



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Peginterferon beta 1a (rch)

Proprietary Product Name: Plegridy

Sponsor: Biogen Idec Australia Pty Ltd

February 2015

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
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- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of commonly used abbreviations

Abbreviation	Meaning
9HPT	9-hole peg test
Ab	antibody
AE	adverse event
ARR	annualised relapse rate
AUC	area under the curve
AUC ₀₋₁₆₈ , AUC ₀₋₂₄₀	AUC up to 168 h post-dose, 240 h post-dose
AUC _{0-inf}	area under the time-concentration curve from time zero to infinity
BAb	binding antibody
BIIB017	peginterferon beta-1a
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL/F	apparent total body clearance
C _{max}	maximum serum concentration
CNS	central nervous system
CPE	cytopathic effect
CSR	clinical study report
CV	coefficient of variation
DMT	disease-modifying treatment
E _{AUCt}	area under the effect-time curve partial
EDSS	Expanded Disability Status Scale
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
E _{max}	peak concentration observed minus baseline concentration

Abbreviation	Meaning
EQ-5D	EuroQoL (quality of life) questionnaire consisting of 5 domains
ESRD	end stage renal disease
Gd	gadolinium
HV	healthy volunteers
IFN β	interferon beta
IFN β -1a	interferon beta-1a
IM	intramuscular
INEC	Independent Neurology Evaluation Committee
ITT	intent-to-treat
IXRS	Interactive Voice/Web Response System
kDa	kiloDalton
MDRD	Modification of Diet in Renal Disease
MIU	million international units
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MS	multiple sclerosis
MSIS	Multiple Sclerosis Impact Scale
MSFC	MS Functional Composite
N/A	not applicable
NAb	neutralising antibody
NC	not calculated
NCA	non-compartmental analysis
OAS, OAS 2',5'	oligoadenylate synthetase
PASAT	Paced Auditory Serial Addition Test
PD	pharmacodynamic
PEG	polyethylene glycol

Abbreviation	Meaning
PFP	prefilled pen
PFS	prefilled syringe
PI	Product Information
PK	pharmacokinetic
PP	per-protocol
PPMS	primary progressive multiple sclerosis
Q2W	every 2 weeks
Q4W	every 4 weeks
qPCR	real-time (quantitative) PCR
RI	renal impairment
RNA	ribonucleic acid
RRMS	relapsing remitting multiple sclerosis
SAE	serious adverse event
SC	subcutaneous
SCE	Summary of Clinical Efficacy
SD	standard deviation
SF-12	12-Item Short Form Health Survey
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	time to peak concentration

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Biological medicine
<i>Decision:</i>	Approved
<i>Date of decision:</i>	29 October 2014
<i>Active ingredient:</i>	Peginterferon beta 1a (rch)
<i>Product name:</i>	Plegridy
<i>Sponsor's name and address:</i>	Biogen Idec Australia Pty Ltd P O Box 380 North Ryde BC NSW 1670
<i>Dose forms:</i>	Solution for injection pre-filled syringe or pre-filled pen
<i>Strengths:</i>	125 microgram/0.5 mL, 94 microgram/0.5 mL and 63 microgram/0.5 mL
<i>Container:</i>	Type 1 glass syringe
<i>Pack sizes:</i>	2 or 6 syringes or pens (125 microgram/0.5 mL)
<i>Approved therapeutic use:</i>	<i>Plegridy is indicated for the treatment of relapsing forms of Multiple Sclerosis (MS) (see Clinical Trials)</i>
<i>Route of administration:</i>	Subcutaneous (SC)

Dosage:

Dose	Time ^a	Amount (µg)	Pen/Syringe label
Dose 1	Day 0	63	Orange
Dose 2	Day 14	94	Blue
Dose 3	Day 28	125 (full dose)	Grey

^aDosed every 14 days (2 weeks)

ARTG numbers: 214197, 214198, 214199, 214200

Product background

This AusPAR describes the application by Biogen Idec Australia Pty Ltd to register the new biological medicine Plegridy, a solution for injection in a pre-filled syringe or pen containing 63 µg, 94 µg or 125 µg peginterferon beta-1a, for:

- Plegridy is indicated for the treatment of relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability.

Interferons are naturally occurring immune-regulating proteins that are usually produced endogenously in response to a number of immune stimuli including viral infection, and which undergo protein folding and glycosylation like many other complex human proteins.

Three main types of interferon are present in humans: interferon alpha, interferon beta, and interferon gamma. These compounds differ substantially in their effects on the immune system.

Recombinant interferon beta has been used for many years in the management of multiple sclerosis. The interferon beta-1a subtype is almost identical to the native human form, sharing its amino acid sequence and glycosylation pattern. Pegylated interferon beta-1a was developed by applying a serum free culture method to interferon beta-1a (Avonex), a registered medicine also sponsored by Biogen Idec Australia and approved for the treatment of relapsing forms of multiple sclerosis and for patients who have experienced a single demyelinating event and are at risk of developing clinically definite MS based on the presence of brain Magnetic Resonance Imaging (MRI) abnormalities characteristic of Multiple Sclerosis (MS).

During pegylation, a 20 kilo Dalton (kDa) methoxypoly (ethylene glycol)-O-2 methylpropionaldehyde (mPEG) moiety is attached to the N-terminus. Peginterferon beta-1a is likely to have a similar mechanism of action as other interferon betas. The proposed dosing regimen requires injections every two weeks rather than weekly as with Avonex. Approved injectable treatments for MS require injection every day, in the case of glatiramer acetate (Copaxone), 3 to 4 times per week, in the case of interferon beta-1b (Betaferon) and interferon beta-1a (Rebif) or once per week in the case of interferon beta-1a (Avonex).

Pegylation to prolong the half-life of an interferon, has previously been undertaken with interferon alpha. Peginterferon alfa-2a (Pegasys) and peginterferon alfa-2b (Peg-Intron) are approved for the treatment of hepatitis C.

Regulatory status

This is a new biological medicine for Australian regulatory purposes.

At the time of submission peginterferon beta-1a had not been approved in any country. Submissions had been made to in the EU, USA, Canada and South Africa. An application had been submitted to Swissmedic.

It was approved by the FDA on the 15 August 2014 for the following indication:

Plegridy (peginterferon beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

On 22 May 2014, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for Plegridy. The European Public Assessment Report (EPAR) was subsequently published on the European medicines Agency (EMA) website on 31 July 2014. The approved indication in the European Union (EU) is:

Plegridy is indicated in adult patients for the treatment of relapsing remitting multiple sclerosis (see section 5.1).

Product Information

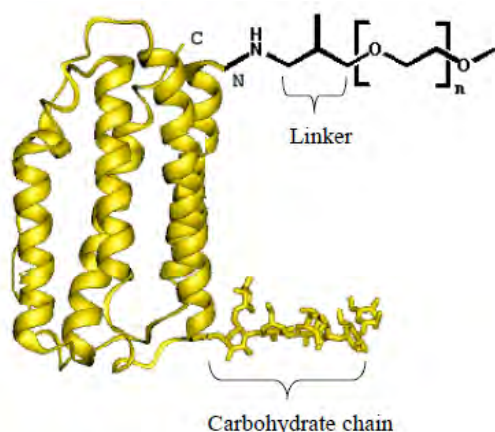
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

Drug substance (active ingredient)

The active substance of Plegridy, peginterferon beta-1a, is a glycosylated recombinant interferon beta-1a (IFN (β -1 a) that is pegylated with a single 20 kDa methoxypoly (ethylene glycol)-O-2 methylpropionaldehyde (mPEG) moiety at the N-terminus. The drug substance is produced by recombinant deoxyribonucleic acid (DNA) technology in Chinese Hamster Ovary (CHO) cells and purified chromatographically. The drug substance has the following structure:

Figure 1. Schematic of the peginterferon beta-1a structure



Hence, it is produced from the same cell line, albeit adapted for serum free culture, as Avonex.

Manufacture

The manufacturing process is comprised of cell culture expansion, clarification of the cell culture fluid and chromatography 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 drug substance.

Cell banking processes are satisfactory.

All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Physical and chemical properties

Peginterferon beta-1a is a 166 amino acid glycoprotein in which the α -amino group of the N-terminal amino acid residue has been modified with a single, linear molecule of 20 kDa methoxy poly(ethyleneglycol)-O-2-methylpropionaldehyde (20 kDa mPEG-O-2-methylpropionaldehyde).

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use were summarised in the submission.

Appropriate validation data have been submitted in support of the test procedures.

Drug product

The drug product is a sterile, liquid formulation in a pre-filled syringe for subcutaneous injection. It has three different fixed dosage strengths and each is filled into the Pre-filled Syringe at a nominal volume of 0.5 mL. The intended dosage forms for use by the patient will include the Pre-filled Syringe with three fixed dosage strengths where the 63 and 94 µg strengths are for initial dose titration and the 125 µg strength is the long term presentation.

Manufacture

The drug product solution is sterilised by filtration and filled into syringes.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product under the following conditions:

- Long term storage at $5 \pm 3^{\circ}\text{C}$
- Accelerated condition storage at $25 \pm 2^{\circ}\text{C}/60 \pm 5\%$ Relative Humidity (RH)
- Photostability
- Supply Chain Simulation
- Ambient Storage and Temperature Excursion Simulation.

Photostability data of the drug product showed that it is not photostable.

The proposed shelf life of 24 months when stored at $5 \pm 3^{\circ}\text{C}$ (protected from light), with an allowance of storage for up to 30 days at room temperature (not to exceed 25°C) within the 24 month shelf life is supported by the stability data.

Biopharmaceutics

Biopharmaceutic/bioavailability data are evaluated separately by the clinical evaluator.

Quality summary and conclusions

The quality evaluators have no objection to the registration of Plegridy peginterferon beta 1a (rch) 125 µg /0.5 mL, 94 µg/0.5 mL and 63 µg /0.5 mL solution for injection pre filled pen/syringe.

Batch release testing of the first five batches by the TGA is recommended to verify quality of the product and consistency of the manufacturing process. Subject to the clinical Delegate's agreement, the batch release conditions, as described below, should be added to the conditions of registration of this product.

Batch release conditions of registration for clinical delegate***Conditions of registration: Batch release testing***

It is a condition of registration that, as a minimum, the first five independent batches of Plegridy peginterferon beta 1a (rch)

- 125 microgram/0.5 mL solution for injection pre-filled pen (AUST R 214197)
- 125 microgram/0.5 mL solution for injection pre-filled syringe (AUST R 214199)

- 63 microgram/0.5 mL and 94 microgram/0.5 mL solution for injection pre-filled pen Titration Pack (AUST R 214200)
- 63 microgram/0.5 mL and 94 microgram/0.5 mL solution for injection pre-filled syringe Titration Pack (AUST R 214198)

imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

III. Nonclinical findings

Introduction

General comments

The general quality of the submitted nonclinical studies was reasonable. The rationale for the nonclinical testing strategy was well presented and justifies the limited number of studies conducted. The range of studies was consistent with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines and the pivotal study examining repeat-dose toxicity in monkeys was conducted under Good Laboratory Practice (GLP) conditions with the proposed peginterferon beta-1a formulation.

Pharmacology

Primary pharmacology

An in vitro study confirmed the ability of peginterferon beta-1a to form a stable complex with the extracellular portion (IFNAR2) of the IFN receptor. The equilibrium dissociation constant (K_d) was similar to that for interferon beta-1a, indicating that pegylation had no significant effect on the affinity of peginterferon beta-1a for the extracellular portion of the IFN receptor. In vivo pharmacology studies with peginterferon beta-1a in animals were not conducted as the efficacy of interferon beta-1a has been demonstrated in MS patients. In addition, mice and rats are not pharmacologically responsive to human interferon beta-1a.

Secondary pharmacodynamics

In vitro studies conducted in human lung carcinoma A549 cells and in SurDaudi human B cells demonstrated, respectively, the anti-viral and anti-proliferative activities of peginterferon beta-1a and interferon beta-1a. The specific antiviral and anti-proliferative activities of peginterferon beta-1a, as measured by the respective 50% effective dose (EC_{50}) values, were approximately 2 times less than those of interferon beta-1a.

In vivo pharmacological responses known to be induced by interferon beta-1a were observed in the 5-week toxicity study in monkeys. These included a transient rise in body temperature, decreases in lymphocyte counts and an increase in serum neopterin concentration. In the pharmacokinetic studies in monkeys, peginterferon beta-1a and interferon beta-1a produced similar neopterin pharmacokinetic parameters following either SC or intramuscular (IM) administration. Peginterferon beta-1a produced a dose-related increase in neopterin serum concentration following SC administration. However,

these pharmacological responses have not been shown to be surrogates for the efficacy of peginterferon beta-1a in patients with MS.

A series of studies demonstrated that peginterferon beta-1a inhibits the growth of various tumours in nude or SCID¹ mice also demonstrated the pharmacological activity of peginterferon beta-1a, although this activity was unrelated to potential efficacy in MS patients. The studies did demonstrate that peginterferon beta-1a with a less frequent dosing regimen maintained equivalent anti-tumour efficacy to interferon beta-1a.

Safety pharmacology

Safety pharmacology endpoints were examined in the 5 week study in monkeys. A transient dose-dependent increase in body temperature was observed at 4 h post-treatment at $\geq 10\mu\text{g/kg}$ SC or IM (equivalent to ≥ 26 times the clinical exposure based on area under the serum concentration versus time curve (AUC)). There was no treatment-related effect on electrocardiogram (ECG) measurements or on respiratory parameters at doses up to $100\mu\text{g/kg}$ SC or IM (equivalent to >300 times the clinical exposure based on AUC).

Pharmacokinetics

Nonclinical pharmacokinetics studies with peginterferon beta-1a which were relevant to MS patients were conducted in rats and monkeys and focused on a comparison with the pharmacokinetics of non-pegylated interferon beta-1a. A pharmacokinetic study in mice was relevant only to tumour growth inhibition in oncology patients.

Absorption:

Absorption following single dose SC or IM administration of peginterferon beta-1a in monkeys was slower than for interferon beta-1a, as evidenced by a longer time to peak serum concentration (T_{max}) (2 fold and 6 fold for IM and SC administration, respectively). The AUC_{inf} , peak serum concentration (C_{max}), half-life ($t_{1/2}$), oral clearance (CL/F), and volume of distribution (V_d/F) were similar for peginterferon beta-1a between the SC and IM routes, but pegylation produced significantly higher exposure (≥ 60 -fold, based on AUC) and slower clearance (≥ 30 -fold). There was a dose-proportional increase in exposure (C_{max} and AUC) following SC administration in monkeys. A similar profile was observed in rats: following single dose IV administration, pegylation of interferon beta-1a produced increased exposure (AUC) (approximately 30 fold) and $t_{1/2}$ while reducing clearance (CL) (approximately 30 fold).

In repeat-dose studies in monkeys, exposure was dose-proportional one day after the initial SC administration of peginterferon beta-1a. Exposure (AUC and C_{max}) was similar following SC or IM administration. Dose proportionality at subsequent time points was difficult to determine due to the development of neutralizing antibodies.

Studies in rats also showed that % sialylation and size of mPEG can influence pharmacokinetic parameters; this study is relevant for the preparation and specifications for purity for peginterferon beta-1a. The pharmacokinetics of peginterferon beta-1a was similar when it was prepared by a serum-containing or serum-free process; this study is relevant for the validation of the Phase I clinical studies and some nonclinical studies conducted with peginterferon beta-1a prepared using the serum-containing process.

¹ SCID=severe combined immunodeficiency

Distribution:

The pharmacological relevance of guinea pig for interferon beta-1a was established in a study which produced a dose-related increase in serum 2',5'-OAS, a biomarker for interferon beta-1a. Tissue distribution of peginterferon beta-1a in guinea pig was extensive with highest distribution in spleen, kidney, liver and lung. The extent of distribution was similar to that seen with interferon beta-1a but overall tissue uptake (AUC) was 20 to 40 fold lower. Peginterferon beta-1a was catabolically more stable in serum than interferon beta-1a up to 72 h post-dosing.

Metabolism:

Peginterferon beta-1a is expected to undergo catabolism to small peptides and amino acids and no specific studies were conducted, consistent with relevant guidelines.² The stability of the linkage between interferon beta-1a and mPEG in peginterferon beta-1a was shown to be 80% in monkey serum and >95% in human serum following incubation at 37°C for up to 2 weeks and is not anticipated to lead to any mPEG-related toxicity.

Excretion:

The distribution study showed that radioactivity associated with peginterferon beta-1a was excreted in the urine with 84% recovery at 72 h. No further specific studies were conducted, consistent with the relevant guidelines.²

Conclusion:

The pharmacokinetics was evaluated in monkeys and the tissue distribution in guinea pigs and both are pharmacologically relevant species. The expected effects of pegylation on pharmacokinetics were observed, namely, increased exposure and reduced clearance, even though the formation of neutralizing antibodies eventually reduced exposure to both pegylated and non-pegylated interferon beta-1a. The tissue distribution of radioactive peginterferon beta-1a was also similar to that of non-pegylated interferon beta-1a. The monkey is considered an appropriate model for the assessment of peginterferon beta-1a-related toxicity in humans.

Pharmacokinetic drug interactions

Peginterferon beta-1a is not considered to be metabolised by hepatic enzyme-mediated pathways and therefore pharmacokinetic drug interactions are not expected.

Toxicology**Acute toxicity**

No acute toxicity studies have been conducted with peginterferon beta-1a or considered necessary since the acute toxicity of interferon beta-1a is low.

Repeat-dose toxicity

An appropriately designed repeat dose toxicity study with weekly treatment with peginterferon beta-1a administered by the SC or IM route was conducted in monkeys up to 5 weeks, consistent with ICH S6 guidelines.² The recommended clinical dose is 125 µg

² ICH Guideline S6 - Preclinical safety evaluation of biotechnology-derived pharmaceuticals.

every two weeks via the SC route. The IM route was also considered in initial studies but ultimately not recommended for clinical use.

Relative exposure

The exposure ratio has been calculated based on animal:human AUC_{tau} (Table 1). Human reference values are from Clinical Study 105MS301. The No Observable Adverse Effect Level (NOAEL) is shown in bold type.

