active substance was sufficiently characterized by state of the art spectroscopic and chromatographic techniques.

The structural characterisation and elucidation of physico-chemical properties using adequate analytical methods presented in the application have confirmed that the structure and properties of peginterferon beta-1a active substance produced by Biogen Idec Inc. have identical features to interferon beta-1a pegylated at the N-terminus.

Specification

The active substance release and stability specification comprises testing of identity, activity, quantity, purity, impurities and other general tests.

The specification is based on batch release data, stability data, clinical batch data and developmental studies. In addition, product and process risk assessments were conducted and a testing strategy was developed to ensure that the critical quality attributes are controlled. Acceptance limits were also set based on criticality of the attribute for pegIFN ß-1a safety and/or efficacy; manufacturing capability and variability; and analytical test method capability.

During the evaluation procedure, the specifications for the active substance have been amended or further justification has been provided.

Analytical Methods

In general, the description of the analytical methods is considered sufficient. Non-compendial tests have been validated. The information provided on batch analyses as well as on the justification of specification is considered acceptable.

Reference Material

Sufficient information on the primary reference standard and on the selection and qualification of future working standards has been provided.

Stability

Sufficient stability data have been provided and no adverse stability trends have been observed at the long-term or accelerated storage conditions. In summary, based on the available data the proposed shelf life is considered appropriate.

2.2.3. Finished Medicinal Product

The finished product is supplied as a sterile, liquid formulation in a pre-filled syringe for subcutaneous injection. The finished product has three different fixed dosage strengths and each is filled into the Pre-filled Syringe at a nominal volume of 0.5 mL. The 63 and 94 µg strengths are for initial dose titration and the 125 µg strength is the administration dose.

In addition to the pre-filled syringe, a single-use, disposable, spring-powered pre-filled pen will be available for patients.

The excipients of the finished product are sodium acetate trihydrate, acetic acid, L-Arginine HCl, Polysorbate 20 and water for injections.

Pharmaceutical Development

The development of the Phase 1 finished product formulation was initiated with the same composition as the Avonex formulation. The pH range and osmolality of the formulation was suitable for subcutaneous use, the intended route of administration for Plegridy.

To evaluate the robustness of the finished product formulation, a partial factorial experimental design study was performed. Overall, these data demonstrated that the finished product manufacturing process is robust and able to remain within stability acceptance limits even if manufacturing variations in the formulation composition occur.

Manufacture of the product

The finished product manufacturing process comprises formulation steps, filtration, aseptic syringe filling, and assembly of pre-filled pen.

Process consistency validation of the finished product process was demonstrated. The overall control strategy applied, taking risk management/mitigation measures into account, is deemed acceptable.

All the excipients used in the manufacture of the finished product are of appropriate compendial grade (USP, Ph. Eur, and/or JP). No excipients of human or animal origin are used for the manufacture of the finished product. No novel or non-novel, non-compendial excipients are used in the manufacture of Plegridy finished product.

Product specification

The pegIFN-β-1a finished product specifications were developed in line with the ICH Q6B guideline: *"Specifications - Test Procedures and Acceptance Criteria for Biotechnological / Biological Products."* The proposed release and stability specifications for pegIFN-β-1a finished product provide assurance of product quality of each finished product lot at release and over its shelf-life.

As a basis for establishing the commercial release specifications, a product risk assessment was conducted and a testing strategy was developed. The risk assessment was conducted as per internal guidelines.

The approach for CQA classification based on risk assessment using impact and uncertainty score and calculated risk priority number is deemed acceptable. However, the approach for setting specification acceptance criteria based on already too wide acceptance criteria for active substance was not accepted. During the initial evaluation the Applicant has revised the specifications or has further provided adequate justification.

Batch analysis results are presented for both the pre-filled syringe component and the final pre-filled pen. A summary of the lots, their manufacturing history and purpose is provided as well as release test results of clinical lots and process validation lots. All results met the release specifications, demonstrating that the manufacturing process is under control to produce pegIFN-β-1a batches of the intended quality.

Container Closure System

The finished product is a sterile, liquid formulation filled in a 1 mL syringe. A pre-filled syringe is contained within a single-use, disposable, spring-powered pen injector called Plegridy Pen. The syringe inside the pen is a 1 mL pre-filled syringe made of glass (Type I) with a bromobutyl rubber stopper and thermoplastic and polypropylene rigid needle shield (RNS), containing 0.5 mL of solution.

Stability of the product

A 2 years shelf life is proposed for pegIFN-β-1a finished product at all strengths (63 µg/syringe, 94 µg/syringe, and 125 µg/syringe) when stored at 2°C to 8°C, with an allowance of storage for up to 30 days at room temperature (2°C to 25°C), protected from light, within the 2 years shelf life.

The cGMP finished product stability studies were designed in accordance with ICH guidelines Q1A (R2), *Stability Testing of New Drug Substances and Products and* Q5C*, Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*.

Results from stability studies have been provided for the pre-filled syringes under long-term storage conditions and accelerated conditions. Furthermore, stability studies have been performed with the pre-filled pen under long-term storage conditions and accelerated conditions in accordance with ICH guidelines. A post-approval stability protocol and stability commitment have been provided.

As PegIFN-β-1a finished product was shown to be sensitive to light, a storage condition of 'Store in the original package in order to protect from light' has been included in the product information.

Additional stability studies were conducted to support an additional storage. The study results confirm that these specified times do not adversely change pegIFN beta-1a finished product quality.

Based on the data provided, a shelf life of 2 years at 2°C to 8°C, with an allowance of storage for up to 30 days at room temperature (2°C to 25°C), protected from light, within the 2 years shelf life for the finished product is considered acceptable. If Plegridy is at room temperature for a total of 30 days, it should be used or discarded. If it is not clear if Plegridy has been stored at room temperature 30 days or more, it should be discarded.

Adventitious agents

The virus safety of Plegridy is controlled by a complementary strategy comprising testing of cell banks, raw materials and the unprocessed bulk harvest for adventitious/endogenous agents and validation of the virus removal/inactivation capacity of the manufacturing process. Process steps have been investigated in virus validations studies and indicate that the process is capable of adequate virus removal/inactivation.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Active substance

The information provided gives a clear overview of development, and production of the active substance. In general the information is well presented and state-of-the-art. However, two major objections have been raised during the initial MA application regarding the control of the purified interferon beta protein prior pegylation and the lack of sufficiently detailed information on the analytical procedures which have been satisfactorily addressed.

The genetic characterisation of the MCB and EEPCB demonstrated that the cells are genetically stable up to the proposed limit of *in vitro* cell age (LIVCA). Data regarding the viable cell density and cell viability at harvest and beyond the proposed LIVCA has been provided and substantiated the proposed LIVCA, as viable cell density and cell viability remain stable.

A list of all materials used in the manufacturing process is presented. For non-compendial or critical raw materials the currently qualified vendors are described. Specifications for non-compendial raw materials as well as specifications for critical raw materials used in cell culture and purification have been added.

The control strategy has been further clarified and/or justified. Updated flowcharts and process descriptions including the entire operating ranges of the controlled parameters were provided and these were considered acceptable. Action limits for key and critical operational parameters as well as specification limits for critical in-process controls have been provided. The information on the analytical methods employed for the depletion/clearance process validation studies was considered acceptable.

Finished product - Plegridy pre-filled syringe

The information provided on the finished product manufacture, control and stability is deemed acceptable. A Major Objection was initially raised on the description and qualification of the analytical procedures (as described in the active substance section) related to the control of the finished product at release and its stability over shelf life. This objection has been sufficiently addressed.

The approach for CQA classification based on risk assessment using impact and uncertainty score and calculated risk priority number is deemed acceptable. However, the approach for setting specification acceptance criteria based on already too wide acceptance criteria for active substance was not accepted. During the initial evaluation the Applicant has revised the specifications or has provided adequate justification.

The batch analyses demonstrated that the finished product manufacturing process is able to produce lots that consistently meet the specifications set.

Based on the data provided, a shelf-life as stated in the SmPC for the finished product is considered acceptable.

Finished Product – Plegridy Pre-filled Pen

All development studies on pen suitability were performed by utilising the intended type of pre-filled pen for commercial production. The established strategy for controlling and monitoring the assembly process provides evidence that the intended product quality of the pen is ensured.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The development, characterisation, and manufacture of the active substance and finished product have been adequately described.

The manufacturing process of the finished product is described in sufficient detail and has been satisfactorily validated. The IPC tests are described and deemed suitable for controlling and monitoring the manufacturing process. The results indicate that active substance as well as the finished product can be reproducibly manufactured. No quality aspects impacting on the Benefit-Risk balance have been identified for Plegridy.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended some points for further investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

The objective of the non-clinical program of Plegridy was to evaluate the pharmacology, pharmacokinetics (PK), and safety of BIIB017 with a view to support up to weekly chronic SC administration in MS patients. The development was based on the experience gained with non-modified interferon beta-1a products (Avonex and Rebif). In addition, results from the non-clinical developments of PegIntron and Pegasys were also considered given that these drugs represent a pegylated version of similar type I interferons that have been approved and marketed.

The non-clinical development program of Plegridy was comprised of:

- Pharmacology studies evaluating the receptor binding affinity and the in vitro antiviral and antiproliferative activity of BIIB017.
- PK studies evaluating the PK profile and tissue distribution of BIIB017, including comparisons to interferon beta-1a.
- Non-clinical safety studies to support the chronic use of BIIB017 for MS at the recommended dose and regime.

The applicant followed the relevant scientific guidelines for the non-clinical development, the ICH S6 guideline for Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

The early peginterferon beta-1a drug substance used in the 5 week repeated-dose toxicity study in rhesus monkeys and the initial phase I trials (BIIB017-A) was derived from a foetal bovine serum-containing production and was later replaced by a serum-free manufacturing process without materials of animal origin (BIIB017-B). This process also utilizes a different purification to increase yield while reducing heterogeneity of the drug product. Comparability between both productions also in relation to Avonex was investigated in physiochemical and biochemical studies and is ensured by quality measures. Moreover, both BIIB017-A and BIIB017-B were compared in non-clinical investigations. BIIB017-B drug product was investigated in two phase I studies and in phase III and will be used for marketing of Plegridy. The commercial formulation contains peginterferon beta-1a in acetic acid/sodium acetate buffer arginine HCl and polysorbate 20.

For all of the non-clinical studies, with the exception of 1 PK study in rats, the 20 kDa mPEG-O-2-methylpropionaldehyde was supplied from a single vendor.

2.3.2. Pharmacology

The pharmacology programme, including primary and secondary in vitro pharmacology studies was designed to determine if the pharmacology of BIIB017 was consistent with that of interferon beta-1a (Avonex) with respect to:

1. Receptor binding affinity to interferon alpha/beta receptor 2 (IFNAR2), the receptor chain mediating high affinity binding of type I interferon beta-1a,

2. Antiviral activity in an assay measuring the ability to protect human A549 lung carcinoma cells from the cytopathic effect of encephalomyocarditis virus,

3. Antiproliferative activity in an assay measuring the ability to inhibit the proliferation of human Daudi B cells.

Pharmacological activity of BIIB017 was further evaluated in the PK and toxicology studies conducted in rhesus monkeys.

In vivo efficacy studies in animal models of MS were not conducted. While mouse and rat experimental autoimmune encephalomyelitis (EAE) models have been developed that reflect certain aspects of the pathophysiology of MS, mice and rats are not pharmacologically responsive to human interferon beta-1a, therefore precluding studies with BIIB017 in these models. Moreover, the applicant considered it not appropriate to test pegylated mouse or rat interferon beta in these EAE models since the data would not necessarily reflect the pharmacology of BIIB017 in humans. Furthermore, there was considerable data on the efficacy of interferon beta-1a in MS.

The exact mechanism of action of interferon beta in MS is not known. However, there are well established biomarkers of the pharmacological activity of interferon beta-1a including serum neopterin levels and decreases in lymphocyte numbers. While it has not been determined whether any of these biomarkers are surrogates for efficacy in MS, they were included in the PK and some of the non-clinical safety studies.

Primary pharmacodynamic studies

According to the commonly held view, type I interferons, including interferon beta-1a, signal through a cell surface receptor composed of the IFNAR1 and IFNAR2 chains. The intracellular portions of IFNAR1 and IFNAR2 associate with Janus tyrosine kinase 2 and Janus kinase 1, respectively. Following ligand binding, the kinases phosphorylate each other and the receptor chains thereby creating binding sites for Signal Transducers and Activators of Transcription (STAT) proteins. The STAT proteins are subsequently phosphorylated, oligomerise, migrate to the nucleus, and drive the expression of interferon-stimulated genes. These genes and their corresponding protein products are responsible for mediating the efficacy of interferon beta-1a in MS. IFNAR2 is the high affinity receptor chain that first binds interferon beta-1a prior to association of IFNAR1 with the interferon beta-1a/IFNAR2 binary complex. Therefore, binding to the type I interferon receptor was studied by investigating the affinity of interferon beta-1a and BIIB017 for the extracellular portion of the IFNAR2 chain.

There was no apparent difference in the affinity of either interferon beta-1a or BIIB017 for IFNAR2 indicating that in solution, the 20 kDa mPEG moiety did not interfere with receptor binding.

Secondary pharmacodynamic studies

The antiviral activity of BIIB017 was determined in an assay measuring the ability of the protein to protect human A549 lung carcinoma cells from the cytopathic effect of encephalomyocarditis virus, and the antiproliferative activity was determined in an assay measuring the ability of the protein to inhibit the proliferation of human Daudi B cells. In these assays, BIIB017 showed a modest ~2-fold loss of potency compared to interferon beta-1a.

These differences in activity of BIIB017 compared to interferon beta-1a suggest that the

affinity for the type I interferon receptor, composed of the full-length IFNAR1 and IFNAR2 chains expressed on the cell surface, may be affected by the attached 20 kDa mPEG. Studies with mouse interferon beta have shown that different gene sets may be activated depending on the mode of activation of the interferon type I receptor (de Weerd et al, 2013). Gene expression profiling of peripheral blood samples, obtained from healthy human subjects in the phase 1 study 105HV101, showed the induction of interferon responsive genes both by IFN beta-1a and BIIB017, albeit with a temporal difference reflecting the slower absorption time of the pegylated form (Allaire et al 2013).

Pharmacodynamic response was also monitored in pharmacokinetic and toxicology studies by determination of serum neopterin, increase of body temperature and (in the repeated dose toxicology study only) decrease in peripheral lymphocyte count. The correlation of these surrogate markers of interferon beta pharmacological activity with efficacy in the claimed indication is not known. As the increase in body temperature is variable, this surrogate marker was considered of little value when evaluating the pharmacodynamic response of interferon beta.

Serum neopterin (D-erythro-1', 2', 3'-trihydroxypropylpterin), a small molecule product of the activity of the interferon-inducible enzyme, GTP-cyclohydrolase I, has been used widely as a PD marker of interferon beta-1a activity in both humans and primates. Neopterin response following a single administration of BIIB017 and interferon beta-1a (100 µg/kg) was similar based on AUClast and Cmax. Yet, BIIB017 showed a longer elimination half-life (t1/2), reduced clearance, and greater exposure than the unmodified protein (see pharmacokinetics section). As shown in a subsequent single dose dose-response study in rhesus monkeys, saturation of biological response occurs above a dose of 10 µg/kg. Thus, the study comparing interferon beta-1a with BIIB017 likley used a dose which was already in the maximum response range, making the study factually non-discriminative.

In the 5-week repeated dose toxicology study, decreases in lymphocyte counts and increases in neopterin concentrations were observed for rhesus monkeys administered BIIB017. However, the pharmacodynamic response diminished from the 3rd dose onwards, which was reflected by waning of the neopterin response, disappearance of the transient increase in body temperature 4 hours post-dose and diminished reduction of lymphocyte count. The most probable explanation for the waning of these PD effects is the appearance of neutralising antibodies (Nabs). However, fading of the effect on lymphocyte count was delayed in the intramuscularly treated animals and the applicant suggested that administration through this route may delay the development of antibodies. Yet, in IM treated animals waning of the neopterin effect was similar to that seen in the subcutaneously treated animals.

Finally, the trend and magnitude of the neopterin response was similar for BIIB017-A and BIIB017-B following a single SC or IM dose of 10 µg/kg in male rhesus monkeys.

Safety pharmacology programme

Safety pharmacological parameters were monitored in the repeated dose toxicology study which is in line with the ICH S6 guideline for biotechnology-derived products. The only BIIB017-related effect was a variable and transient increase in body temperature in some animals, which was expected.

Pharmacodynamic drug interactions

Due to the lack of drug-drug interactions reported for other interferon beta products in the clinical and commercial settings and to the limited value in the qualitative and quantitative projection of interactions between therapeutic proteins and drug metabolising enzymes from *in vitro* or non-clinical studies, nonclinical drug interaction studies of BIIB017 were not carried out.

2.3.3. Pharmacokinetics

The non-clinical pharmacokinetic studies were designed to characterise the PK profile of BIIB017 in comparison with unmodified interferon beta-1a, particularly with regards to clearance, exposure, and tissue distribution. In addition, dose linearity, gender differences and route of administration (SC and IM) were studied.

Although not a pharmacologically relevant species, the rat was used as a pre-clinical model for PK studies to evaluate the changes in renal clearance and enzymatic proteolysis due to pegylation. More detailed PK studies were then conducted in rhesus monkeys, the pharmacologically relevant species to interferon beta-1a that has been used in pharmacology and toxicology studies. Finally, the guinea pig, also considered a pharmacologically relevant species, was used to study tissue distribution.

The serum concentrations of BIIB017 in serum samples of rats and rhesus monkeys were determined by a validated enzyme linked immunosorbent assay (ELISA) using a purified goat anti-human interferon beta antibody. Furthermore, BIIB017 concentrations were determined during early research in rodents by a cytopathic effect bioassay which measures the ability of the protein to protect human lung carcinoma A549 cells challenged with encephalomyocarditis virus . The serum and tissue concentrations of BIIB017 in the tissue distribution study were determined by radioactivity (^{125}I). The PK analysis was conducted using a non-compartmental analysis extravascular input model. Moreover, the metabolic stability of BIIB017 was evaluated in human and monkey serum by Western blot in vitro.

Following SC **single dose** administration in rhesus monkeys, BIIB017 exposure increased in an approximately dose-proportional manner from 2 to 100 µg/kg. The concentration peaked at ~12-24 h post-dose and $t_{1/2}$ ranged from 14 to 21 h. The PK parameters were similar following SC and IM administration at 100 µg/kg, except faster absorption and slightly greater exposures (AUC_{last} and C_{max} were 1.3 and 2-fold greater, respectively, following IM administration). Supportive data were also available from other studies in nude mice, rats and rhesus monkeys.

Following **repeated dosing** in a 5-week toxicology study in rhesus monkeys, dose-proportional exposure of BIIB017 was confirmed for up to 3 doses (SC or IM). Thereafter, BIIB017 exposure decreased and was not detectable in 29 out of 40 BIIB017-treated monkeys after the 5th dose, likely due to the development of Nabs. Similar PK data were available from another 5-week repeat dose toxicity study, investigating the effect of BIIB017 on the menstrual cycle of female rhesus monkeys.

In order to understand the impact of sialyation and mPEG molecular weight on BIIB017 PK parameters, and to provide guidance for BIIB017 specification, a **single dose structure**

activity relationship study was conducted in rats. BIIB017 exposure in rats was markedly reduced by major decreases in the percentage of sialylation and the molecular weight of the mPEG used for pegylation, while a smaller reduction in the percentage of sialylation from 95% to 81% had minimum impact on the PK in rats. Furthermore, a 25% difference in exposure between BIIB017 manufactured with 20 kDa mPEG obtained from two independent vendors was observed (see section 2.3.6. for related discussions).

To support the pharmaceutical development of a serum-free production, the pharmacokinetic properties of pegylated interferon beta-1a derived from an early serum-containing manufacturing process (BIIB017-A) was compared in rhesus monkeys with material, which was subsequently produced without serum (BIIB017-B). Generally, the PK profiles of both BIIB017-A and BIIB017-B were similar after IM or SC administrations, but a 40% difference in C_{max} was observed after SC dosing. The mean concentration difference was limited to the first few hours post-dose and converged at later time points.

The **tissue distribution** of ^{125}I-BIIB017 and ^{125}I-interferon beta-1a was compared in guinea pigs after a single intravenous dose. Compared to non-pegylated interferon beta-1a, BIIB017 showed similar tissue distribution pattern, but was more restricted to serum, and less distributed to tissues, likely due to increased molecular size. The tissue/serum exposures ratios of BIIB017 was reduced as much as 20-40 fold for highly distributed tissues, and 3-4 fold for poorly distributed tissues. The rank order of $AUC_{last72h}$ ratios was consistent with that of C_{max}, where the highest tissue:serum $AUC_{last72h}$ ratios were observed for spleen, kidney, liver, and lung. Elimination of radioactivity from all tissues was gradual over time, and by 72 h post-dose all tissues examined retained measurable levels of radioactivity. The majority of the radioactivity was recovered in urine as catabolic products (84.5% and 63.6% recovered for BIIB017 and interferon beta-1a, respectively) with no intact protein detected, indicating renal clearance as the major elimination pathway for both BIIB017 and interferon beta-1a. SDS-PAGE analysis confirmed that the radioactivity present in serum (up to 72 hours post-dose), in spleen and kidney (up to 24 hours post-dose), and in liver (up to 6 hours post-dose) was primarily associated with the intact pegylated Interferon beta-1a. The concentration versus time profiles of BIIB017 of kidney, liver, lung, and spleen were generally in line with that of serum, indicating that the estimated half-life of BIIB017 in tissues with the highest exposures was similar to that in serum.

In line with ICH S6 recommendations, a **metabolism** study specific to BIIB017 was not performed. However, the stability of the linker between the mPEG and interferon beta-1a moieties of BIIB017 was evaluated in serum of rhesus monkeys and humans in vivo. Limited degradation of BIIB017 in serum was observed. Both deconjugation, producing low molecular weight (LMW) BIIB017, presumably free interferon beta-1a, and the formation of high molecular weight (HMW) product-related substances, presumably aggregates of BIIB017 with serum protein or oligomers, occurred, amounting to 30% HMW BIIB017 and 20% (rhesus monkey serum) or <5% (human serum) LMW BIIB017 after 2 weeks. Since half-life of BIIB017 in humans is approximately 2-3 days, the contribution of degradation in serum is considered limited.

Reference to the literature regarding catabolism of interferon in vivo was also provided. The studies by Bino et al. (J Gen Virol. 1982; J Interferon Res. 1982) and Bocci et al. (J Interferon Res. 1981) mostly concern rat data, but also some rabbit and cynomolgus monkey data. The

authors studied interferon alfa, instead of interferon beta-1a. Similar to the tissue distribution study conducted with BIIB017 in guinea pigs, these studies indicated that catabolism mostly occurs in the kidneys. The guinea pig study showed that 43% of radioactivity appeared in urine within the first 8 hours, which accumulated to 85% after 72 hours. Thus, although no direct proof was provided, it appears reasonable to assume that it is likely that BIIB017 will be catabolised renally, including presumably other mammals, and humans. A preclinical hepatic metabolizing enzyme-mediated metabolism study of BIIB017 was not conducted.

For the same reasons mentioned before (section 2.3.2.), pharmacokinetic drug interaction studies of BIIB017 were not carried out.

2.3.4. Toxicology

The rhesus monkey was chosen as the toxicology species for BIIB017 as it is was demonstrated to be pharmacologically responsive to the human interferon-beta-1a protein in an in vitro 2',5'-oligoadenylate synthetase induction (2',5- OAS) assay in peripheral blood lymphocytes (PBL).

The nonclinical toxicology programme for BIIB017 was designed to support chronic administration for the treatment of MS and consisted of:

- 5-week repeat-dose toxicology study (with a 4-week recovery period) in rhesus monkeys,
- *In vitro* genotoxicity studies (Ames and chromosomal aberrations, and
- 5-week repeat-dose study in female rhesus monkeys to evaluate effects of BIIB017 on hormones involved in pregnancy and effects on the menstrual cycle.

Exposure to BIIB017 was determined using an ELISA assay. Furthermore, pharmacological markers of interferon beta activity, body temperature and serum neopterin, were included in the 5-week repeat dose toxicity study. Studies were limited to a duration of no longer than 5 weeks because, consistent with the effects of observed with non-pegylated interferon beta-1a, the administration of BIIB017 resulted in the development of neutralising antibodies that significantly reduced and in some animals ablated exposure after repeated dosing. Animals used in in vivo toxicology studies were administered BIIB017 in the same vehicle and routes (SC or IM) used for BIIB017 administered in the clinic to human subjects.

BIIB017-A, the pegylated form of interferon beta-1a derived from serum-containing manufacturing process, was used in the 5- week toxicity study in rhesus monkeys. BIIB017-B, produced by a serum-free process intended for commercialisation that uses no materials of direct animal origin, was used for the 5-week hormone study in female rhesus monkeys and for the in vitro genotoxicity assays.

Single dose toxicity

In line with ICH S6, single-dose toxicity studies with BIIB017 were not conducted.

Repeat dose toxicity

The potential toxicity of BIIB017 was evaluated by administration to male and female rhesus monkeys once weekly for 5 weeks of up to 100 µg/kg via SC or IM injection, followed by a

four-week treatment-free recovery period. No relevant changes have been observed in this toxicology study, besides the expected mild pharmacological effects and the anticipated generation of neutralising antibody (NAbs). Based on the results of this study, the applicant calculated a 400-fold safety margin over the clinical maintenance dose (125 µg). However, the difference in sensitivity for pharmacology related adverse effects between rhesus monkeys and humans was not considered in this calculation. Furthermore, chronicity of exposure is excluded from the monkey study since repeated exposure causes formation of ADA, greatly diminishing exposure. ADAs were formed in most monkeys and these antibodies appeared quickly. Almost all of these antibodies were neutralising antibodies. Consequently, after 3 weeks of weekly repeated dosing, BIIB017 serum levels were diminished. Similarly, the pharmacodynamic parameters (transient rise in body temperature and elevation of serum neopterin and reduction in peripheral blood lymphocyte count) also diminished in the course of the study.