Table 1. Relative exposure in the repeat-dose toxicity monkey study

Species	Study duration	Dose (µg/kg/week)	AUC** (ng·h/mL)	Exposure ratio***
Monkey (Rhesus)	5 weeks	2	171	4
		10	1063	26
		100	13339	325
Human*	48/96 weeks	125 µg every 2 weeks or 4 weeks	41 (20 th percentile)	–

*Subjects with relapsing MS. ** Measured at day 1 (AUC_{inf}) in animal study; measured as AUC_{tau} in human studies. *** Animal: human serum AUC

Major toxicities

The nonclinical changes associated with peginterferon beta-1a in monkeys were a dose-related transient increase in body temperature and a decrease in lymphocyte counts. The increase in body temperature (1 to 2°C) was significant at 10 and 100 µg/kg and returned to normal by 8 h post-treatment. The decrease in lymphocyte counts was also significant at 10 and 100 µg/kg after the 1 and 3 week treatments, but not at subsequent times. These changes were related to the pharmacological activity of peginterferon beta-1a and not considered toxicologically significant. The pharmacological response decreased with the production of neutralising antibodies which occurred after approximately 2 weeks of treatment. The transient pharmacological effects are not considered clinically relevant. The NOAEL was the highest dose tested, namely, 100 µg/kg/week (equivalent to >300 times the anticipated clinical exposure, based on AUC).

Genotoxicity

The genotoxic potential of peginterferon beta-1a was examined in a bacterial reverse mutation assay and in a test for chromosomal aberrations in human blood lymphocytes. Both assays were negative, consistent with the negative results obtained for interferon beta-1a (Avonex®).

Carcinogenicity

As peginterferon is not pharmacologically active in rodent species, a weight-of-evidence approach has been used to assess potential carcinogenicity, consistent with ICH S6 guidelines.² With respect to interferon beta-1a, there was no evidence of carcinogenicity in a 6-month study in monkeys with NAb suppression. Interferon beta-1a demonstrates anti-tumour activity both in vitro and in vivo, and in 15 years clinical use there is no evidence of increased cancer risk. Peginterferon beta-1a also demonstrates anti-tumour activity *in*

vivo. On the basis of these data, no further carcinogenicity investigation on peginterferon beta-1a is considered necessary.

Reproductive toxicity

Interferon beta-1a was tested for reproductive and developmental toxicity previously and shown to be an abortifacient in monkeys but not to affect fetal development (Avonex®), consistent with the results for other type 1 interferons. Clinical use of interferon beta-1a has also not been shown to increase the rate of spontaneous abortion. Testing on peginterferon beta-1a was therefore limited to a study of hormone and menstrual cycling in monkeys to confirm its abortifacient potential. The study confirmed the potential of peginterferon beta-1a to prolong the menstrual day of peak estradiol and progesterone at 125µg/kg/week (equivalent to 170 times the clinical exposure based on serum AUC), consistent with the effects observed with interferon beta-1a (Avonex®) and with peginterferon α-2b (Peg-intron® Product Information). At 2.5 µg/kg/week minimal changes were observed (equivalent to 2.5 times the clinical exposure, based on AUC). No further reproductive studies with peginterferon beta-1a were considered necessary. The abortifacient effect is considered to be clinically relevant.

Relative exposure

The following table describes the relative exposure in menstrual cycle study.

Table 2. Relative exposure in menstrual cycle study

Species	Study duration	Dose (µg/kg/week)	AUC (ng·h/mL)	Exposure ratio [#]
Monkey (Rhesus)	5 weeks	2.5	109	2.5
		125	6990	170
Human*	48/96 weeks	125 µg every 2 weeks or 4 weeks	41 (20 th percentile)	–

*Subjects with relapsing MS. ** Measured at day 1 (AUC_{0-168h}) in animal study; measured as AUC_{tau} in human study. *** Animal: human serum AUC

Pregnancy classification

The sponsor has proposed pregnancy Category D³, which is appropriate and consistent with the pregnancy Category for interferon beta-1a.

Local tolerance

There were no treatment-related macroscopic or histopathological changes observed at the injection site in the 5 week repeat dose toxicity study in monkeys following either the SC or IM route of administration.

³Australian Pregnancy Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Antigenicity

Administration of peginterferon beta-1a by the SC or IM route was shown to elicit the production of neutralizing antibodies after about 2 weeks, followed by subsequent reduced levels of exposure to peginterferon beta-1a.

Immunotoxicity

In the 5 week toxicity study in monkeys, there was no evidence of adverse effects on tissues associated with the immune system. The transient decrease in lymphocytes was not associated with a decreased immune response. Similar results were obtained with interferon beta-1a.

Paediatric use

Peginterferon beta-1a is not currently proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary

- The nonclinical data provided were adequate to analyse and assess the nonclinical pharmacological, pharmacokinetic and toxicological properties of peginterferon beta-1a in relation to its proposed clinical use. The data were in general accordance with the ICH guidelines. The pivotal studies were GLP compliant and conducted with the proposed clinical formulation. The exposure ratios are adequate to address the clinical relevance of the observed toxicities.
- The primary pharmacology in vitro studies confirm the ability of peginterferon beta-1a to form a stable complex with the extracellular portion of the IFN receptor, with a similar dissociation constant to that for non-pegylated interferon beta-1a. In vivo studies were not conducted as rodents are not pharmacologically responsive to human interferon beta-1a, and the efficacy of interferon beta-1a has been demonstrated in MS patients.
- In vitro secondary pharmacodynamic studies have demonstrated anti-viral and anti-proliferative activities of peginterferon beta-1a with EC₅₀ values 2 fold less than for interferon beta-1a. In a repeat dose monkey study, peginterferon beta-1a induced pharmacological responses similar to interferon beta-1a, namely, a transient rise in body temperature, a decrease in lymphocyte counts and an increase in serum neopterin concentration. These pharmacological responses, however, are not surrogates for the efficacy of peginterferon beta-1a in MS patients.
- Safety pharmacology endpoints were examined in the 5 week study in monkeys. A transient increase in body temperature was observed at >20 times the clinical exposure. There was no treatment-related effect on ECG measurements or on respiratory parameters at >300 times the clinical exposure.
- Pharmacokinetic studies focused on a comparison with the pharmacokinetics of non-pegylated interferon beta-1a. Following a single SC administration of peginterferon beta-1a in monkeys, absorption was 6 fold slower, AUC exposure was 100 fold higher, and clearance was approximately 40 fold slower than for interferon beta-1a. In a repeat dose study in monkeys, exposure to peginterferon beta-1a was dose proportional one day after SC administration but could not be measured at subsequent time points due to the development of neutralizing antibodies. Tissue distribution in guinea pigs was high with a similar extent of distribution for pegylated and non-pegylated interferon beta-1a. As with other interferons, peginterferon beta-1a is expected to undergo catabolism to small peptides and amino acids. The linkage

between mPEG and interferon beta-1a was relatively stable in both monkey and human serum following incubation for 2 weeks. Excretion of peginterferon beta-1a-related radioactivity was via the urine. The pharmacokinetics results support the monkey as an appropriate model for assessment of peginterferon beta-1a-related toxicity in humans.

- In the 5 week repeat-dose toxicity study in monkeys, the only changes observed were a transient increase in body temperature and a decrease in lymphocyte counts, both of which were considered to be related to the pharmacological activity of peginterferon beta-1a, and not toxicologically significant. These pharmacological effects decreased with the production of neutralizing antibodies after about 2 weeks and are not considered clinically relevant. The exposure (AUC) at the NOAEL in this study was >300 times the clinical exposure.
- The genotoxicity data were adequate and produced negative results in in vitro and in vivo studies. No carcinogenicity studies were performed and after consideration of all available evidence, no further carcinogenicity investigation is considered necessary. This is consistent with the weight-of-evidence approach recommended by the ICH guidelines.
- In reproductive and developmental toxicity studies, interferon beta-1a and other interferons have been shown previously to be abortifacents in monkeys but not to affect fetal development. Similar studies have not been conducted with peginterferon beta-1a but a 5 week SC study in monkeys confirmed its potential to prolong the menstrual day of peak estradiol and progesterone, consistent with the effects produced by interferon beta-1a in relation to its abortifacient effect. The potential abortifacient effect is considered to be clinically significant. The sponsor has proposed pregnancy Category D, which is considered appropriate.
- Local tolerance at the injection site was examined in the 5 week monkey toxicity study. No macroscopic or histopathological changes were observed.
- No adverse effects associated with the immune system were observed in the 5 week monkey toxicity study.
- Peginterferon beta-1a is not currently proposed for paediatric use.

Nonclinical conclusions and recommendation

- There were no major deficiencies in the nonclinical data on peginterferon beta-1a.
- The pharmacology data on peginterferon beta-1a confirm that it has similar in vitro and in vivo pharmacological activity to non-pegylated interferon beta-1a, supporting its use for the proposed indication.
- The safety pharmacology data did not indicate any clinically relevant adverse effects.
- The pharmacokinetic properties of peginterferon beta-1a confirmed the expected changes related to the pegylation of interferon beta-1a.
- The repeat-dose toxicity study did not reveal any evidence of toxicity related to treatment with peginterferon beta-1a. The observed changes related to the pharmacological activity were not considered clinically relevant.
- There was no evidence of genotoxic potential and carcinogenicity studies were not considered necessary.
- The potential abortifacient activity of peginterferon beta-1a was confirmed. No further reproductive studies were considered necessary. This effect is considered clinically relevant.

- Based on the nonclinical data evaluated in this report, registration of peginterferon beta-1a is supported, provided clinical efficacy and safety can be demonstrated.
- Amendments to the draft Product Information document were recommended but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Multiple sclerosis (MS) is the most common chronic neurological disease of young adults. It is an inflammatory disease of the central nervous system (CNS), with characteristic plaques of demyelination, which represent sites of myelin destruction. Plaques are most common in the white matter of the CNS but may also affect the grey matter.

MS may show a number of different temporal patterns. In the most common form, relapsing and remitting MS (RRMS), patients experience bouts of inflammation ('relapses') followed by complete or partial recovery ('remissions'). The symptoms of each relapse depend on which part of the CNS is affected and may involve focal weakness, incoordination, sensory loss, visual disturbance or bladder and bowel dysfunction.

Most subjects with RRMS eventually show sustained progression of disability, arising from a combination of incomplete recovery from discrete relapses, the cumulative effect of poorly defined or subclinical relapses, and background progression of disease between relapses. This phase is known as secondary progressive MS. It is usually subdivided according to whether identifiable relapses are still occurring.

In the less common form of the disease, primary progressive MS (PPMS), patients show progressive disease from the onset of the disease, without ever exhibiting identifiable relapses. Such patients generally show a poor response to immune-modifying treatments.

The aetiology of MS remains unclear despite decades of research but it is widely considered to be an autoimmune disease. Active plaques show lymphocytic infiltration of the brain parenchyma, the cerebrospinal fluid shows bands of antibodies on electrophoresis and immunosuppressive treatments including steroids can suppress disease activity.

The treatment of MS usually involves a combination of symptomatic treatments (such as antispasm agents or analgesia), corticosteroids for acute relapses and disease-modifying agents that seek to alter the course of the disease. The beta interferons (Avonex, Rebif and Betaferon) have been used for many years as disease-modifying agents in the treatment of RRMS. Along with glatiramer acetate (Copaxone), these injectable agents have been considered first-line treatments, capable of reducing relapse rate and slowing progression of disease.

More recently, several oral therapies have been developed and monoclonal antibodies such as natalizumab have been employed, directed at various targets in the immune system. None of the treatments is capable of suppressing all disease activity, though some patients achieve lasting states of remission. Natalizumab is particularly effective but its use is associated with a risk of progressive multifocal leukoencephalopathy (PML), a very serious cerebral disease caused by opportunistic infection with the JC virus. The oral

treatments are associated with some safety concerns. Fingolimod may cause macular swelling with visual loss, as well as first-dose bradycardia that has at least once been fatal. Teriflunomide has some nuisance side effects and exhibits only moderate efficacy compared to the interferons. Dimethyl fumarate appears to be reasonably safe but can cause flushing and diarrhoea. Cladribine is no longer marketed because of safety issues. The chemotherapy agent mitoxantrone has been used as a second-line MS agent but it causes cumulative cardiac toxicity that limits its use.

The traditional first-line injectable agents, including Avonex, also have a number of side effects but most of these represent tolerability issues rather than safety concerns. The interferons can cause flu-like malaise, mood changes, fatigue, an increase in spasm and derangements of liver and thyroid function tests. Subjects can develop antibodies to the injected treatment, which is usually considered an efficacy concern rather than a safety issue because the antibodies may neutralise the desired pharmacological effects of the interferon. Glatiramer acetate is often better tolerated but may cause flushing. All of the injectable treatments can cause injection-site reactions. Patients may also develop 'injection fatigue', characterised as an increasing reluctance to inject, increasing problems with compliance and eventual abandonment of the treatment.

Peginterferon does not offer a new mechanism of action and its side effects are expected to be similar to existing interferons but the proposed dosing regimen with injections every two weeks is likely to be welcomed by patients. Existing injectable treatments require injection every day, in the case of glatiramer acetate, 3 to 4 times per week in the case of Betaferon and Rebif or once per week, in the case of Avonex. If peginterferon delivered the same efficacy as these existing treatments but with less injections this would reduce the overall burden of treatment. There could be resulting improvements with compliance, though this has not been directly demonstrated.

Guidance

Related submissions

There have been no closely related submissions but the current submission draws strongly on previous experience with existing interferon beta therapies including Avonex, Betaferon and Rebif. Only a single, Phase III efficacy study has been completed for peginterferon (with a dose-blinded extension study), which would normally be considered inadequate if this were an entirely new agent with a novel mechanism of action. Given that peginterferon is expected to have the same biological activity as Avonex and is thought to differ from it structurally and on pharmacokinetic grounds, a relatively small set of clinical trials is acceptable but a more complete exploration of different dosing regimens would have been more appropriate. The original Avonex submission and the extensive published literature on the use of interferon beta therapies provide indirect support.

European guidelines for the conduct of MS studies

The Committee for Medicinal Products for Human use (CHMP) of the European Medicines Agency has produced guidelines relevant to this submission, entitled 'Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis.'

The key points from this guideline are as follows:

- For RRMS relapse rate is an acceptable primary endpoint but disability should be monitored and should at least be shown not to worsen as a result of treatment.
- Suitable secondary endpoints include disability, proportion of patients relapsed and MRI measures.

- The EDSS⁴ is recommended as the most suitable primary measure for disability endpoints.
- MRI reading should be centralised and blinded.
- McDonald's criteria⁵ for diagnosis of MS should be applied.
- Superiority over placebo or active treatment should be demonstrated; non-inferiority studies are inadequate.
- The minimum duration of a confirmatory efficacy trial should be two years but in view of the availability of effective treatments, the guideline acknowledges that long-term placebo treatment may not be feasible or ethical. *'An option is to compare the new treatment to placebo in a short duration phase (e.g. one year or until patients have a new relapse) and thereafter to switch placebo-treated patients to a predefined active treatment or randomise them to the experimental product or a predefined active treatment. The proportion of subjects with no relapses over two years of follow-up then may be the primary endpoint.'*
- Where un-blinding is possible (for instance, due to side effects), a separate examining and treating clinician should be used.
- Safety data for at least two years should be available.
- For biological agents, immunogenicity should be assessed.
- For immunomodulating agents, autoimmune disorders and malignancy should be assessed, including postmarketing surveillance for a heightened risk of tumours.

The sponsor has complied with all of these guidelines, with the exception of the recommended study duration (the pivotal trial was only placebo-controlled in the first year). The design of the pivotal study is similar, however, to an option described in the guideline in which placebo subjects are changed to a different therapy after one year (italicised above). The sponsor *did not* follow the advice to use the two year results as the primary endpoint (underlined above) but the two year results were positive, and generally consistent with the one year results, so this is not a major deficiency.

Contents of the clinical dossier

The submission contained the following clinical information:

- 4 clinical pharmacology studies, all of which provided pharmacokinetic and 3 of which provided pharmacodynamic data.
- 1 population pharmacokinetic analysis based on the pivotal efficacy study.

⁴ The Expanded Disability Status Scale (EDSS): The score is based upon neurological testing and examination of functional systems (FS), which are areas of the central nervous system which control bodily functions. The functional systems are:

- Pyramidal (ability to walk)
- Cerebellar (coordination)
- Brain stem (speech and swallowing)
- Sensory (touch and pain)
- Bowel and bladder functions
- Visual
- Mental
- Other (includes any other neurological findings due to MS).

These rankings are especially important in the 'less severe' lower numbers of the scale, when a patient is still ambulatory, yet experiencing some abnormal signs or disability in other areas.

⁵ McDonald's criteria are MRI criteria used in the diagnosis of multiple sclerosis were introduced in 2001, revised in 2005 and again recently in 2010.

- 1 pivotal efficacy/safety study with its dose-blinded extension.

Paediatric data

The submission did not include paediatric data. The draft PI includes the comment:

‘The safety and efficacy of PLEGRIDY in patients below 18 years of age has not been studied.’

Good clinical practice

The clinical summaries and individual study reports contained assurances that the studies were performed in accordance with Good Clinical Practice (GCP) and the studies described appear to have been conducted in a professional and ethical manner.

Pharmacokinetics

Studies providing pharmacokinetic data

The sponsor submitted four Phase I PK studies, as well as a pharmacokinetic/pharmacodynamic (PK/PD) substudy based on intensive sampling of a small group of subjects from the pivotal efficacy study and a population PK report based on sparse sampling of all subjects in the pivotal efficacy study. Table 3 below shows the studies relating to each pharmacokinetic topic.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Table 3. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	105HV101	*
	- Multi-dose	105HV102	*
	Bioequivalence of different routes of administration - Single dose, SC versus IM	105HV101	
	- Single dose, PFP versus AI	105HV103	*
	- Multi-dose	n/a	
	Food effect	n/a	
PK in special populations	Target population §- Single dose	n/a	
	- Multi-dose	Intensive PK substudy of 105MS301	
	Hepatic impairment	n/a	
	Renal impairment	105RI101	*

PK topic	Subtopic	Study ID	*
	Neonates/infants/children/adolescents	n/a	
	Elderly	n/a	
Genetic/gender-related PK	Males vs. females	Pop-PK analysis of 105MS301	
PK interactions	Multiple drugs	Pop-PK analysis of 105MS301	
Population PK analyses	Healthy subjects	n/a	
	Target population	105MS301	

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. PFP – pre-filled pen, AI – auto-injector

Evaluator's conclusions on pharmacokinetics

The pharmacokinetics of peginterferon show substantial inter-individual variability, with exposure in some subjects greatly reduced compared to the median exposure in a cohort of healthy subjects, as illustrated in the figure below (Figure 2) from the intensive PK cohort of the pivotal MS study.