Genotoxicity

The class of type I interferons, as well as higher molecular weight poly(ethyleneglycol) molecules (i.e. 12 kD mPEG) have not been demonstrated to be genotoxic. Furthermore, according to ICH S6 guidance, proteins are not expected to have genotoxic potential and standard genotoxicity assays are not appropriate to assess the genotoxic potential of process impurities.

However, as in silico results from a DEREK analysis of the 20 kDa mPEG-O-2-methylpropionaldehyde moiety of BIIB017 revealed a structural alert for chromosomal damage, genotoxicity, and mutagenicity, BIIB017 was tested in an Ames mutagenicity assay and in a chromosomal aberration assay). Both tests were negative.

Carcinogenicity

Consistent with the ICHS6 Addendum, a weight of evidence approach was taken in the evaluation of the potential carcinogenicity risk of BIIB017 for humans. The nonclinical toxicology profile of BIIB017 as well as of type I interferons as described in the scientific literature did not indicate a cause for concern and BIIB017 was negative in the *in vitro* genotoxicity assessment. Finally, though limited in duration, no concern arose from the preclinical safety assessments for BIIB017 or Avonex. Thus, the weight of evidence did not suggest a potential human risk for cancer and no carcinogenicity studies were conducted.

Reproduction Toxicity

A reproductive and developmental toxicity study was not conducted due to the known abortifacient activity of interferon beta-1a in rhesus monkeys (Avonex EPAR). Instead, the reproductive toxicity of BIIB017 was evaluated in a 5-week study in sexually mature female rhesus monkeys that was designed to determine if BIIB017 caused hormonal changes (progesterone and 17-beta estradiol) in sexually mature, non-pregnant monkeys consistent with the anovulatory and abortifacient interferon class effects. Results from this study were meant to serve as a bridge to the developmental and reproductive toxicity studies conducted for Avonex.

Treatment with 125 µg/kg/week of BIIB017 for up to 5 doses was associated with a reversible prolongation of menstrual cycles and reductions in serum 17-beta estradiol and progesterone levels. Two out of five animals in the high dose group (125 ug/kg/week) and one out of five in

the low dose group (2.5 ug/kg/week) showed prolonged menstrual cycles. In one of the high dose animals with a prolonged menstrual cycle, hormone levels did not show a peak in the acclimatisation period either, and in the other animal, no clear hormone peak could be observed in the post-dose recovery period, which might have been an early sign of the animal phasing out the breeding season. No effects on menstrual cycle or serum hormone levels were observed following treatment of 2.5 µg/kg/week of BIIB017, at approximately a 10-fold exposure-based safety margin over the clinical dose.

Toxicokinetic data

The pharmacokinetic data from the 5-week repeated dose toxicology study are described in the pharmacokinetic section of this report (see section 2.3.3.). The relevance of this study for evaluation of long-term safety was limited due to the reduction in exposure following formation of NAbs.

Local Tolerance

Local tolerance, as measured by injection site reactions, was evaluated in the 5 week repeat-dose study in rhesus monkeys. There were no adverse BIIB017-related changes at any injection site for any dose tested up to 100 µg/kg (11 MIU/kg) following SC or IM administration.

Other toxicity studies

Antigenicity

Formation of binding and neutralising antibodies was monitored in the 5-week repeated dose study of BIIB017 in rhesus monkeys with a 4-week recovery period (see above).

Immunotoxicity

Consistent with ICH S8, potential immunomodulatory effects of BIIB017 were evaluated in the repeat dose toxicology study by evaluation of haematology, and of macro- and microscopic analysis of tissues. There was no indication for any immune modulatory effects of BIIB017 suggestive of a cause for concern.

Studies on impurities

The applicant did not perform any studies on impurities, which is in agreement with ICH S6, where it is stated that it is preferable to rely on purification processes to remove impurities and contaminants rather than to establish a preclinical testing program for their qualification. Consequently, the safety assessment for the process-related impurities was based on the clearance validation.

Concerning product-related impurities, free interferon beta-1a is of no concern as per the specification. Likewise, free residual mPEG is of no toxicological concern since the aldehyde form is quenched to produce the arginine conjugate and the maximum daily dose is 0.2 µg. No information was provided on peginterferon dimers and oligomers. As PK, PD and immunogenic potential may be affected, the CHMP considered it to be important that these impurities are kept consistently at a low level. However, there is no need to investigate these properties of the impurities per se.

2.3.5. Ecotoxicity / environmental risk assessment

Peginterferon beta-1a is not a persistent, bioaccumulative and toxic (PBT) substance as log Kow does not exceed 4.5. Furthermore, the predicted environmental concentration in surface water (PECsw) was 4.1 x 10-6 µg/L, which is below the action limit of 0.01 µg/L. Therefore, in line with the Guideline on the environmental risk assessment of medicinal product for human use (EMEA/CHMP/SWP/4447/00 corr 1), no further (phase II) studies were performed.

Table 1 - Table with environmental endpoints

Substance (INN / Invented Name): PEG-Interferon beta 1a			
PBT screening		Result	**Conclusion**
Bioaccumulation potential – log K_{ow}	OECD107	Log K_{ow} -1.98	Not B
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	Log K_{ow} -1.98	Not B
PBT-statement			Not PBT, nor vPvB
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	4.1 x 10^{-6}	µg/L	< 0.01 threshold
Other concerns (e.g. chemical class)			Not applicable

2.3.6. Discussion on non-clinical aspects

Pharmacology

Regarding non-clinical pharmacology, the applicant provided in vitro data showing that Plegridy (BIIB017), like Avonex (interferon beta 1a) binds to the extracellular domain of IFNAR2. However, when tested in cell assays, compared to interferon beta 1a, a modest 2-fold reduction of in vitro antiviral and antiproliferative activity was demonstrated, suggesting that the affinity for the type I interferon receptor, composed of the full-length IFNAR1 and IFNAR2 chains expressed on the cell surface, may be affected by the attached 20 kDa mPEG. This may lead to differences in gene expression. However, there was no indication for a differential activation of interferon responsive genes other than a temporal difference reflecting the longer elimination time of peginterferon beta-1a.

The justification by the applicant to limit the pharmacology studies to the above mentioned *in vitro* studies and to gather data on pharmacological surrogate markers in pharmacokinetic and safety studies was considered acceptable by the CHMP.

These studies showed that BIIB017 is pharmacologically active *in vivo* in rhesus monkeys as expressed by increased serum neopterin, transient mild body temperature elevations in some, but not all monkeys and reduction of peripheral blood lymphocyte count. All shifts in these parameters, as well as BIIB017 plasma levels were diminished after the 3rd weekly dose due to the formation of NAbs. After 5 weeks, practically no BIIB017 could be confirmed in plasma samples and the pharmacodynamic response had disappeared. Therefore, no conclusions on the long-term safety of BIIB017 could be drawn.

With regards to long-term safety, renal epithelial vacuolation was described in the literature after 3 month exposure to pegylated proteins in rats. However, since the dose of BIIB017 in patients will be more than 2000-fold lower on a mg/kg bodyweight basis, similar renal effects in patients treated with BIIB017 were considered unlikely.

Pharmacokinetics

PK studies in both rats and rhesus monkeys indicated that the pegylation reduced clearance, prolonged half-life, and increased exposure of BIIB017 compared to the unmodified interferon beta-1a as expected.

Furthermore, PK profiles of both BIIB017-A and BIIB017-B were generally similar following IM or SC administration, but a 40% difference in C_{max} was observed during the first few hours post SC-dosing. However, considering that most clinical studies were performed with BIIB017-B derived material, which will be used commercially, the CHMP considered that this difference could be acceptable, since conclusions on tolerability in humans would not solely be based on data from studies performed with BIIB017-A.

A rat study showed that BIIB017 exposure was markedly affected by major changes in the percentage of sialylation and the molecular weight of the mPEG. Furthermore, a 25% difference in exposure between BIIB017 manufactured with 20 kDa mPEG obtained from two independent vendors was observed, raising questions on the inter-changeability of the two mPEGs. The applicant considered that the difference in point estimates was due to the variability observed in the PK study (16-35%) and in the bioanalytical assay (<10%), as well as due to the small study size (N=10). Further to the review of additional analyses, the CHMP concluded that the apparent differences were unlikely to cause a clinically relevant PK difference in humans

The tissue distribution pattern of BIIB017 was generally similar to non-modified interferon beta-1a, but was more restricted to serum, and less distributed to tissues, likely due to increased molecular size. No metabolism studies were performed with BIIB017, which is agreed considering the protein nature of the product. Although no direct proof was provided, based on the available data, the CHMP considered that BIIB017 was likely to be catabolised renally. The fate of the PEG moiety was not further studied, but in view of the clinical experience with pegylated proteins, no further study was considered necessary by the CHMP at the time of this report.

Toxicology

The CHMP agreed that the lack of single dose toxicity studies and carcinogenicity studies was in line with ICH S6 and therefore acceptable. Likewise, in line with ICH S8, no immunotoxicity studies were needed. While no concerns arose from the repeated toxicity study, the estimate of a 400-fold safety margin over the clinical maintenance dose (125 µg) as proposed by the applicant was not agreed by the CHMP for the reasons described above.

Finally, the CHMP considered, after critical review of the results of the study performed in sexually mature female rhesus monkeys, that no firm conclusions could be drawn from these data. Prolongation of menstrual cycles might have been due to other reasons than treatment with BIIB017. Furthermore, variability in hormone levels was high and the number of animals in the study was low. In general, the evidence for an abortifacient effect caused by interferon

betas was considered to be very limited altogether and it was not considered evident that the temporal changes in hormone level can be extrapolated to pregnant animals. Effect in pregnancy was included as missing information in the risk management plan (RMP) of Plegridy and data on pregnancy outcomes will be collected post-marketing in the European Interferon Beta Pregnancy Registry.

As the predicted environmental concentration in surface water was below the action limit and since no other environmental concerns were apparent, peginterferon beta 1a was not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The CHMP concluded that BIIB017 has been shown to have qualitatively similar pharmacological properties compared to interferon beta-1a in vitro and in vivo, which would support the use of Plegridy in the proposed indication from a non-clinical point of view. Non-clinical PD and PK comparisons have shown that the addition of 20 kDal mPEG to the interferon protein prolongs the duration of its pharmacodynamic activity, but does not clearly affect its pharmacological response qualitatively.

Overall, the CHMP was of the opinion that the non-clinical program presented with this application was acceptable and that relevant data were adequately reflected in the product information.

2.4. Clinical aspects

2.4.1. Introduction

Figure 1 provides an overview of the clinical trials program conducted in support of the application for a marketing authorisation of Plegridy in MS.

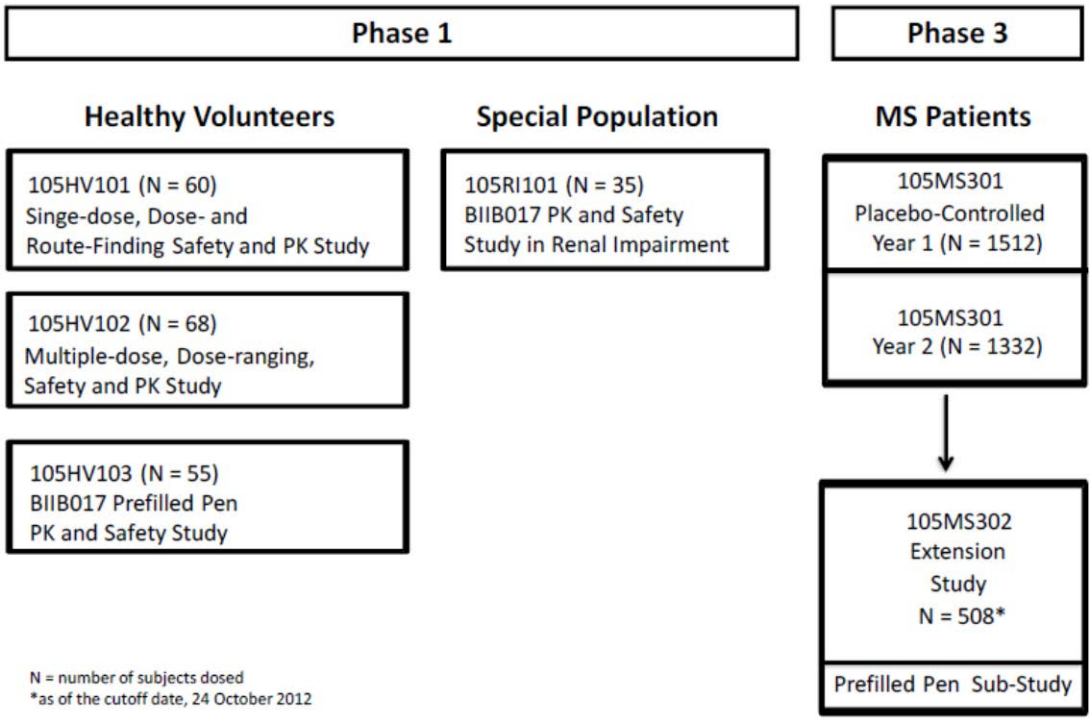


Figure 1 – Overview of the clinical development program for BIIB017

Good Clinical Practice (GCP)

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

The applicant has provided a statement that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	105HV103	Evaluate the PK profile, safety, and tolerability of BIIB017 delivered by pre-filled syringe and autoinjector	Phase 1, randomized, open-label, crossover	BIIB017; One dose each of BIIB017 125 mcg SC, delivered by pre-filled syringe and autoinjector	55 enrolled; 24 completed	Healthy subjects	Subjects dosed on day 1 and day 22	Complete; Full
Safety PK/PD	105HV101	Identify the highest safe and well-tolerated dose of BIIB017 given IM or SC	Phase 1, single-dose, blinded, randomized, dose escalation	BIIB017 or Avonex; 3 dose cohorts: • BIIB017 SC (63, 125, and 188 mcg) • BIIB017 IM (63, 125, and 188 mcg) • Avonex 30 mcg IM	60 enrolled and dosed; 58 completed	Healthy subjects	Single dose	Complete; Full
Safety PK/PD	105HV102	Identify the highest safe and well-tolerated dose and frequency of BIIB017 SC given every other week or every 4 weeks	Phase 1, double-blind, randomized, placebo-controlled, multiple-dose, dose-ranging, parallel-group	BIIB017; 7 treatment groups: • BIIB017 63 mcg SC every 2 weeks and every 4 weeks • BIIB017 125 mcg SC every 2 weeks and every 4 weeks • BIIB017 188 mcg SC every 2 weeks and every 4 weeks • Placebo SC every 2 weeks	69 subjects enrolled; 68 subjects dosed; 65 subjects completed	Healthy subjects	6 weeks	Complete; Full
PK/PD Safety	105RI101	Estimate the effect of renal impairment on the PK/PD and safety profile of BIIB017	Phase 1, single-dose, open-label, multicenter, non-randomized, serial-group	BIIB017; Single-dose of BIIB017 63 mcg SC or BIIB017 125 mcg SC	35 enrolled, dosed, and completed	Healthy subjects and subjects with renal impairment	Single dose	Complete; Full
Efficacy, Safety, PK/PD	105MS301	Evaluate the efficacy and safety of BIIB017 in subjects with relapsing remitting multiple sclerosis	Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled	BIIB017; Year 1: • Placebo every 2 weeks, or • BIIB017 125 mcg SC every 2 weeks, or • BIIB017 125 mcg SC every 4 weeks Year 2: • BIIB017 125 mcg SC every 2 weeks, or • BIIB017 125 mcg SC every 4 weeks	At time of data cutoff (24 October 2012): 1516 randomized; 1512 dosed; 1332 completed year 1; 608 completed year 2	Relapsing Remitting Multiple Sclerosis	96 weeks	Ongoing; Full

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Long-term Safety and Efficacy	105MS302	Evaluate the long-term safety and efficacy of BIIB017 in subjects with relapsing remitting multiple sclerosis	Phase 3, multicenter, parallel-group, dose-frequency blinded extension	BIIB017; BIIB017 125 mcg SC every 2 weeks or BIIB017 125 mcg SC every 4 weeks	At time of data cutoff (24 October 2012): 517 enrolled; 508 dosed; 0 completed	Relapsing Remitting Multiple Sclerosis	96 weeks	Ongoing; Interim
	105MS302 AI Sub-Study	Evaluate the safety, tolerability, subject ease of use, and satisfaction with the single-use BIIB017 autoinjector (prefilled pen)	See above	Either BIIB017 125 mcg SC every 2 weeks or BIIB017 125 mcg SC every 4 weeks, delivered by a single-use autoinjector device	39 subjects enrolled and dosed; 39 completed treatment; 34 completed follow up	Relapsing Remitting Multiple Sclerosis	6 weeks	Complete; Full sub-study report appended to main interim study report

2.4.2. Pharmacokinetics

A total of 5 clinical studies were performed to study the pharmacokinetics and pharmacodynamics of peginterferon-beta 1a (BIIB017): three Phase 1 studies in healthy subjects (studies 105HV101, 105HV102 and 105HV103), one Phase 1 study in subjects with renal impairment (Study 105RI101) and one Phase 3 study in MS patients (Study 105MS301).

Among these studies, 3 were single dose studies (studies 105HV101, 105HV103, and 105RI101) and 2 were multiple-dose studies (studies 105HV102 and 105MS301). Study 105HV103 is considered a biopharmaceutical study, which characterised the PK of the prefilled syringe (PFS) and prefilled pen (PFP).

BIIB017 was administered subcutaneously in all studies. Intramuscular route of administration was also evaluated to compare BIIB017 with non-pegylated interferon beta-1a (Avonex).

The BIIB017 doses evaluated in Phase 1 studies ranged from 63 to 188 µg in healthy subjects, and from 63 to 125 µg in subjects with renal impairment.

In the Phase 3 study (105MS301) with MS patients, 63 and 94 µg were used as titration doses and 125 µg as the therapeutic dose. Blood samples were taken from all subjects at Week 4 and 24, using a combination of intensive (frequent sampling) and sparse sampling strategy. For PK/PD evaluation, result from the intensive sampling group were used. Only a small group of patients agreed and was eligible for participation in the intensive sampling schedule at Weeks 4 and 24 (44 subjects total, placebo group included, 25 subjects in the BIIB017 group).

The PK profile of BIIB017 was determined by a validated ELISA assay in all studies and a validated cytopathic effect bioassay in selected studies. Results from a cell-based myxovirus resistance protein A (MxA) gene assay were not considered for the PK assessment as the validation parameters did not meet all target criteria. The cytopathic effect assay has traditionally been used to measure unmodified interferon concentrations, but is unable to discriminate between different interferon types.

For the initial PK comparison between BIIB017 and interferon beta-1a, conclusions were drawn based on results from the cytopathic effect assay. The ELISA assay was used in subsequent studies. Both cytopathic effect and ELISA assays showed similar PK properties for BIIB017 in 2 studies (105HV101 and 105HV102).

Finally, a population PK/PD analysis study (CPP-12-016-BIIB017) was performed to characterise the PK profile of BIIB017 in the MS population, identify intrinsic and extrinsic factors which affect BIIB017 disposition, characterise exposure-response relationships with neopterin and identify covariates that were significant determinants of variability of neopterin response. The population PK model was developed using data from study 105MS301 and based on a one-compartment linear model with a first-order absorption rate. For the population PD model, data from study 105HV102 and 105MS301 were pooled and an indirect stimulatory response (E_{max}) model was applied.

Absorption

Bioavailability

The absolute bioavailability of BIIB017 SC has not been compared to the intravenous route of application since only the SC route was evaluated in the pivotal clinical study, which is also the proposed route for commercial use. Like other biologics, peginterferon beta-1a is believed to be absorbed through the lymphatic system and by blood capillaries after SC administration.

Generally, the estimated inter-subject variability was high (AUC: 56–88% and C_{max}: 47–75%). Likewise, a high intra-subject variability was observed (AUC: 26–46% and C_{max}: 38–55%).

In order to study the effect of pegylation, the applicant compared the PK profile of BIIB017 with non-pegylated interferon beta-1a in healthy subjects (study 105HV101).

In study 105HV101, a single SC injection of BIIB017 resulted in approximately 4-, 9-, and 13-fold higher exposure (AUC_{168h}) values and approximately 2-, 3.5- and 5-fold higher C_{max} values, following single doses of 63 (6 MIU), 125 (12 MIU), and 188 µg (18 MIU) respectively, compared to intramuscular administration of 30 µg (6 MIU) non-pegylated interferon beta-1a.

Following SC administration of BIIB017 in MS patients (study 105MS301), the peak concentration was reached between 1 to 1.5 days post-dose. After repeat dosing of 125 µg, the observed C_{max} (mean ± SD) was 280 ± 249 pg/ml with every two weeks (q2W) dosing and 305± 225 pg/ml with every 4 weeks dosing (q4W). The concentration at the end of the dosing interval (mean ± SD) was 34.8± 17 and 32.9 ± 20 h*ng/ml for the q2W and q4W dosing, respectively and the AUC_{168h} (mean ± SD) was 29.9 ± 18 h*ng/ml and 29.5 ± 18 h*ng/ml for the q2W and q4W dosing, respectively. BIIB017 exposures based on median values (C_{max} and AUC_{168h}) decreased by 6% and 3% (q2W) and by 23% and 27% (q4W) from Week 4 to Week 24.

In order to facilitate assessment of possible differences between healthy subjects and MS patients, exposure variables AUC and C_{max} were compared across studies (see Figure 2).

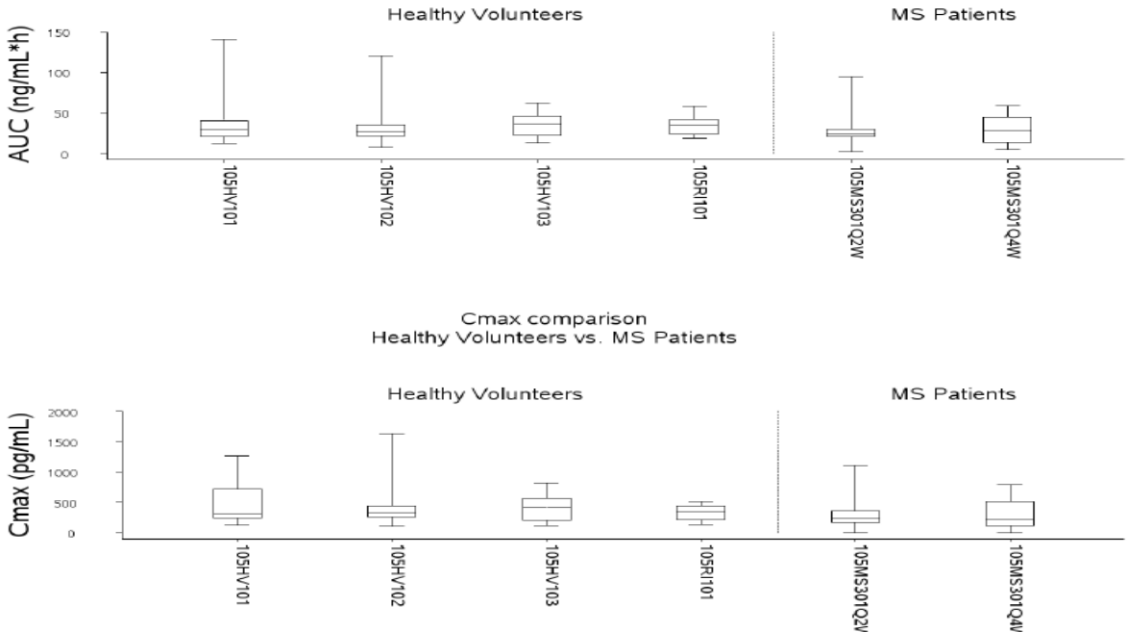


Figure 2 - AUC and Cmax Comparison Between Healthy Volunteers and MS Patients

No study was performed comparing different injection sites (thigh, arm or abdomen). However Pop PK analysis showed that injection site was not a significant covariate.

Bioequivalence

No bioequivalence study was carried between the products manufactured with and without serum (BIIB017-A and BIIB017-B). The pivotal study and its extension study were performed with the serum-free manufactured product, which is the proposed commercial formulation.

Study 105HV103 was conducted to compare the pharmacokinetics of BIIB017 between the two delivery systems applied for, the pre-filled syringe (PFS) and the pre-filled pen [PFP or AI (autoinjector)]. No formal statistical testing was performed as the study was not powered to show bioequivalence and the inter-subject variability was high. However, study 105HV103 was submitted as a descriptive study to characterise the PK profiles of the two delivery systems. The serum concentration-time curves obtained with both devices are depicted in Figure 3. BIIB017 exposure with the autoinjector/PFP was only slightly higher (AUC: 7% and C_{max}: 18%) and compared to the PFS. Furthermore, the interquartile range of the two devices overlapped.

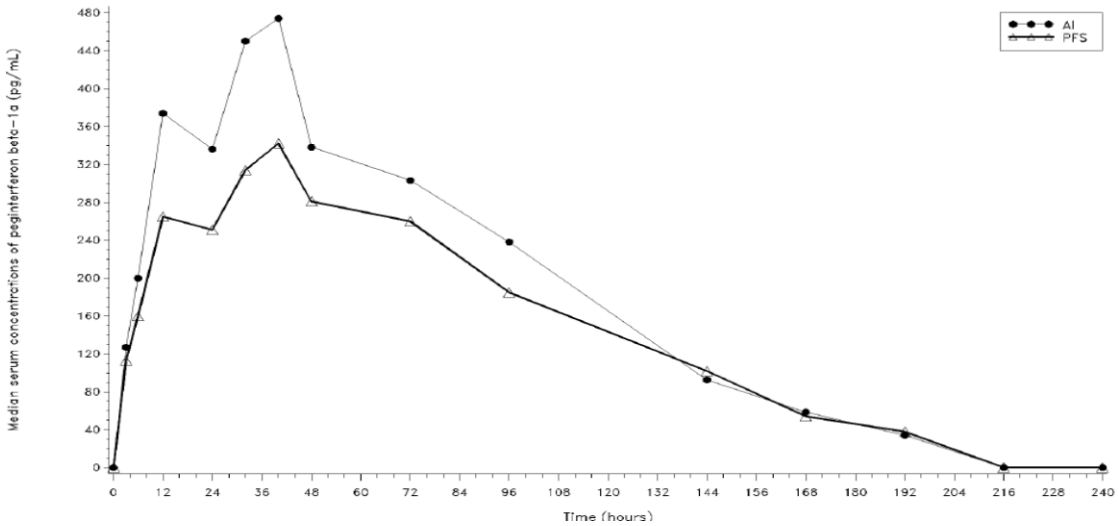


Figure 3 - Median Serum Concentrations of Peginterferon Beta-1a PFS versus PFP / AI

Food interaction

No food interaction study was done and this is not necessary as BIIB017 will be administered subcutaneously.

Distribution

No protein binding study was performed as this is not required for pegylated proteins.

Following repeat dosing of 125µg SC BIIB017, the apparent volume of distribution was 481 ± 105 l (mean ± SE).

Elimination

No mass balance study was conducted in humans for BIIB017.

Pegylation is known to alter the PK properties of a protein, which includes decreased renal clearance and decreased proteolysis leading to an extended circulating half-life ($t_{1/2}$). This has been substantiated for BIIB017 in study 105MS301 as follows: The $t_{1/2}$ of BIIB017 in healthy volunteers was approximately 2-fold longer than of the non-pegylated interferon beta-1a (study 105HV101). In MS patients, the steady-state $t_{1/2}$ (mean ± SE) of BIIB017 was 78 ±15 hours and the steady state clearance was 4.1 ± 0.4 l/h (mean ± SE).

Based on a simple linear regression model predicting clearance as a function of estimated glomerular filtration rate, total renal clearance was estimated to be due to 42% renal clearance and 58% non-renal clearance.

Dose proportionality and time dependencies

Following SC administration of BIIB017, linear pharmacokinetics were observed.

In both single dose and repeat dose studies (105HV101 and 105HV102), systemic exposure (AUC_{168h} and C_{max}) increased in an approximately dose-proportionate manner following SC administration of doses of 63, 125 and 188 µg BIIB017.

No accumulation was observed in BIIB017 exposure following multiple doses of 125µg once every 2 weeks or once every 4 weeks in MS subjects (study 105MS301).

Special populations

Impaired renal function

The renal impairment study (105RI101) showed that increasing severity of renal impairment resulted in a corresponding increase in BIIB017 exposures. In subjects with mild, moderate and severe renal impairment based on glomerular filtration rate classification (mL/min/1.73m^2) and median values, the AUC_{336h} increased by 13, 22 and 62%, respectively, and C_{max} increased by 32, 38, and 44%, respectively, compared to normal renal function. The AUC_{336h} and C_{max} of the normal renal function and end-stage renal disease (ESRD) groups were similar, which was partly due to BIIB017 removal by dialysis as shown by a 24% (geometric mean) reduction from pre- to post-haemodialysis.

Impaired hepatic function

No hepatic impairment study was conducted as the liver is only one of many other catabolic organs (e.g. spleen, lung, lymph nodes and pancreas) involved in the metabolism of interferon beta-1a and therefore hepatic impairment was considered by the applicant not likely to have a significant effect on the PK profile of BIIB017.

However, hepatic function was tested in the population PK/PD study (CPP-12-016- BIIB017). The population PK (PopPK) analysis showed no hepatic function effect. However, the analysis has limited value as, in line with the inclusion criteria of the pivotal trial, which was used to build the model, subjects had normal laboratory values.

Age

No patients older than 65 years of age were included in the Phase 3 studies.

No data were available in children at the time of this report. A study in the MS paediatric population (10 years to 17 years old) is being planned. A waiver for a PIP has been granted for children younger than 10 years since MS is exceedingly rare in this age group.

The PopPK analysis showed that age did not impact on the PK of BIIB017.

Weight

Body weight did not affect the PK parameters of BIIB017 in the PopPK analysis. However, the model predicted a less than proportional increase in clearance (CL) with body mass index (BMI). A 50% increase in BMI corresponded to a 24% increase in CL, which translates into a decrease in BIIB017 median AUC of about 40% in the highest BMI quintile (80%) compared to the lowest quintile (20%).

Race

The PopPK analysis showed that race did not influence BIIB017 PK parameters.

Gender

The PopPK analysis showed that gender did not influence BIIB017 PK parameters.

Pharmacokinetic interaction studies

No drug-drug interaction studies were conducted due to the lack of drug-drug interaction observed for existing beta interferons used in the treatment of MS.

However, in the pivotal Phase 3 study and its extension, patients were allowed to received IV corticosteroids to treat relapses and the study data suggested that concomitant use of both products was well tolerated. Furthermore, other concomitant medication including paracetamol, ibuprofen, mepresone, naproxen, modafinil, gabapentin, and baclofen, selected based on the high frequency of use in MS subjects in study 105MS301 and their potential influence on renal and hepatic functions, did not significantly affect the PK parameters of BIIB017 in the PopPK analysis.

No data on consequences of possible genetic polymorphism were provided.

2.4.3. Pharmacodynamics

Mechanism of action

The mechanism of action of BIIB017 is considered to be the same as for interferon beta. BIIB017 binds to the type I interferon receptor on the surface of cells and elicits a cascade of intracellular events leading to the regulation of interferon-responsive gene expression. These genes, and their gene products, are believed to mediate the efficacy of BIIB017 in MS.

Interferon beta modulates immune responses that are believed to play a role in the pathogenesis of MS. While the pathogenesis of the disease is complex and multifaceted, BIIB017 may act at several levels including up-regulation of anti-inflammatory cytokines (e.g. IL-4, IL-10,IL-27), down-regulation of pro-inflammatory cytokines (e.g. IL-2, IL-12, IFN-γ, TNF-α) and inhibiting the migration of activated T cells across the blood brain barrier. Furthermore, it has been shown that interferon beta-1a induces the synthesis of Interleukin-10. This cytokine contributes to slow down auto immunological processes in the disease course of MS.

Primary and Secondary pharmacology

The pharmacology of peginterferon beta-1a was investigated in 4 studies, including 3 phase 1 studies (studies 105HV101, 105HV102, 105RI101) and 1 phase 3 study (study 105MS301).

The assessment of the pharmacological activity of BIIB017 was based on study results for the elevation of serum neopterin concentration and whole blood 2',5'-oligoadenylate synthetase (2',5'-OAS) expression. Neopterin is a well-characterised biomarker induced by type I interferons and was determined using a competitive, validated ELISA in all PD studies, i.e. in both healthy subjects and MS patients. Expression of 2',5'-OAS, an interferon-induced protein important in the antiviral actions of interferons, was determined only in study 105HV101 using a real-time polymerase chain reaction to quantify OAS messenger RNA. PD parameters, including the maximum serum concentration (E_{max}), time to reach E_{max} (E_{Tmax}) and area under the concentration-time curve (EAUC) were determined based on the respective median values after baseline adjustment. In addition, for the neopterin response, EAUC and ET for concentrations above 1.5ng/ml ($EAUC_{dur}$ and ET_{dur}) were determined as these were considered most likely treatment-related in Study 105HV101.

In the single dose study 105HV101, levels of both neopterin serum concentration and 2',5'-OAS expression increased in less than a dose proportionate manner with increasing concentrations of BIIB017. The maximum neopterin concentrations were attained at about 48 h. Neopterin and 2',5'-OAS profiles obtained for SC and IM route of administration were comparable. Compared to non-pegylated interferon beta-1a, the neopterin and 2',5'-OAS responses to BIIB017 were augmented ($EAUC_{336h}$ and E_{max}) and a longer duration of effect was observed as shown by the neopterin median $EAUC_{dur}$ and ET_{dur} (591 versus 289 h*ng/ml and 167 versus 109 ng/ml, respectively).

Similar to the single-dose study, neopterin serum concentrations increased in a less than dose-proportionate manner in the multiple-dose study in healthy volunteers (105HV102). In general, neopterin profiles obtained for both the q2W and q4W regimes were comparable. However, there was a slight reduction in the neopterin levels with the q2W dosing scheme from Day 1 to Day 29 while no such reduction was observed when BIIB017 was dosed q4W. For the 125 µg dose at Day 29, the $EAUC_{336h}$ was slightly lower (10%) for the q4W regime than with the q2W dosing frequency (1145 versus 1270 h*ng/ml, respectively) but the induction ratio (ratio of peak to baseline) was slightly higher (6%) for q4W compared to q2W (4.7 versus 4.4-fold, respectively).

In MS patients (study 105MS301), the maximum neopterin levels were attained at about 72 hours post-dose. Levels returned to near baseline values at about 10 to 14 days for both q2W and q4W dosing. Neopterin levels decreased with repeated dosing particularly for the q2W dosing regimen. From Week 4 to Week 24, E_{max} and $EAUC_{336h}$ decreased by 40% and 48%, respectively following q2W dosing and by 8% and 20%, respectively with q4W dosing. In terms of $EAUC_{336h}$ at week 24 dose, a higher value was obtained for q4W (47%) compared to q2W (1397 versus 956 h*ng/ml, respectively).

In renally impaired patients (study 105RI101), neopterin baseline values, $EAUC_{672h}$ and E_{max} increased with worsening renal impairment. The baselines in the ESRD groups were 5-fold greater compared with the normal renal function group. $EAUC_{672h}$ and E_{max} in the ESRD group were about 10-fold greater compared with the normal renal function group.

Immunogenicity

A tiered testing scheme was used to measure immunogenicity. Firstly, sera samples were tested for the presence of antibodies that bind to interferon beta-1a (binding antibodies, BAbs) using ELISA. Samples that generated a positive response were further tested for the presence and titer of interferon beta-1a neutralising antibodies (Nabs) in a validated cell-based assay measuring the induction of MxA expression by ELISA. All samples were also tested for the presence and titer of antibodies to PEG. Evaluation of the immunogenic potential of BIIB017 was conducted by initially categorising subjects negative at baseline and positive post-baseline.

The incidence of treatment-emergent antibodies to interferon beta-1a or PEG was low in both healthy volunteers and MS subjects. In Year 1 of the pivotal study 105MS301, the incidence was 4% and 8% in the q4W and q2W groups, respectively. With regards to Nabs, less than 1% were seen in both BIIB017 treatment groups. Anti-PEG antibodies were observed in 9% and 7% in the q4W and q2W groups, respectively. The majority of treatment-emergent antibodies were transient responses. Additional data from 2 and 3 years exposure indicated

that the level of antibodies remained low throughout, with Nabs remaining at an incidence below 1% and overall, 3% of patients developing persistent antibodies to the PEG moiety of peginterferon.

In the intensive PK/PD group in study 105MS301, 2 subjects each were tested positive for anti-interferon Babs and anti-PEG antibodies. No patient in this group had Nabs. In the Bab positive subjects, significantly reduced BIIB017 serum concentrations (in one case not detectable) were observed at Week 24 compared to the group median, while the neopterin response was not affected. Neopterin response and BIIB017 serum concentration were comparable to the group median for the two patients testes anti-PEG positive.

The effect of anti-interferon binding antibodies (BAbs) could not be reliably predicted in the PopPK analysis, as the anti-interferon BAbs positive subjects and BLQ (below the limit of quantitation) concentrations due to BAbs were excluded from analysis.

2.4.4. Discussion on clinical pharmacology

The CHMP considered that the bioanalytical methods used for PK/PD analyses were generally acceptable. While the cytopathic effect assay was not discriminatory between interferon types, the lack of specificity was considered to be compensated by the parallel use of the selective and validated ELISA method.

The absolute bioavailability of BIIB017 SC has not been studied. However, the PK profile of peginterferon beta-1a was characterised after single and repeated dose in healthy subjects and MS patients, and compared with non-pegylated interferon beta-1a as well as for the q2W and q4W dosing regimens and for the IM and SC route of administration.

The pharmacokinetic profiles in MS patients and healthy subjects were considered to be generally similar.

With regards to BIIB017 SC administration, the CHMP noted that bioavailability might differ between administration sites as observed for another pegylated interferon protein (Pegasys). In the pivotal study with MS patients, BIIB017 was injected either in the thigh, arm or abdomen while in the phase 1 single- and multiple-dose studies, BIIB017 was injected in the thigh only. Pop PK analysis showed that injection site was not a significant covariate. Therefore, the CHMP considered that no differences in exposure were to be expected.

The two delivery systems, pre-filled syringe (PFS) and pre-filled pen (PFP), were compared in study 105HV103, whereby no formal statistical testing was performed as the study was not powered to show bioequivalence and the inter-subject variability was high. The mechanism of needle penetration is similar for both PFS and PFP. Patients manually insert the needle into the injection site to complete the needle penetration into the subcutaneous tissue. Therefore, use of the PFP was considered not to impact the route or dose of administration for delivery of BIIB017 drug product. The serum levels available from study 105HV103 demonstrated that the drug was reliably delivered from the auto injector and the serum levels indicated no essential differences of clinical relevance between the two delivery systems. The CHMP considered the two devices qualitatively similar and, since the formulation, route of administration and the injected volume is the same, that similarity of both devices can be assumed.

No bioequivalence study was conducted to compare products manufactured with and without

serum (BIIB017-A and BIIB017-B). This was considered by the CHMP not to be a major issue as it is not planned to use both products interchangeably in the commercial setting. The pivotal study and its extension study used the serum-free manufactured product, which is the proposed commercial formulation.

The CHMP noted that the apparent volume of distribution was considerably larger compared to other approved pegylated proteins, possibly due to a low bioavailability from the injection site.

The lack of a mass balance study to characterise elimination was considered acceptable by the CHMP, as, like for other proteins, catabolism and excretion are expected to be the clearance mechanisms for peginterferon beta 1a. This is supported by animal studies, suggesting renal clearance as the main elimination pathway, as well as data from the scientific literature for free PEG showing that hepatic metabolism and biliary excretion are minor routes for clearance.

Elimination PK parameters showed a prolonged half-life compared to unmodified substances, as could be expected.

With regards to special populations, the applicant conducted a study in renally impaired patients. Increased exposures due to reduce renal clearance were observed in the different renal impairment groups compared to subjects with normal renal function. To further explore the clinical relevance of this observation, the applicant referred to the comparison performed in different BMI categories resulting in different exposure similar to levels observed for renal impairment (see discussion below). Furthermore, a PK simulation comparing MS subjects with normal and severely impaired renal function, showed that concentration-time profiles at steady state greatly overlapped, but an increased exposure in severely renally impaired patients could not be excluded. Tolerability was comparable across all groups, however, the data were limited due to the small size of the study. Overall, the CHMP considered that a warning for patients with severe renal impairment should be included in SmPC section 4.4, but no dose adjustment was considered necessary.

The CHMP furthermore noted that the increased neopterin levels in patients with ESRD compared to patients with normal renal function was not in line with the corresponding PK parameters, which were comparable in both groups. However, published data obtained in ESDR patients who had undergone haemodialysis (Fuchs et al. 1988, Estelberger et al, 1993; Lhee et al, 2006), showed as well high neopterin levels, which were attributed to interactions between blood coagulation molecules and the haemodialysis membrane, as well as to the activated cellular immune response to exposure to the dialysis membrane.

No hepatic impairment study was carried out. In the SmPC, the absence of hepatic impairment studies is stated in the posology section and caution and monitoring is recommended when administering BIIB017 to patients with severe hepatic impairment. This was considered acceptable by the CHMP.

The body mass index (BMI) has been found in the Pop PK model to significantly influence the clearance and volume of distribution of BIIB017. A 50% increase in BMI corresponded to a 24% increase in clearance, which translates into a 40% decrease in BIIB017 median AUC in the highest BMI quintile (80%) in comparison with the lowest quintile (20%). Post hoc efficacy subgroup analysis of data from study 105MS301 with stratification by BMI showed that a 40%

decrease did not lead to significant loss of efficacy and hence can be considered not clinically relevant. The CHMP agreed that no dose adjustment in relation to BMI was necessary.

The lack of drug-drug interaction studies was considered acceptable by the CHMP. However, as a class, interferons are known to be weak inhibitors of Cytochrome P450 1A2. Upon request of the CHMP, this was reflected in section 4.5 of the SmPC in line with other approved interferon MS products.

There was no data on consequences of possible genetic polymorphism. An exploratory genetic analysis was planned to identify genetic factors that contribute to the safety and efficacy of BIIB017. The CHMP requested that the results of the exploratory genetic analyses should be submitted upon completion.

When comparing PD results with PK parameters measured in MS patients, the attainment of the peak levels of neopterin (72h) was delayed in comparison to that of the BIIB017 serum levels which occurred at about 36 hours post dose. Both neopterin and serum BIIB017 levels reduced from Week 4 to Week 24, but the magnitude of the reduction differed. However, the available clinical data after 2 years treatment with BIIB017 did not suggest a reduction in efficacy (see also section 2.5.), which was reassuring.

Some differences between neopterin and BIIB017 serum levels were also noted with regards to the area under the curve for the two tested dosing regimens, q2W and q4W, after repeat dosing (Week 24). However, the CHMP considered that data obtained in healthy volunteers, showing similar profile of gene expression in peripheral blood, was more relevant. Still, no study was performed on the relationship between serum concentration and effect. Additional analyses performed by the applicant in this context, based on the primary clinical end-points used in the pivotal study, indicated that the q2W dose produced a 2-fold higher monthly cumulative exposure which correlated with higher neopterin induction and less gadolinium (Gd)-enhanced lesions and new/newly enlarged T2 lesions using magnetic resonance imaging (MRI). However the pivotal trial was not powered to detect differences in the annualized relapse rates (ARR) between the two doses. Therefore, the CHMP considered that correlation between exposure and efficacy can be considered confirmed for PD parameters (neopterin) and MRI outcomes, but not for the most relevant clinical outcomes ARR and disability progression. The dosing regimen is further discussed in section 2.5.3.

With regards to immunogenicity, the occurrence of antibodies was observed in several studies. In both dose regimens in study 105MS301, anti-interferon Nabs, which are the most relevant antibodies from a clinical point of view, were found in less than 1% of patients. The presence of non-neutralising antibodies to interferon beta-1a appeared to decrease the concentration of BIIB017 in serum, but did not impact the pharmacological activity as measure by neopterin response. The evaluation of the influence of the anti-interferon NAbs on PK and PD (neopterin) parameters was not possible due to the low incidence of NAbs and visit time for PK and neopterin sample collection. Neither could a reliable estimate be obtained from Pop PK/PD analysis. Anti-PEG antibodies did not significantly affect BIIB017 serum concentrations or neopterin PD effects, at least for titer values ≤ 800. Overall, based on the provided study results , the CHMP considered that the potential impact of antibodies is likely to be minor.

Taken together, based on the data provided The CHMP concluded that the pharmacodynamic response correlates with the dose of BIIB017 in a nonlinear relationship.

2.4.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology data submitted were considered satisfactory.

As there were no data on consequences of possible genetic polymorphism, the CHMP recommended that the applicant should provide the results of the exploratory genetic analyses with the final study report of study 105MS301.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

No dose-response studies were performed.

In phase 1 studies, SC doses of 63, 125 and 188 µg peginterferon beta-1a were tested. All doses resulted in higher exposure than non-pegylated interferon beta-1a 30 µg IM (Avonex) and were well tolerated by both healthy volunteers and subjects with renal impairment.

A dose of 125 µg every 2 weeks (q2W) was chosen for the phase 3 studies as it provides an equivalent biological activity (24 MIU per month) and produces at least equivalent neopterin induction over a 4-week dosing interval as compared to interferon beta-1a 30 µg IM once a week, which is an approved MS treatment (Avonex). Furthermore, accumulation was not observed in subjects receiving q2W dosing in phase 1 studies. A dose of 125 µg every 4 weeks (q4W) was also included in phase 3 trials to study the efficacy and safety of a lower monthly dose.

2.5.2. Main study(ies)

Introduction

To support this application, the applicant submitted results from two phase 3 studies, study 105MS301 (also referred to as study 301) and its extension 105MS302. Both studies were randomised, multicentre, double-blind studies, with a duration of 2 years.

The first year of study 301 included a placebo arm. In both studies, 2 dosing regimens of peginterferon beta-1a were administered: once every 2 weeks (q2W) and once every 4 weeks (q4W). At the time of the application, the first year of study 301 was completed, and year 2 was on-going. During the procedure the full 2-years of study 301 were completed.

Table 2 – Summary of Phase 3 Clinical Study Program with BIIB017

Study ID	# Sites	Study Dates[1]/ Status[2]	Study Design	Treatment	Duration	Objectives	No. Subjects Treated (M/F) Age range	Diagnosis	Primary Endpoint
105MS301	182	2009 Enrollment and placebo-controlled phase complete; Year 2 of the study is ongoing	Phase 3 multicenter, randomized, double-blind, parallel-group, placebo-controlled	Year 1: Placebo BIIB017 125 µg SC Q2W BIIB017 125 µg SC Q4W Year 2: BIIB017 125 µg SC Q2W BIIB017 125 µg SC Q4W	2 years	Efficacy, Safety, PK/PD	N = 1512 (441M/1071F) 18-61 yrs	RRMS	Annualized relapse rate at 1 year
105MS302	101	2011 Enrollment not complete, Ongoing	Phase 3 multicenter, parallel-group, dose-frequency blinded extension	BIIB017 125 µg SC Q2W or Q4W	2 years	Long-term Safety and Efficacy	N = 508 (141M/367F) 20-57 yrs	RRMS	Safety

F = female; M = male; PD = pharmacodynamic; PK = pharmacokinetic; Q2W = every 2 weeks; Q4W = every 4 weeks; RRMS = relapsing multiple sclerosis; SC = subcutaneous.
[1] As defined by first subject enrolled.
[2] As of 24 October 2012.

2.5.2.1. Study 105MS301 and 105MS302

2.5.2.1.1. Methods

The pivotal trial (105MS301) was a multicentre, randomised, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of pegylated interferon beta-1a (BIIB017) in subjects with relapsing multiple sclerosis.

The total study treatment period was 96 weeks. Year 1 of the study (Week 0 to Week 48) was placebo-controlled and double-blinded. Year 2 of the study (Week 48 to Week 96) was dose-blinded.

At the beginning of Year 1, subjects were randomised to 1 of 3 treatment groups:

- Placebo,
- BIIB017 125 µg administered once every 4 weeks, or
- BIIB017 125 µg administered once every 2 weeks.

At the end of Year 1, subjects in the placebo group were re-randomised to BIIB017.

Study 105MS302 was a dose-frequency blinded, multicenter, extension study to determine the long-term safety and efficacy of pegylated interferon beta-1a (BIIB017) in subjects with relapsing multiple sclerosis. The extension period is 2 years (the study was on-going at the time of this report). Subjects who completed study 301 were eligible to enrol in study 302 and would continue to receive BIIB017 in the dosing regimen followed during Year 2 of study 301.

Study Participants

A total of 1512 subjects with relapsing-remitting multiple sclerosis (RRMS) from 26 countries were enrolled and dosed in study 301.

Main inclusion criteria:

- Age of 18 to 65 years, inclusive.

- Confirmed diagnosis of relapsing MS, as defined by McDonald criteria 1 through 4.

- Expanded Disease Severity Scale (EDSS) score between 0.0 and 5.0.

- Experienced at least 2 relapses that had been medically documented within the last 3 years with at least one of these relapses having occurred within the past 12 months prior to randomisation (Day 1).

Main exclusion criteria:

- Primary progressive, secondary progressive, or progressive relapsing MS. Subjects with these conditions may also have had superimposed relapse, but were distinguished from relapsing subjects by the lack of clinically stable periods or clinical improvement.

- Prior treatment with interferon could not exceed 4 weeks and subjects must have discontinued interferon treatment 6 months prior to Baseline.

- History or presence of any clinically significant medical condition or abnormal laboratory findings that could affect subject safety or interpretation of test results, including malignant disease, seizure disorder or unexplained blackouts or history of a seizure, suicidal ideation or an episode of severe depression within 3 months prior to Baseline as well as history of human immunodeficiency virus, history or positive test result for hepatitis C antibody, or current hepatitis B infection at screening.

- Prior treatment with total lymphoid irradiation, cladribine, fingolimod, T cell or T cell receptor vaccination, or any therapeutic monoclonal antibody (e.g., rituximab, natalizumab, alemtuzumab).

- Prior treatment with interferon could not exceed 4 weeks and subjects must have discontinued interferon treatment 6 months prior to Baseline.

Treatments

All subjects enrolled in this study were to receive a subcutaneous (SC) injection (pre-filled syringe) every 2 weeks to maintain the blind, starting on Day 1 and ending at Week 96. All three treatment groups were equally sized (approximately 500 patients each). Subjects randomised to BIIB017 125 µg SC every 2 weeks were to receive an injection of BIIB017 125 µg SC every 2 weeks and subjects randomised to BIIB017 125 µg SC every 4 weeks were to alternate between placebo and BIIB017 125 µg SC injections every 2 weeks. Subjects randomised to placebo were to receive an injection of placebo every 2 weeks. Subjects who received placebo in Year 1 were re-randomised to one of the dosing regimens (q2W or q4W) for BIIB017 in Year 2.