With this limitation in mind, the overall PK of peginterferon has been adequately characterised by the sponsor. When administered subcutaneously, at the proposed dose of 125 µg, the serum levels of peginterferon peak in 1 to 1.5 days and then decline over the course of a week to ten days. Thus, the drug is *not* expected to maintain significantly elevated levels throughout the proposed two week dose cycle.

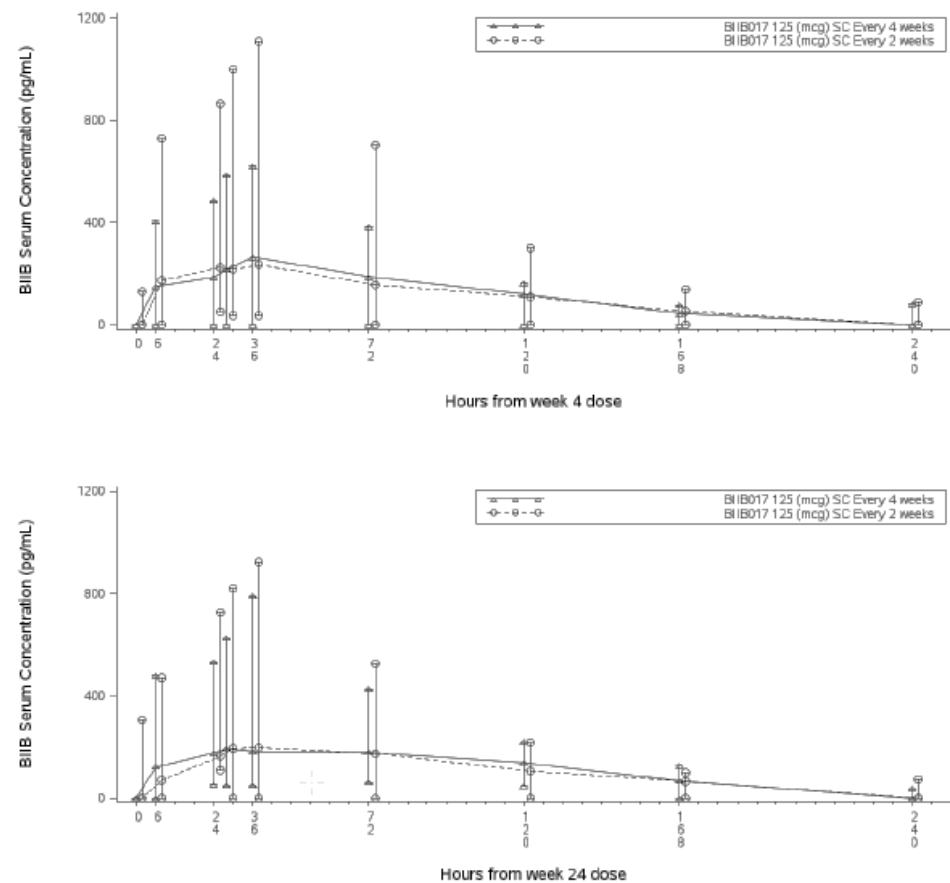
The drug is associated with an apparent volume of distribution of 481 ± 105 L (mean \pm standard error (SE)). It undergoes proteolysis and renal clearance, with renal clearance accounting for about half (approximately 47%) of the elimination of the drug. The elimination half-life is approximately 78 ± 15 h at steady state but varies considerably between subjects and across studies. In healthy volunteers, the elimination half-life of peginterferon was approximately double that of non-pegylated interferon beta-1a (Avonex) when both were administered as 6MIU⁶ and the AUC and C_{max} were also increased with the pegylated form.

Exposure is increased in subjects with renal impairment and in those with a low body mass index (BMI) but exposure does not appear to be affected by race or gender. The effect of hepatic impairment has not been studied. A population-PK analysis did not find that concomitant drugs had a major effect on the PK of peginterferon but the power of this analysis is unclear. Historically, beta interferons have not been associated with clinically significant pharmacokinetic drug interactions and this is expected to be true of peginterferon as well but the question has not been directly addressed.

The PK details provided in the draft PI are consistent with the submitted evidence. The PI does not discuss the metabolism or excretion of peginterferon and some additional comments would be appropriate.

⁶ MIU=Million International Units

Figure 2. Medians and ranges of serum BIIB017 concentrations (pg/mL) from ELISA by treatment group and time-evaluable subjects in Intensive PK population



Pharmacodynamics

Studies providing pharmacodynamic data

All submitted clinical studies except 105HV103 included a PD assessment using established surrogate biomarkers for the immunomodulatory actions of beta-interferon, such as neopterin and OAS (2',5'-oligoadenylate synthetase, 2', 5'-OAS).

Table 4 below shows the studies relating to each pharmacodynamic topic.

Table 4. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	N/a – primary mechanism of action for beta-interferon in MS remains unclear		
Secondary Pharmacology (surrogate markers)	Effect on neopterin & OAS	101HV101	
		101HV102	
Gender, other	Effect of gender	see Pop-PK/PD	

Genetic and Age-Related Differences in PD Response		analysis	
	Effect of renal impairment	105RI101	
	Effect of BMI	see Pop-PK/PD analysis	
	Effect of age	see Pop-PK/PD analysis	
PD Interactions	Multiple concomitant drugs	Pop-PK/PD analysis	
Population PD and PK-PD analyses	Healthy subjects	N/a	
	Target population §	105MS301, Report CPP-12-016-BIIB017	

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. N/a – not applicable.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

The primary PD effects of peginterferon were not studied but the primary effects of interferon betas are complex and poorly understood. Using the secondary biomarker neopterin, the sponsor has demonstrated that the peak PD response to peginterferon is slightly delayed relative to non-pegylated interferon but also more prolonged. Neopterin levels fall to baseline after about 10 days but this part of the proposed two-week dose cycle was not adequately studied. It seems likely that neopterin levels are low for the last few days of each dose-cycle and it is unclear if this compromises efficacy. Based on the interferon literature discussed below it seems likely that the waning of PD response after 10 days would compromise efficacy but this has not been directly addressed.

Dosage selection for the pivotal studies

The sponsor reports that the following issues were considered when choosing the 125 µg (12MIU) two-weekly regimen for further study:

- the single-dose and multiple-dose PK and PD (neopterin) responses
- the comparison with non-pegylated interferon beta-1a PK and PD
- the likelihood of accumulation with repeated dosing
- in vitro biological activity
- the safety and tolerability data from Phase I studies

The guiding principle in dose selection appears to have been *matching the approved dose of Avonex while aiming for the lowest feasible dosing frequency*. It is not clear that this approach has led to the sponsor choosing the most efficacious regimen. Low dosing frequency is likely to represent a major *marketing* advantage for peginterferon but indirect evidence suggests that it may compromise efficacy.

Overall conclusions on the appropriateness of dose selection

On balance, the sponsor has provided good evidence that peginterferon 125mcg two weekly (the proposed dose) provides a broadly similar pharmacodynamic effect as Avonex 30 µg weekly (the approved dose) as indicated by total dose administered per 4 week period (24MIU) and the resulting cumulative AUC for the biomarker neopterin. They have also shown that 125 µg is likely to be better tolerated than 188 µg and to have similar tolerability to Avonex 30 µg. The sponsor therefore selected the dose of 125 µg two-weekly for further study, and also assessed a less frequent dosing regimen (125 µg four-weekly) on the grounds that, if effective, this would provide greater convenience to patients.

What the sponsor has not done, however, is test a dosing regimen likely to give a continuous pharmacodynamic response throughout the dose cycle, such as 125 µg weekly. Firstly, the PK/PD studies did not assess the PD response in detail between 7 and 14 days, so it remains unclear when neopterin levels fall to baseline over the course of a two-week dose cycle and thus how long patients are effectively left untreated by the proposed two-weekly regimen. Secondly, the sponsor did not include a treatment arm in the pivotal studies assessing the safety and efficacy of 125 µg weekly.

The limited evidence from head-to-head studies of Avonex against its competitors suggests that infrequent interferon beta dosing, although more convenient for patients, is less effective than more frequent dosing. Avonex treatment produces a pharmacodynamic response that does not last through the weekly dose cycle and this appears to compromise efficacy. Pegylation could have been adopted as a means of addressing the deficiencies of a once-weekly Avonex regimen but this opportunity has not been pursued. Instead, the sponsor has used pegylation to find a dosing regimen even lower in frequency than is the case with Avonex, and which still leaves some patients with a weak or nonexistent pharmacodynamic response for the last part of each dose cycle.

The proposed peginterferon regimen is likely to have market appeal with patients because of its convenience but it is probably not the most effective possible regimen. This represents the single biggest deficiency in the sponsor's submission.

Efficacy

Studies providing efficacy data

The submission rests on the first year of a single, pivotal efficacy study, 105MS301 (Study 301). The study was designed to follow patients for two years but only the first year was placebo-controlled so the second year data is merely supportive.

Patients completing the second year were invited to join a follow-up study, 105MS302 (Study 302) but this study was ongoing at the time of submission and very few patients had completed an additional year of follow-up. The follow-up study also lacks a placebo control group. Thus, in its current incomplete form Study 302-should be rejected as an efficacy study though it does provide useful safety data.

These were the only two clinical studies performed in MS patients. The sponsor wrote a justification of their decision to perform just one adequate efficacy study, and this is considered in *Section Sponsor's justification for performing a single pivotal efficacy study* (Attachment 2).

The study conforms to recommendations on the conduct of studies in MS. Although the European Guidelines for the conduct of MS studies generally recommend a two year duration of placebo-controlled treatment, an accepted alternative explicitly discussed in

the Guidelines is a one year placebo-controlled efficacy phase followed by a switch to active treatment.

A significant deficiency in the study program was the sponsor's failure to perform a study assessing the efficacy and safety of more frequent dosing regimens of peginterferon, such as 125 µg weekly in comparison to peginterferon 125 µg once every two weeks (Q2W).

Evaluator's conclusions on efficacy

The efficacy of peginterferon has been established through a single year of placebo-controlled treatment, with some supportive data gathered from a second year of dose frequency blinded treatment in the same study and further dose frequency blinded treatment in an extension study. The placebo-controlled phase of the pivotal study had no substantial methodological flaws, reasonable attempts were made to preserve blinding where possible and the results were robust enough that they do not appear likely to have arisen from any systemic bias.

Relative to placebo, peginterferon at the proposed dose of 125 µg Q2W was associated with a reduction in annualised relapse rate of 35.6% ($p=0.0007$), a reduction in the proportion relapsed after one year of 39% ($p=0.0003$) and a reduction in sustained disability progression of 38% ($p=0.0383$). With respect to MRI endpoints, peginterferon 125mcg Q2W was associated with a reduction in new or newly enlarged T2 lesions of 67% ($p<0.0001$), a reduction in Gd-enhancing lesions of 86% ($p<0.0001$) and a reduction in new T1 hypointensities of 53% ($p<0.0001$).

The pivotal study also assessed a less frequent dose regimen, 125 µg Q4W, but this regimen was clearly inferior, achieving reductions for most of the endpoints that were intermediate between the placebo and Q2W results. An exception was disability progression, which was reduced by the same extent in each active group. Most Q4W endpoints achieved statistical significance in comparison to placebo, apart from Gd-enhancing lesions and T1 hypointense lesions. All of these endpoints are summarised in Table 5 below.

Most tertiary endpoints, including quality-of-life measures, were too insensitive to show a significant benefit.

Subgroup analyses did not reveal any significant reduction in efficacy in groups defined by demographic or disease characteristics, or by the presence or absence of potential telltale side effects that could have led to un-blinding.

Rough post hoc calculations with pessimistic imputation suggest that withdrawal bias did not play a major role in producing the positive findings.

The second year of the pivotal study and the on-going extension study in the same population are difficult to interpret because they lacked a placebo control. The efficacy data from the second and third year of treatment were generally reassuring, however, in that the relapse rate in the Q2W group continued to stay low and was similar to that seen in the placebo-controlled first year. Continued treatment with the Q4W regimen did not produce comparable efficacy and was clearly inferior.

The efficacy of peginterferon 125 µg weekly remains untested but on pharmacodynamic grounds appears likely to be more effective than the proposed regimen.

Table 5. Study 301 summary of key efficacy results at one year by treatment group

Endpoint	Statistic	Placebo	BIIB017 125 µg Q4W	BIIB017 125 µg Q2W
Clinical endpoints				
Annualized relapse rate	N	500	500	512
	Adjusted rate (95% CI)	0.397 (0.328, 0.481)	0.288 (0.234, 0.355)	0.256 (0.206, 0.318)
	% reduction vs. placebo	—	27.5	35.6
	p-value vs. placebo ^a	—	0.0114	0.0007
Proportion of subjects relapsed	N	500	500	512
	Estimated proportion ¹	0.291	0.222	0.187
	% risk reduction vs. placebo	—	26	39
	p-value vs. placebo ^b	—	0.0200	0.0003
Disability progression	N	500	500	512
	Estimated proportion of subjects progressed ²	0.105	0.068	0.068
	% risk reduction vs. placebo	—	38	38
	p-value vs. placebo ^b	—	0.0380	0.0383
MRI endpoints				
New or newly enlarging T2 hyperintense lesions	N (# of imputed values)	476 (18)	462 (23)	457 (18)
	Adjusted mean	10.9	7.9	3.6
	% reduction vs. placebo	—	28	67
	p-value vs. placebo ^a	—	0.0008	<0.0001
Gd enhancing lesions	N (# of imputed values)	477 (19)	463 (25)	457 (18)
	Mean	1.4	0.9	0.2
	% reduction vs. placebo	—	36	86
	p-value vs. placebo ^c	—	0.0738	<0.0001
New T1 hypointense lesions	N (# of imputed values)	476 (18)	462 (24)	457 (18)
	Mean	3.8	3.1	1.8
	% reduction vs. placebo	—	18	53
	p-value vs. placebo ^c	—	0.0815	<0.0001

Note: All p-values compare each active treatment group versus placebo based on: (a) negative binomial regression (b) Cox proportional hazards model; (c) multiple logit regression.

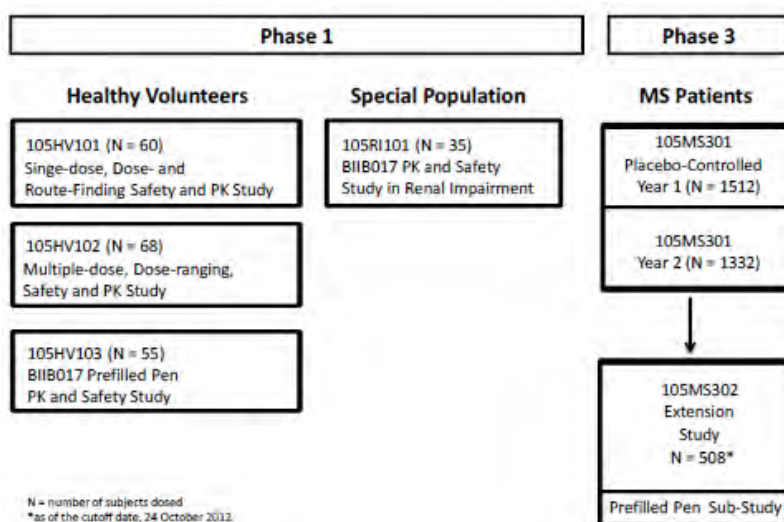
¹ From Kaplan-Meier curve of time to relapse.

² From Kaplan-Meier curve of time to progression (12-week confirmation).

Safety

Studies providing safety data

The following figures describe the six studies which provided evaluable safety data:

Figure 3. Overview of the clinical development program of BIIB017

Patient exposure

Exposure to peginterferon is summarised in Attachment 2.

Allowing for the persistence of biological effects for up to two weeks after the last dose, the mean duration of exposure to peginterferon in Year 1 of Study 301 was 44.3 weeks, with a similar duration of exposure between the two dose frequency groups. The total number of subject-years of placebo-controlled exposure was 429.2 subject-years for the Q4W group and 430.5 subject-years for the Q2W group and the vast majority of this exposure was to the proposed dose of 125 µg, apart from initial titration with lower doses.

In the overall experience (Studies 301 and 302 pooled), a total of 1468 subjects were exposed to at least 1 dose of peginterferon. The mean time on study was 68.7 weeks and the total exposure was 1932.0 subject-years. Total exposure to the Q4W regimen was 960.5 subject-years and to the Q2W regimen 971.9 subject-years. Overall, 1093 subjects were exposed for ≥48 weeks, and 415 subjects for ≥96 weeks. This represents an adequate overall exposure for the detection of uncommon side effects.

In the Phase I program in which exposure was generally brief (Table 6). Subjects in the PK/PD Study 105HV101 received a single dose of Avonex or peginterferon. In Study 105HV102, subjects received 2 to 4 injections, depending on dose frequency: subjects in the Q2W group received 4 injections of active peginterferon and subjects in the Q4W group received 2 injections of active peginterferon and two injections of placebo. In Study 105HV103, subjects received one dose of peginterferon by pre-filled syringe and another by auto-injector.

Table 6. Phase I Exposure. Extent of exposure to BIIB017 in Phase I studies in healthy volunteers and in subjects with renal impairment.

Clinical Study	BIIB017 Dose (µg)			Total (N)
	63	125	188	
105HV101 (Healthy Volunteers)	16	16	16	48
105HV102 (Healthy Volunteers)	19	19	20	58
105HV103 (Healthy Volunteers)	-	55	-	55
105RI101 (Subjects with Renal Impairment)	5	30	-	35 ^a
Total Number of Subjects Exposed	40	120	36	196
a. Includes 29 subjects with renal impairment and 6 healthy volunteers.				

Safety issues with the potential for major regulatory impact

Liver toxicity

Hepatic abnormalities are known to be increased by interferon beta treatment. In the placebo-controlled experience, the incidence of hepatic disorders was low but increased in the active groups (2 subjects in the placebo group and 4 subjects in each of the peginterferon groups), as indicated below in Table 7. The incidence of abnormal liver function tests is considered in Attachment 2 Section *Liver function*.