In order to mitigate flu-like symptoms, all subjects randomised to receive BIIB017 began treatment with a lower dose of BIIB017, starting at 63 µg and increasing in steps of 2 weeks to the target dose of 125 µg by Week 4. This same dose titration process was followed in Year 2 for placebo-group subjects who were re-randomised to BIIB017.

Subjects were to participate in this study for up to 108 weeks (2 years, 3 months), which consisted of a 6-week screening period, a 96-week (2-year) treatment period that included a

4-week titration period, and up to a 4- or 8-week safety follow-up period for subjects who did not enter the extension study under a separate protocol. Subjects who prematurely discontinued study treatment and switched to an approved open-label MS medication were to remain in the study for up to 24 weeks of follow-up evaluations.

Subjects were to self-administer study treatment every 2 weeks and to return to the clinic as scheduled for data collection. Unscheduled relapse assessment visits were to occur within 72 hours of the onset of any new neurological symptoms that might indicate the onset of a clinical relapse.

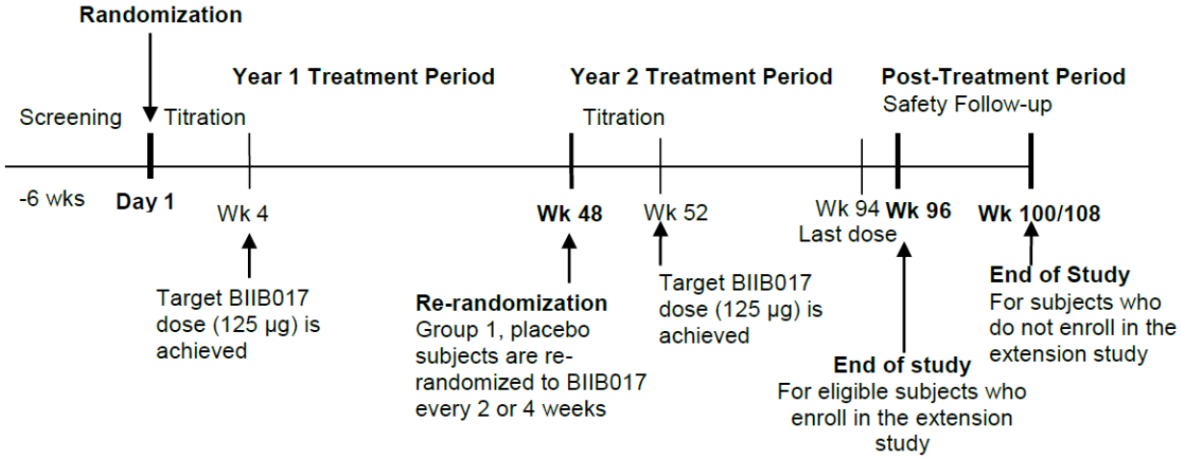


Figure 4 – Study Scheme

Treatment compliance

Treatment compliance was monitored by syringe-count at scheduled visits and patient diaries on self-administration. Patients who missed more than 2 consecutive doses or more than 4 total doses during the study were defined as non-compliant.

Other allowed therapies

To further reduce the flu-like symptoms, patients were instructed to take paracetamol, ibuprofen, non-steroidal anti-inflammatory drugs or naproxen prior to injection and for 24 hours following each treatment injection during the first 26 weeks of the study.

Symptomatic therapy was allowed. Protocol-approved relapse-treatment was either 3 days or 5 days with IV methylprednisolone 1000 mg/day. Steroid re-treatment of the same relapse was not allowed unless approved by the advisory committee.

Rescue medication was allowed per protocol if

- patients had completed 48 weeks of blinded study treatment and experienced or 2 more relapses confirmed by the Independent Neurology Evaluation Committee (INEC), or
- patients experienced significant disability progression i.e. at least a 1.0-point increase on the EDSS from a baseline EDSS≥ 1.0 that was sustained for 12 weeks, or at least a 1.5-point increase on the EDSS from a baseline EDSS = 0 that was sustained for 12 weeks

In these cases patients could either choose to remain on study treatment, to discontinue the study treatment and switch to approved, open-label MS therapy or to discontinue the study and decline switching to another therapy.

For relapse definition, see section on outcomes/endpoints.

Objectives

Study 301

The primary objective of study 301 was to determine the efficacy of BIIB017 in reducing the annualized relapse rate (ARR) in subjects with RMS at 1 year.

The secondary objectives were to determine whether BIIB017, at 1 year as compared with placebo was effective in:

- Reducing the total number of new or newly enlarging T2 hyperintense lesions on brain MRI scans;
- Reducing the proportion of subjects who relapsed;
- Slowing the progression of disability (see outcomes/endpoints for the definition of sustained progression).

The additional, tertiary objectives of this study were to determine:

- The safety, tolerability, and immunogenicity of BIIB017 over a 2-year treatment period;
- The PK and PD profile of BIIB017 in subjects with RMS;
- The maintenance of efficacy of BIIB017 over a 2-year treatment period.

As an exploratory objective, the potential biomarkers from RNA gene-expression profiling and serum cytokine/chemokine panel that may be associated with treatment response to BIIB017, as well as potential genetic polymorphisms from DNA that may be associated with treatment response to BIIB017, were to be determined.

Study 302

The primary objective of this study was to evaluate the long-term safety and tolerability of BIIB017 in subjects originally treated in Study 105MS301 who continue BIIB017 treatment.

The secondary objective of this study was to describe the long-term multiple sclerosis (MS) outcomes in subjects originally treated in Study 105MS301 who continue BIIB017 treatment.

Outcomes/endpoints

Study 301

The primary endpoint was the annualized relapse rate (ARR) at 1 year.

Secondary endpoints were in order of relative importance:

- Number of new or newly enlarging T2 hyperintense lesions at 1 year;
- Proportion of subjects relapsing at 1 year;

- Disability progression measured by EDSS at 1 year.

Tertiary endpoints included the above mentioned endpoints at year 2 as well as the number of Gd-enhancing lesions at 1 year and the number of new T1 hypointense lesions at 1 year. Other tertiary endpoints included clinical measures (such as relapses requiring steroid use, MS-related hospitalizations, Multiple Sclerosis Functional Composite); MRI measures (including new active lesions, lesion volumes, brain atrophy, and magnetization transfer ratio); and assessments of cognition, visual function, and various patient-reported outcomes relevant to MS.

Study 302

Study 302 employed the same endpoints as study 301. These endpoints were analysed at baseline and the Week 48 and Week 96 visits.

Definitions of MS relapses

A relapse was documented when a subject informed study site personnel of any symptoms that might indicate that a relapse was occurring or had occurred.

All relapses: Any event suspected of being a relapse by a subject whether or not the event met the criteria for protocol-defined or INEC-confirmed relapse.

Protocol-defined relapses*:* New or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, with onset more than 30 days after the last relapse, and accompanied by new objective neurological findings upon examination by the examining neurologist. Protocol-defined relapses may or may not have been confirmed by INEC.

INEC-confirmed relapses (only for study 301)*:* protocol-defined relapses that were evaluated by 3 INEC members and confirmed by a majority vote (2 out of 3 members confirmed the event as a MS relapse). Only INEC-confirmed relapses were included in the primary endpoint analysis.

Relapses not evaluated by the treating neurologist within 72 hours of onset of symptoms or not evaluated by the examining neurologist within 5 days of onset of of symptoms were not sent to INEC for confirmation, and could not be INEC confirmed.

Definition of disability progression

The outcome measure was the sustained disability progression, defined as a 1.0 point increase on EDSS score from baseline (for baseline EDSS score ≥1.0) or 1.5 point increase on EDSS score from baseline (for baseline EDSS score = 0) and this increase in EDSS score had to persist for at least 12 weeks (study 301). In study 302, disability progression had to persist for 24 weeks.

Sample size

Sample size calculation was based on the type I error rate of 0.05 and a dropout rate of 10%. It was assumed that the treatment effect for BIIB017 would be a 32% reduction from placebo in the Year 1 ARR.

Initially, a sample size of 420 per treatment group was planned to provide approximately 90%, 87%, and 85% power when the placebo Year 1 annualized relapse rate is 0.6, 0.55, or 0.5, respectively. Following blinded monitoring of the pooled Year 1 ARR, the sample size was increased from 420 to 500 subjects per group.

Randomisation

Randomisation to one of the three treatment groups in year 1 was done in a 1:1:1 ratio using a centralized interactive voice/web response system. Randomisation was stratified by study centre. After completion of Year 1, subjects on the placebo group were re-randomised to receive BIIB017 every 2 or 4 weeks for the duration of Year 2, and the extension study 302.

Blinding (masking)

Study 301 was a double-blind, rater-blinded study. All subjects and study staff were blinded to the treatment assignment. Patients receiving BIIB017 once in 4 weeks received placebo injection every 2 weeks in order to maintain the blind. On the second year of the study, the blinding of dosing frequency was sustained but patients were told that they received the active treatment.

As for study 301, in study 302, subjects, study staff and examining physicians are blinded to dose frequency and clinical assessment is performed by blinded neurologists.

Statistical methods

All efficacy endpoints were evaluated on the intent-to-treat (ITT) population including all randomised subjects who received at least 1 dose of study treatment (BIIB017 or placebo). In addition, the primary and secondary efficacy endpoints were also analysed based on the per-protocol (PP) population, defined as a subset of the ITT population without major protocol deviation. The analyses performed on the ITT population were considered the primary analyses, and the analyses based on the PP population were considered supportive.

While statistical comparisons were made between the placebo and BIIB017 groups during the placebo-controlled period in Year 1, data from Year 2 were descriptive only, and unless otherwise specified, no formal comparisons were made between the treatment groups.

Due to the multiplicity of endpoints and dose regimens, a hierarchical testing procedure was used to control the type I error rate for the primary and secondary endpoints: For the primary endpoint, the BIIB017 q2W group was compared to placebo and if the difference was statistically significant ($p \leq 0.050$), then the comparison of BIIB017 q4W versus placebo could also be performed and considered statistically significant if $p \leq 0.05$. Secondary endpoints were ranked and each dose group was compared to placebo in the same manner as the primary endpoint. If statistical significance was not achieved for an endpoint for a particular dose frequency group, all comparisons for endpoint(s) of lower rank for that dose frequency group were not considered statistically significant.

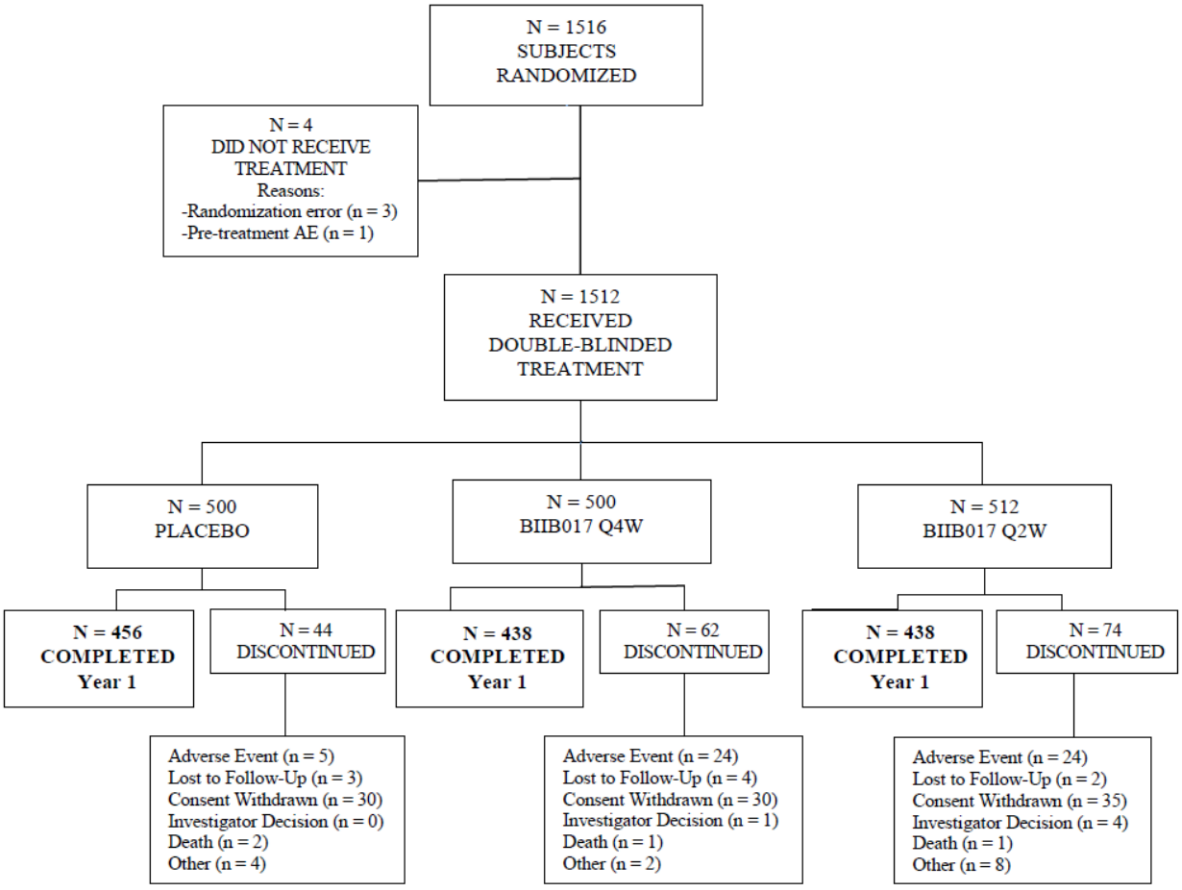
The analysis of the primary endpoint used negative binominal regression on INEC-confirmed relapses with time of study as offset parameter. In case of under-dispersion or if the negative binominal regression model did not converge, a Poisson regression model was used instead. Dispersion was evaluated from the Pearson Chi-Square statistic. The response variable was the total number of relapses. Logarithmic transformation of the time on study was included as an independent variable in the model. The model variables included treatment, baseline relapse rate, age (<40 vs. >40) and EDSS (<4 vs. >4).

Negative binominal regression was also used to analyse the number of new or newly enlarging T2 hyperintense lesions at 1 year, while a Cox proportional hazards model was applied to the other two secondary endpoints.

Two-sided 95% confidence intervals (CI) of the rate ratio were provided for the comparisons of each active treatment versus placebo. The estimated relapse rate and its 2-sided 95% CIs and the gross estimate of ARR are provided for each treatment group.

2.5.2.1.2. Results

Participant flow in study 105MS301 for Year 1



Recruitment

The study started on 13 March 2009 and the placebo-controlled phase of the study (Year 1) was completed on 24 October 2012.

A total of 1936 subjects were screened for enrolment in study 301. Of these, 1516 subjects were randomised, 1512 subjects received at least 1 dose of study treatment, and 1332 subjects completed Year 1. Of the subjects who received BIIB017 during Year 1, a total of 876 subjects continued treatment in Year 2 at the same dose (438 in each dose group). The 456 subjects in the placebo group who completed Year 1 were re-randomised to the BIIB017 treatment groups,

with 228 subjects in the q2W and q4W group, respectively. A total of 1198 patients completed study Year 2 (200 and 196 patients who switched from placebo to BIIB017 q2W and q4W, respectively, and 391 and 411 patients continuing on BIIB017 q2W and q4W, respectively).

Study 302 was on-going at the time of this report. At the time of data cutoff (24 October 2012), 517 subjects had entered study 302, and 508 subjects had received at least 1 dose of study treatment. Only 17 subjects in the BIIB017 q4W and 13 subjects in the BIIB017 q2W groups who were continuously exposed to BIIB017 in study 301 had completed Year 1 of study 302 and consequently had 3 years of exposure to BIIB017.

Conduct of the study

Study 301 and 302 were performed in 26 countries world-wide including countries in Europe.

Enrolment began under global protocol Version 1, dated 13 March 2009. The protocol was subsequently amended 4 times with all changes made to the protocols occurring prior to breaking the blind of the study. In the latest protocol update, the age limit for subject enrolment into the study was increased to include patients of 56-65 years of age to better reflect the age range of the treated MS population.

All patients who completed study 301 were eligible for the extension study 302 thus the study population originates from the same geographic areas. Study 302 was initiated in 2011.

Baseline data

See Table 3 and Table 4 for an overview of patient demographics and baseline disease characteristics and MRI evaluation.

Geographically, 70% of subjects in the ITT population were from Eastern Europe (Bulgaria, Croatia, the Czech Republic, Estonia, Greece, Latvia, Poland, Romania, the Russian Federation, Serbia, and the Ukraine), 11% were from India, 8% were from Western Europe (Belgium, France, Germany, the Netherlands, Spain, and the UK), 7% were from the rest of the world (Chile, Colombia, Georgia, Mexico, New Zealand, and Peru), and 3% were from North America (Canada and the US). Therefore, the majority of the recruited patients represented the European target population [1183 (78%) out of 1512 patients].

With regards to patient demographics, the majority of patients were Caucasians (82%) and females (71%). The mean age was 36.5 years. Less than 1% of the patients were over the age of 59.

The mean EDSS score at baseline was 2.46 representing mild to moderate neurological impairment. A total of 436 patients with EDSS scores ≥3.5 were included. The mean number of relapses within the past year was 1.5. The mean time since the occurrence of the first symptoms of MS was 6.6 years, with a wide range of individual subject values (0 to 40 years). The mean time since MS diagnosis was 3.6 years (range: 0 to 40 years).

With regard to MRI parameters, the majority of subjects (61%) had no Gd-enhancing lesions at baseline. Compared with placebo and BIIB017 q4W, slightly more subjects in the BIIB017 q2W had no Gd-enhancing lesions at baseline (59%, 59%, and 65%, respectively). The overall mean number of Gd-enhancing lesions was 1.5. The mean number of Gd-enhancing lesions was 1.6, 1.8 and 1.2 in the placebo group, the BIIB017 q4W and the BIIB017 q2W groups, respectively. The mean number of T2 hyperintense lesions at baseline was 50.6, 51.4, and 48.7 in the

placebo, BIIB017 q4W and BIIB017 q2W groups, respectively. The overall mean number of T2 hyperintense lesions was 50.2. Overall, a majority of subjects (92%) had ≥9 T2 hyperintense lesions at baseline. The percentage of subjects with ≥9 T2 hyperintense lesions at baseline was 94%, 93%, and 90% in the placebo, BIIB017 q4W and BIIB017 q2W groups, respectively.

Of the 1512 patients included in the ITT population, the majority were naïve to previous MS medication (83%). The most common pre-study MS medication was glatiramer acetate (5%), corticosteroids (4%), followed by interferon beta-1b and azathioprine (1% of subjects each).

The medications most frequently used (≥10% of subjects) in Year 1 included paracetamol (88%), ibuprofen (37%), methylprednisolone (22%), and omeprazole (10%). Paracetamol, ibuprofen, naproxen, and aspirin were protocol-specified medications that subjects were instructed to take for the first 26 weeks of the study to reduce flu-like symptoms, and additional dosing was allowed as necessary. Methylprednisolone for the treatment of an MS relapse while on blinded treatment was used by more subjects in the placebo group (29%) compared to BIIB017 q4W (21%) and BIIB017 q2W (17%).

Concomitant medications used by ≥10% of subjects in Year 2 included paracetamol, being the most commonly used (81% of subjects) followed by ibuprofen (33%), and methylprednisolone (16%).

In Year 1, 16 subjects (1%) of the ITT population switched to open-label treatment with approved alternative MS medications. Interferon beta-1a, glatiramer acetate, and interferon beta-1b were the alternative MS medications most commonly used.

Table 3 – Demography of Patients Recruited for Study 105MS301

	Placebo	BIIB017 125 (mcg) SC		Total
		Every 4 weeks	Every 2 weeks	
Number of subjects in ITT population	500 (100)	500 (100)	512 (100)	1512 (100)
Age (yrs)				
< 18	0	0	0	0
18-19	12 (2)	5 (1)	10 (2)	27 (2)
20-29	122 (24)	144 (29)	121 (24)	387 (26)
30-39	176 (35)	155 (31)	189 (37)	520 (34)
40-49	139 (28)	140 (28)	128 (25)	407 (27)
50-59	48 (10)	54 (11)	63 (12)	165 (11)
60-65	3 (<1)	2 (<1)	1 (<1)	6 (<1)
>65	0	0	0	0
n	500	500	512	1512
Mean	36.3	36.4	36.9	36.5
SD	9.74	9.87	9.79	9.80
Median	37.0	36.0	37.0	36.0
Min, Max	18, 61	18, 61	18, 60	18, 61
Age (yrs)				
< 40	310 (62)	304 (61)	320 (63)	934 (62)
>= 40	190 (38)	196 (39)	192 (38)	578 (38)
Gender				
Female	358 (72)	352 (70)	361 (71)	1071 (71)
Male	142 (28)	148 (30)	151 (29)	441 (29)
Race				
White	412 (82)	409 (82)	416 (81)	1237 (82)
Asian	56 (11)	56 (11)	59 (12)	171 (11)
Other	29 (6)	32 (6)	33 (6)	94 (6)
Black	3 (<1)	1 (<1)	3 (<1)	7 (<1)
Not reported (a)	0	2 (<1)	1 (<1)	3 (<1)
Height (cm)				
n	492	493	506	1491
Mean	167.5	167.6	167.8	167.6
SD	9.11	9.17	9.55	9.28
Median	167.0	167.0	167.0	167.0
Min, Max	142, 194	144, 192	140, 201	140, 201
Weight (kg)				
n	498	497	511	1506
Mean	69.19	68.32	69.57	69.03
SD	16.164	14.634	17.376	16.107
Median	66.00	67.00	65.60	66.00
Min, Max	42.0, 139.2	38.5, 147.4	36.0, 176.9	36.0, 176.9
Body mass index (kg/m^2)				
n	492	493	506	1491
Mean	24.61	24.25	24.59	24.48
SD	4.896	4.531	5.097	4.849
Median	23.60	24.00	23.58	23.67
Min, Max	16.6, 54.9	15.6, 57.6	14.8, 45.1	14.8, 57.6
Geographic areas (b)				
India	56 (11)	56 (11)	58 (11)	170 (11)
North America	17 (3)	16 (3)	19 (4)	52 (3)
West Europe	38 (8)	39 (8)	41 (8)	118 (8)
East Europe	354 (71)	355 (71)	355 (69)	1064 (70)
Rest of World	35 (7)	34 (7)	39 (8)	108 (7)

NOTE: Numbers in parentheses are percentages.
(a) Race was not reported due to local ethics committee requirements.
(b) North America includes Canada, United States. West Europe includes Belgium, France, Germany, Netherlands, Spain, and United Kingdom. East Europe includes Bulgaria, Croatia, Czech Republic, Estonia, Greece, Latvia, Poland, Romania, Russia, Serbia, and Ukraine. Rest of World includes Chile, Colombia, Georgia, Mexico, New Zealand and Peru.

Table 4 - Patient Disposition including Baseline Disease Characteristics and MRI Evaluation (ITT Population)

	Placebo	BIIB017 q2W	BIIB017 q4W
N dosed (year 1)	500	512	500
N completed	456	438	438
Reason for discontinuation			
Adverse event	1%	5%	5%
Lost to follow-up	<1%	<1%	<1%
Consent withdrawn	6%	7%	6%
Investigator decision	-	<1%	<1%
Death	<1%	<1%	<1%
Other	<1%	2%	<1%
N dosed (year 2)	n.a.		
Placebo -> active		228	228
Continuing active		438	438
Total		666	666
N completed (Placebo → active / continuing active)	n.a	196 / 411	228 / 438
Reason for discontinuation			
Adverse event		4% / 2%	4% / 2%
Lost to follow-up		2% / <1%	<1% / <1%
Consent withdrawn		7% / 3%	6% / 6%
Investigator decision		<1 / <1%	0% / 1%
Death		0% / <1%	<1% / 0%
Other		<1 / <1%	2% / <1%
Median EDSS score(range)	2.0 (0.0-5.0)	2.5 (0.0-5.5)	2.5 (0.0-5.0)
Median no. of relapses within past 3 years (range)	2.0 (1-9)	2.0 (1-12)	2.0 (1-7)
Mean time since first symptoms , years (SD)	6.3 (6.28)	6.9 (6.61)	6.5 (6.07)
Time since diagnosis, years (SD)	3.5 (4.63)	4.0 (5.09)	3.4 (4.36)
Previous MS treatments (The most important, approved therapies presented)			
None	83%	83%	83%
Glatimer Acetate	5%	5%	6%
Interferon β-1B	1%	2%	1%
Interferon β-1A	1%	<1%	1%
Natalizumab	0%	0%	0%
Median no. of Gd lesions (range)	0 (0-38)	0 (0-32)	0 (0-68)
Median no. of T2 lesions (range)	43.0 (1-212)	39.0 (0-249)	45.0 (0-206)
Median no. of T1 hypointense lesions (range)	20.0 (0-212)	18.0 (0-185)	19.0 (0-213)

*Completed Year 2 as of the data cut-off date, 24 October 2012

Numbers analysed

Of the 1516 subjects randomised for the study, 4 subjects were never treated (3 had been randomised in error, and 1 reported a pre-treatment adverse event and became ineligible to participation in the study). The 1512 subjects who received at least 1 dose of study treatment comprised the ITT and safety populations.

The PP population included 1465 subjects (97%) overall with 482, 486, and 497 subjects in the placebo, BIIB017 every 4 weeks, and BIIB017 every 2 weeks groups, respectively.

Data were analysed for the study 302 ITT population, which included 247 subjects in the BIIB017 q4W and 261 subjects in the BIIB017 q2W at the time of data cut-off.

Outcomes and estimation

Primary endpoint

The adjusted ARR at Year 1 was 0.397 in the placebo group, 0.288 in the BIIB017 q4W arm and 0.256 in the BIIB017 q2W arm, translating into a reduction of 27.5% and 35.6% in the active treatment groups, respectively (see Table 5), compared to placebo. The improvement in ARR for both BIIB017 treatment arms was statistically significant with slightly numerically better results for the higher BIIB017 dose (q2W).

Table 5 – Annualized Relapse Rate (INEC-Confirmed Relapses) at Year 1-(ITT Population)

	Placebo	BIIB017 q2W	BIIB017 q4W
Year 1			
N	500	512	500
ARR (adjusted) **Rate ratio** **95% CI** **P**	0.397	0.256 0.644 0.500 – 0.831 p=0.0007	0.288 0.725 0.565 0.930 p=0.0114

There was a higher relapse rate in the placebo group, but relapse rates were in general low in al there groups. Table 6 provides an overview of the reported relapses in each group during Year 1 (see section 2.5.2.1.1. , outcomes/endpoints, for the definition of relapses). Most of the patients in all treatment groups experienced zero relapses (placebo: 72%, BIIB017 every 4 weeks: 79%, BIIB017 every 2 weeks: 82%).

Table 6 – Number of Reported Relapses at Year 1

	Placebo	BIIB017 q4W	BIIB017 q4W	Total
All relapses	213	142	132	487
Protocol-defined relapses	204	134	126	464
INEC-confirmed relapses	181	125	116	422

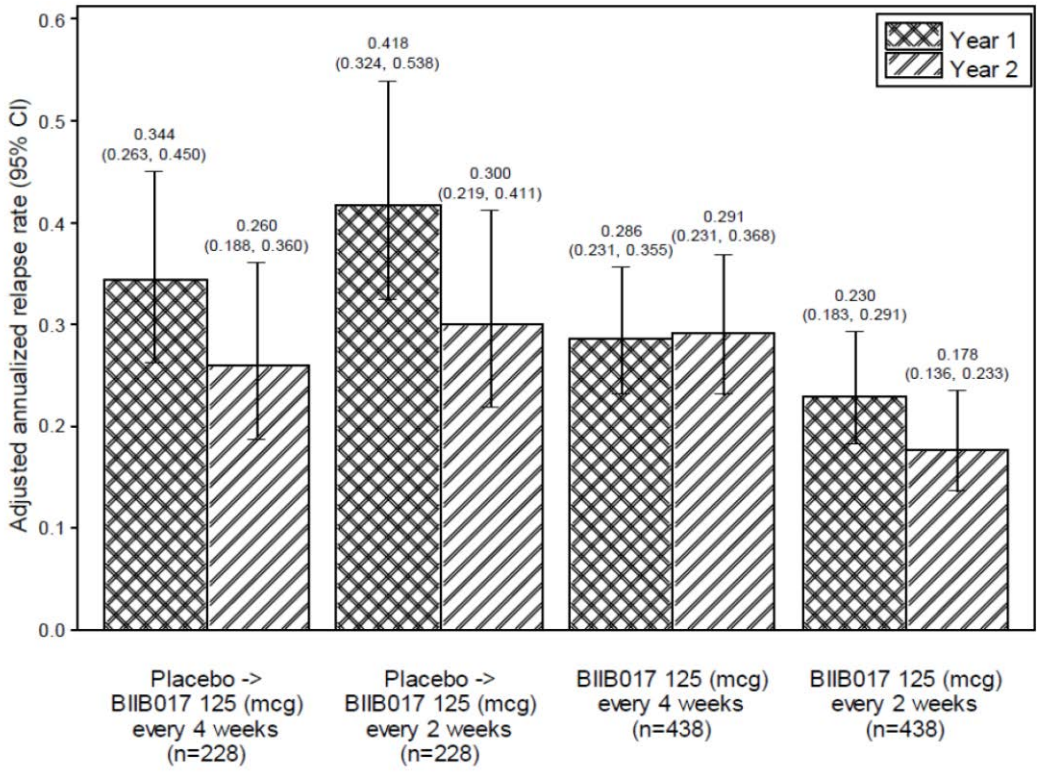
A post-hoc analysis of study participation status to evaluate the effect of early withdrawal on the primary endpoint showed a similar trend in reduction of ARR compared to all subjects in the primary analysis.

Furthermore, results of an analysis of adverse events known to occur in subjects receiving interferon treatment, including influenza-like symptoms and injection-site reactions, to evaluate the effect of potential un-blinding of subjects or investigators on the primary endpoint at Year 1 showed consistency with the conclusions from the primary analysis.

Figure 5 provides an overview of the ARR by study year.

For patients who received BIIB017 q4W, the ARR in Year 2 seemed to be comparable to the ARR in Year 1. For patients who received BIIB017 q2W, the ARR in Year 2 seemed to show a reduction compared to the ARR in Year 1.

Also for patients who received placebo in Year 1 and who were re-randomized to BIIB017 in year 2, the ARR in Year 2 was lower than the ARR in Year 1.



NOTE 1: Only relapses confirmed by INEC are included in the analysis.
2: Data after subjects switched to alternative MS medications during the period are excluded.
3: Adjusted annualized relapse rate and 95% CI are based on negative binomial regression, adjusted for baseline EDSS (<4 vs. >=4), baseline relapse rate and age (<40 vs. >=40).

Figure 5 - Summary of Annualized Relapse Rate (INEC-Confirmed Relapses) by Study Year – ITT Population Dosed in Year 2

Secondary endpoints

- Number of new or newly enlarging T2 hyperintense lesions at 1 year

The adjusted mean number of new or newly enlarging T2 hyperintense lesions was 10.9 in the placebo group, compared to 7.9 in subjects who received BIIB017 q4W and 3.6 in subjects who received BIIB017 q2W (see Table 7). Treatment with BIIB017 q4W and BIIB017 q2W significantly reduced the number of new or newly enlarging T2 hyperintense lesions that developed over 1 year by 28% (p=0.0008) and 67% (p<0.0001), respectively, compared to placebo, which was statistically significant.

Table 7 – Number of New or Newly Enlarging T2 Lesions - Year 1 (ITT Population)

	Placebo	BIIB017 q2W	BIIB017 q4W
Year 1			
N	500	512	500
Median no. of new or newly enlarging T2 hyperintense lesions (range)	6.0 (0 – 148)	1.0 (0-69)	3.0 (0-113)
Mean no. of new or newly enlarging T2 hyperintense lesions (range)	13.3	4.1	9.2
Adjusted mean no. of new or newly enlarging T2 hyperintense lesions	10.9	3.6	7.9
lesion mean ratio (95% CI) p-value	n.a.	0.33 (0.27 – 0.40) p=<0.0001	0.72 (0.60 – 0.87) p=0.0008

Sensitivity analyses also provided statistically significant results for both active treatment arms in comparison to placebo.

Among the subjects who continued into Year 2 of the study, the effect of BIIB017 on the occurrence of new or newly enlarging T2 hyperintense lesions was maintained in subjects who continued to receive BIIB017. Subjects who started on BIIB017 in Year 2 saw improvements as compared to Year 1.

- Proportion of subjects relapsing at 1 year

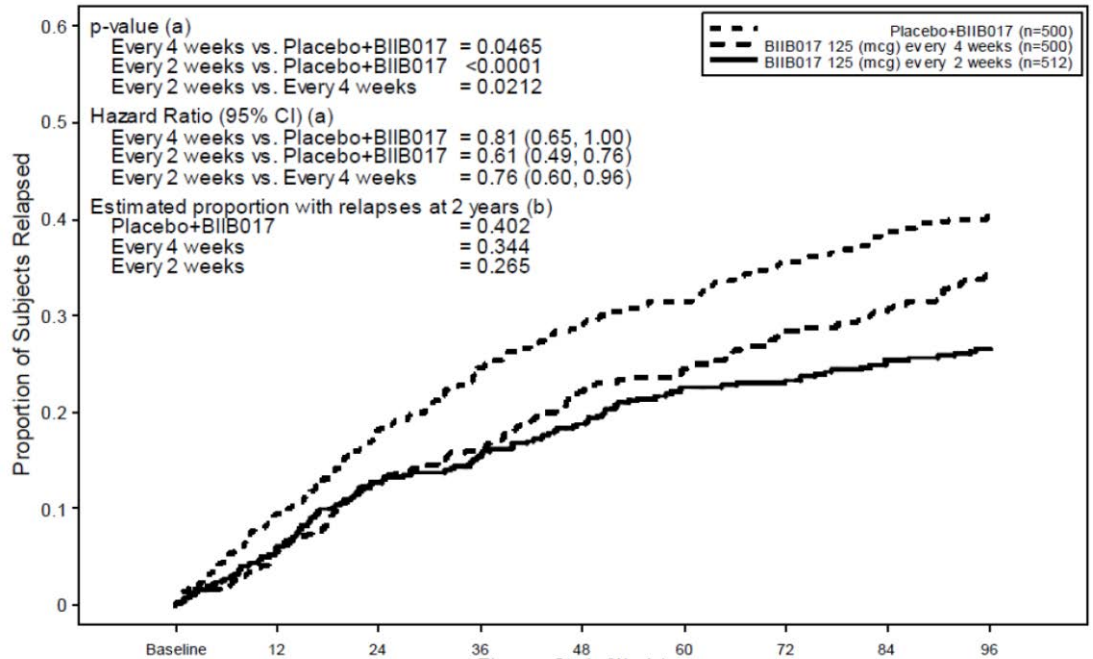
The proportion of subjects that relapsed at Year 1 was 0.291 in the placebo group compared with 0.222 in the BIIB017 q4W group and 0.187 in the BIIB017 q2W group (see Table 8). The hazard ratios were 0.74 for the BIIB017 q4W group versus placebo and 0.61 for the BIIB017 q2W group versus placebo. The risk of relapse was statistically significantly reduced by 26% (p = 0.0200) following treatment with BIIB017 q4W and 39% (p = 0.0003) following treatment with BIIB017 q4W.

Table 8 – Proportion of Subjects Relapsed (INEC Confirmed Relapses) at Year 1 (ITT Population)

	Placebo	BIIB017 q2W	BIIB017 q4W
Year 1			
N	500	512	500
Proportion of subjects relapsed	0.291	0.187	0.222
HR		0.61	0.74
95% CI		0.47 – 0.80	0.57 – 0.95
P		p=0.0003	p=0.0200

Similar results were obtained for the PP population analysis and a sensitivity analysis using all relapses.

Kaplan-Meier plots (see Figure 6) of the time to first relapse revealed a separation between the curves of the two active arms around Week 36, which is maintained over time.



NOTE 1: Only relapses confirmed by the INEC are included in the analysis.
2: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrawal from study are censored at the time of switch/withdrawal.
3: Subjects in placebo+BIIB017 group received placebo in year 1, and either BIIB017 125 (mcg) every 4 weeks or every 2 weeks in year 2 if they continued study treatment in year 2.
(a) P-value and hazard ratio (active/placebo+BIIB017, q2w/q4w) are based on Cox proportional hazards model, with adjustment for baseline EDSS (<4 vs. >=4), age (<40 vs. >=40), baseline relapse rate, and baseline Gd enhancing lesions (presence vs. absence).
(b) Kaplan-Meier estimate of the proportion of subjects relapsed within 2 years.

Figure 6 - Time to First Relapse (INEC-Confirmed Relapses) over 2 Years (ITT Population)

- Disability progression measured by EDSS at 1 year

Disability progression was measured in terms of 12 weeks confirmed increase in EDSS score. The proportion of subjects with sustained disability progression at Year 1 was 0.105 in the placebo group as compared to 0.068 in both BIIB017 q4W and BIIB017 q2W (Table 9). The risk of progression of disability over 1 year was reduced by 38% following treatment with BIIB017 q4W and 38% following treatment with BIIB017 q2W relative to placebo. Both active treatment arms reached statistical significance when compared to placebo.

Table 9 – Sustained Disability Progression at 1 Year as Measured by Increase in EDSS as defined in study 301 over 12 Weeks (ITT Population)

	Placebo	BIIB017 q2W	BIIB017 q4W
Year 1			
N	500	512	500
Proportion of subjects with a 3-month sustained disability progression	0.105	0.068	0.068
HR		0.62	0.62
95% CI		0.40 – 0.97	0.40 – 0.97
P		p=0.0383	p=0.0380

Further to a request by the CHMP, the applicant provided additional analyses applying a definition of sustained worsening in line with the CHMP Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis (CPMP/EWP/561/98 Rev. 1) as follows:

- increase of the EDSS score of 1.0 point from baseline (if the baseline EDSS score was ≤5.5) or increase by 0.5 point from baseline (if the baseline EDSS score was >5.5);

- increase of EDSS score as defined above persisting for 6 months (24 Weeks).

The results of this analysis are shown in Table 10.

Table 10 - Confirmed Disability Progression

		BIIB017 Q2W	BIIB017 Q4W
Prespecified analysis			
12-week confirmation over 1 year (prespecified analysis and definition)	HR vs. placebo (95% CI)	0.62 (0.40, 0.97)	0.62 (0.40, 0.97)
	p-value	*0.0383*	*0.0380*
Additional post hoc sensitivity analyses			
24-week confirmation over 1 year	Prespecified definition	0.46 (0.26, 0.81)	0.67 (0.41, 1.10)
	p value	*0.0069*	*0.1116*
	Alternate definition	0.59 (0.36, 0.98)	0.73 (0.46, 1.18)
	p value	*0.0402*	*0.1994*
24-week confirmation over 2 years[a] (complete 2 year results)	Prespecified definition	0.59 (0.38, 0.90)	0.91 (0.63, 1.33)
	p value	*0.0137*	*0.6243*
	Alternate definition	0.65 (0.44, 0.98)	0.95 (0.66, 1.37)
	p value	*0.0394*	*0.7877*

CI = confidence interval; HR = hazard ratio; Q2W = every 2 weeks; Q4W = every 4 weeks.
[a] All comparisons at 2 years are by original randomization against the subjects who received placebo and then switched to BIIB017.

The Kaplan-Meier plots for patients with sustained disability progression over time revealed a separation between the placebo group and the 2 BIIB017 groups from Week 12 through Week 48 both for the original definition of sustained disability progression (see Figure 7) and the alternate definition in line with the multiple sclerosis guideline (see Figure 8). However, when calculating disability progression sustained over 24 weeks, only results for BIIB017 q2W, but not for q4W, were statistically significantly better than placebo (see also Table 10).

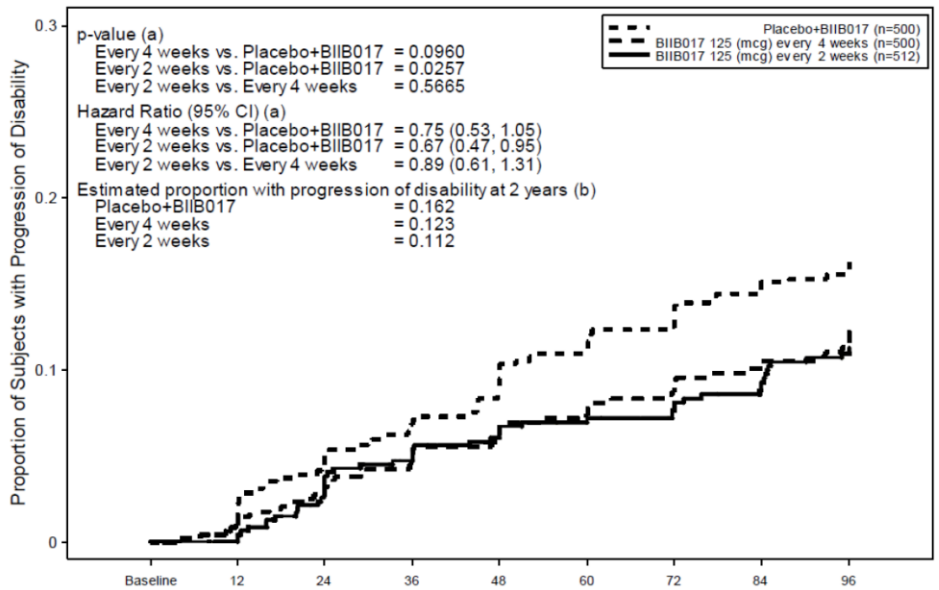


Figure 7 - Time to Sustained Disability Progression over 2 Years (Original Study 301 Definition)

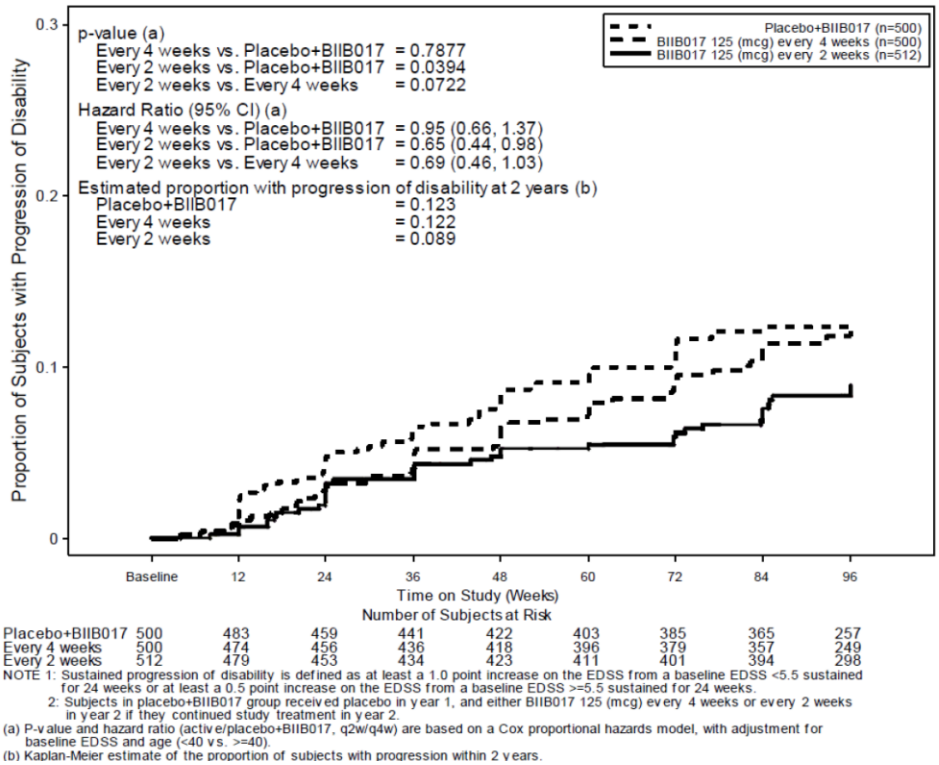


Figure 8 - Time to Sustained Disability Progression over 2 Years (Alternate Definition in line with the MS guideline)

Tertiary endpoints

Results for selected relevant tertiary endpoints are presented in Table 11.

Table 11 – Summary of the Main Efficacy Results for Selected Tertiary Endpoints Study 301 at Year 1

	Placebo	BIIB017 q2W	BIIB017 q4W
Year 1			
N	500	512	500
Median no. of Gd-enhancing lesions (range)	0.0 (0 – 39)	0.0 (0 – 13)	0.0 (0 -41)
Mean no. of Gd-enhancing lesions **% reduction vs placebo** **P**	1.4	0.2 86% <0.0001	0.9 36% 0.0738
Median no. of new T1 hypointense lesions (range)	1.0 (0 – 56)	0.0 (0 - 39)	1.0 (0 – 61)
Mean no. of new T1 hypointense lesions **% reduction vs placebo** **P**	3.8	1.8 53% <0.0001	3.1 18% 0.0815

The mean number of Gd-enhancing lesions in the placebo group was 1.4, compared to 0.9 and 0.2 in the BIIB017 q4W and in the BIIB017 q2W group, respectively. The difference was only statistically significant for BIIB017 q2W ($p < 0.0001$).

The mean number of new T1 hypointense lesions was 3.8 in the placebo group and 3.1 in the BIIB017 q4W group at Week 48 and was significantly lower in the BIIB017 q2W group (mean 1.8). This translated into a reduction of new T1 hypointense in Year 1 of 18% ($p=0.0815$) under treatment with BIIB017 q4W and 53% ($p<0.0001$) in the BIIB017 q2W group respectively, compared to placebo. Only the difference for BIIB017 q2W was statistically significant.

Tertiary endpoints relating to 2-year results for outcome measures representing primary and secondary endpoints at Year 1 are summarised together with results of the primary and secondary endpoints (see above).

Interim results for study 302

At Year 1 in study 302, 30 subjects in the BIIB017 q4W group had experienced 37 relapses, and 14 subjects in the BIIB017 q2W group had experienced 18 relapses. The corresponding adjusted ARR were 0.410 in the BIIB017 q4W group and 0.203 in the BIIB017 q2W group.

The estimated proportion of subjects relapsed at Week 36 was 0.186 and 0.104 in the BIIB017 q4W and q2W groups, respectively.

At the time of data cut-off, 24-week sustained disability progression (based on combined study 301 and 302 data) had been confirmed for 21 subjects (8.5%) in the BIIB017 q4W group and 16 subjects (6.1%) in the BIIB017 q2W group.

Among the 37 subjects with available MRI data at the time of data cut-off, a mean of 3.7 new or newly enlarging T2 lesions was detected among the 19 subjects in the BIIB017 q4W group, and a mean of 1.1 lesions was detected among the 18 subjects in the BIIB017 q2W group.

Discontinuation

The majority of discontinued subjects were patients who withdrew their consent. The majority of these patients withdrew due to personal reasons, which included relocation, wish to receive approved MS treatment, wish not to receive placebo, plans of pregnancy and other. A limited number of patients withdrew due to lack of efficacy (9, 5 and 5 in the placebo group and the BIIB017 q4W and q2W groups, respectively). Discontinuation due to adverse events is presented in section 2.6.

Ancillary analyses

Subgroup analyses

The applicant performed a number of subgroup analyses for the most important clinical endpoints in study 301. The results of the analysis of ARR in the BIIB017 groups were in general similar among the demographics (gender, age, weight, geographic origin) and baseline disease characteristics subgroups.

In the subgroup analysis of patients with different numbers of relapses within 3 years prior to study entry, patients that had suffered 4 or more relapses showed results comparable to placebo. However, the number of patients in this subgroup was rather small (66 patients receiving placebo, 52 patients receiving active treatment).

With regards to 3-month sustained disability progression, results for patients without prior MS treatment favoured active treatment against placebo for both dosing regimens. No treatment effect was detected for BIIB017 in the subgroup of patients who already were treated with MS substances. However, the number of patients in this subgroup was rather small.

Immunogenicity

The MAH investigated the impact of immunogenicity on the efficacy of BIIB017 for BAbs to interferon beta-1a, NAbs to interferon beta-1a, and BAbs to PEG (anti-PEG). Subjects who were positive at any time point during Year 1, including baseline, were categorized as ‘ever positive’ to assess the impact of antibodies on efficacy. In the BIIB017 q4W and q2W groups, respectively, 28/500 subjects (6%) and 54/512 subjects (11%) were ever positive for anti-interferon BAbs, 4/500 subjects (0.8%) and 12/512 subjects (2.3%) were ever positive for anti-interferon NAbs, and 70/500 subjects (14%) and 56/512 subjects (11%) were ever positive for anti-PEG antibodies. Although the impact on efficacy measurements was difficult to interpret due to the low incidence of antibodies found, the unadjusted ARR at 1 year for both groups of BIIB017-treated subjects who were ‘ever positive’ or ‘never positive’ was lower than the ARR observed for placebo-treated subjects.

Dosing regimens

A direct comparison of the two dosing regimens showed that dosing every 2 weeks resulted into better efficacy compared to q4W for all main endpoints.

Summary of main study(ies)

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

Table 12 Summary of Efficacy for Study 105MS301

Title: A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of PEGylated Interferon Beta-1a (BIIB017) in Subjects with Relapsing Multiple Sclerosis			
Study identifier	105MS301 (study 301)		
Design	Multicenter, randomised, double-blind, parallel-group, placebo-controlled study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		96 weeks (2 years) including 4 weeks titration for active groups 6 weeks screening 96 weeks (2 years; 4 years in total: study 302)
Hypothesis	Superiority of BIIB017 over placebo in reducing the annualized relapse at year 1		
Treatments groups	Group 1 (placebo)		500 patients to receive SC injection of placebo every 2 weeks.
	Group 2 (BIIB017 Q4W)		500 patients to receive SC injection of 125 µg BIIB017 every 4 weeks (alternating placebo and BIIB017 injections every 2 weeks)
	Group 3 (BIIB017– Q2W)		512 patients to receive SC injection of 125 µg BIIB017 every 2 weeks
Endpoints and definitions	Primary endpoint	Annualized relapse rate at 1 year (week 48)	Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist. Only relapses confirmed by the Independent Neurology Evaluation Committee (INEC) were included.
	Secondary endpoint (1)	Number of new or newly enlarging T2 hyperintense lesions at 1 year (week 48)	MRI scans were performed during the screening period (30 days prior to the first dose, and not less than 5 days prior to the first dose) as well as at week 24 and 48. Brain scans were reviewed by 2 qualified MRI readers, who independently reviewed all brain scans and identified the gadolinium-enhancing lesions.
	Secondary endpoint (2)	Proportion of subjects relapsed at 1 year	Only protocol-defined relapses (see primary endpoint) confirmed by INEC.