Table 7. Incidence of hepatic disorders by System Organ Class and Preferred Term. Year 1.

	Placebo	BIIB017 125 (mcg) SC		
		Every 4 weeks	Every 2 weeks	Total
Number of subjects in safety population	500 (100)	500 (100)	512 (100)	1012 (100)
Number of subjects with an event	2 (<1)	4 (<1)	4 (<1)	8 (<1)
HEPATOBIILIARY DISORDERS	2 (<1)	4 (<1)	4 (<1)	8 (<1)
HEPATIC PAIN	2 (<1)	2 (<1)	2 (<1)	4 (<1)
HYPERBILIRUBINAEMIA	0	1 (<1)	2 (<1)	3 (<1)
ACUTE HEPATIC FAILURE	0	1 (<1)	0	1 (<1)

NOTE 1: Numbers in parentheses are percentages.

2: For subjects who switched to alternative MS medications, data after switch and 14 days after last dose of study treatment are excluded.

3: A subject was counted only once within each system organ class/preferred term.

4: Preferred terms are presented by decreasing incidence in the total BIIB017 column within each system organ class.

In the overall experience, the incidence of hepatic disorders was higher, consistent with the increased duration of monitoring. The incidence was similar between the two dose frequency groups (5 and 6 subjects [$<1\%$] in the Q4W and Q2W groups, respectively). Hepatic pain was the most common disorder (2 and 3 subjects in Q4W and Q2W groups, respectively).

A list of all hepatic adverse events (AEs) leading to discontinuation in Study 301 is tabulated below; there were no discontinuations due to hepatic AEs in Study 302.

The most significant hepatic event was an episode of acute hepatic failure thought not to be related to study treatment. The subject developed liver failure in the setting of corticosteroid treatment, recovered and then months later while off BIIB017 had another

episode when corticosteroids were used to treat another MS relapse. An independent liver specialist assessed the liver failure as being due to the corticosteroids.

Table 8. List of adverse events that led to discontinuation of study treatment or study withdrawal associated with hepatic disorder or elevated liver enzymes.

Treatment Group	Onset Day of Event	AE Preferred Term(s)	Investigator Term(s)	Relationship to Study Treatment Per Investigator	Liver Function Test Maximum Level of Abnormality	Serious (Yes/No)	Outcome at of Data Cutoff Date
Placebo-Control Experience (Year 1 of Study 301)							
Placebo	5	Hepatic Enzyme Increased	Liver Enzymes – Upper Above Normal Level	Related (as assessed during blinded treatment)	ALT/AST >5×ULN	No	Not resolved
BIIB017 Q4W	48	Acute Hepatic Failure	Acute Hepatic Failure	Not related	ALT/AST >5 × ULN Total bilirubin >2 × ULN	Yes	Resolved
BIIB017 Q4W	57	ALT Increased	Serum ALT >5 × ULN	Related	ALT/AST >5 × ULN	No	Resolved
BIIB017 Q4W	1	Liver Function Test Abnormal	Abnormal LFT (ALT, AST, and LDH Elevation)	Not related	ALT/AST >5 × ULN	No	Resolved
BIIB017 Q2W	270	Transaminases Increased	Transaminitis	Related	ALT/AST >5 × ULN	Yes	Resolved
BIIB017 Q2W	57	Transaminases Increased	High Level of Hepatic Transaminase	Related	ALT/AST >5 × ULN	No	Resolved
BIIB017 Q2W	1	ALT and AST Increased	High Level of ALT and AST	Related (both)	ALT/AST >5 × ULN	No	Not resolved
Year 2 of Stud							
Placebo to BIIB017 Q2W	394	Drug-Induced Liver Injury	Acute Drug-Induced Hepatitis	Not related	ALT/AST >5 × ULN	Yes	Resolved
BIIB017 Q4W	336	ALT Increased	Elevated Level of ALT	Related	ALT >5 × ULN, AST ≥3 × ULN	No	Not resolved
Treatment Group	Onset Day of Event	AE Preferred Term(s)	Investigator Term(s)	Relationship to Study Treatment Per Investigator	Liver Function Test Maximum Level of Abnormality	Serious (Yes/No)	Outcome at of Data Cutoff Date
BIIB017 Q4W	435	Increased Level of ALAT, AST, and GGT	ALT, AST, and GGT Increased	Related (all)	ALT/AST >5 × ULN	No	Not resolved
BIIB017 Q2W	338	ALT Increased	Elevated Laboratory Values of ALT	Related	ALT/AST >5 × ULN	No	Resolved
ALT = alanine transferase, AST = aspartate transaminase; ULN = upper limit of normal; Q4W = every 4 weeks; Q2W = every 2 weeks; GGT = gamma-glutamyl transaminase Source: Appale 30 and Table 134; Study 301 Appendix 16.2.7, Table 2 and Table 9; Individual Subject Narratives, Study 301, Section 14.3.3 * There were no discontinuations or withdrawals due to hepatic disorders or hepatic enzyme elevations during Study 302.							

This table has been edited to remove individual patient information (patient numbers).

The draft PI contains the following warning, which fairly summarises this data:

‘Hepatic injury, including elevated serum hepatic transaminase levels, hepatitis, and autoimmune hepatitis, and rare cases of severe hepatic failure, has been reported with interferon beta. Elevations in hepatic enzymes and hepatic injury have been observed with the use of PLEGRIDY. Patients should be monitored for signs of hepatic injury.’

Haematological toxicity

As discussed in Attachment 2 Section *Haematology*, peginterferon treatment was associated with a decline in mean white blood cell (WBC) counts across the active groups and an increased incidence of shifts to low WBC, lymphocyte and neutrophil counts. There were also minor declines in mean red blood cell counts and platelet counts. Abnormal counts did not usually lead to withdrawal (white cells, no withdrawals; red cells, no withdrawals; platelets, n=2). All subjects recovered without sequelae.

The incidence of haematological abnormalities was low and there is no evidence of permanent bone marrow suppression in the safety experience so far but caution is advised when administering peginterferon. Routine haematological monitoring at baseline and after commencing the drug could be useful to detect abnormal counts and the drug should be used with particular caution in those with a history of abnormal counts.

The proposed PI contains the following warning, which is appropriate:

'Decreased peripheral blood counts in all cell lines, including rare pancytopenia and severe thrombocytopenia, have been reported in patients receiving interferon beta. Cytopenias, including rare severe neutropenia and thrombocytopenia, have been observed in patients treated with PLEGRIDY. Patients should be monitored for symptoms or signs of decreased peripheral blood counts.'

Serious skin reactions

Not counting injection-site reactions, which have already been considered, dermatological reactions to peginterferon were uncommon. AEs in the body system 'skin and subcutaneous tissue disorders' occurred in 9% of the placebo group and 15% of the Q2W group, with pruritus as the only individual AE that was at least 2% more common with Q2W treatment (4%) than with placebo (1%).

Rash was reported in 6 subjects (1%) in the Q2W group of the placebo-controlled dataset but was not rated as severe in any subject. Erythema was reported in 8 subjects (2%) and was again not rated as severe in any subject. All other dermatological AEs occurred in <1% of the Q2W group. Results in the Q4W group were similar (pruritus 2%, rash 1%, erythema <1%).

Amongst serious adverse events (SAEs) in the overall experience of peginterferon, rash did not appear as a preferred term, but two subjects in the Q2W group had angioedema.

Overall, peginterferon appears to be associated with a relatively low incidence of serious skin reactions.

Cardiovascular safety

Cardiovascular events were assessed by the sponsor as an AE of special interest, because of isolated reports of a potential link with interferon beta therapy. Generally, interferon beta is not considered to pose a significant cardiovascular risk. In the placebo-controlled experience, the incidence of cardiovascular AEs was similar between the active and placebo groups (7% placebo versus 9% Q4W and 7% Q2W). Individual cardiovascular AEs reported by ≥2 subjects included syncope, loss of consciousness, tachycardia, palpitations, angina pectoris, sinus bradycardia, right bundle branch block, arrhythmia, chest pain and abnormal ECGs. Most the cardiovascular AEs were assessed as mild or moderate; the only severe AE (one subject with chest pain) was reported in the placebo group.

In the overall experience, the incidence of cardiovascular AEs was similar between dose frequency groups (10% and 9% in the Q4W and Q2W groups, respectively).

Unwanted immunological events

Hypersensitivity reactions have been reported with protein-based biological therapies, including interferon beta. Peginterferon appears to pose a low risk of hypersensitivity reactions, similar to that seen with other interferon beta therapies.

In the placebo-controlled dataset, the incidence of hypersensitivity events was similar between treatment groups (14%, 13% and 16% in the placebo, Q4W and Q2W groups, respectively). The most common AEs potentially linked to hypersensitivity were cough (6%, 5% and 4% in the placebo, Q4W and Q2W groups, respectively) and pruritus (1%, 2% and 4% in the placebo, Q4W and Q2W groups, respectively).

Most hypersensitivity AEs were rated as mild or moderate; severe AEs were reported in 2 subjects in the placebo group (<1%), 3 in the Q4W group (<1%), and 4 subjects in the Q2W group (<1%).

In the placebo-controlled dataset, there were 3 hypersensitivity SAEs in the active groups and none in the placebo group. One SAE (asthma) was reported in 1 subject in the Q4W group and 2 SAEs (anaphylactic reaction and hypersensitivity) were reported in the Q2W

group. None of these events was considered related to treatment and none were associated with the presence of antibodies to the interferon or the mPEG moiety of peginterferon. Two of these events had alternative potential causes: the asthma case occurred in a patient with pre-existing asthma who did not develop asthma following a subsequent rechallenge with peginterferon; the anaphylactic reaction appeared to be secondary to MRI contrast in a patient with known allergy to MRI contrast agents. In the third case, the event was entered as an SAE of 'hypersensitivity' but was not diagnosed as an allergic reaction by the dermatologists who evaluated the patient; furthermore, it resolved with continued peginterferon treatment.

In the overall experience, there were 4 additional SAEs in the hypersensitivity category (shock, angioedema, angioneurotic edema, and urticaria). The case of shock appeared to be related to sepsis and not to study treatment but the 3 other cases appeared to be related to peginterferon. All resolved with standard medical treatment.

The incidence of hypersensitivity reactions did not appear to be increased in subjects with antibodies. The number of subjects with hypersensitivity events was 18% and 22% in the Q4W and Q2W groups, respectively, amongst those with positive binding antibodies (BAb) at any time-point, compared to 14% and 16%, respectively, in subjects that never had BAb.

Overall, the incidence of hypersensitivity reactions with peginterferon appears to be low, and hypersensitivity events observed so far have all resolved without serious sequelae. As a protein-based agent, peginterferon should be used with the usual caution.

Postmarketing data

At the time of submission, peginterferon is an investigational product that has not been marketed in any countries so there is no postmarketing experience with the pegylated form of interferon beta-1a.

On the other hand, there is extensive experience with non-pegylated forms of interferon beta. The known side effect profile of interferon beta includes flu-like symptoms, injection site reactions, mood changes, abnormalities of liver function and reductions in white blood cell counts, all of which are considered in Attachment 2 Section *Adverse events of special interest*. Overall, peginterferon appears to have a safety and tolerability profile that is consistent with the profile expected from the pivotal studies and postmarketing experience of other interferon beta therapies.

Evaluator's conclusions on safety

The safety of peginterferon has been adequately studied in the Phase III program, with an overall exposure of 1932 patient-years in 1468 patients.

The evidence suggests that the safety and tolerability of peginterferon is similar to other interferon beta products. Most of the adverse events observed in the safety database relate to tolerability, rather than to severe health risks. The main tolerability issues are flu-like symptoms and injection-site reactions. Another issue is a tendency for peginterferon recipients to have asymptomatic abnormalities on blood tests, including reduced white cell counts and elevated liver enzymes.

More serious toxicity was rare but isolated case of severe injection site reactions, hypersensitivity reactions or haematological disturbances were observed, including one case of severe thrombocytopenia and one of severe neutropenia both of which resolved on cessation of treatment. The incidence of *serious* hypersensitivity events was <1% and all serious hypersensitivity reactions resolved with discontinuation of peginterferon and standard medical treatment; none were associated with hypotension. A single case of anaphylaxis was likely to be due to an allergy to MRI contrast. Reduced white cell counts

were not associated with an increased risk of infection. Combined elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >3 times upper limit of normal (ULN) and total bilirubin >2 times ULN were very uncommon and were reported in only 2 of 1468 peginterferon -treated subjects ; one of these case was more likely to be attributable to steroids and the other was asymptomatic and resolved on discontinuation of peginterferon.⁷

Treatment with peginterferon was *not* associated with an increased incidence of cardiovascular events, depression and suicidal ideation, malignancy, infections, seizures, or autoimmune disorders compared with placebo. Based on previous experience with interferon beta, however, it is expected that more extensive use of peginterferon might eventually reveal an increased risk of depression, seizures, spasms and fatigue.

Most side effects were equally prevalent with the Q2W and Q4W regimen but injection-related symptoms would clearly occur less frequently with less frequent injections. There was a trend suggesting that white cell counts were less likely to be depressed by the Q4W regimen.

Peginterferon had low immunogenicity and the incidence of hypersensitivity reactions and other AEs was not affected by the presence of antibodies (neutralising antibodies (Nabs), BAbs or anti- polyethylene glycol (PEG) antibodies).

In conclusion, the safety and tolerability of peginterferon is acceptable, and similar to other agents in its class. Furthermore, the description of adverse effects in the draft PI appears to be consistent with the submitted data.

First round benefit-risk assessment

First round assessment of benefits

The benefits of peginterferon in the proposed usage are:

- a reduction in annualised relapse rate of 35.6% (p=0.0007);
- a reduction in the proportion relapsed after one year of 39% (p=0.0003);
- a reduction in sustained disability progression of 38% (p=0.0383);
- a reduction in new or newly enlarged T2 lesions of 67% (p<0.0001);
- a reduction in Gd-enhancing lesions of 86% (p<0.0001);
- a reduction in new T1 hypointensities of 53% (p<0.0001).

This represents similar efficacy to that provided by existing interferon beta treatments but with the advantage of only needing 2 injections per four week cycle, compared to 4 with Avonex, 12 with Rebif, or 14 with Betaferon.

First round assessment of risks

The main risks of peginterferon in the proposed usage are:

- flu-like symptoms
- injection-site reactions
- elevated liver enzymes

⁷ Sponsor comment: 'Three of 1468 peginterferon -treated subjects ; one of these events was more likely to be attributable to steroids and was assessed as unrelated to BIIB017. The other two events resolved on discontinuation of peginterferon.'

- reduced white cell counts

A more complete discussion of safety issues can be found in Attachment 2 Section *Evaluator's overall conclusions on clinical safety*.

Overall, these risks are comparable to those that subjects would face with competing interferon beta products so that there is no definite increase in risk when using peginterferon in place of another agent from its class.

First round assessment of benefit-risk balance

The benefit-risk balance of peginterferon, given the proposed usage, is favourable, and appears to be similar to other agents in its class. Compared to other interferon beta preparations, peginterferon offers the potential advantage of less frequent injections for broadly similar overall benefit, though it is not possible to compare agents in the absence of head-to-head studies.

The sponsor has not adequately confirmed that the proposed regimen is the optimal regimen and it seems at least possible that weekly treatment with the same dose would offer a more favourable benefit-risk balance – that it would be more effective than two-weekly treatment with no major change in safety. Firstly, the submitted pharmacodynamic studies suggest that the biological effects of peginterferon wane after about 10 days, leaving a gap of about 4 days prior to the next dose in which the patient does not experience any effective immunomodulation. Secondly, the sponsor did not perform any Phase II dose-finding studies that could have explored the efficacy of more frequent dosing, so the efficacy of a weekly regimen is completely untested. Thirdly, the literature on non-pegylated interferon beta suggests that more frequent dosing is generally more effective – that pulsatile regimens, which allow biomarkers to fall between doses, are less effective than more frequent regimens which maintain elevation of biomarkers. Thus, it is expected that peginterferon Q2W would be less effective than other interferon betas with more frequent dosing.

First round recommendation regarding authorisation

Recommendations regarding authorisation depend on policy considerations. If it is considered that the sponsor's obligation is merely to demonstrate that peginterferon has acceptable safety and is more effective than placebo, then the submitted evidence is sufficient to support the application. If the sponsor is considered to have an obligation to find the most effective regimen, with the best trade-off between efficacy and tolerability, it appears that they have not fully discharged that obligation.

In general, marketing applications to the TGA are approved if the proposed regimen is safe and more effective than placebo. On this basis, approval is recommended in this report but it would also be reasonable to reject the sponsor's application until the efficacy of peginterferon 125 µg weekly has been assessed.

- Peginterferon should be authorised for use at a dose of 125 µg two-weekly, for the prevention of relapses in subjects with relapsing and remitting multiple sclerosis.
- The sponsor should be encouraged to explore the efficacy and safety of more frequent dosing regimens.

Clinical questions**Pharmacokinetics**

No questions.

Pharmacodynamics

Most PD studies assessed biomarkers only sparsely between 7 and 14 days post-dose. As a result, the proportion of subjects with clinically meaningful elevation of biomarkers in the last few days of the proposed two-week dose cycle is unclear.

This raises four closely related questions:

1. What levels of neopterin are consistent with a clinically meaningful response to immunomodulation with interferon beta?
2. What levels of neopterin are associated with the optimal clinical response to immunomodulation with interferon beta?
3. With the proposed dosing regimen, what proportion of subjects have clinically meaningful elevations of neopterin throughout the proposed two week cycle?
4. With the proposed dosing regimen, what proportion of subjects have optimal elevations of neopterin throughout the proposed two-week cycle?

Efficacy

5. Why was no attempt made to assess the efficacy of peginterferon 125 µg once-weekly?
6. Does the sponsor concede that previous published experience with non-pegylated interferons suggests that, in general, greater efficacy is achieved with more frequent dosing?
7. It would be of interest to report the adjusted annualised relapse rate (ARR) results in a post hoc analysis in which Gd+ status was included in the binomial regression model but such an analysis would carry less weight than the prospectively defined primary analysis.

Safety

No questions.

Second round evaluation of clinical data submitted in response to questions

The clinical evaluator asked questions regarding the pharmacodynamics of peginterferon beta-1a. While these questions are of interest responses are unlikely to alter the decision on registration of peginterferon beta-1a. For this reason a second round evaluation was not requested.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) Peginterferon beta-1a Australian RMP (AUS-RMP) version 01, dated 14 August 2013 (data lock point 24 October 2012), AUS-RMP version 2, dated 23 May 2014 (data lock point 24 October 2012) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 9.

Table 9. Summary of Ongoing Safety Concerns

Important identified risks	Serious hypersensitivity reactions Hepatic injury Decreased peripheral blood cell counts Serious injection site reactions
Important potential risks	Depression and suicidal behaviour Seizure disorders Cardiac disorders Thyroid disorders Malignancies Immunogenicity
Important missing information	Safety profile in patients over the age of 65 years Safety profile in children and adolescents Effect on pregnancy outcomes Exposure during lactation Safety profile in patients with hepatic impairment Safety profile in patients with decreased peripheral blood counts

Pharmacovigilance plan

Table 10 is a summary of the pharmacovigilance activities proposed in the AUS-RMP.

Table 10. Summary of sponsor's proposed pharmacovigilance activities

Safety concern	Planned action(s)
Important identified risks	
Serious hypersensitivity reaction	Routine pharmacovigilance, and additional data collection in the 302 safety extension study.
Hepatic injury	Routine pharmacovigilance, and additional data collection in the 302 safety extension study.
Decrease in peripheral blood cell count	Routine pharmacovigilance, and additional data collection in the 302 safety extension study.
Serious injection site reactions	Routine pharmacovigilance, and additional data collection in the 302 safety extension study.
Important potential risks	
Depression and suicidal behaviour	Routine pharmacovigilance, and additional data collection in the 302 safety extension study.
Seizure disorders	Routine pharmacovigilance, and additional data collection in the 302 safety extension study.
Cardiac disorders	Routine pharmacovigilance, and additional data collection in the 302 safety extension study.
Thyroid disorders	Routine pharmacovigilance, and additional data collection in the 302 safety extension study.
Malignancies	Routine pharmacovigilance, and additional data collection in the 302 safety extension study.
Immunogenicity	Routine pharmacovigilance, and additional data collection in the 302 safety extension study.
Important missing information	
Use in elderly (>65years)	Routine pharmacovigilance
Use in paediatrics	Routine pharmacovigilance, Clinical study in patients between ages 10 and 17-years-old.
Pregnancy and lactation	Routine pharmacovigilance, European Interferon Beta Pregnancy Registry
Safety profile in patients with hepatic impairment	Routine pharmacovigilance
Safety profile in patients with decreased peripheral blood counts	Routine pharmacovigilance

Risk minimisation activities

The sponsor proposes routine risk minimisation through information provided in the PI for all the safety concerns identified.

Reconciliation of issues outlined in the RMP report

Table 11 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 11. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the	<p><i>No safety considerations were raised in the Nonclinical and Clinical Evaluation Reports.</i></p> <p><i>The Australian Product Information will be updated based on the TGA's request, and the Risk Management</i></p>	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.</p>	<p><i>Plan will be updated accordingly, as necessary.</i></p>	
<p>2. It is noted that the following safety risks have been identified with recombinant interferon beta-1a:</p> <ul style="list-style-type: none"> a. Thrombotic thrombocytopenic purpura; b. Retinal vascular disorders; c. Autoimmune disorders such as autoimmune hepatitis; d. Serious infection; 	<p><i>The sponsor has given the TGA's requests due consideration and, based on the data from Phase III studies of peginterferon beta-1a and when applicable Phase III placebo-controlled studies and postmarketing data for Avonex, and proposes to update the risk management documents as described below.</i></p> <p><i>a. Thrombotic Thrombocytopenic Purpura</i></p> <p><i>The Sponsor, based on the recommendation of the TGA, will include thrombotic thrombocytopenic purpura (TTP) as an important potential risk for peginterferon beta-1a in the Risk Management Plan (RMP).</i></p> <p><i>TTP is not proposed to be added to</i></p>	<p>The sponsor's response is satisfactory.</p>

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>e. Systemic lupus erythematosus and drug induced lupus erythematosus.</p> <p>The sponsor should provide justification as to why these safety risks are not considered relevant to PEGylated interferon beta-1a. Otherwise, these safety risks should be added to the list of ongoing safety concerns. The pharmacovigilance and risk minimisation sections in the AUS-RMP should be updated consequently to provide plans for managing these safety issues, including proposed update to the PI and CMI.</p>	<p><i>the Australian Product Information (PI) as there were no reported cases of TTP in peginterferon beta-1a clinical studies and it is not considered to be a class effect as it is not listed in the beta interferon Australian PIs across the class.</i></p> <p><i>The sponsor has also conducted a cumulative search of the Biogen Idec Avonex lobal Safety Database for the reporting interval from International Birth Date (IBD) 17 May 1996 to 01 November 2013 using the Medical Dictionary for Regulatory Activities (MedDRA; Version 16.1) preferred terms of haemolytic uraemic syndrome (HUS), TTP, and thrombotic microangiopathy (TMA).</i></p> <p><i>From this analysis, the sponsor analysed reported cases of TTP, HUS, and TMA in patients treated with Avonex® and determined that they were within the expected background rate observed in the general population. From these reports and analyses, there was no clear evidence of a causal association between TTP, HUS, and TMA and Avonex. The overall reporting rate of postmarketing reports of TTP, HUS, and TMA with Avonex is estimated to be 6.83 per million person-years (95% confidence interval [CI]: 3.13-11.20), which is below the background incidence of 11.3 per million for suspected TTP-HUS [Terrell 2005].</i></p> <p><i>However, when strictly considering only reports of TTP, HUS, or TMA considered to be potentially related to Avonex (excluding reports with alternative etiology, etc.), the cumulative reporting rate is 1.71 per million person-years (95% CI: 0.35-4.99), which is well below the incidence in the general population.</i></p> <p><i>If, during postmarketing surveillance, data become available</i></p>	

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	<p><i>to suggest a signal, it will be evaluated, and if appropriate, the sponsor will inform the Agency and update the RMP and, if necessary, labelling documents accordingly.</i></p> <p><i>b. Retinal Vascular Disorders</i></p> <p><i>There is no evidence of increased risk of retinal vascular disorders associated with peginterferon beta-1a. During the placebo-controlled Year 1 of Study 105MS301, 1 (<1%) subject in the peginterferon beta-1a every 4 week group and 2 subjects in the placebo group experienced nonserious retinal vascular disorders (preferred terms: vitreous floater, vitreous haemorrhage, and retinal vascular disorder, respectively) (Study 105MS301 Clinical Study Report, Table 193).</i></p> <p><i>The sponsor has reviewed the available peginterferon beta-1a and Avonex (interferon [IFN] beta-1a intramuscular [IM]) clinical trial data along with the Avonex post-marketing reports to assist with the assessment of whether retinal vascular disorders are a safety risk for peginterferon beta-1a.</i></p> <p><i>Similarly, there is no evidence of increased risk of retinal vascular disorders associated with Avonex. The incidence of events associated with retinal vascular disorders in Phase III studies of Avonex was also very low, with 2 Avonex-treated subjects experiencing nonserious events (<1%) and no events in placebo-treated subjects over two years of treatment.</i></p> <p><i>The overall reporting rate of post-marketing reports of retinal vascular disorders with Avonex was 7.4 per 100,000 patient-years. The estimated reporting rate of serious cases of retinal vascular disorders with Avonex is 1.3 per 100,000 patient-years. Assuming a constant risk over</i></p>	

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	<p><i>10 years, the annual incidence of retinal vascular disorders is estimated as 163 per 100,000 persons in the general population [Cugati 2006]. These Avonex post-marketing reporting rates are well below the estimated incidence rates for retinal vascular disorders within the general population.</i></p> <p><i>Retinal vascular disorders are not considered to be a class effect because they are not listed in the Australian PI across the class (only listed within Rebif PI).</i></p> <p><i>In summary, there is no evidence of a risk for retinal vascular events with peginterferon beta-1a as a class. Hence, the sponsor proposes that retinal vascular disorders should not be included as a safety risk in the peginterferon beta-1a RMP.</i></p> <p><i>If, during postmarketing surveillance, data become available to suggest a signal, it will be evaluated, and if appropriate, the sponsor will inform the Agency and update the RMP and, if necessary, labelling documents accordingly.</i></p> <p><i>c. Autoimmune Disorders Such as Autoimmune Hepatitis</i></p> <p><i>The sponsor, based on the recommendation of the TGA, will include autoimmune disorders as an important potential risk for peginterferon beta-1a in the RMP.</i></p> <p><i>It is proposed not to add autoimmune disorders in general to the Australian PI as there were no reported cases in peginterferon beta-1a clinical studies and it is not considered to be a class effect as it is not listed in the Australian PI across the class.</i></p> <p><i>Autoimmune disorders such as autoimmune hepatitis and thyroid disorders have been associated with interferon beta-1a use. Autoimmune</i></p>	

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	<p><i>hepatitis will be discussed here. Thyroid disorders are discussed in further detail in the response to TGA Question 8, Part c. Events of autoimmune hepatitis are currently captured in the Australian RMP within the important identified risk of hepatic injury, and autoimmune hepatitis is included in the Warnings and Precautions section of the proposed PI. No further update to the PI is considered necessary in response to this question.</i></p> <p><i>d. Serious Infection</i></p> <p><i>The sponsor has reviewed the available peginterferon beta-1a and Avonex clinical trial data together with all IFN-beta product labelling to assess whether serious infection is a safety risk for peginterferon beta-1a.</i></p> <p><i>Results from Phase III studies of peginterferon beta-1a showed no evidence of an increased risk of serious infections in subjects treated with peginterferon beta-1a. The incidence of serious infections was low and similar, with overlapping CIs for peginterferon beta-1a- and placebo-treated subjects in the placebo-controlled Year 1 of Study 105MS301. Similarly, for the overall peginterferon beta-1a experience at the time of the most recent safety analysis (as of 27 March 2013), including all peginterferon beta-1a-treated subjects from Studies 105MS301 and 105MS302 with up to 3.5 years of exposure, the incidence of serious infections remained low and similar to the incidence observed in the placebo-controlled phase. In Phase III clinical studies of Avonex, the incidence of serious infections was also low and similar to placebo, with overlapping CIs.</i></p> <p><i>Serious infection is not considered to be a class effect because, currently, it is not listed within the Australian PI</i></p>	

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	<p><i>of any of the IFN-beta products within the class.</i></p> <p><i>Patients with multiple sclerosis (MS) are at a greater risk for developing serious infections compared with the general population. According to 1 Swedish MS registry study, patients with MS (n = 20,276) had an increased risk of infection-related hospital admissions compared with patients without MS in the general population (n = 203,951), with a relative risk of 4.26 (95% CI: 4.13 to 4.40) [Montgomery 2013].</i></p> <p><i>The risk for patients with MS developing serious infections appears similar for patients treated with IFN-beta therapies and is comparable to those patients not receiving a disease-modifying therapy, suggesting that IFN-beta is not associated with an increased risk of serious infections. An internally conducted database study of insurance claims in the United States (Impact database) between 2004 and 2012 showed a slightly lower incidence of serious infections among patients with MS treated with IFN-beta (n = 13,000) than those unexposed to any disease-modifying therapy (n = 26,289) [incidence rate ratio: 0.71, 95% CI: 0.66 to 0.76]. Infections in the study were indicated by the first hospitalisation as standardised by the Ninth Revision of the International Classification of Diseases. More common infections observed in both cohorts included pneumonia, sepsis, urinary tract infection, and staphylococcal infection. The annualised incidence of each of these specific infections in the IFN-beta group is noted to be similar to, or lower than, the MS unexposed cohort. Hence, current data demonstrate that there is an increased risk of serious infections within the MS population compared</i></p>	

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	<p><i>with the general population; however, there is no clear evidence that the use of IFN-beta increases the risk of serious infections compared to that of MS patients not exposed to a disease-modifying therapy.</i></p> <p><i>In summary, several sources of evidence argue against serious infections being classified as a safety risk for peginterferon beta-1a. Review of the peginterferon beta-1a and Avonex placebo-controlled studies does not show evidence of an imbalance in the incidence of serious infections compared with placebo. Additionally, incidence estimates of the overall and most common serious infections observed in a large claims study demonstrate that patients with MS receiving IFN-beta are at the same or lower risk for serious infections compared with unexposed patients with MS. Finally, serious infections are not considered to be a class effect because this risk is not currently listed within the Australian PI for any approved IFN-beta therapy. For all of the above reasons, the sponsor proposes exclusion of serious infections as a safety risk.</i></p> <p><i>If, during postmarketing surveillance, data become available to suggest a signal, it will be evaluated, and if appropriate, the sponsor will inform the Agency and update the RMP and, if necessary, labelling documents accordingly.</i></p> <p><i>e. Systemic Lupus Erythematosus and Drug-Induced Lupus Erythematosus</i></p> <p><i>The sponsor, based on the recommendation by TGA, will include systemic lupus erythematosus (SLE) and drug-induced lupus erythematosus (DILE) as an important potential risk for peginterferon beta-1a in the RMP.</i></p> <p><i>It is proposed that SLE including drug induced lupus erythematosus</i></p>	

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	<p><i>not be added to the Australian PI as there were no reported cases of SLE or DILE in peginterferon beta-1a clinical studies. Additionally, although the Avonex Australian PI has lupus erythematosus listed, SLE is not considered to be a class effect of beta-IFNs as it is not listed in the Australian PI across the class.</i></p> <p><i>The sponsor conducted a cumulative search from IBD to 28 February 2013 of the Biogen Idec Global Safety Database for cases of lupus erythematosus (including subtypes) and the PTs of neonatal lupus-erythematosus, neuropsychiatric lupus, systemic lupus erythematosus (SLE) arthritis, SLE disease activity index abnormal, SLE disease activity index increased, and SLE disease activity index decreased. From this analysis the sponsor analysed reported cases of SLE in patients treated with Avonex and determined that they were within the expected background rate observed in the general population. It is concluded that there is no clear evidence of a causal association between lupus and Avonex. The overall reporting rate of postmarketing reports of SLE was 1.76 per 100,000 person-years, which is below the overall-incidence of SLE in the general population (5.1 per 100,000 person-years) [Naleway 2005]. However, when strictly considering only reports considered to be potentially related to Avonex (excluding reports with alternative etiology, etc.) and new onset SLE reports, the cumulative reporting rate is 0.47 per 100,000 person-years.</i></p> <p><i>If, during postmarketing surveillance, data become available to suggest a signal, it will be evaluated, and if appropriate, the sponsor will inform the Agency and update the RMP and, if necessary,</i></p>	

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	<p><i>labelling documents accordingly.</i></p> <p>Risk Management Plan</p> <p><i>Part II, Module SVII.3: Details of important identified and potential risks from clinical development and post-authorisation experience (including newly identified)</i></p>	
<p>3. The sponsor should provide protocols of the study 105MS302 and the planned paediatric study to the TGA for review.</p>	<p><i>The protocol for study 105MS302 was included in the original MAA in Module 5.3.5.1 (105MS302 Clinical Study Report, Appendix 16.1.1), and was also provided within this response (not in AusPAR) for ease of review. This study is ongoing.</i></p> <p><i>A draft synopsis of the planned paediatric study is also provided. A full protocol is not currently available, as the sponsor has committed to modify the attached study design upon completion of the Phase III study and prior to initiating the paediatric study.</i></p>	<p>The sponsor's response is satisfactory.</p>
<p>4. As the European pregnancy registry does not include Australia patients, the sponsor should clarify what it plans to do in case its application in the EU is rejected or deferred. It should be noted, Section 4.3 of 'Guideline on Similar Biological Medicinal Products Containing Interferon Beta' (EMA/CHMP, date for coming into effect 01 September 2013) requires 'a pregnancy registry for IFN-beta (interferon beta) containing products is mandatory'.</p>	<p><i>Biogen Idec has proposed, and the Pharmacovigilance Risk Assessment Committee (PRAC) has agreed, that peginterferon beta-1a will be added to the European Union beta-interferon (EU IFN) pregnancy registry, which collects information on all marketed beta-interferons. This recommendation is anticipated to be endorsed at the forthcoming Committee for Medicinal Products for Human Use (CHMP) opinion. In addition, global pregnancy reports collected through routine pharmacovigilance, including pregnancies in Australian patients, will be included in the periodic benefit-risk evaluation reports (PBRERs).</i></p>	<p>It is noted that on 22 May 2014, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for Plegridy. In the context of this information, the sponsor's response is acceptable.</p>

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>Although the TGA has not adopted the Guideline in Australia, an Australian pregnancy registry should be established to ensure collection and reporting of the data on the use of peginterferon beta-1a in pregnancy if application in the EU is rejected or deferred.</p>		
<p>5. Due to the limited information that could be provided during the pre-marketing clinical trials, the evaluator recommends that a postauthorisation observational safety study be conducted to monitor safety concerns and identify new safety issues. This is in line with postmarketing pharmacovigilance measures for recombinant interferon beta-1a and 'Guideline on Similar Biological Medicinal Products Containing Interferon Beta'.</p>	<p><i>The sponsor acknowledges the benefit of additional safety data regarding peginterferon beta-1a. The pre-authorisation Study 105MS302 has been extended to September 2015 to capture additional safety data. Although peginterferon beta-1a is not a biosimilar and does not claim to be similar to any other interferon beta product, the sponsor agrees in principle with the 'Guideline on Similar Biological Medicinal Products Containing Interferon Beta,' which outlines various mechanisms that could be used to manage pharmacovigilance. Hence, the extension of the pre-authorisation study to September 2015 is sufficient to monitor longterm safety.</i></p> <p><i>The safety of peginterferon beta-1a will also continue to be monitored through routine pharmacovigilance activities.</i></p>	<p>The sponsor's response is acceptable. The sponsor should undertake to report safety findings from Study 105MS302 in the Periodic Safety Update Reports to the TGA.</p>
<p>6. The sponsor should address the follow issues in the RMP:</p> <p>a. Potential for overdose</p>	<p><i>Content addressing the potential for overdose, transmission of infectious disease, off-label use, and paediatric off-label use is included in the updated version of the Australian Risk Management Plan (RMP)</i></p>	<p>The sponsor's response is satisfactory.</p>