	Secondary endpoint (3)	Progression of disability as measured by EDSS score at 1 year (week 48)	Disability progression was defined as a minimum change (i.e. at least a 1.0 point increase on the EDSS from baseline EDSS ≥1.0 or at least a 1.5-point increase on the EDSS from baseline EDSS = 0) that was present on a scheduled or unscheduled study visit and where this minimum EDSS change was present on the next study visit occurring after 74 days from the initial observation.
Database lock	Year 1 (48 weeks) for primary and secondary endpoints and Year 1 and 2 (48 and 96 weeks) for tertiary endpoints		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat: All subjects who were randomised and received at least 1 dose of study treatment (BIIB017 or placebo)			
Descriptive statistics and estimate variability	Treatment group	Group 1 (placebo)	Group 2 (BIIB017 Q4W)	Group 3 (BIIB017 Q2W)
	Number of subject	500	500	512
	Annualized (adjusted) relapse rate	**0.397**	**0.288**	**0.256**
	95% CI	0.328, 0.481	0.234, 0.355	0.206, 0.318
	Adjusted mean (new/newly enlarging T2 hyperintense lesions	**10.9**	**7.9**	**3.6**
	Statistical variability	n/a	n/a	n/a
	Estimated proportion of subjects relapsed (from Kaplan-Meier curve of time to relapse)	**0.291**	**0.222**	**0.187**
	Statistical variability	n/a	n/a	n/a

	Estimated proportion of subjects with disability progression (From Kaplan-Meier curve of time to progression)	**0.105**	**0.068**	**0.068**
	Statistical variability	n/a	n/a	n/a

Effect estimate per comparison	Primary endpoint: Reduction in annualized relapse rate	Comparison groups	(1) Group 2 (BIIB017 Q4W) vs. Group 1 (placebo) (2). Group 3 (BIIB017 Q2W) vs. Group 1 (placebo)
		% Reduction of relapse rate	**(1) 27.5%** **(2) 35.6%**
		P-value (negative binomial regression)	(1) 0.0114 (2) 0.0007
	Secondary endpoint (1): New/newly enlarging T2 hyperintense lesions	Comparison groups	See primary endpoint
		% Reduction in lesions	**(1) 28 %** **(2) 67 %**
		P-value (negative binomial regression)	(1) 0.0008 (2) 0.0001
	Secondary endpoint (2): Proportion of subjects relapsed	Comparison groups	See primary endpoint
		% Reduction in the risk of relapse	**(1) 26 %** **(2) 39 %**
		P-value (Cox proportional hazards model)	(1) 0.0200 (2) 0.0003
	Secondary endpoint (3): Disability progression	Comparison groups	See primary endpoint
		% Reduction in the risk of disability progression	**(1) 38 %** **(2) 38 %**
		P-value (Cox proportional hazards model)	(1) 0.0380 (2) 0.0383

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

No clinical efficacy studies in special populations were performed. A study in paediatric patients above 10 years of age will be performed according to the paediatric investigation plan (PIP).

Considering the target population for interferons, a specific study in elderly was not considered necessary by the applicant.

The applicant has performed a phase 1 PK/PD study in patients with renal impairment (see discussion on clinical pharmacology in section 2.4.4.).

Supportive study(ies)

The main interim results of study 302 were presented with the results of study 301, as relevant. At the time the interim analysis was provided, the study was still on-going.

A small usability study (n=39) was performed (as a sub-study of study 302) to assess the ease of use of the auto-injector device (pre-filled pen) as well as its safety as compared to the pre-filled syringe. No comparisons on exposure or efficacy were made. Based on the results derived from patient questionnaires, the majority of patients found the device easy to use. However, the study did not include any comparisons between the auto-injector and pre-filled syringe in terms of ease of use.

2.5.3. Discussion on clinical efficacy

Peginterferon beta-1a is a new formulation of an existing, established class of products in the treatment of multiple sclerosis (MS), beta interferons. In light of the extensive experience gained with this class, the CHMP was of the opinion that the requirements laid down in the current MS guideline (CHMP Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis, CPMP/EWP/561/98 Rev. 1) would apply only partially, for example in terms of study duration and the duration of placebo control.

Design and conduct of clinical studies

No conventional dose-response studies were performed. The lack of such studies was considered acceptable by the CHMP, as the main clinical studies included 2 dose regimens, once every 2 weeks (q2W) and once every 4 weeks (q4W), with a two-fold difference in exposure. The justification for selection of 125 µg as the maintenance dose in the pivotal trial was also considered acceptable in light of the fact that no accumulation was observed in PK studies.

In support of this application, results from two phase 3 studies, 301 and its extension 302, were provided. Both studies were randomised, multicentre, double-blind studies with a duration of 2 years, whereby the first year of study 301 included a placebo arm.

Overall, the study design and methodology was considered acceptable.

The studied patient population with respect to patient demographics and disease characteristics was considered by the CHMP to be generally in line with the expected MS patient population to use interferons. A sufficiently high number of patients from the European target population was included in the trial. Generally, all treatment groups were comparable with respect to baseline disease characteristics. The mean age of 36.5 years was considered acceptable, but the CHMP requested to reflect the limited data in patients over the age of 59 years in the product information. Of note, patients had rather mild disease activity at the time of enrolment and the majority were naïve to previous MS treatments.

The CHMP furthermore noted, that, based on the inclusion/exclusion criteria, only patients with relapsing-remitting MS (RRMS) were included, which was not in line with the initially claimed target population of relapsing MS (RMS) patients. The applicant argued that one in five recruited subjects could actually be considered most similar to patients with secondary progressive MS (SPMS). While the CHMP agreed that for some patients the exact definition of RRMS and SPMS may be difficult to achieve, in order to extend the indication to a wider population, efficacy would have needed to be demonstrated in a clearly defined population of SPMS patients with superimposed relapse. However, no subgroup analysis was provided by the applicant to that effect.

The studies did not include an active comparator. The applicant's original plan was to include non-pegylated beta interferon-1a (Avonex) as an active arm. The reasoning for dropping the active arm from the final investigational plan was not clarified. The CHMP considered that the lack of an active comparator makes it difficult to conclude if the efficacy of peginterferon beta-1a is the same as of other beta interferons products, an issue which is further discussed below.

Both studies covered a period of 2 years, which is in line with the current recommendation for MS studies. However, the efficacy claim was primarily supported by the one-year placebo-controlled data derived from study 301. Two year efficacy data were provided during the course of the assessment, which was considered sufficient by the CHMP to provide supportive data for the demonstration of maintenance of the effect.

The primary endpoint, annualized relapse rate (ARR), is the recommended endpoint for MS studies in the chosen population. The chosen definition of relapses was in accordance with the widely accepted clinical definition. Disability (3-month sustained disability progression) was included as a secondary endpoint, however, it was only ranked 3rd among the secondary endpoints. In this assessment, disability was considered to be the most important secondary endpoint. Furthermore, the CHMP noted that the applied definition of sustained disability progression was unconventional and not in line with the MS guideline as regards the required increase in EDSS score based on baseline EDSS as well as duration of persistence of disability worsening (3 months versus 6 months). Hence, the applicant was requested to re-analyse the data in line with the guideline requirements. Finally, several MRI endpoints provided supportive efficacy data. These were considered adequate by the CHMP.

Efficacy data and additional analyses

Efficacy in terms of ARR for RRMS patients was demonstrated with both dosing regimens of peginterferon beta-1a over a study period of one year in the placebo-controlled study 301. The effect size was modest, i.e. an ARR of 0.40 for placebo versus 0.26 and 0.29, for peginterferon beta-1a q2W and peginterferon beta-1a q4W, respectively. However the relative effect size of around 30% reduction in relapse rate was comparable to that of other interferons, which was considered clinically relevant.

Efficacy was also investigated for sustained disability progression over 1 year as defined in study 301 as well as when applying the proposed definition according to the MS guideline (post hoc analysis upon CHMP request). When applying the definition of 24-week sustained disability progression, the effect size was smaller compared to the results from the primary analysis. Furthermore, for the q4W regimen, statistical significance was not achieved. From this sensitivity analysis it can be concluded that efficacy in preventing disability progression (although smaller in size) over 1 year was confirmed for the Q2W regimen while data for Q4W were less convincing.

Efficacy was also investigated for MRI endpoints. BIIB017 treatment with both dosing regimens resulted in a statistically significant reduction in the number of new or newly enlarging T2 hyperintense lesions compared to placebo. However, only the BIIB017 q2W regimen demonstrated statistically significant differences against placebo on the endpoints of Gd-enhancing lesions and T1 hypointense lesions at Year 1, but not the q4W regimen.

Data over the full 2-year treatment period were considered by the CHMP supportive of the maintenance of the treatment effect of BIIB017 seen at Year 1.

Sub-group analyses revealed generally similar results with regard to demographics (gender, age, weight, geographic origin) and baseline disease characteristics. However, in the subgroup of patients with the highest number of relapses (≥ 4) in the 3 years prior to study entry, no effect of BIIB017 was seen neither with regard to ARR nor disability progression. While the number of patients was too small to draw firm conclusions, in light of the fact that the study participants generally presented with mild disease activity, the CHMP considered that clear information on the available data should be provided in section 5.1 of the SmPC to inform prescribers. Furthermore, in the subgroup of patients who received disease modifying MS treatment prior to study start, no effect of BIIB017 compared to placebo was seen with regard to sustained disability progression. However, these results are probably explained by the rather small number of patients in this subgroup.

No discernible negative impact on primary or secondary endpoints of clinical efficacy was associated with antibodies against either interferon beta-1a or PEG.

With regard to the tested dosing regimens, the CHMP considered that, generally, the two regimens showed comparable effect sizes at Year 1 with slightly better results for the q2W scheme. Comparative efficacy analyses for clinical and key MRI outcomes performed post-hoc supported the position that the q2W regimen could be advantageous as compared to the less frequent q4W dosing regimen. The difference between the two regimens increase with time of treatment, at least in terms of ARR and disability progression, but remained overall rather small. Taken together, from an efficacy point of view, the CHMP considered the proposed dose regimen of 125 µg every 2 weeks acceptable and preferable over the q4W dosing schedule.

Finally, the CHMP discussed the impact of the absence of an active comparator in the pivotal study, which raised the question if the efficacy of peginterferon beta-1a was comparable to that of other interferon beta products. To address this question, the applicant performed an across-study comparison of efficacy and safety data between peginterferon beta-1a and the non-pegylated beta-interferons as well as other MS products available in the EU at the time of this report. However, indirect comparison to historical data was considered problematic due to differences in the MS patient populations recruited in these studies, background therapy, endpoints (3 month- or 6 month sustained disability progression), duration of the studies (one or two years) and standards of care. Still, with all caveats of such a comparison, the CHMP agreed that the relative reduction of ARR and time to sustained disability progression observed for peginterferon beta-1a and the non-pegylated beta-interferons were in a comparable range, which provides some reassurance. Overall, as superiority of BIIB017 over placebo has been shown for the duration of one year, and was supported by 2 years of data on maintenance of effect, the lack of an active comparator was not considered an essential issue with respect to establishing efficacy of Plegridy.

However, since the magnitude of effect of beta interferons is modest, any potential difference in the effect size was considered by the CHMP to be critical with a view to switching patients from one interferon product to the other. Given the fact that peginterferon beta-1a is recommended to be given subcutaneously every 2 weeks, while non-pegylated interferon beta-1a has to be injected more frequently (e.g. Avonex IM injection once a week), switches

from non-pegylated interferons to peginterferon beta-1a, once available, may occur. While it was acknowledged by the CHMP that loss of efficacy could be difficult to detect in clinical practice, especially in a rather mild MS patient population as relapses usually occur infrequently and even in some cases with years in between consecutive relapses, comparative data would have been valuable for prescribers and patients. Since the active principle and mechanism of action of pegylated and non-pegylated interferons are the same, clinical data focussing on MRI endpoints to assess the relative anti-inflammatory effect may have been considered to indicate comparable efficacy. However, the CHMP pointed out that this was a specific case and that, generally, clinical endpoints in line with the CHMP MS guideline have to be investigated to establish patient benefit of a new active substance in the treatment of MS and that approval of disease-modifying therapies based only on MRI endpoints would not be acceptable.

Taken together, the CHMP was of the opinion that the SmPC should provide adequate information in sections 4.2 and 5.1 on the lack of comparative clinical data, which should be considered when switching patients between pegylated and non-pegylated interferons.

2.5.4. Conclusions on the clinical efficacy

The CHMP considered that the data provided demonstrated efficacy of Plegridy, at the proposed maintenance dose of 125 µg SC every 2 weeks, in patients with RRMS as compared to placebo for a one-year study period. Efficacy was shown in terms of effects on the ARR and on disability progression, with a modest effect size that seemed to be comparable to that of already approved interferon beta products. However, the effect on disability progression was not considered to have robustly been shown and therefore did not support a specific claim in the indication. The placebo-controlled study period of one year was considered to be sufficient in this particular case of a pegylated form of interferon beta-1a, a well-known class of MS products for which extensive clinical experience exists. Data for 2 years treatment supported maintenance of the effect beyond year 1.

Unfortunately, the relative efficacy of pegylated and non-pegylated interferon beta-1a has not been directly investigated, although this information would have been valuable for treating physicians and patients when switching between these treatments.

Altogether the CHMP considered the data from the clinical development programme satisfactory to support an indication of Plegridy for the treatment of adult patients with relapsing-remitting multiple sclerosis.

2.6. Clinical safety

The clinical safety development program focused on the results of the phase 3 study 301 and its extension 302, forming the integrated safety database of BIIB017. Doses administered during these studies were 125 µg SC in two dosing regimens, q4W or q2W (see section 2.5.2.1.1. for a detailed description of the study design and methodology).

Results of the phase 1 clinical studies were considered to be supportive and employed different doses and routes of administration (105HV101, 105HV102), safety of a prefilled pen (autoinjector in Study 105HV103), and safety of BIIB017 in a special population with varying degrees of renal impairment (105RI101) (see also section 2.4.).

Phase 3 studies 301 and 302 were pooled for the integrated analysis of safety. Phase 1 studies were not included because the design, objectives, and/or populations in these studies were significantly different from the Phase 3 studies.

At the time of submission, both study 301 and 302 were on-going. Data used for the safety analysis were therefore initially based on a cut-off date of 24 October. These were later complemented with additional data provided during the assessment of this application with a cut-off date of 27 March 2013, which translated into safety data up to a duration of 3.5 years.

The safety analysis population is based on subjects who received at least 1 dose of study treatment (ITT populations). Safety data after subjects switched to alternative MS medications were excluded from the overall safety analysis. Two study safety populations were defined:

- **Study 301 Safety Population** or **Placebo-Experience Population**, defined as all subjects who received at least 1 dose of study treatment with placebo or BIIB017 in study 301 Year 1.
- **Overall BIIB017 Safety Population,** defined as all subjects who received at least 1 dose of study treatment with BIIB017 in Study 301 or 302. This was the analysis population for the overall BIIB017 experience. Subjects were analysed in the treatment groups according to the treatment.

Patient exposure

As of the data cut-off date of 24 October 2012, a total of 608 subjects had completed both years of study 301, and 625 subjects were continuing year 2 of Study 301. At cut-off date, 508 subjects were receiving treatment in the extension study 302.

In Table 13, exposure as indicated by subject years, number of patients by duration of treatment, by study arm and compliance is presented.

Table 13 – Summary of Exposure in the Placebo-Experience and Overall Safety Populations

Placebo Experience Safety Population			
	Placebo	BBII017/4 weeks	BBII017/ 2 weeks
n-in safety population	**500**	**500**	**512**
Subjects years	442.4	429.2	430.5
Compliance (mean , sd)) *	99.6% (1.44%)	99.6% (2.16%)	99.4% (2.72%)
>= 4 weeks	498	493	504
>= 8 weeks	495	483	495
>= 16 weeks	487	471	478
>= 24 weeks	478	465	462
>= 32 weeks	474	456	452
>= 40 weeks	464	448	445
>= 48 weeks	457 (91%)	438 (88%)	435 (85%)

Placebo Experience Safety Population			
	Placebo	BBII017/4 weeks	BBII017/ 2 weeks
Overall BIIB017 safety population: Cumulative exposure (data cut-off 2012-10-24)			
		BBII017/4 weeks	BBII017/ 2 weeks
n-in safety population		**728**	**740**
Subjects years		960.5	971.9
Compliance (mean , sd)) *		99.5% (2.15%)	99.5% (2.53%)
>= 4 weeks		715	721
>= 8 weeks		693	698
>= 16 weeks		647	649
>= 32 weeks		589	598
>= 48 weeks		544	549
>= 64 weeks		361	376
>= 80 weeks		289	304
>= 96 weeks		209	206
>= 112 weeks		95	92
>= 128 weeks		59	58
>= 136 weeks		20	23
>= 144 weeks		17	13

Long-term safety data were collected in accordance with ICH E1 guidance (CPMP/ICH/375/95).

As of the data cut-off date, **1249 subjects** had been exposed to BIIB017 for **more than 6 months**, 1093 subjects for more than 1 year (≥48 weeks), and 415 subjects for more than 2 years (≥96 weeks). As of this date, a total of 1468 subjects received at least one dose of BIIB017.

Adverse events

In Table 14 an overview is given of the adverse events (AE) encountered in the Placebo Experience Safety Population by system organ class (SOC), including the most frequent AEs by preferred term (PT) in each SOC, highlighted in italics.

Table 14 – Overview of adverse events reported in the study 301 safety population

	Placebo	**BIIB017 q4W**	**BIIB017 q2W**
n	**500**	**500**	**512**

	Placebo	BIIB017 q4W	BIIB017 q2W
Overall			
No of subjects with an AE in %	83%	94%	94%
Any treatment related AE in %	53%	90%	90%
n-Deaths	2	1	1
Discontinuing study or treatment due to AE in %	1%	5%	5%
% with serious AE	15%	14%	11%
% with moderate or severe AE	57%	65%	66%
% with severe AE	11%	16%	18%
By SOC			
Infections and infestations	39%	37%	33%
Urinary tract infection	*4%*	*6%*	*5%*
Oral herpes	*1%*	*3%*	*2%*
Neoplasms benign, malignant and unspecified incl cysts and polyps	<1%	<1%	<1%
Blood and lymphatic system disorders	2%	5%	3%
Lymphadenopathy	*0%*	*2%*	*<1%*
Immune system disorders	1%	1%	1%
Endocrine disorders	1%	1%	<1%
Metabolism and nutrition disorders	2%	5%	3%
Psychiatric disorders	15%	12%	15%
Nervous system disorders	60%	58%	59%
Headache	*33%*	*41%*	*44%*
Somnolence	*1%*	*3%*	*2%*
Eye disorders	9%	8%	9%
Ear and labyrinth disorders	11%	7%	7%
Cardiac disorders	3%	4%	4%

	Placebo	BIIB017 q4W	BIIB017 q2W
Vascular disorders	6%	4%	5%
Respiratory, thoracic and mediastinal Disorders	15%	12%	13%
Gastrointestinal disorders	20%	24%	24%
Nausea	*6%*	*8%*	*9%*
Vomiting	*2%*	*7%*	*5%*
Hepatobiliary disorders	<1%	1%	<1%
Skin and subcutaneous tissue disorders	9%	12%	15%
Pruritus	*1%*	*2%*	*4%*
Musculoskeletal and connective tissue Disorders	33%	42%	40%
Myalgia	*6%*	*19%*	*19%*
Arthralgia	*7%*	*11%*	*11%*
Backpain	*11%*	*13%*	*12%*
Renal and urinary disorders	5%	7%	4%
Pregnancy, puerperium and perinatal Conditions	0%	<1%	<1%
Reproductive system and breast disorders	7%	7%	6%
General disorders and administration Site conditions	45%	89%	88%
Injection site erythema	*7%*	*56%*	*62%*
Influenza like illness	*13%*	*47%*	*47%*
Pyrexia	*15%*	*44%*	*45%*
Chills	*5%*	*18%*	*17%*
Injection site pain	*3%*	*13%*	*15%*
Asthenia	*8%*	*14%*	*13%*
Injection site pruritus	*1%*	*11%*	*13%*
Pain	*3%*	*6%*	*5%*
Hyperthermia	*1%*	*5%*	*4%*

	Placebo	BIIB017 q4W	BIIB017 q2W
Injection site warmth	*0%*	*2%*	*3%*
Injection site haematoma	*1%*	*2%*	*3%*
Injection site oedema	*0%*	*4%*	*3%*
Injection site rash	*0%*	*<1%*	*2%*
Malaise	*1%*	*3%*	*1%*
Investigations	15%	18%	21%
Body temperature increased	*3%*	*7%*	*6%*
ALA increased	*3%*	*4%*	*6%*
ASA increased	*2%*	*3%*	*4%*
GGT increased	*1%*	*3%*	*3%*
Injury, poisoning and procedural Complications	7%	4%	4%
Surgical and medical procedures	1%	1%	1%
Social circumstances	0%	0%	<1%

For the placebo-controlled BIIB017 experience, the overall incidence of AEs was higher in the BIIB017 treatment groups compared to placebo (83% placebo versus 94% and 94% in the BIIB017 q4W and q2W, respectively).

Differences in the AE profile between the placebo and BIIB017 treatment groups were primarily driven by events in the SOC of general disorders and administration-site conditions (45% for placebo versus 89% and 88% for BIIB017 q4W and q2W, respectively), musculoskeletal and connective tissue disorders (33% for placebo versus 42% and 40% for BIIB017 q4W and q2W, respectively), investigations (15% for placebo versus 18% and 21% for BIIB017 q4W and q2W, respectively), and skin and subcutaneous tissue disorders (9% for placebo versus 12% and 15% for BIIB017 q4W and q2W, respectively).

The most commonly reported AEs by PT with an incidence ≥10% in any treatment group included injection-site erythema, influenza-like illness, pyrexia, headache, MS relapse, myalgia, chills, injection-site pain, asthenia, back pain, injection-site pruritus, nasopharyngitis, arthralgia, fatigue, and pain in extremity.

With the exception of relapse, nasopharyngitis, fatigue, and pain in extremity, all other commonly reported AEs were reported at a higher incidence in the BIIB017 treatment groups compared to placebo.

The most common ADRs (incidence ≥10% in the BIIB017 group) in the BIIB017 q4W group were similar to the BIIB017 q2W.

The overall incidence of treatment-related AEs was higher with BIIB017 treatment compared to placebo and similar between the BIIB017 treatment groups (53% placebo versus 90% in each of the two BIIB017 treatment groups).

The overall incidence of severe AEs was higher in the BIIB017 treatment groups compared with placebo (11% placebo versus 16% BIIB017 q4W and 18% BIIB017 q2W). The incidence of the following severe events was higher in the BIIB017 treatment groups compared with placebo: headache (2% placebo versus 4% and 5% in the BIIB017 q4W and q2W groups, respectively), myalgia (<1% placebo versus 1% and 2% in the BIIB017 q4W and q2W groups, respectively), influenza-like illness (<1% placebo versus 4% and 5% in the BIIB017 q4W and q2W groups, respectively), pyrexia (0% placebo versus 3% in each of the BIIB017 treatment groups), and injection-site erythema (0% placebo versus 2% in each of the BIIB017 treatment groups).

Discontinuation from treatment due to an adverse event was overall low but higher in the BIIB017 groups (5% each) compared to placebo (1%). Withdrawal from study due to an adverse event was higher in the BIIB017 groups (4% and 5% for BIIB017 q4W and q2W) compared to placebo (1%).

The incidence of AEs was analysed in 12-week time intervals. When examined at both the SOC and PT level, the incidence of AEs for the placebo-controlled BIIB017 experience remained stable or decreased at each time interval in both the placebo and the BIIB017 treatment groups. There were no increases over time in the incidence of any AE by PT or SOC in any treatment group.

Adverse events reported from the overall BIIB017 experience were similar to those reported from the placebo-controlled experience (study 301, Year 1), giving an overall consistent picture of controlled and controlled/uncontrolled studies.

Adverse events of special interest

AEs identified of special interest for beta-interferons include

- flu-like symptoms (FLS),
- injection site reactions,
- cardiovascular disorders,
- hepatic disorders,
- autoimmune disorders,
- seizures,
- depression and suicide ideation,
- hypersensitivity reactions,
- haematological laboratory abnormalities, and
- abnormal liver function tests.

AEs identified of special interest for immunomodulation are

- infections and
- malignancies.

Furthermore, development of anti-interferon beta or anti-PEG antibodies was also an event of special interest as it may affect both efficacy (lack of efficacy) and safety.

- Flu-like symptoms (FLS)

FLS were defined and described using 2 definitions. The narrow definition of FLS was based on the single PT of influenza-like illness whereas the broad definition included the PTs chills, hyperpyrexia, influenza-like illness, musculoskeletal pain, myalgia, pain, and pyrexia.

Incidence of flu-like symptoms is presented in Table 15.