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>b. Potential for transmission of infectious disease</p> <p>c. Potential for off-label use</p> <p>d. Potential for paediatric off-label use</p>	<p><i>provided to the TGA in response to the received Notification Letter-Not Effective (01 October 2013). These specific sections are also included below.</i></p> <p><i>Risk Management Plan</i></p> <p><i>Part II: Module SVI - Additional Requirements for the Safety Specification</i></p> <p><i>SVI.1 Potential for harm from overdose</i></p> <p><i>The presentation of peginterferon beta-1a is a single dose pre-filled syringe and pre-filled pen. Packs provided to patients will generally contain two 125 µg doses. Some countries may use packs with a maximum of six 125 µg doses. It is possible that overdose could occur with peginterferon beta-1a, but the potential for overdose is judged to be very low. In case of overdose, appropriate supportive treatment should be given.</i></p> <p><i>SVI.2 Potential for transmission of infectious agents</i></p> <p><i>Peginterferon beta-1a is manufactured from working cell banks using a serum free process. All the materials used in the manufacturing of peginterferon beta 1-a are controlled in accordance with international industrial standards. The possibility of transmission of infectious agents from these substances is very low.</i></p> <p><i>SVI.5 Potential for off-label use</i></p> <p><i>The proposed indication for peg interferon beta-1a is relapsing forms of MS. There is no information available regarding potential off-label use with peginterferon beta-1a. The potential for off-label use for other indications cannot be excluded.</i></p> <p><i>SVI.6 Specific paediatric issues</i></p>	

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	<p><i>Peginterferon beta-1a has not been used in any clinical study in MS to treat patients younger than 18 years and is currently not recommended for paediatric use. Please refer to SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes for a summary of the limited short-term safety information with use of interferon beta in paediatric patients with relapsing MS.</i></p>	
<p>7. Rather than 'refer to Australian PI', the sponsor should provide wording pertaining to important safety concerns in the proposed Australian PI and CMI in table IV.1.1</p>	<p><i>Wording pertaining to important safety concerns from the proposed Australian Product Information is included in the updated version of the Australian Risk Management Plan (RMP) provided to the TGA in response to the received Notification Letter-Not Effective (01 October 2013). These specific sections are also included below.</i></p> <p><i>In addition, the Australian RMP has been updated to include wording pertaining to important safety concerns from the Consumer Medicine Information (CMI). An outline of the changes to the Australian RMP in response to the addition of content from the CMI was provided.</i></p> <p>Risk Management Plan</p> <p><i>Part V: Risk Minimisation Measures</i></p> <p><i>V.1 Risk minimization measures by safety concern</i></p>	<p>The sponsor's response is satisfactory.</p>
<p>8. In regard to the proposed routine risk minimisation activities, the evaluator makes the following recommendations to the Delegate on the content of the proposed PI:</p>	<p><i>The sponsor agrees to harmonise the wording regarding the use of peginterferon beta-1a in pregnancy, severe depression and/or suicidal ideation, and thyroid disorder in the Australian Risk Management Plan (RMP) and Product Information (PI). Specifically:</i></p> <p><i>a. Based on the request from the TGA, the sponsor proposes additional text</i></p>	<p>The sponsor's response is satisfactory.</p> <p>The recommendations on the draft Product Information remain, awaiting</p>

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>a. Use in pregnancy: the current Australian PI and SmPC appear to provide contradictory information on the use of a non-PEGylated interferon beta-1a (Avonex): 'Exposure to AVONEX did not increase the rate of spontaneous abortion or alter the pattern of defects compared to the general population' in the Australian PI compared to 'available data indicates that there may be an increased risk of spontaneous abortion' in SmPC. Nonetheless, 'initiation of treatment in pregnancy' is listed as a contraindication in both product packaging. The evaluator recommends that the Delegate assesses</p>	<p><i>for the Contraindications and Use in Pregnancy sections of the Australian PI for Plegridy similar to that in the approved PI for other interferon beta products to include a contraindication for initiation of therapy during pregnancy.</i></p> <p><i>The outcome of the United States Avonex Pregnancy registry was recently included in the Australian Avonex PI (approved 5 December 2013), resulting in the addition of the sentence 'Exposure to AVONEX did not increase the rate of spontaneous abortion or alter the pattern of defects compared to the general population' to the Use in Pregnancy section.</i></p> <p><i>b. Use in patients with current severe depression and/or suicidal ideation will be listed as contraindicated for peginterferon beta-1a in the Australian PI and RMP.</i></p> <p><i>c. Text regarding thyroid disorders will be included in the 'Precautions' section of the Australian PI. The Australian RMP currently includes thyroid disorders as an important potential risk.</i></p> <p><i>An outline of the changes to the Australian RMP and PI in response to this question is provided below (new text is in bold font).</i></p> <p>Risk Management Plan</p> <p><i>Part V: Risk Minimisation Measures</i></p> <p><i>V.1 Risk minimization measures by safety concern</i></p> <p>Product Information</p> <p>CONTRAINDICATIONS</p> <p><i>PLEGRIDY is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta or peginterferon, or any other component of the formulation.</i></p>	<p>consideration by the Delegate.</p>

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>whether 'initiation of treatment' should be a contraindication for PEGylated interferon beta-1a based on the evaluation of the safety data.</p> <p>b. Use in patients with current severe depression and/or suicidal ideation: this is a contraindication in the current Australian PI for interferon beta-1a. Depression and suicidal behaviour is a pharmacological class effect. The sponsor stated: 'In summary, the incidence of depressive disorders with peginterferon beta-1a treatment was comparable with that of Avonex and Rebif with no meaningful difference between active treatment group and placebo groups. The incidence of serious events</p>	<p><i>The initiation of treatment is contraindicated during pregnancy, and in patients with current severe depression and/or suicidal ideation.</i></p> <p><i>PRECAUTIONS</i></p> <p><i>Effects on Fertility</i></p> <p><i>The weekly subcutaneous administration of peginterferon beta-1a at 170 times the clinical exposure (based on serum AUC) to sexually mature female rhesus monkeys over the course of one menstrual cycle (up to 5 weeks), resulted in menstrual irregularities, anovulation, and decreased serum progesterone. This is consistent with the effects observed with non-pegylated interferon beta. These effects were reversible after discontinuation of drug. The significance of these nonclinical effects to humans is unknown.</i></p> <p><i>Use in Pregnancy (Category D)</i></p> <p><i>Initiation of treatment is contraindicated during pregnancy (see CONTRAINDICATIONS).</i></p> <p><i>Peginterferon beta-1a has not been tested for reproductive toxicity in pregnant animals. Non pegylated interferon beta-1a has shown no evidence of teratogenicity in pregnant animals.</i></p> <p><i>There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should take appropriate contraceptive measures during treatment. If a patient becomes or plans to become pregnant whilst on therapy, they should be informed of the potential hazards to the foetus. PLEGRIDY should be used during pregnancy only if the potential benefit justifies the</i></p>	

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>was low and was similar among all 3 interferon beta-1a treatments.' (Section SVI.4, AUS-RMP). Based on this statement, 'use in patients with current severe depression and/or suicidal ideation' should be listed as a contraindication for PEGylated interferon beta-1a.</p> <p>c. Thyroid disorder: this is a pharmacological class effect that has not been addressed in the proposed PI.</p>	<p><i>potential risk to the foetus.</i></p> <p><i>Use in Lactation</i></p> <p><i>It is not known whether PLEGRIDY is excreted in human milk.</i></p> <p><i>Effects on Laboratory Tests</i></p> <p><i>Laboratory abnormalities are associated with the use of interferons. Complete and differential white blood cell counts, platelet counts, and blood chemistry, including liver function tests, are recommended using PLEGRIDY therapy. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.</i></p> <p><i>Hypothyroidism and hyperthyroidism have been observed with the use of interferon beta products. Regular thyroid function tests are recommended in patients with a history of thyroid dysfunction or as clinically indicated.</i></p>	
<p>9. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that where changes to the PI are required, the content of the proposed CMI be updated accordingly.</p>	<p><i>The proposed Consumer Medicine Information (CMI) will be updated with all of the applicable changes to the Product Information (PI). An outline of these changes to the CMI is provided below (new text is in bold font).</i></p> <p><i>Consumer Medicine Information</i></p> <p><i>Before you use Plegridy</i></p> <p><i>When you must not use it</i></p> <p><i>Do not use Plegridy:</i></p> <ul style="list-style-type: none"> <i>If you have severe depression or think about committing suicide</i> 	<p>The sponsor's response is satisfactory.</p> <p>The recommendations on the draft CMI remain, awaiting consideration by the Delegate.</p>

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	<ul style="list-style-type: none"> • <i>If you are already pregnant</i> <i>If you are not sure whether you should use this medicine, talk to your doctor or pharmacist.</i> <i>Before you use it</i> <i>Tell your doctor if you have or have had:</i> • <i>Depression or problems with your moods, or if you have ever considered</i> • <i>committing suicide</i> • <i>A seizure, fit or convulsion</i> • <i>Liver problems</i> • <i>Bleeding problems</i> • <i>A problem with your heart</i> • <i>Thyroid problems</i> • <i>Bone marrow suppression</i> <p><i>Do not start using Plegridy if you are already pregnant. If you could get pregnant, you need to use contraception while you use Plegridy</i></p> <p><i>Tell your doctor:</i></p> <ul style="list-style-type: none"> • <i>If you are pregnant or plan to become pregnant.</i> • <i>If you want to breastfeed.</i> <i>Your doctor can discuss with you the risks and benefits involved.</i> 	

Cugati S. et al (2006). Ten-year incidence of retinal vein occlusion in an older population. The Blue Mountains Eye Study. Arch Ophthalmol 124:726-732.

Montgomery S. et al (2013). Hospital admission due to infections in multiple sclerosis patients. European Journal of Neurology 20: 1153–1160.

Naleway A.L. et al (2005). Epidemiology of systemic lupus erythematosus in rural Wisconsin. *Lupus* 14: 862-866.

Summary of recommendations

It is considered that the sponsor's response to the TGA's consolidated request for further information has adequately addressed issues identified in the RMP evaluation report. Outstanding issues are addressed below.

Issues in relation to the RMP

Recommendation 5: The sponsor's response is acceptable. The sponsor should undertake to report safety findings from Study 105MS302 in the Periodic Safety Update Reports to the TGA.

Recommendation 8 and 9: The recommendations on the draft Product Information and Consumer Medicine Information remain, awaiting consideration by the Delegate.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

In its response to the TGA's consolidated request for further information, the sponsor provided an updated AUS-RMP version 2, dated 23 May 2014. Key changes from the version evaluated at Round 1 are summarised below in Table 12.

Table 12: Key changes to the AUS-RMP

Safety specification	<p>Important identified risks: 'Flu-like symptoms' is added;</p> <p>Important potential risks: 'Systemic lupus erythematosus including drug-induced lupus erythematosus', 'autoimmune disorders', 'thrombotic microangiopathies including TTP' are added;</p> <p>Additional requirements for the safety specification: section SVI.1 'Potential for harm from overdose', SVI.2 'Potential for transmission of infectious disease', SVI.5 'Potential for off-label use', SVI.6 'Specific paediatric issues' are added.</p>
Pharmacovigilance activities	Additional data collection in the 302 safety extension study are added for 'flu-like symptoms', systemic lupus erythematosus including drug-induced lupus erythematosus', 'autoimmune disorders', and 'thrombotic microangiopathies including TTP'.
Risk minimisation activities	<p>Product Information:</p> <ul style="list-style-type: none"> 'Contraindication': 'initiation of treatment during pregnancy' and 'patients with current severe depression and/or suicidal ideation' are added; 'Precautions': warnings are added for thyroid disorders and use in pregnancy. <p>Consumer Medicine Information: additional warnings are added for 'serious hypersensitivity reactions', 'hepatic injury', 'decreased peripheral blood cell counts', 'serious injection site reactions', 'flu-like symptoms', 'depression and suicidal behaviour', 'seizure disorder', 'cardiac disorders', 'children and adolescents under the age of 18 years', 'effects on pregnancy outcomes and lactation', and 'patients with hepatic impairment'.</p>

These changes addressed relevant issues raised by the evaluator during the first round RMP evaluation. The evaluator has no objection to the above changes and recommends to the Delegate that the updated version is implemented (see below).

Suggested wording for conditions of registration***RMP***

Implement AUS-RMP version 2, dated 23 May 2014 (data lock point 24 October 2012) and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluators have no objection to the registration.

The active substance of peginterferon beta-1a, is a glycosylated recombinant interferon beta-1a (IFN (beta-1 a) that is pegylated with a single 20kDa methoxypoly (ethylene glycol)-O-2 methylpropionaldehyde (mPEG) moiety at the N-terminus. The drug substance is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells and purified chromatographically. The non-pegylated interferon beta-1a is produced from the same cell line, albeit adapted for serum free culture, as Avonex. Cell banking processes are satisfactory.

All viral/prion safety issues have addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

The proposed shelf life of the drug substance is 60 months at $-70 \pm 10^{\circ}\text{C}$. However, only up to 24 months data from validation batches are available. The company has agreed to limit the shelf life of the drug substance to 36 months at $-70 \pm 10^{\circ}\text{C}$.

Batch release testing of the first five batches by the TGA is recommended to verify quality of the product and consistency of the manufacturing process. The biochemistry evaluator recommended batch release conditions to be included as conditions of registration for this product.

Nonclinical

There were no objections to approval based on the nonclinical data. The nonclinical evaluator noted that there were no major deficiencies in the nonclinical data. The pharmacology data confirmed that it has similar in vitro and in vivo pharmacological activity to non-pegylated interferon beta-1a, supporting its use for the proposed indication.

The pharmacokinetic properties of peginterferon beta-1a confirmed the expected changes related to the pegylation of interferon beta beta -1a.

There was no evidence of genotoxic potential and carcinogenicity studies were not considered necessary.⁸

The potential abortifacient activity of peginterferon beta-1a was confirmed. No further reproductive studies were considered necessary. This effect was considered clinically relevant by the nonclinical evaluator. A pregnancy Category of D, as for Avonex, has been recommended.

⁸ As peginterferon is not pharmacologically active in rodent species, a weight-of-evidence approach has been used to assess potential carcinogenicity, consistent with ICH S6 guidelines. See *Nonclinical findings, Carcinogenicity* above.

Clinical

Pharmacology

Pharmacokinetics:

The sponsor anticipated that peginterferon beta-1a would have the same biological activity as interferon beta-1a (Avonex) and would differ from it only on pharmacokinetic grounds. Four clinical pharmacology studies and a population pharmacokinetic analysis based on the pivotal efficacy study were performed.

Following SC injection, peginterferon beta-1a reaches a peak concentration in 1 to 1.5 days post-dose. The median T_{max} for IM and SC peginterferon beta-1a ranged from 30 to 36 h compared to 12 h with IM interferon beta-1a. The median C_{max} for peginterferon beta-1a was approximately 2 times higher with peginterferon beta-1a 63 µg (6MIU) than with interferon beta-1a 30 µg (also 6MIU), reaching 41.6 IU/mL via the IM route and 38.9 IU/mL via the SC route, compared to 20.8 IU/mL with IM interferon beta-1a. Higher doses of peginterferon beta-1a (125 µg/12MIU and 188 µg/18MIU) produced proportionately higher C_{max} values, with a similar T_{max} . The AUC for peginterferon beta-1a was also increased but this partly reflects delayed clearance rather than differences in absorption.

The bioavailability of intravenous versus intramuscular or subcutaneous administration was not assessed. The availability of peginterferon beta-1a from sites of injection appears to be incomplete in some subjects, given the high degree of inter-individual variability in exposure that was observed after SC or IM injection of standardised amounts in the Phase I studies. The % coefficient of variation (CV) ranges for the major parameters in these studies were: AUC_{tau} – 41% to 68%; C_{max} – 74% to 89%; and half-life ($t_{1/2}$) – 45% to 93%. Figure 3 in the CER shows the distribution of C_{max} and AUC for healthy volunteers and MS patients in the clinical studies submitted. There are no systematic differences between MS subjects and healthy volunteers, with the ranges for AUC and C_{max} showing substantial overlap across studies. There were no data on intra-individual variability.

Exposure is increased in subjects with a low BMI but exposure does not appear to be affected by race or gender. The effect of hepatic impairment has not been studied. A population PK analysis did not find that concomitant drugs had a major effect on the PK of peginterferon beta-1a but this analysis was based on small sample numbers.

Study 105RI101 was conducted in volunteers with various degrees of renal impairment who did not have MS. Increasing degrees of renal impairment resulted in increasing exposure to peginterferon beta-1a. The differences are of a similar magnitude to those seen with inter-subject variability. No dose adjustment is required for patients with renal impairment.

Based on a linear regression model, renal clearance was estimated to account for 47% of the total clearance of peginterferon beta-1a, with non-renal clearance accounting for the other 53% (90% CI, 33%, 77%). When given by subcutaneous injection to healthy adults the median $t_{1/2}$ was from 2 to 3 days across dose groups (63, 125 and 188 µg). The apparent Vd volume of distribution was 481 ± 105 L (mean \pm SE).

Antibodies to peginterferon beta-1a were assessed in the pivotal study, and the incidence is summarised in the Tables 4 and 5 in the CER. Three types of antibodies need to be distinguished: antibodies that bind to interferon (binding antibodies, BAbs); antibodies that bind to interferon and neutralise its biological effects (neutralising antibodies, NABs); and antibodies to the PEG moiety (anti-PEG Abs). In Study 301, two intensive PK sub-study subjects developed anti-PEG antibodies on treatment but they showed no reduction in peginterferon beta-1a levels or PD effects. The population PK and PD model, derived from sparse sampling in all subjects from the pivotal study, showed no PK impact of anti-PEG antibodies.

Pharmacodynamics:

No studies to examine the primary PD effect of peginterferon beta-1a in humans were included in the submission. Secondary PD effects via surrogate biomarkers known to be induced by interferon beta-1a were examined. Neopterin was the primary biomarker in the PK component of the Phase I and III studies. Neopterin acts as a biomarker of pro-inflammatory activity and also as a marker of treatment with interferons intended to prevent inflammatory episodes. The apparent contradiction reflects the fact that interferon beta has complex actions, inducing a relative shift in various components of immune responses rather than merely suppressing immune responses. OAS (2',5'-oligoadenylate synthetase, 2', 5'-OAS) was an additional biomarker in some studies. OAS is an antiviral enzyme that counteracts viral infections by degrading viral RNA, and levels increase in response to beta interferons.