Table 15 – Incidence of flu-like symptoms in the BIIB017 safety populations

Study 301 Safety Population			
	Placebo	BIB017 /4 weeks	BIB017 /2 weeks
N	**500**	**500**	**512**
FLS narrow definition			
Incidence –overall	13%	47%	47%
Incidence week 0-12 /4 weeks (range)	5%-7%	19%-30%	25%-29%
Incidence week 12-48 by 4 weeks interval (median, range)	3% 2%-3%	22% 19%-24%	24% 23%-26%
Incidence severe FL-illness	<1%	4%	5%
Serious FL-illness	-	-	-
Event rate per subject year	0.8	3.7	5.7
Percentage days FL symptoms by 12 week intervals (median, range)	2.08% 0.3%-66.7%	4.76% 0.3%-99.7%	6.25% 0.3% - 100%
FLS broad definition			
Incidence –overall	33%	77%	78%
Incidence first 12 weeks	20%-11%	59%-39%	57% - 48%
Incidence week 12-48 (median, range)	6% 5% - 9%	39% 35%-42%	42% 39%-45%
Incidence severe FL-illness	1%	8%	9%
Serious FL-illness	-	-	-
Event rate per subject year	1.9	8.5	11.8
Discontinuations treatment	0%	2%	2%
Discontinuations study	0%	1%	1%
Percentage days FL symptoms by 12 week intervals (median, range)	2.68% 0.3%-100%	5.06% 0.3%-99.7%	7.14% 0.3% - 100%
Overall BIIB experience			
		BIB017 /4 weeks	BIB017 /2 weeks

n		**728**	**740**
FLS narrow definition			
Incidence		50%	51%
Incidence severe FL-illness		4%	5%
Serious FL-illness		-	-
Event rate per subject year		3.4	5.4
FLS broad definition			
Incidence		76%	78%
Incidence severe FL-illness		Not retrievable	Not retrievable
Serious FL-illness		0%	<1%
Event rate per subject year		7.1	10.1
Discontinuations treatment		2%	2%
Discontinuations study		2%	1%

For the placebo-controlled BIIB017 experience, FLS occurred most frequently over the first 12 weeks of treatment and decreased slightly thereafter within both BIIB017 dose frequency groups. Analysis of FLS over time for the overall BIIB017 experience showed the same pattern for FLS seen for the placebo-controlled BIIB017 experience.

The mean percentage of days with FLS using the narrow definition (excluding subjects without FLS in the analysis) from 0 to 48 weeks was 5.2% in the placebo group versus 6.9% and 9.6% days in the BIIB017 q4W and q2W groups, respectively. When including all subjects in the analysis the mean percentage of days with FLS was lower, but the outcome was similar with a higher mean percentage of days with FLS in subjects receiving BIIB017 (3.2% and 4.5% days in the BIIB017 q4W and q2W groups, respectively) compared with placebo (0.7%) The same outcome was observed when using the broad FLS definition.

The incidence of FLS that occurred within 2 days of the most recent injection was higher in the BIIB017 treatment groups compared with the placebo group (78% placebo versus 95% and 96% in the BIIB017 q4W and q2W groups, respectively). The duration of FLS that occurred within 2 days of the most recent injection was similar between the BIIB017 and placebo treatment groups (2.6 to 3.0 days).

In the overall BIIB017 experience, the percentage of days with FLS by 12-week intervals was similar to the placebo-controlled BIIB017 experience and similar between BIIB017 dose frequency groups. The same outcome was observed when using the broad FLS definition.

The time course of FLS events indicated a peak during the first 12 weeks of treatment followed by a slightly lower plateau phase in the subsequent weeks up to Week 48. However, the overall BIIB017 experience revealed higher incidences in the subsequent months of treatment up to three years of treatment, especially with BIIB017 q2W. The updated analysis with a data cut-off of 27th March 2013 showed no increase in FLS towards the end of the study period in contrast to the original analysis.

Discontinuations from treatment and withdrawals from study due to flu-like illness AEs were overall low and similar across treatment groups (<2%).

- Injection-site reactions

Injection-site reactions were commonly reported by subjects receiving BIIB017 treatment and occurred at a higher incidence compared with the placebo group. The incidence of injection-site reactions tended to be dose-frequency related in both the placebo-controlled BIIB017 experience and in the overall BIIB017 experience.

Injection-site erythema, injection-site pain, and injection-site pruritus were the most commonly reported adverse events in relation to injection-site reactions.

The incidence of reported injection-site reactions and percentage days did not change significantly over time when examined by 12-week intervals.

The majority of the injection-site reactions were mild or moderate in severity. There was one serious case (BIIB017 q2W), including erythema, oedema, pain, and pruritus, which was treated with IM dexamethasone and oral cetirizine and resulting in discontinuation and withdrawal. This was described as a local hypersensitivity reaction with no systemic hypersensitivity symptoms involved others than the skin reactions described. One further SAE was reported in the overall BIIB017 experience (gangraneous cellulitis, resulting in necrosis).

In general, injection-site reactions only led to study drug discontinuations and withdrawals from studies in few cases only.

Injection Site Reactions in Relation to Antibody Status

Because of the low incidence of neutralising antibodies (NAbs: 12 out of 676), binding antibodies (BAbs: 63/625) and anti-PEG antibodies (87/601) in the placebo-controlled BIIB017 population, no meaningful conclusion could be drawn regarding the presence of NAbs, BAbs or anti-PEG antibodies and occurrence of injection-site reactions. In the overall BIIB017 population, the incidence of injection-site reactions by antibody status (ever positive versus never positive; any post-baseline positive versus rest) was similar in the overall BIIB017 experience. There was no increase in the incidence of injection-site reactions in subjects who were anti–interferon beta-1a BAb-, NAb-, or anti-PEG antibody-positive at any point in time.

- Infections

There was no evidence for an increased risk of infections, serious infections or opportunistic infections in subjects treated with BIIB017. Severe infections concerned in the BIIB q4W group 15 subjects. Most frequent were urinary tract infections (n=6), influenza (n=2) and sepsis (n=2). In the BIIB q2W group 13 subjects had severe infections. Most frequent were urinary tract infections (n=4), urosepsis (n=2), sepsis (n=2) and pneumonia.

A total of 12 and 11 subjects treated with BIIB017 q4W and q2W, respectively, had serious infections.

Opportunistic infections were reported in 2 subjects in the placebo group [cryoptosporidial gatrosenteritis (NZ), dissiminated tuberculosis (India)] and in 1 subject receiving BII017 q2W [positive cytomegalovirus immunoglobiline G test without associated symptoms (UKR)].

- Cardiovascular disorders

There was no evidence of an increased risk of cardiovascular disorders or serious cardiovascular disorders in patients treated with BIIB017. Most of the reported cardiovascular disorder AEs were assessed as mild or moderate.

In the placebo-controlled safety population, serious cardiovascular disorders were reported by 3 subjects (paraparesis, monoparesis, paresis) in the BIIB017 q4W group, 3 subjects (paraparesis, cerebral ischemia, cerebrovascular insufficiency) in the BIIB017 q2W group and 2 subjects (subarachnoid haemorrhage, chest pain) in the placebo group. All events except for 1 were considered not related to study treatment by the Investigator.

In the overall BIIB017 population, serious cardiovascular disorders were reported by 9 and 4 subjects In the BIIB017 q4W and q2W respectively. These concern: paraparesis, paresis (n=2), lacunar infarction, monoparesis, syncope, myocardial infarction (n=2) cardiac failure) in the BIIB017 q4W group and paraparesis, cerebral ischemia, cerebrovascular insufficiency, cardiopulmonary failure in the BIIB017 q2W group.

- Autoimmune disorders

In the placebo-controlled population, 3 cases were reported: 1 rheumatoid arthritis and 2 autoimmune thyroiditis. In the BII017 2qW group there was one report of autoimmune thyroiditis. There were no autoimmune disorder events that were assessed as severe or serious.

In the overall BIIB017 safety population, 2 subjects in each BIIB017 group reported an autoimmune disorder AE. None was reported as severe. One event in the BIIB017 q4W group concerned a serious autoimmune disorder i.e. Basedow's Disease. This event was not considered related to study treatment, because this patient had hyperthyroidism prior to the onset of BIIB017 treatment and the diagnosis of Basedow's disease was made shortly after the initiation of BII017 treatment in year 2.

There were no autoimmune disorders that led to study treatment discontinuation or withdrawal from study.

- Hepatic disorders

Hepatic injury, ranging from asymptomatic elevated serum hepatic enzyme levels, hepatitis, and autoimmune hepatitis to severe hepatic failure, has been associated with the use of IFN-β. There was a dose-dependent increase in alanine transaminase (ALT) and aspartate aminotransferase (AST) levels from baseline in BIIB017-treated subjects, but the majority of these elevations were less than 3 times the upper limits of normal (ULN).

In the placebo-controlled BIIB017 population, the incidence of elevated ALT and AST ≥3 × ULN was slightly higher in BIIB017-treated subjects compared with subjects receiving placebo. However, elevations of ALT and AST >5 × ULN were balanced between BIIB017 and placebo treated subjects.

One severe AE was reported each in the BIIB017 q4W and q2W groups.

In clinical trials with BIIB017, there were a total of 3 cases of concurrent elevations of transaminases ⩾3 × ULN and total bilirubin >2 × ULN. All 3 cases were on the BIIB017 Q4W

dose frequency group. One of these cases (Acute hepatic failure) was reported during the Year 1 of Study 301 (placebo controlled experience) and was assessed as not related to BIIB017 treatment (and related to corticosteroid treatment) and the 2 other cases (one reported during the Year 2 of Study 301 and the other reported from the Study 302) were assessed as related to BIIB017 treatment.

Severe AEs were reported in 3 subjects.

Serious hepatic disorders were reported in 1 subject in the BIIB017 q4W group (see above) and 1 subject (drug-induce liver injury) in the BIIB017 q2W group.

- Hypersensitivity Events

The majority of hypersensitivity events were non-serious and mild to moderate in severity.

In the placebo-controlled BIIB017 population, the overall incidence of hypersensitivity events was 14% (n=71), 13% (n=67) and 16% (n=82) for placebo, BIIB017 q4W and BIIB017 q2W, respectively. Three serious hypersensitivity events were reported all in the BIIB017 groups. None of these events were related to BIIB017 treatment, and none were associated with the presence of antibodies to the interferon or PEG components of BIIB017.

In the overall BIIB017 population, the incidence of hypersensitivity events was 14% (n=105) and 17% (n=125) for BIIB017 q4W and BIIB017 q2W, respectively.

The most frequent events concerned (BIIB017 q4W / BIIB017 q2W): skin and subcutaneous tissue disorders (47/68), cough (40/31), pruritus (19/23), erythema (7/15), urticaria (7/12), oedema peripheral (14/5), dyspnoea (7 /9), dermatitis allergic (6/4), pruritus generalised (3 /6), eye disorders (3/6), drug hypersensitivity (2/4), hypotension (2/4), face oedema (0/4), flushing (1/3), sneezing (3 /1).

The rates of hypersensitivity events in subjects who were anti–interferon beta-1a BAb-, NAb-, or anti- PEG antibody-positive at any time during the study were either similar to rates observed in antibody-negative subjects or too low to draw a conclusion.

- Malignancies

Malignancies were identified in four subjects (breast cancer, cervix carcinoma, Squamous cell carcinoma lip/oral cavity, Basal cell carcinoma) treated with BIIB017. In one case the malignancy (Squamous cell carcinoma lip/oral cavity under BIIB017 q4W treatment) was assesses as related to treatment.

- Seizure

There was a similar incidence of seizures occurring across all treatment groups in the placebo-controlled BIIB017 experience. The majority of seizure events reported occurred in subjects with medical histories of seizure disorders. One SAE was considered related to BIIB017 treatment due to its onset shortly after injection of BIIB017.

- Depression and suicide

In the placebo-controlled experience there was no excess of AEs related to depression and suicidal ideation of BIIB017 over placebo (8% placebo vs. 9% BIIB017 q4W and 8% BIIB017 q2W). Suicidal ideation was reported in single subjects only across treatment groups (<1%).

Serious depression and suicide-related AEs were reported in one single subject per treatment group.

Regarding the overall BIIB017 experience, the incidence of depression or suicide AEs was 10% and 9% in the BIIB017 q4W and q2W groups, respectively, with suicidal ideation only occurring in single subjects (<1% in each treatment group). The only two SAE of depression and suicidal ideation were already included in the placebo-controlled experience.

There were no cases of completed suicide.

The Beck Depression Inventory II (BDI-II) scores were similar across treatment groups in Year 1 and in Year 2. The incidence of depression, suicidal tendency, and suicide attempt according to BDI-II (score >18) were similar across treatment groups and remained stable over time.

- Immunological events

Table 16 provides an overview of the incidence of antibody formation observed in studies 301 and 302.

Table 16 – Incidence of antibody formation in the BIIB017 safety populations

Study 301 Safety Population			
	Placebo	BIB017 /4 weeks	BIB017 /2 weeks
N	**500**	**500**	**512**
Binding antibodies	12/482	20/485	38/480
Persistent Binding antibodies	1/12	4/20	18/38
Neutralizing antibodies	2/490	2/491	4/488
Anti-PEG antibodies	24/454	43/465	31/471
Persistent anti-PEG antibodies	6/24	25/42	10/31
Overall BIIB experience			
		BIB017 /4 weeks	BIB017 /2 weeks
N		**728**	**740**
Binding antibodies		37/706	58/706
Persistent binding antibodies		18/37	34/58
Neutralizing antibodies		6/716	7/715
Persistent neutralizing antibodies		1/6	5/7
Anti-PEG antibodies		55/682	42/681
Persistent pos anti-PEG antibodies		35/55	19/681

Overall, over the period of >96 weeks, there was a low rate of immunogenicity detected for BIIB017, which was similar across the BIIB017 dose frequency groups. The overall incidence of NAbs to interferon beta-1a was low (<1%) in the BIIB017 treatment groups. The overall incidence of anti-PEG antibodies was similar between BIIB017 dose frequency groups, but about half of these subjects had persistent anti-PEG antibodies.

Serious adverse event / deaths / other significant events

Deaths

Eight deaths have been reported in Year 1 and Year 2 of study 301. No deaths have been reported in study 302 as of the data cut-off date.

In Year 1 of study 301, 4 deaths were reported. None of the deaths were considered related to study treatment by the investigator. Cause of death was unknown (n=2, one in placebo and one in the BIIB017 q2W arm), subarachnoid haemorrhage (n=1, placebo) and septicemic shock (n=1, BIIB017 q4W).

In year 2 of study 301, 4 additional deaths were reported. Causes of death concerned lip/oral cavity squamous cell carcinoma rated as related to treatment (BIIB q4W), cranio-cerebral injury due to motor vehicle accident rated as not related to treatment (BIIB q2W), sepsis due to cardiorespiratory failure rated as related to study treatment (BIIB q2W) and an unknown cause of death (BIIB q2W, lost in follow-up).

Other serious adverse events (SAE)

- Study 301 Safety Population (Placebo-Experience Population)

For the placebo-controlled BIIB017 experience, the percentage of subjects reporting an SAE was similar across treatment groups (15% placebo versus 14% and 11% in the BIIB017 q4W and q2W groups, respectively). MS relapse was the most frequent SAE reported in Year 1 across treatment groups. Other SAEs occurring in ≥2 subjects included pneumonia and urinary tract infection. All other SAEs were reported by at most 1 subject in each treatment group with an incidence of ≤1%.

The distribution of SAEs considered related to study treatment by the investigator was 2 subjects (<1%) in the placebo group (both with MS relapse); 6 subjects (1%) in the BIIB017 q4W group (2 subjects with MS relapse, 1 subject with pneumonia, 1 subject with febrile neutropenia, 1 subject with overdose and 1 subject with deep vein thrombosis); and 4 subjects (<1%) in the BIIB017 q2W group (1 subject with transaminase levels increased, 1 subject with partial seizures, 1 subject with injection-site reactions and 1 subject with paraparesis).

- Overall Safety Population (Placebo-Experience Population)

For the overall BIIB017 experience, the overall incidence of SAEs was lower in the BIIB017 q2W group (16%) compared with BIIB017 q4W (21%). MS relapse was the most frequent SAE reported in the overall BIIB017 experience. Other SAEs occurring in ≥3 subjects included urinary tract infection, pneumonia, sepsis and fall.

The incidence of SAEs considered related to study treatment between the 2 BIIB017 dose frequency groups was: 16 subjects (2%) in the BIIB017 every 4 weeks group and 13 subjects (2%) in the BIIB017 every 2 weeks group.

Laboratory findings

- White blood cell (WBC) Parameters

There were small BIIB017 dose-related decreases from baseline and shifts to low counts observed in WBC, lymphocytes, and absolute neutrophil counts in BIIB017-treated subjects compared with placebo.

Mean values remained within normal limits at all evaluations across all treatment groups.

Monocytes, eosinophils, and basophils did not change markedly from baseline in BIIB017-treated subjects compared with placebo-treated subjects.

- Red blood cells (RBC)

RBC (RBC counts, haemoglobin, and haematocrit) and platelets were found to be moderately decreased in BIIB017-treated subjects compared to placebo.

Data on the overall BIIB017 experience at Year 3 (week 144) revealed no further decrease in mean RBC counts and mean haemoglobin levels relative to Year 2. Clinically significant values for RBC counts, haemoglobin, and platelets were not different across groups in general. However, one SAE was reported with significant haemoglobin decrease resulting in hospitalisation of a woman, who already had a relevant medical history and therefore the SAE was not rated related to treatment. Another SAE was reported as severe thrombocytopenia and was considered to be related to BIIB017 treatment. In addition, one subject discontinued due to thrombocytopenia.

- Blood Chemistry Results

Liver Function Tests

There was a dose-related increase in the incidence of elevated liver transaminase levels in BIIB017 treated subjects. This increase was primarily due to differences that occurred in the first 3 months of BIIB017 treatment. For the majority of subjects treated with BIIB017 who experienced elevated transaminase levels, the maximum post/baseline values for ALT and AST were <3 times ULN and were not associated with any corresponding increase in total bilirubin. ALT or AST values ≥3 x ULN and total bilirubin >2 x ULN, which defines Hy's law, was reported in one subject from the BIIB017 q2W group (acute hepatic failure due to corticosteroids) during the placebo-controlled experience and in two subject from the overall experience.

Three SAEs included drug-induced liver injury, transaminitis, and AST/ALT increased.

Kidney Function

Mean values and change from baseline for blood urea nitrogen (BUN) and creatinine were similar across treatment groups and showed no meaningful changes over time; mean values were within the normal range in both groups at all time points during the study. Kidney function parameters were similar in the overall BIIB017 experience population compared to those reported in the placebo-controlled BIIB017 experience and were similar between BIIB017 treatment groups.

Other Blood Chemistry

Mean values for bicarbonate, sodium, potassium, chloride, glucose, and thyroid-stimulating hormone (TSH) were similar across the placebo and BIIB017 treatment groups at all time points, did not change significantly from baseline, and remained within normal range at all times through Week 48. Results in the overall BIIB017 experience safety population were comparable to the placebo-controlled BIIB017 experience.

Urinalysis

In the placebo-controlled BIIB017 experience, the proportion of subjects with shift from baseline to low or high/positive values in the urinalysis was similar between the placebo and BIIB017 treatment groups. Shifts to high across treatment groups were more commonly reported in descending order in urine protein, blood, RBC, WBC, and ketones. No subjects in any treatment group had shifts to high (or low) values for urine bilirubin. Similar results were observed in the overall BIIB017 experience and results were similar between the BIIB017 dose frequency groups.

Vital signs, physical findings

In the placebo-controlled BIIB017 experience, the mean baseline values for vital signs (body temperature, pulse, and systolic and diastolic blood pressure), weight were similar across the treatment groups. There were no significant changes from baseline values over time for any vital sign across treatment groups.

No clinically significant changes were observed between placebo and the BIIB017 treatment groups for QTc interval or any other parameter.

Body weight changes

Safety data for the overall BIIB017 experience at the cut-off date of 27th March 2013 comprised 196 weeks of exposure and revealed no significant change of body weight for the active treatment groups.

Safety in special populations

The overall incidence of AEs by demographic characteristics was consistent with the incidence of AEs in the overall safety population, and there were no clinically relevant differences in the incidence of AEs between BIIB017 treatment groups with respect to age (subjects <40 years and subjects ≥40 years), sex (female and male), race (white, Asian, black, and other), body weight, BMI, and antibody status (NAbs, BAbs, and anti-PEG antibodies).

Some minor and clinically non-relevant differences in the incidence of AEs were observed by region (North American and Western European countries versus Eastern European countries versus rest of the world) in the placebo-controlled BIIB017 experience whereas the incidence of AEs in the overall BIIB017 experience was similar between BIIB017 dose frequency groups within a region.

Due to the low number of subjects in studies 301 and 302 who used prior MS therapies, an analysis of the incidence of AEs by prior MS therapy was inconclusive.

Twelve pregnancies in BIIB017-treated women were identified in the clinical program. There were no safety signals concerning fetal abnormalities. However, spontaneous abortion was reported in one patient from the placebo group versus two patients from the BIIB017 group. Three pregnancies were still on-going at the time of database closure.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been conducted with BIIB017.

As corticosteroids are commonly used in MS subjects for the treatment of relapses, and since complications arising from high-dose corticosteroids can occur, an analysis of the incidence of AEs in subjects who had IV corticosteroid treatment for an MS relapse compared with subjects

who did not have IV corticosteroid treatment during the studies has been performed. With the exception of events of MS relapse, no considerable differences in the incidence of AEs for subjects who received IV corticosteroid treatment versus subjects who did not receive IV corticosteroid treatment were observed.

Discontinuation due to adverse events

Discontinuation from study due to AEs

In the placebo-controlled BIIB017 experience the overall incidence of AEs that led to discontinuation of study treatment was higher in the BIIB017 treatment groups (24 subjects [5%] in the BIIB027 q4W group, and 25 subjects [5%] in the BIIB017 q2W group) compared with the placebo group (7 subjects [1%]). The data from the overall experience were similar to the placebo-controlled experience for the BIIB017 groups.

The most common AEs that led to study treatment discontinuation in BIIB017-treated subjects were influenza-like illness, injection-site erythema, and pyrexia; and the incidence of each of these was ≤2% in each BIIB017 treatment group.

Withdrawal from study due to AEs

In the placebo-controlled BIIB017 experience the overall incidence of AEs that led to withdrawal from the study was higher in the BIIB017 treatment groups (22 subjects [4%] and 25 subjects [5%] in the BIIB017 every 4 and every 2 weeks groups, respectively) compared with the placebo group (6 subjects [1%]).

The data from the overall experience were similar to the placebo-controlled experience for the BIIB017 groups. In general, the pattern of AEs leading to withdrawal from the study was similar to that observed for AEs leading to discontinuation of study treatment. Influenza-like illness leading to study withdrawal was reported by 1% of subjects in the BIIB017 treatment groups as the most common AE leading to study withdrawal.

Dose interruptions

In the placebo-controlled BIIB017 experience, the incidence of AEs that led to dose interruption was similar between treatment groups. The results for the overall BIIB017 experience were comparable to the placebo-controlled BIIB017 experience.

Withdrawal and rebound

In the placebo-controlled BIIB017 experience the number of subjects in the placebo-controlled BIIB017 population who discontinued study treatment but remained in the study for follow-up and had an AE was low (5 [11%] subjects in the placebo group, 7 [11%] subjects in the BIIB017 every 4 weeks group, and 9 [12%] subjects in the BIIB017 every 2 weeks group).

For the overall BIIB017 experience, the number of subjects who discontinued study treatment and remained in the study for follow-up evaluations was similar between the BIIB017 dose frequency groups: 16.9% and 18.1% in the BIIB017 q2W and q4W groups.

The number of subjects who discontinued study treatment and reported an AE after study treatment discontinuation was low.

Post marketing experience

Postmarketing experience was not available for BIIB017, but for other interferon-beta 1a therapies like Avonex (IM) and Rebif (SC). A comparison of the safety profiles of BIIB017, Avonex, and Rebif, mainly based on placebo-controlled experience, revealed high similarities in the adverse events of special interest. BIIB017 tended to be favourable regarding hypersensitivity reactions, depression and suicidal ideation, infections, cardiovascular disorders and the formation of NAbs. Incidences of all other AEs of special interest including FLS, hepatic disorders, seizures, autoimmune disorders, and malignancies were similar.

Regarding injection-site reactions, there was a significantly higher event rate following BIIB017-treatment compared to IM Avonex (60%-66% vs. 3%). This higher incidence is well in line with Rebif (89%-92%), which is also administered SC.

2.6.1. Discussion on clinical safety

The safety database presented with this application was considered by the CHMP to be acceptable both in term of numbers of patients as well as considering the duration of use. The CHMP noted that, at the time of this report, study 302 was on-going and hence, long-term data were still being generated.

The definition of two safety populations, i.e. placebo-experience population and overall BIIB017 safety population, was suitable to enable overall safety assessment as well as comparison of active test drug versus placebo. Since the placebo-experience population is included in the overall population, it was not unexpected that the safety of BIIB017 in these two populations was similar.

No formal drug-drug interaction studies have been conducted with BIIB017.

Compared to placebo the overall incidence of any adverse events as well as for any treatment-related AEs was higher in both active arms. Most common adverse events concerned injection-site events and influenza-like illness and symptoms e.g. headache, myalgia, chills, asthenia, arthralgia, fatigue, and pain in extremities.

Apart from local site reactions and flu-like syndrome, no specific pattern of serious adverse events, that could be associated with active treatment, emerged. Eight cases of death occurred. Overall there was no specific pattern regarding the nature of these cases of death.

Adverse events of special interest, based on previous experience with beta-interferons were flu-like symptoms (FLS), injection site reactions (ISRs), hepatic disorders, autoimmune disorders, seizures, depression and suicide ideation, hypersensitivity reactions, haematological laboratory abnormalities and abnormal liver function tests. AEs identified of special interest due to the immunomodulatory mechanism of action were infections and malignancies.

Flu-like symptoms are a common adverse reaction to beta interferons. They typically occur at the beginning of treatment and are mild and moderate in severity. In the safety population, FLS was recognised as one of the major reason for treatment failure. However, the low incidence of severe flu-like illness, low percentage days of flu-like symptoms and low rate of discontinuation due to flu-like syndrome indicated that for BIIB017 this was not a large issue. Flu-like symptoms were referred to as important identified risk in the risk management plan (RMP, see

section 2.8.). The CHMP agreed that dose titration at treatment initiation may help to ameliorate flu-like symptoms. As already recommended with other interferon-beta therapies, concomitant administration of anti-inflammatory, analgesic and/or antipyretic treatments may help to ameliorate these symptoms. This was considered to be adequately reflected in section 4.2 of the SmPC.

Injection-site reactions are also common with interferon-beta treatment. There was a slight but consistent disadvantage in adverse events related to injection site for the BIIB017 q2W dose versus the BIIB017 q4W dose, which is likely explained by the larger dose interval. Serious injection-site reactions were mentioned as an important identified risk in the RMP. Regarding the warning in section 4.4 of the SmPC (and respective section in the PIL), following a recommendation by CHMP, a more precise instruction on the injection technique and alertness on the occurrence of symptoms of injection-site reactions has been included.

BIIB017 treatment carries the risk for the development of (serious) hypersensitivity reactions, which is already known for other interferon-beta treatments. Therefore, the CHMP agreed that use of Plegridy should be contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta or peginterferon. Additional appropriate warnings and instructions were included in the SmPC. Furthermore, serious hypersensitivity reactions were included as important identified risk outlined in the RMP.

Preclinical data for non-pegylated interferons have indicated hepatic toxicity in animals and furthermore, clinical studies with Plegridy/BIIB017 confirmed hepatic damage, e.g. by increases in liver enzymes and rare cases of hepatic injury. BIIB017-related liver enzyme abnormalities were found to be generally in line with data for Avonex and Rebif, with incidences ranging somewhere in between the two non-pegylated products. Since rare serious adverse events of hepatic injury with BIIB017 have been reported to be related to elevated ALT/AST and bilirubin (Hy's Law), routine monitoring of liver parameters (and laboratory parameters in general) should be performed at pre-specified time points as known from other interferon-beta MS therapies (section 4.4 of the SmPC). Furthermore, hepatic injury was included in the RMP as potential important risk.

For injection-site reactions, hepatic disorders, elevated liver function tests, and hypersensitivity reactions there was a slight advantage of the BIIB017 q4W dose versus the q2W dose. Although the differences in frequencies for the two dose regimens were small, taken together, this resulted in a less favourable safety profile of the q2W regimen compared to the q4W dosing schedule.

Based on the safety database presented with this application it appeared that BIIB017 was not associated with an increased risk of infections, opportunist infections, autoimmune disorders, seizures or depression/suicidal ideation. Depression and suicidal behaviour were however considered a potential important risk within the RMP and the CHMP agreed that Plegridy was contraindicated in patients with current severe depression and/or suicidal ideation, as depression is known to occur with increased frequency in MS patients and in association with interferon use.

No conclusion could be drawn based on the low incidence and pattern of malignancies.

The changes in haematology and chemical variables other than liver function parameters described above were considered by the CHMP to be consistent with what is known for non-pegylated beta interferons. Specification of routine blood monitoring in accordance with other interferon-beta therapies has been implemented in the SmPC and decrease in peripheral blood cell count was reflected in the RMP (important identified risk).

Anti–PEG antibodies were found to be higher for subjects in the BIIB017 groups compared to placebo. Many of these patients showed persistent anti-PEG antigenicity and the impact for the therapy with Plegridy was not clear. Additional analyses provided by the applicant showed that the emerging of anti-PEG antibodies during BIIB017 treatment did not lead to altered PK/PD, efficacy and safety profiles. However, the findings were only representative for a 2-year period. Immunogenicity was an important potential risk in the RMP and the CHMP considered that long-term data from the extension study 302 would help to better characterise this safety concern.

Overall, the occurrence of antibodies, especially neutralising anti-bodies to interferon beta-1a was low. Therefore and since the duration of treatment was considered to be too short, the CHMP was unable to draw firm conclusions on the immunogenicity of Plegridy and the impact of antibody formation on safety. However, overall, the CHMP considered that the immunogenic potential of BIIB017 was low.

No direct comparison of safety between BIIB017 and other beta-interferons could be made due to a lack of active controlled studies. Based on a review of data from the BIIB017 placebo-controlled pivotal study and available data from controlled clinical studies for other approved interferon beta-1a products (Avonex and Rebif) the CHMP agreed that the safety profile of BIIB017 was generally consistent with that of approved non-pegylated beta-interferon therapies and relevant parts of the product information were aligned.

Available data from other interferon-containing products were indicative for a slightly higher risk of spontaneous abortion

Overall, from the safety database all relevant adverse reactions reported in clinical trials have been included in the SmPC. Furthermore, the product information was brought in line with wording previously agreed further to two recent signals at the time of this report for beta interferons concerning nephrotic syndrome with different underlying nephropathies including collapsing focal segmental glomerulosclerosis and thrombotic microangiopathy.

2.6.2. Conclusions on the clinical safety

Overall the clinical safety data set was considered acceptable.

Based on the review of the available safety data, the CHMP concluded that the safety profile of Plegridy was comparable to already approved interferon beta products and overall acceptable. Numerically, more hepatic events, elevated liver function tests and hypersensitivity reactions were observed in the q2W dose regimen as compared to the q4W regimen, resulting in a slightly less favourable safety profile of the q2W dosing scheme. Long-term data from study 302 were considered to be needed to further elucidate the immunogenic potential of Plegridy.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. Risk Management Plan (RMP)

The CHMP received the following PRAC Advice on the submitted RMP:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1.2, the PRAC considers by consensus that the risk management system for Peginterferon Beta 1a (Plegridy) in the proposed indication of adult treatment of relapsing multiple sclerosis to slow the progression of disability and decrease the frequency of relapses is acceptable.

The CHMP endorsed this advice with changes. These changes concerned the Pharmacovigilance plan of the Risk Management Plan following a request of the applicant to introduce a minor correction to the objective of the pregnancy registry to clarify that the registry will not be able to characterise patterns of congenital abnormalities.

The approval of Risk Management Plan version 1.3 is based on the following content:

- **Safety concerns**

Summary of safety concerns	
Important identified risks	Serious hypersensitivity reactions Hepatic injury Decreased peripheral blood cell counts Serious injection site reactions Flu-like symptoms Depression and suicidal behaviour Seizure disorders Thyroid disorders
Important potential risks	Cardiac disorders Malignancies Immunogenicity Systemic lupus erythematosus Thrombotic microangiopathies including TTP and HUS Nephrotic syndrome and glomerulosclerosis
Missing information	Safety profile in children and adolescents under the age of 18 years Safety profile in patients over the age of 65 years Effect on pregnancy Exposure during lactation Safety profile in patients with hepatic impairment Safety profile in patients with decreased peripheral blood counts Drug-drug interactions

- **Pharmacovigilance plan**

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Paediatric study, Clinical trial, Category 3	To evaluate safety, tolerability, and descriptive efficacy of pegylated human interferon beta-1a	Growth (height, weight, Tanner stage); psychiatric monitoring, including depression (assessed by MINI-KID); vital signs, ECG, changes in laboratory values		2021
European Interferon Beta Pregnancy Registry (3)	To evaluate pregnancy outcomes, including frequency of spontaneous abortion and frequency of congenital anomalies	To address preclinical finding with non-pegylated interferon beta-1a[1] of abortifacient activity in monkeys	Initiated with premarketing clinical trials and will continue post-marketing	Updates provided in PSURs and an MAH collective annual report via the European Interferon Beta Pregnancy Registry
Phase 3 Extension Study 105MS302 (3)	To evaluate the long-term safety, tolerability, and MS outcomes of peginterferon beta-1a in subjects originally treated in Study 105MS301 who continue peginterferon beta-1a treatment.	Clinical safety assessments, including AEs, physical exam, vital signs, Beck depression inventory, changes in laboratory values and immunogenicity (development of BAbs and NAbs).	Ongoing	Final report by March 2016

- **Risk minimisation measures**

Important identified risks

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Serious Hypersensitivity (allergic) Reactions	SmPC text: Contraindication in section 4.3 of the SmPC. Warning in section 4.4 of the SmPC. Listed as an ADR in section 4.8 of the SmPC.	No additional risk minimisation measures are proposed

[1] This document has been updated; the previous version referred to 'peginterferon beta-1a'

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Hepatic (liver) Injury	SmPC text: Warning in section 4.4 of the SmPC. Elevation of liver enzymes listed as ADRs in section 4.8 of the SmPC.	No additional risk minimisation measures are proposed
Decreased peripheral blood cell counts	SmPC text: Warning in section 4.4 of the SmPC. Relevant preferred terms listed as ADRs in section 4.8 of the SmPC.	No additional risk minimisation measures are proposed
Serious injection site reactions including injection site necrosis (sores)	SmPC text: Warning in section 4.4 of the SmPC. Relevant preferred terms listed as ADRs in section 4.8 of the SmPC.	No additional risk minimisation measures are proposed
Flu-like symptoms	SmPC text: Recommendations for helping ameliorate symptoms provided in section 4.2 of the SmPC. Listed as ADR in section 4.8 of the SmPC.	No additional risk minimisation measures are proposed
Depression, suicidal behaviour	SmPC text: Contraindication in section 4.3 of the SmPC. Warning in section 4.4 of the SmPC. Listed in section 4.8 of the SmPC.	No additional risk minimisation measures are proposed
Seizure disorders (fits or convulsions)	SmPC text: Warning in section 4.4 of the SmPC. Listed as an ADR in section 4.8 of the SmPC.	No additional risk minimisation measures are proposed
Thyroid disorders	SmPC text: Warning in section 4.4 of the SmPC.	No additional risk minimisation measures are proposed

Important potential risks

Safety Concern	Routine Risk minimisation measures	Additional risk minimisation measures
Cardiac disorder	SmPC text: Warning in section 4.4 of the SmPC.	No additional risk minimisation measures are proposed
Malignancies	None proposed	None
Immunogenicity	SmPC text: Warning in section 4.4 of the SmPC.	No additional risk minimisation measures are proposed
SLE	None Proposed	None
Thrombotic microangiopathies	SmPC text	No additional risk minimisation

Safety Concern	Routine Risk minimisation measures	Additional risk minimisation measures
including TTP and HUS	Warning in section 4.4 of the SmPC. Listed as ADRs in section 4.8 of the SmPC.	measures are proposed
Nephrotic syndrome and glomerulosclerosis	SmPC text Warning in section 4.4 of the SmPC. Listed as ADRs in section 4.8 of the SmPC.	No additional risk minimisation measures are proposed

Missing information

Safety Concern	Routine Risk minimisation measures	Additional risk minimisation measures
Population not studied: children and adolescents under the age of 18 years	SmPC text: Information on the absence of data in children and adolescents aged 0 to 18 years provided in section 4.2 of the SmPC.	No additional risk minimisation measures are proposed
Populations not studied: patients over the age of 65 years	SmPC text: Information on the limited data in patients over 65 years of age is provided in sections 4.2 and 5.2 of the SmPC. Information on the pharmacokinetic profile based on the data available is provided in section 5.2 of the SmPC.	No additional risk minimisation measures are proposed
Population not studied: Effects on pregnancy outcomes and lactation	SmPC text: Contraindication for the initiation of treatment in pregnancy in section 4.3 of the SmPC. Information in section 4.6 of the SmPC including recommendations for women of child-bearing potential (have to take appropriate contraceptive measures) and a recommendation to discontinue breastfeeding or Plegridy therapy during breastfeeding.	No additional risk minimisation measures are proposed
Population not studied: patients with hepatic impairment	SmPC text: Information on the absence of data in patient with hepatic impairment included in section 4.2 of the SmPC. Warning in section 4.4 of the SmPC.	No additional risk minimisation measures are proposed
Drug-drug interaction	SmPC text: Information on the absence of interaction studies included in section 4.5 of the SmPC, as well as information regarding potential interactions with products with a	No additional risk minimisation measures are proposed

Safety Concern	Routine Risk minimisation measures	Additional risk minimisation measures
	narrow therapeutic index and largely dependent on cytochrome P450 for clearance.	
Safety profile in patients with decreased peripheral blood counts	SmPC text: Warning in section 4.4 of the SmPC on patients with myelosuppression.	No additional risk minimisation measures are proposed

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The active substance of Plegridy is peginterferon beta-1a, which represents a polyethylene glycol (PEG)-conjugated form of interferon beta-1a in order to protect the interferon moiety from enzymatic degradation and other clearance mechanisms. Medicinal products including beta interferon are established treatments in MS as 1st line therapy.

Data in support of efficacy of a therapeutic dose of 125 µg peginterferon beta-1a has been generated in two randomised, multicentre, double-blind phase 3 studies, 105MS301 (study 301) and its extension, 105MS302 (study 302). As study 302 was still on-going at the time of this report and since the study was not controlled, data from this study were considered descriptive and supportive.

Both studies only tested one of the two proposed delivery systems, the pre-filled syringe, but not the pre-filled pen. However, since the formulation, route of administration and the injected volume is the same, and as the PK profiles of both devices were similar, CHMP agreed that both devices could be used inter-changeably.

In study 301, a statistically significant reduction in the adjusted annualised relapse rate (ARR) at Year 1 was observed for both active treatment arms when compared to placebo (ARR was 0.397 for placebo, 0.256 for Plegridy every 2 weeks and 0.288 for Plegridy every 4 weeks). Although the observed effect size was rather modest (relative reduction of about 30%), it was considered clinically relevant. The CHMP agreed that it could be considered comparable to other interferons, based on historical comparison. Amongst the secondary endpoints, the CHMP considered the time to 12-weeks sustained disability progression as the most clinically relevant endpoint. The proportion of patients with progression at Year 1 was higher in the placebo group (0.105) compared to both Plegridy every 2 weeks and Plegridy every 4 weeks (both 0.068). The difference between placebo and both active arms was statistically significant. However,

when sustained disability progression was assessed over 6 months, statistical significance after one year was only maintained for Plegridy every 2 weeks.

Efficacy was also shown in MRI endpoints for both dosing regimens. The percentage reduction of new/newly enlarging T2 hyperintense lesions compared to placebo was 67% and 28% for Plegridy every 2 weeks and Plegridy every 4 weeks, respectively, which was statistically significant. However, Plegridy only demonstrated statistically significant differences against placebo on the number of Gd-enhancing lesions and T1 hypointense lesions at Year 1 when administered every 2 weeks.

The available data over 2 years of treatment from study 301 showed that efficacy in terms of ARR was maintained beyond Year 1. In terms of disability progression, a statistically significant effect over placebo was only apparent for Plegridy every 2 weeks.

The two dosing regimens tested in the pivotal trial (every 2 weeks versus every 4 weeks) generally showed comparable effect sizes at Year 1 of study 301. The difference became larger, though still rather small, over 2 years of treatment, at least in terms of ARR. This was supported by comparative efficacy analyses for clinical and key MRI outcomes.

Uncertainty in the knowledge about the beneficial effects.

Efficacy of Plegridy was primarily supported by one-year placebo-controlled data from study 301. However, the CHMP Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis (CPMP/EWP/561/98 Rev. 1, hereafter referred to as MS guideline) requires that efficacy is confirmed over a period of 2 years. Two-year results were available and despite the lack of a comparator arm, they provided some support for maintenance of the effect.

Only patients with relapsing-remitting MS (RRMS) were included in the studies; they were rather mildly affected and mostly treatment-naïve to MS medications. The CHMP considered that the lack of data in patients with high disease activity and prior MS treatment was adequately reflected in SmPC section 5.1. However, while the CHMP agreed that efficacy of Plegridy has been demonstrated in RRMS patients, this was not the case for a wider MS population, i.e. RMS as initially proposed by the applicant, and therefore only an indication in RRMS was supported.

The age limit for subject inclusion was increased while the study was on-going for two years. However, less than 1% of the enrolled patients were over the age of 59 years. Therefore, lack of data in the elderly was reflected in the product information.

The definition of sustained progression to disability was unconventional. Based on the MS guideline, sustained worsening is defined as an increase in EDSS score by 1 point in patients with a baseline EDSS <5.5 points and by 0.5 point if the EDSS at baseline is ≥5.5 points. Furthermore, accurate and reliable definition of sustained worsening for this chronic disease should include an assessment of disability over 6 months (24 weeks). Analyses in line with this definition were only generated post-hoc and showed smaller effect sizes as compared to the results from the primary analysis. Results for the dosing regimen every 4 weeks did not reach statistical significance. Overall, considering shortcomings in the study design with regard to the lack of placebo-controlled data beyond Year 1, the CHMP considered that the effect on disability

progression has not robustly been shown and therefore did not support a specific claim in the indication.

The pivotal study did not include an active comparator, which, although not essential in establishing a favourable benefit/risk balance, would have provided valuable additional information on relative efficacy for treating physicians and patients switching between pegylated and non-pegylated interferon-beta. Only data from an indirect across-study comparison was available. While supportive, these data cannot be taken as proof of similar effects. This is also true for the comparison of neopterin, a secondary PD marker, in healthy volunteers and of profiles of interferon-responsive genes expression, which did not further elucidate similarities or potential differences.

One of the possible advantages of Plegridy could be an increased patient adherence and convenience due to a less frequent dosing scheme compared to non-pegylated beta interferons as well as due to the SC route of administration. Based on the available data, treatment compliance and adherence appeared indeed to be good, but as direct comparison to non-pegylated interferon treatment (e.g. Avonex) was missing, no firm conclusions could be drawn.

While generally, the effect of Plegridy was similar across demographics and baseline disease characteristics, in two subgroups representing patients with[2] higher disease activity (≥ 4 relapses within 3 years prior to study entry) and patients who prior to study start had received other MS treatments, no benefit over placebo was seen for some of the relevant endpoints. However, the number of patients was too small to draw firm conclusions and information on the patient population was adequately reflected in SmPC, section 5.1.

Risks

Unfavourable effects

The safety database presented with this application was considered by the CHMP to be acceptable both in term of numbers of patients as well as considering the duration of use. Overall, the BIIB017 experience amounted to 1468 patients (1932 patient years) and a maximum of 196 weeks of exposure, with about 800 patients treated up to 2 years and about 100 patients with up to 3 years exposure. At the time of this report, long term safety data were still being generated (study 302).

Compared to placebo the overall incidence of any adverse events was higher, i.e. 83% for placebo versus 94% in both BIIB017 treatment groups. The overall incidence of any treatment-related adverse event was also higher, i.e. 53% for placebo versus 90% in both BIIB017 treatment groups. Most common adverse events concerned injection-site events and influenza-like illness and symptoms including headache, myalgia, chills, asthenia, arthralgia, fatigue, and pain in the extremities. The majority of these events were mild or moderate in severity.

Adverse events of special interest were flu-like symptoms, injection site reactions, hepatic disorders, autoimmune disorders, seizures, depression and suicide ideation, hypersensitivity reactions, haematological laboratory abnormalities and abnormal liver function tests. AEs identified of special interest due to the immunomodulatory mechanism of action were infections and malignancies.

[2] This paragraph has been updated to correct one of the two referenced subgroups of patients, i.e. those with prior MS medication rather than those without prior therapy (treatment-naïve)

Flu-like symptoms were common in the active study arms and one of the main reasons for treatment failure. While the safety profile of Plegridy was overall comparable with non-pegylated beta interferons in this respect, the low incidence of severe flu-like illness, low percentage days of flu-like symptoms and low rate of discontinuation due to flu-like syndrome (1%, 74/740) indicated that this was not a major issue for Plegridy. As for other interferons, dose titration is recommended to ameliorate flu-like symptoms at the beginning of treatment.

Based on the current safety database, it appeared that Plegridy was not associated with an increased risk of infections, opportunist infections, autoimmune disorders, seizures or depression/suicidal ideation. Nevertheless relevant safety information for these events related to the class of interferons was included in the product information and the risk management plan of Plegridy, as appropriate.

Cases of hepatic damage and liver enzyme abnormalities were observed in clinical trials with Plegridy as were decreases of cell counts in all blood cell lines. These effects were not unexpected and, overall, Plegridy showed an hepatic and haematological safety profile in between non-pegylated interferon beta-1a products (Avonex and Rebif). Therefore, regular monitoring of these parameters was considered appropriate, which has been reflected in SmPC section 4.4 similar to other beta interferons.

Numerically, more events of injection site reactions, hepatic disorders, liver function abnormalities and hypersensitivity reactions were observed for the every 2 weeks dose regimen as compared to the every 4 weeks dose regimen. Although the differences were small, taken together they sum up to a slightly less favourable safety profile of the every 2 weeks dosing schedule compared to the every 4 weeks regimen.

Uncertainty in the knowledge about the unfavourable effects

Based on the available data, there were uncertainties with regards to the immunogenic potential of Plegridy. While overall there was no clear signal for increased immunogenicity with prolonged use of the product, the duration of treatment was considered by the CHMP to be too short to fully elucidate the exact degree and impact. Further monitoring was encouraged and to this end immunogenicity has been referred to in the RMP as important potential risk and will be further addressed throughout extension study 302.

No direct comparison of safety between Plegridy and other beta interferons could be made due to the lack of an active control in the pivotal trial. Based on a review of data from the placebo-controlled pivotal study 301 and available data from controlled clinical studies for other approved non-pegylated interferon beta-1a products (Avonex and Rebif), the safety profile of Plegridy appeared generally consistent with that of existing non-pegylated beta interferon MS therapies. However, the CHMP noted that a comparative exercise involving a non-pegylated interferon beta-1a based on e.g. PK/PD parameters, would further clarify the safety profile of Plegridy.

Benefit-risk balance

Importance of favourable and unfavourable effects

Efficacy of peginterferon beta-1a was demonstrated in terms of effects on annual relapse rate and time to sustained disability progression. Whilst modest, the effect size appeared to be comparable to that of other beta-interferons approved for MS treatment, which was considered

clinically relevant. The patient population was representative of the target population for interferons, i.e. rather mildly affected RRMS patients, and efficacy of Plegridy was considered demonstrated in this population.

Overall the safety profile of Plegridy appeared to be comparable to non-pegylated beta interferon MS therapies. Flu-like symptoms and injection-site reactions were common under treatment with Plegridy and were generally mild or moderate in severity. Efficacy and safety remained unaltered for subjects with and without antibody formation and overall the immunogenic potential was considered to be likely small.

A slightly inferior safety profile was observed for the every 2 weeks dosing scheme compared to the every 4 weeks regimen. However, safety was generally manageable for doses every 2 weeks. At the same time, a numerical advantage of the every 2 weeks regimen was observed in terms of efficacy. This was further supported by comparative efficacy analyses for clinical and key MRI outcomes.

Discussion on the benefit-risk balance

Despite the deficiencies in the clinical development programme, in particular the lack of an active comparator and the fact that placebo-controlled data were only available for one year, which is not in line with the requirements stated in the MS guideline, overall, the CHMP considered that the programme was satisfactory, taking into account that Plegridy is a pegylated form of beta-interferons, a well-established class of MS products for which extensive clinical experience existed at the time of this report.

The CHMP did not agree that the benefit/risk profile could be extrapolated from RRMS patients, included in the pivotal trial, to the wider population of RMS patients. In addition, the effect on disability progression has not robustly been shown.

The magnitude of the observed treatment effect was rather modest. The observed reduction in relapse rate would mean that a patient will suffer on average one relapse in 4 years with peginterferon beta-1a treatment as compared to one relapse in 3 years without disease modifying treatment. However, the effect size was in line with that of non-pegylated beta interferon, which was considered of clinical relevance.

The safety profile of Plegridy appeared to be comparable to the known safety profile of non-pegylated beta-interferons and no new unexpected safety issues emerged from the available data.

The benefit-risk profile of peginterferon beta-1a would position Plegridy as a first line therapy amongst other interferons in patients with RRMS. The less frequent SC dosing schedule was considered by the CHMP of benefit to patients as other interferons require more frequent dosing and some need to be injected via the IM route. However, due to the lack of comparative data, it was not possible to exclude without doubt differences in the effect size of non-pegylated interferon-beta and peginterferon-beta. Considering the modest magnitude of effect, any difference in the effect size was considered by the CHMP to be important with a view to switching patients from one interferon product to the other, which may be expected in clinical practice given the less frequent need for injections with Plegridy. While it was acknowledged by the CHMP that loss of efficacy could be difficult to detect in clinical practice, especially in a rather mild MS population, as relapses usually occur infrequently and even in some cases with

years in between consecutive relapses, comparative data would have been valuable for prescribers and patients. Since the active principle and mechanism of action of pegylated and non-pegylated interferons are the same, clinical data focussing on MRI endpoints to assess the relative anti-inflammatory effect may have been considered sufficient to indicate comparable efficacy. However, the CHMP pointed out that this was a specific case and that, normally, clinical endpoints in line with the MS guideline were required to establish patient benefit of a new active substance in the treatment of MS and approval of disease-modifying therapies based on MRI endpoints only was not possible. Overall, the CHMP considered that prescribers should be informed about the lack of direct comparative data through adequate information in the SmPC.

With regard to the two dosing regimens tested in the pivotal trial, the CHMP concluded that the every 2 weeks dosing regimen, on balance, offered a slightly more favourable benefit/risk balance, based on better efficacy, for all patient groups and that no subgroup could be identified for which the less frequent dosing regimen (every 4 weeks) would be more appropriate.

All adverse reactions and safety concerns associated with Plegridy were considered adequately described in the product information and the RMP, which was considered by the CHMP to be sufficient to manage the risks. Long-term data will become available from the extension study 302 and these data will allow to further characterise the benefit/risk balance of Plegridy.

Benefit-risk balance

Based on the available quality, efficacy and safety data, the CHMP considered that the benefits of Plegridy in the treatment of relapsing-remitting multiple sclerosis in adult patients and subject to the agreed product information and the risk management plan, outweigh its risks. Therefore, the CHMP concluded that the benefit/risk balance was favourable.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Plegridy in the treatment of relapsing remitting multiple sclerosis in adult patients is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the

requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that peginterferon beta-1a is qualified as a new active substance.