Using neopterin concentration as the primary measure of interferon effect, the sponsor defined E_{\max} as the maximum baseline-subtracted neopterin concentration reached, E_{AUC} as the area under the baseline-subtracted neopterin concentration time curve and ET_{\max} as the time taken to reach maximum neopterin concentration.

Figure 6 in the CER shows neopterin concentration over time following a single 30 µg intramuscular dose of interferon beta-1a and of 3 subcutaneous doses of peginterferon beta-1a (63 µg, 125 µg and 188 µg). The proposed dose of peginterferon beta-1a is 125 µg every 2 weeks. While the neopterin response was larger and more prolonged with that dose compared to the 30 µg dose of interferon-beta 1a, the response did not persist throughout the whole two week dosing period. All doses of peginterferon beta-1a were associated with substantial declines in neopterin concentration during days 7 to 14 after administration. The duration of the neopterin response was longer than the concentration-time profile of peginterferon beta-1a which peaked at 1 to 1.5 days and reduced to low levels between 7 and 10 days. Neopterin peaked at approximately 3 days and returned to baseline after >10 days.

Figure 7 in the CER shows the concentration of neopterin over time in the intensively monitored subgroup in the Study 301, the pivotal study. Neopterin levels to 24 h post the Week 4 and Week 24 doses are shown for the 125 µg dose given either Q2W or Q4W. At Week 4 there is little difference between the 2 dose groups and at Week 24 the Q4W group has higher median neopterin concentrations however there was a wide range in both dose groups. Neopterin levels during the last four days of the two week dose cycle were not studied in the Phase III study. Given the results from the single dose studies it is likely that neopterin concentrations would be substantially reduced in the last four days of a two week cycle compared with earlier in the cycle. The sponsor stated that the dose regimen of 125 µg every two weeks was selected because 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 with IFN beta-1a 30 µg IM.

The results with OAS as a secondary marker were qualitatively similar to those seen with neopterin, as shown in the summaries of individual PK/PD studies.

No specific PD interaction studies were performed however interferon beta-1a was given with corticosteroids (methylprednisolone and prednisolone), which are widely used to treat acute relapses in MS regardless of whether subjects are on disease-modifying agents. Steroids were used as needed in the pivotal study.

There was no evidence of a significant reduction in neopterin response in the setting of antibodies to interferon or PEG, even in subjects who appeared to have reduced levels of peginterferon in association with antibodies. The preservation of the PD response in the setting of apparently low peginterferon levels is likely to reflect that peginterferon levels were higher than measured and that the antibodies interfered with the drug assay, as discussed in Section *Pharmacokinetics related to anti-interferon and anti-PEG antibodies* of

the CER (Attachment 2). In volunteers with renal impairment there was an increased exposure to peginterferon beta-1a and to neopterin. This is discussed in section *Pharmacokinetics in subjects with impaired renal function* in Attachment 2.

Efficacy

Justification of dose regimen:

Comprehensive dose-response studies to establish optimal dose and frequency of dosing have not been conducted with peginterferon-beta-1a. The clinical evaluator has considered that the guiding principle in dose selection appears to have been matching the approved dose of interferon beta-1a (Avonex) while aiming for the lowest feasible dosing frequency. Because of delayed clearance of the pegylated form, the cumulative AUC for peginterferon beta-1a 6MIU is higher than for a single dose of Avonex 6MIU (5.7 versus $3.1 \times 10^3 \text{h} \cdot \text{IU/mL}$). Over 4 weeks at the proposed dose, the AUC for peginterferon beta-1a ($14.3 \times 10^3 \text{h} \cdot \text{IU/mL}$) is considerably higher than that achieved with Avonex ($3.1 \times 10^3 \text{h} \cdot \text{IU/mL}$) even though both amount to the same total administered activity (24MIU).

In this sense, the proposed dose of peginterferon beta-1a could be considered to be higher than the approved Avonex dose. The other factor to be considered in determining dose selection is neopterin response. Neopterin induction increased in a less than proportional fashion to higher doses and decreased between less frequent doses, so that higher doses cannot fully compensate for low-frequency dosing (for the same total monthly dose).

A discussion on the appropriate dosing interval for interferons used in the treatment for MS is in section *Accumulation between doses* of the CER (Attachment 2). The evaluator has noted differences in outcome in a published study of the two non-pegylated interferon-beta-1a products approved for the treatment of MS (Avonex and Rebif) and noted the different dosing intervals and total dose given as potential factors influencing efficacy.

Study 301:

The pivotal efficacy and safety study is described in section *Pivotal efficacy study, 105MS301* of the CER (Attachment 2). This study was randomised, double-blind, and placebo-controlled and conducted in 2 stages. The first 48 weeks compared placebo with two dosing frequencies of peginterferon beta-1a (125 µg Q2W or 125 µg Q4W) in subjects with relapsing MS (RMS). In the second 48 weeks, subjects initially randomised to placebo were reassigned to active treatment and received peginterferon beta-1a 125 µg at either Q2W or Q4W. Subjects initially randomised to active treatment continued active treatment at their original dosing frequency. All subjects in the second year remained blinded to dosing frequency and to their original treatment allocation.

The primary objective of this study was to determine the efficacy of peginterferon beta-1a in reducing the annualised relapse rate in subjects with RMS at 1 year. The final study report was available at the time of submission, 46% of subjects entering Year 2 had completed it at the time of data cut-off.

Major inclusion criteria were:

- EDSS score between 0.0 and 5.0, this equates to mild to moderate functional impairment⁹.

⁹ The Expanded Disability Status Scale (EDSS):

0.0: Normal neurological exam.

1.0: No disability, but minimal signs in one functional system (FS) are present.

1.5: No disability, but minimal signs in more than one FS are present.

2.0: Minimal disability in one FS is present.

2.5: There is mild disability in one FS or minimal disability in two FS.

- At least 2 documented relapses within the last 3 years, at least 1 of which was within the past 12 months; and
- Age 18 to 65 years.

Recent treatment with an interferon was not permitted as was prior treatment with agents expected to produce long-lasting immunosuppression, including total lymphoid radiation, fingolimod, cladribine, T cell or T-cell receptor vaccine, or therapeutic monoclonal antibodies, such as rituximab, natalizumab or alemtuzumab.

The primary efficacy endpoint was the annualised relapse rate at 1 year. Secondary efficacy endpoints were ranked with statistical significance required for the preceding endpoint before the subsequent endpoint could be considered for statistical significance. The ranked secondary endpoints were: number of new or newly enlarging T2 hyperintense lesions at 1 year; proportion of subjects relapsing at 1 year; and disability progression measured by EDSS at 1 year. 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. Disease progression was defined as an increase in EDSS sustained for 12 weeks. A 24 week sustained disability progression analysis was also performed as a sensitivity analysis. The number of T2 hyperintensities is a marker of the number of 'plaques', or areas of inflammation in the brain. Lesions appearing between scans indicate new areas of inflammation whereas enlarging lesions reflect new activity at old sites of inflammation.

A total of 1512 subjects received at least 1 dose of study treatment (placebo n=500, peginterferon beta-1a Q4W n=500, and peginterferon beta-1a Q2W n=512) and were included in the Intent-to-Treat (ITT) (primary) analysis. Of these 1332 subjects (88%) completed 48 weeks of treatment. Study participants were predominantly from Eastern Europe. At baseline mean age was 36.5 years, median EDSS was 2.5, mean time since the occurrence of the first symptoms of MS was 6.6 years (range 0 to 40 years) and the mean time since MS diagnosis was 3.6 years (range 0 to 40 years). The majority of subjects (83%) in the ITT population had not been treated with any MS medication prior to study entry, and this proportion was consistent across the treatment groups.

3.0: There is moderate disability in one FS or mild disability in three or four FS. However, the person is still fully ambulatory.

3.5: The person is fully ambulatory, but has moderate disability in one FS and mild disability in one or two FS; or moderate disability in two FS; or mild disability in five FS.

4.0: The person is fully ambulatory without aid, and is up and about most of the day (12 hours) despite relatively severe disability. He or she is able to walk 500 meters without aid or rest.

4.5: The person is fully ambulatory without aid, and is up and about much of day. He or she is able to work a full day, but may otherwise have some limitations of full activity or require minimal assistance. This is considered relatively severe disability. Able to walk 300 meters without aid.

5.0: The person is able to walk 200 meters without aid or rest. Disability impairs full daily activities, such as working a full day without special provisions.

5.5: The person is able to walk 100 meters without aid or rest. Disability precludes full daily activities.

6.0: The person needs intermittent or unilateral constant assistance (cane, crutch or brace) to walk 100 meters with or without resting.

6.5: The person needs constant bilateral support (cane, crutch or braces) to walk 20 meters without resting.

7.0: The person is unable to walk beyond five meters even with aid, and is essentially restricted to a wheelchair. However, he or she wheels self and transfers alone, and is active in wheelchair about 12 h a day.

7.5: The person is unable to take more than a few steps and is restricted to wheelchair, and may need aid to transfer. He or she wheels self, but may require a motorized chair for a full day's activities.

8.0: The person is essentially restricted to bed, a chair or a wheelchair, but may be out of bed much of day. He or she retains self care functions and has generally effective use of arms.

8.5: The person is essentially restricted to bed much of day, but has some effective use of arms and retains some self care functions.

9.0: The person is confined to bed, but still able to communicate and eat.

9.5: The person is totally helpless and bedridden and is unable to communicate effectively or eat and swallow.

10.0: Death due to MS.

There were small differences among the dose groups in the prevalence of Gd-enhancing (Gd+) lesions (mean number of lesions 1.6 for placebo, 1.8 for peginterferon beta-1a Q4W and 1.2 for peginterferon beta-1a Q2W). The peginterferon beta-1a Q2W dose group also had the highest proportion of subjects with no Gd+ lesions at baseline (65% versus 59% in the placebo and peginterferon beta-1a Q4W group). There were also small differences in the number of relapses in the last 3 years (worst in the peginterferon beta-1a Q2W group) and the proportion with EDSS ≥ 4 (14% in placebo and 17% in each of the active treatment groups).

The primary and secondary efficacy endpoint results are shown in Table 21 in section *Results for secondary endpoints* of the CER (Attachment 2). The adjusted, annualised relapse rates (Independent Neurology Evaluation Committee confirmed) were 39.7%, 28.8% and 25.6% for the placebo, peginterferon beta-1a Q4W and peginterferon beta-1a Q2W groups respectively, with a 27.5% relative reduction from placebo in relapse rate for the peginterferon beta-1a Q4W group ($p=0.0114$) and 35.6% relative reduction ($p=0.0007$) for the peginterferon beta-1a Q2W group. The absolute reduction in annualised relapse rate compared with placebo for the peginterferon beta-1a Q2W group was 14.1%.

Sensitivity analyses were consistent with the primary analysis. Various subgroup analyses of the annualised relapse rate were performed with results shown in Figure 14 in Attachment 2. These were supportive of efficacy across the patient population, including patients with interferon antibodies.

The major secondary efficacy endpoints were also all statistically significant. The major efficacy results at one year are shown in Table 21 in Attachment 2. Results of particular interest are:

- The mean number of new or newly enlarging T2 hyperintense lesions at Year 1 was 10.9 in the placebo group, 7.9 in the peginterferon beta-1a Q4W group and 3.6 in the peginterferon beta-1a Q2W group. Compared with placebo this was a 28% relative reduction ($p = 0.0008$) and 67% relative reduction ($p < 0.0001$) for the peginterferon beta-1a Q4W and peginterferon beta-1a Q2W groups, respectively.
- The proportion of subjects relapsed after one year, broadly followed the results for the primary endpoint. The proportion relapsed is potentially a less sensitive endpoint than ARR because only first relapses in the period of interest are counted but a high level of significance was nonetheless demonstrated ($p=0.0003$). After adjustment, approximately 29.1% of placebo subjects relapsed after one year, compared to 22.2% of subjects receiving peginterferon Q4W and 18.7% of subjects receiving peginterferon Q2W.
- 12 week sustained disability progression at one year was reported in 10.5% given placebo and 6.8% in each of the peginterferon beta-1a dose groups. Compared with placebo this was a relative reduction of 38% in both peginterferon beta-1a dose groups ($p = 0.0380$ for both groups). The absolute annualised reduction in 12 week sustained disability was 3.7% for the proposed peginterferon beta-1a dose regimen of Q2W.

Final data from the second year of this study were not available at the time of submission and the study was not placebo-controlled after the first 12 months. Available data from the second year of this study showed that patients who received the longest period of treatment with peginterferon beta-1a Q2W, that is, patients randomised to Q2W at the beginning of the study and who continued into the second year had the lowest annualised relapse rate of groups in the study. Relapse rates for the continuing Q4W group and the placebo groups that switched to either Q4W or Q2W had similar relapse rates. Results are shown in Figure 17 in Attachment 2.

Various post hoc comparisons of efficacy endpoints for the peginterferon beta-1a Q2W versus Q4W dose groups were performed and are tabulated in section *Post hoc comparison of Q2W vs Q4W dosing* in Attachment 2. Cross study comparisons with available data from related beta-interferon studies are summarised in section *Supportive evidence from related beta-interferon studies* in Attachment 2. These comparisons suggest broadly similar efficacy of the proposed dose regimen of peginterferon beta-1a with that of Avonex and Rebif.

In summary, compared to placebo after 12 months of study, peginterferon beta-1a at the proposed dose of 125 µg Q2W was associated with a relative reduction in annualised relapse rate of 35.6% ($p=0.0007$), a relative reduction in the proportion relapsed after one year of 39% ($p=0.0003$) and a relative reduction in sustained disability progression of 38% ($p=0.0383$). With respect to MRI endpoints, peginterferon 125µg Q2W was associated with a relative reduction in new or newly enlarged T2 lesions of 67% ($p<0.0001$), a reduction in Gd-enhancing lesions of 86% ($p<0.0001$) and a reduction in new T1 hypointensities of 53% ($p<0.0001$).

Study 302:

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.

This study was designed as an extension of Study 301. The primary objective was to obtain long-term safety and tolerability data. Efficacy follow-up was a secondary objective. This study was ongoing at the time of submission. It began on 11 April, 2011, with a data cut-off at the time of submission of 24 October 2012. At that time 517 subjects had enrolled with 508 subjects having received at least 1 dose and 407 subjects having received at least 1 dose and attended for a post-baseline safety follow-up.

The primary eligibility criterion was completion of Study 301. Major exclusion criteria were: a period of >6 weeks since completion of the Week 96 Visit of Study 301; or any significant change in medical condition that, in the opinion of the Investigator, would have excluded the subject from participation in Study 301.

Subjects continued to receive peginterferon beta-1a 125 µg at the same randomised dosing frequency they had received in the second year of the pivotal study (Q2W or Q4W). This included patients who had received the same regimen from the start of the pivotal study, as well as those who had switched to active treatment from placebo.

The sponsor did not designate a single efficacy variable as primary. In general the results were presented descriptively. All subjects were already receiving active treatment with alternate placebo and active injections in the Q4W group to maintain blinding. This treatment continued in a double-blind fashion through to the extension study. Selected efficacy analyses, including annualised relapse rate, proportion of subjects relapsed and disability progression used the Study 302 ITT Population with Combined Treatment Grouping and Combined Data. At data cut-off exposure to peginterferon beta-1a ranged from 2 weeks to 80 weeks with 46 subjects having completed one year of treatment. No subjects had completed the planned two years. Relapses during the first year of the extension study are shown in Figure 23 in section Attachment 2.

The number of subjects with 48 weeks of data is very low (at risk $n=31$), so it is not possible to infer annualised relapse rates or proportion of subjects relapsed with confidence, but the curves suggest that the superiority of Q2W versus Q4W dosing continued through the third year of treatment.

Safety

Six studies provided safety data which was presented separately for the overall experience and the placebo-controlled exposure. A total of 1486 individuals received any peginterferon beta-1a in clinical trials. The extent of exposure is shown in Table 29 in Attachment 2. The overall exposure to peginterferon beta-1a in the Phase 3 program was 1932 patient-years in 1468 patients.

The evidence suggests that the safety and tolerability of peginterferon is similar to other interferon beta products. Most of the adverse events observed in the safety database relate to tolerability rather than to severe health risks. The main tolerability issues are flu-like symptoms and injection-site reactions. Another issue is a tendency for peginterferon recipients to have asymptomatic abnormalities on blood tests, including reduced white cell counts and elevated liver enzymes.

Most exposure to peginterferon beta-1a occurred in Study 301. In the first 12 months of Study 301 there were 11% more subjects with any adverse event reported in each of the active treatment groups compared with the placebo group (AEs in 83% of patients given placebo compared to 94% given either dose regimen of peginterferon beta-1a). The most common side effects were: headache (placebo 33% versus Q2W 44%), myalgia (placebo 6% versus Q2W 19%) arthralgia (placebo 7% versus Q2W 11%), injection-site erythema (placebo 7% versus Q2W 62%), influenza-like illness (placebo 13% versus Q2W 47%), pyrexia (placebo 15% versus Q2W 45%), chills (placebo 5% versus Q2W 17%), various other injection-site terms (see table), and abnormal liver function tests (increased ALT, placebo 3% versus Q2W 6%).

Serious events were less frequent with active treatment, occurring in 15%, 14% and 11% of the placebo, Q4W and Q2W groups, respectively. Serious AEs reported in at least 2 subjects are shown in Table 37 in Attachment 2. These events were: pneumonia, upper respiratory infection (URIs) and MS relapse. Serious infections were not more frequent in the active treatment groups compared with placebo. The pattern of serious AEs in the overall population was similar, with the addition of sepsis (n=4) and falls (n=3) to the causes of AEs reported in at least 2 subjects.

In Year 1 of Study 301 there were 4 deaths reported (2 subjects in the placebo group and 1 subject each in the peginterferon beta-1a groups). None of the deaths were considered related to study treatment by the Investigator. A further 4 deaths were reported in the second year. Causes of death are shown in Table 39 in Attachment 2. Investigators considered 2 of these deaths possibly related to study drug (sepsis and oral cavity cancer).

Peginterferon beta-1a had low immunogenicity, and the incidence of hypersensitivity reactions and other AEs was not affected by the presence of antibodies (NAbs, BAbs or anti-PEG Abs). There was a trend suggesting that white cell counts were less likely to be depressed by the Q4W regimen.

Treatment with peginterferon beta-1a was not associated with an increased incidence of cardiovascular events, depression and suicidal ideation, malignancy, infections, seizures, or autoimmune disorders compared with placebo. Based on previous experience with interferon beta, however, it is expected that more extensive use of peginterferon might eventually reveal an increased risk of depression, seizures, spasms and fatigue. However, it should be noted that subjects with a history of any clinically significant (as determined by the Investigator) cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric and renal or other major disease were excluded from participation in the pivotal study and its extension study.

Clinical evaluator's recommendation

Recommendations regarding authorisation depend on policy considerations. If it is considered that the sponsor's obligation is merely to demonstrate that peginterferon has acceptable safety and is more effective than placebo, then the submitted evidence is sufficient to support the application. If the sponsor is considered to have an obligation to find the most effective regimen, with the best trade-off between efficacy and tolerability, it appears that they have not fully discharged that obligation.

In general, marketing applications to the TGA are approved if the proposed regimen is safe and more effective than placebo. On this basis, approval is recommended in this report but it would also be reasonable to reject the sponsor's application until the efficacy of peginterferon 125 µg weekly has been assessed.

- Peginterferon should be authorised for use at a dose of 125 µg two-weekly, for the prevention of relapses in subjects with relapsing and remitting multiple sclerosis.
- The sponsor should be encouraged to explore the efficacy and safety of more frequent dosing regimens.

Risk management plan

There are no RMP issues that preclude approval. The RMP evaluator considered that the sponsor has adequately addressed the issues identified in the RMP evaluation report. The only outstanding issue in relation to the RMP is that the sponsor should provide undertaking to report safety findings from Study 302 in the Periodic Safety Update Reports to the TGA. Study 302 is intended to evaluate the long-term safety, tolerability, and MS outcomes of peginterferon beta-1a in subjects originally treated in Study 301 who continued peginterferon beta-1a treatment. The amendments to the Product Information that were recommended by the RMP evaluator were addressed by the sponsor in its response to TGA's request for further information.

Risk-benefit analysis

Delegate's considerations

Pharmacology:

When administered subcutaneously, at the proposed dose of 125 µg Q2W serum levels of peginterferon beta-1a peak in 1 to 1.5 days and then decline over the course of 7 to 10 days. Thus, peginterferon beta-1a is not expected to maintain significantly elevated levels throughout the proposed two-week dose cycle. The serum concentration of Avonex also does not remain elevated throughout its approved dose interval of one week.

The assessments of neopterin concentrations during the dosing interval suggest that levels fall during the last 7 to 10 days of treatment. Whether this would have an effect on disease activity in MS is not known. Neopterin is a surrogate marker and it is not known whether either total exposure (as assessed by AUC) or by a threshold C_{min} or C_{max} for effect would correlate with an effect on MS disease activity.

The optimal dose regimen has not been fully explored. As noted by the clinical evaluator, a dosing regimen likely to give a continuous pharmacodynamic response throughout the dose cycle such as 125 µg weekly has not been assessed. The PK/PD studies did not assess the PD response in detail between 7 and 14 days, so it remains unclear when neopterin levels fall to baseline over the course of a two-week dose cycle and thus how long patients are effectively left untreated by the proposed two weekly regimen.

Very limited data on drug interactions were available from the pivotal efficacy and safety study and that did not suggest clinically significant interactions with any medications. Beta interferons have not been associated with clinically significant pharmacokinetic drug interactions. While this is expected to be true of peginterferon beta-1a as well, it has not been directly examined.

Efficacy:

Data included with this submission are not sufficient to satisfy current EMA guidelines. The application appears to have been submitted prematurely in that efficacy has not been assessed throughout two years of treatment.

Assessment of efficacy to two years is ongoing and is not placebo-controlled beyond the first 12 months. Section 6.5 (Confirmatory trials) of the EMA *Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis* states the following: The annual relapse rate in RRMS is usually low and, in general, progression of disability takes years. Consequently, confirmatory studies with products intended to modify the course of the disease should be large scale and long enough to have a substantial proportion of patients suffering relapses or showing progression of disability. Two years is considered the minimum duration to demonstrate efficacy.

Of particular concern is the proposed claim for reduction in disability progression. While a statistically significant difference in 12 week disability progression was demonstrated, a difference should have been demonstrated over two years. This lack of prolonged assessment of disability progression is of particular concern given the indication for Avonex does not include this claim. Additionally the absolute difference from placebo in annualised disability progression of 3.7% is quite small.

The pivotal study population was drawn primarily from Eastern Europe and the majority of the study population were not given disease modifying treatment in the years immediately after diagnosis. As previously noted at baseline median EDSS was 2.5, mean time since the occurrence of the first symptoms of MS was 6.6 years (range 0 to 40 years), and the mean time since MS diagnosis was 3.6 years (range 0 to 40 years). The majority of subjects (83%) in the ITT population had not been treated with any MS medication prior to study entry. This population may not be typical of the population commenced on interferon treatment in Australia consequently the disability reduction estimates are likely to be different in the Australian population.

With regard to study design, Section 6.5 of the guideline also states the following: *An option is to compare the new treatment to placebo in a short duration phase (e.g. one year or until patients have a new relapse) and thereafter to switch placebo-treated patients to a predefined active treatment or randomise them to the experimental product or a predefined active treatment. The proportion of subjects with no relapses over two years of follow-up then may be the primary endpoint.* The guideline states that two years is considered the minimum duration to demonstrate efficacy. However, a difference in disability progression that was both clinically and statistically significant was demonstrated in patients treated for 12 months. That difference was similar to that of interferon beta-1a in cross-study comparison, however cross-study comparisons do not provide a rigorous comparison of the relative efficacy of treatments and Avonex does not have an indication that includes either a reduction in relapse rate or in progression of disability.

Safety:

The safety profile of peginterferon beta-1a appears to be similar to that of interferon beta-1a.

The clinical evaluator asked questions regarding the pharmacodynamics of peginterferon beta-1a. While these questions are of interest responses are unlikely to alter the decision

on registration of peginterferon beta-1a. For this reason a second round evaluation was not requested.

Given the lack of finalised efficacy and safety data in the pivotal study, the Delegate proposes that this lack of data be specifically stated in the indications for Plegridy. The indication could be amended should the final report for Study 301 confirm a persistence of efficacy and safety to two years. Given the absence of a comparator over the full two years of treatment, other than the Q4W dose regimen of interferon beta-1a, it will not be possible to obtain a direct comparison of efficacy with either placebo or any current treatment to two years.

At this stage the Delegate is proposing to restrict the indication for Plegridy so that there is no specific claim on reduction in relapse rate or in disability progression and to specify that the indication is based on 12 months of safety and efficacy data. The submission of the final reports of Study 301 and of Study 302, and the long term extension of Study 301 are to be conditions of registration. The indication could be amended on submission of the final study reports for Studies 301 and 302.

The Delegate does not propose to limit the indication to adults, though only patients aged between 18 and 65 years were enrolled in the pivotal clinical trial. This approach is similar to the approach taken with Avonex where the Paediatric Use section reflects the lack of data in children and adolescents.

Summary of issues

1. The optimum dose regimen for interferon beta-1a has not been ascertained. Based on pharmacology data Q2W and Q4W dose regimens for peginterferon beta-1a were examined in a randomised, placebo-controlled study. It may be that a higher or lower dose/injection or more frequent dosing would have a better risk/benefit profile but this has not been assessed.
2. With regard to efficacy this submission was premature. The final results of the pivotal study were not available at the time of submission. Efficacy data to 12 months were submitted and partial data for 24 months.
3. The pivotal study to support the proposed indication used a design which limits the efficacy claims that can be made. It did not enrol patients who are aged under 18 years or over 65 years.

The pivotal efficacy study was placebo-controlled for 12 months. Subsequent efficacy assessments have not been submitted but in any case the data to two years would allow only comparisons of the Q2W and Q4W dose regimens of the active against an historical control. Subjects initially randomised to placebo were re-randomised to one of the two dose regimens of the active after the first 12 months of treatment.

The efficacy assessment at 12 months showed clinically and statistically significant superiority of the proposed dose regimen of peginterferon beta-1a over placebo for both a reduction in relapse rate and in annualised disability progression in patients with RRMS. This is a lesser standard of efficacy than is recommended in the TGA adopted EMA document: *Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis*. That guideline recommends a minimum duration of treatment of two years for safety and efficacy assessment.

The guideline allows for the study design used in the pivotal study for this submission but states that if this design is used, the primary endpoint should be the proportion of subjects with no relapses over two years of follow-up. That is not the case for the pivotal study in this submission where the annualised relapse rate over the first 12 months of treatment was the primary efficacy endpoint. At 48 weeks the absolute difference in annualised relapse rates between placebo and the proposed treatment regimen was 14.1% and the

absolute difference in 12 week sustained disability progression was 3.7%. While differences from placebo were statistically significant they are quite small in absolute terms particular for disability progression.

Given the low numbers of subjects with disability progression, the short assessment interval and likely differences between the study population and the Australian population with MS likely to be offered treatment with an interferon the Delegate is not satisfied that this is a sufficient basis to justify a claim for reduction in disability progression.

The Delegate proposes an indication similar to that of Avonex. It should not specify a reduction in the frequency of relapses or delay to the progression of disability. This approach could be modified, to allow a claim for reduction in frequency of relapses, when the final two year data are available. The Delegate does not propose to specify use in adults in the indication. That information can be included in the Paediatric Use section in the PI, consistent with PI for Avonex.

Should the sponsor wish to submit the final report for the pivotal study, this will require further evaluation by the TGA and another submission will be required.

4. The available safety data suggests that the safety profile of peginterferon beta-1a is similar to that of interferon beta-1a however longer term safety assessment is quite limited. The sponsor has committed to longer term safety assessment in an extension study.

Proposed action

The Delegate is not in a position to say, at this time, that the application for Plegridy (interferon beta-1a) should be approved for registration. Should the indication the Delegate has proposed be accepted by the sponsor the Delegate would reconsider this position.

Request for Advisory Committee on Prescription Medicines (ACPM) advice

The committee is requested to provide advice on the following specific issues:

1. The final study report of the pivotal efficacy and safety study which will provide efficacy and safety data to two years was not completed at the time of submission. No patients aged under 18 years or over 65 years have been assessed for efficacy or safety. The study was not designed to provide a comparison with placebo in disability progression over two years. Given the similarity of peginterferon beta-1a to interferon beta-1a the Delegate is inclined to accept this reduced level of evidence to support an indication similar to that of Avonex but with a specific statement that efficacy beyond 12 months have not been adequately assessed. The Delegate requests the committee's advice on whether the indication below is acceptable or whether the statistically significant differences in relapse rate and/ or in disability progression over 12 months are sufficient to support the indication proposed by the sponsor. The indication the Delegate proposes is:

PLEGRIDY is indicated for the treatment of relapsing forms of multiple sclerosis. (efficacy has been assessed over 12 months see CLINICAL TRIALS)

2. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Biological, nonclinical, and RMP evaluations

The sponsor acknowledges the Delegate's summary of the quality, nonclinical, and RMP evaluations and has no further comments. As mentioned in the summary, safety findings from Study 302 will be provided in the Periodic Safety Update Reports to the TGA.

Clinical evaluation

The sponsor acknowledges the Delegate's summary of the clinical evaluation and has the following comments:

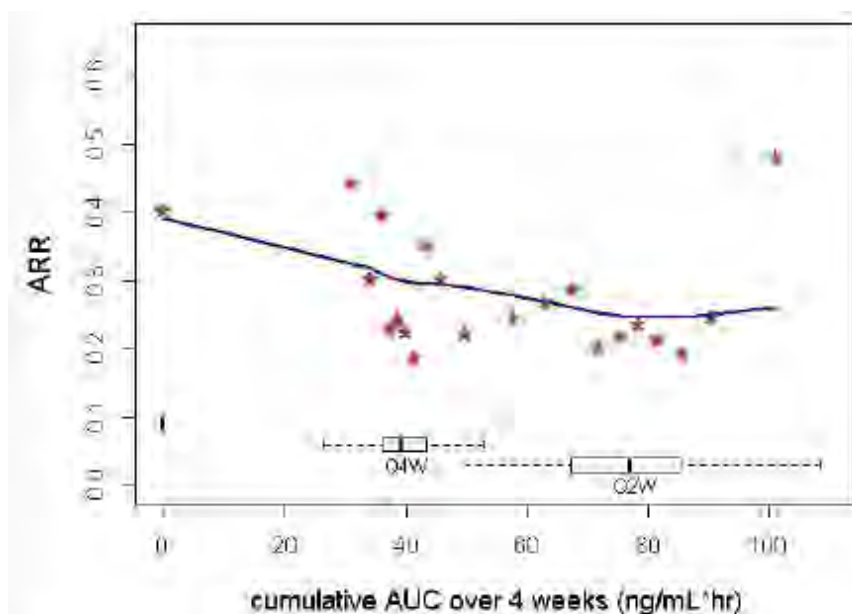
Optimal dose regimen

The primary goal of developing BIIB017 (peginterferon beta-1a) was to provide an immunomodulatory therapy that offers patients with relapsing multiple sclerosis (RMS) the benefits of efficacy and safety that are similar to existing first-line therapies while addressing the unmet need of improved convenience by lowering the burden of injections on patients. Existing first-line injectable therapies in MS require injections as frequently as every day. The least frequently administered currently available injectable first-line therapy requires weekly injections. Therefore, once weekly dosing of BIIB017 would not offer the benefit of reduced injection frequency compared to existing injectable therapies.

To identify the dose regimen which provides the optimal benefit-risk profile with less frequent than weekly dosing, the sponsor evaluated different doses (63, 125 and 188 µg) and 2 injection frequencies (every 2 weeks (Q2W) and every 4 weeks (Q4W)) of BIIB017. The selection of dose and dosing frequency evaluated in the Phase III program was based on tolerability, PK and PD data from the Phase I studies and leveraged non-pegylated interferon beta-1a (Avonex) as a reference point. The BIIB017 125 µg dose was the highest dose with a favourable tolerability profile in the Phase I studies. On a per-month basis, BIIB017 125 µg Q2W provided similar biologic activity and exposure in the PD parameter BIIB017 125 µg Q4W was also tested to identify a minimally efficacious dose.

The efficacy and safety of BIIB017 Q2W was demonstrated convincingly in the Phase III Study 105MS301. At Year 1, BIIB017 Q2W provided numerically superior results compared to the Q4W dose in the reduction in ARR, the proportion of patients relapsed and magnetic resonance imaging endpoints, and similar results in the reduction of the proportion of patients with 12 week confirmed disability progression. The safety profiles of both doses were similar.

While these results suggested a favourable benefit-risk of BIIB017 at 125 µg Q2W compared to that of 125 µg Q4W, visual examination of the exposure and response relationship does not appear to support a substantially increased treatment effect with further increases of exposure provided by dosing more frequently than Q2W. Figure 4 shows ARR plotted against the cumulative AUC of BIIB017. A lower ARR was associated with the Q2W dose compared to the Q4W dose and within the range of AUC offered by the Q4W dose there was a downward trend in ARR with greater exposures (that is, those overlapping with the exposures generated by the Q2W regimen). However, within the range of AUC offered by the Q2W dose, there was no discernable difference in ARR at the low or high end of the AUC range, suggesting that further increasing the AUC by increasing the frequency of injections would not lead to further lowering of ARR.

Figure 4: Relationship between cumulative AUC and ARR at Year 1. Study 105MS301

BIIB017-treated subjects (n=1012) were binned based on each subject's monthly cumulative AUC, and each bin included an approximately equal number of subjects. Red asterisks represent observed data; solid line represents Friedman's super smoother line, indicating the trend of the data; horizontal bars at the bottom indicate cumulative AUC for the Q4W and Q2W groups, respectively. The observed ARR in the last bin was out of trend; sensitivity analysis showed that this was driven by 4 subjects with AUC below or close to median of the last binning subgroup. Exclusion of these 4 subjects yielded a result consistent with the overall trend (ARR=0.306 for the last group).

As mentioned by the reviewer, while both dose regimens were efficacious, BIIB017 125 µg Q2W has demonstrated a favourable benefit-risk profile which appears to be superior to that of BIIB017 125 µg Q4W. For this reason, the sponsor believes the optimal dose of BIIB017 is 125 µg Q2W. Furthermore, as once weekly dosing of BIIB017 would not reduce the injection burden of currently available first-line therapies and existing data did not seem to indicate that further increasing the frequency of injections would result in significantly improved efficacy; it was not deemed necessary to assess the efficacy of BIIB017 125 µg once weekly.

Indication statement

In the Delegate's overview, it is noted that the indication statement should be revised to include the statement '*efficacy has been assessed over 12 months see Clinical Trials*' and to remove specification of a reduction in frequency of relapses or delay to the progression of disability. The sponsor respectfully disagrees with the Delegate's proposal to specify that efficacy has only been assessed over 12 months as this would exclude relevant outcome data that have been collected over two years of treatment, thus potentially misleading the prescriber. While the primary and secondary endpoints demonstrating efficacy of peginterferon beta-1a 125 µg against placebo were assessed at the end of Year 1, interim data supporting maintenance of efficacy over two years were provided in this application. Included were data from 608 subjects who had completed two years of treatment as of the data cutoff for the original filing (24 October 2012).

These data demonstrate that efficacy is maintained beyond the placebo-controlled first year of the study, particularly for the BIIB017 Q2W dosing regimen. The complete 2 year data confirm these findings.

This pivotal study, which was designed in consultation with regulatory agency advice and the European regulatory guideline for the development of treatments for MS (CHMP 2006), is two years in duration, of which the first year sponsor recognises that this aspect

of the study design diverges from the abovementioned guidance, prior to initiating Study 301, Biogen Idec obtained regulatory advice on the design of the study from the Dutch and Swedish national health agencies in the European Union (EU).

These agencies agreed that in principle, a single pivotal trial with a one year efficacy endpoint demonstrating superiority versus placebo could be sufficient for registration.

Despite the fact that the majority of participants in Study 301 were from Eastern Europe, it was shown through subgroup analyses that the overall patient characteristics and outcome were consistent among patients from various geographic regions and the overall population in the study. Using inclusion and exclusion criteria similar to recent Phase III clinical trials in relapsing MS, the baseline characteristics including demographics and MS disease characteristics of the patient population in Study 301 were comparable to those in recent Phase III clinical trials. As the vast majority of patients with relapsing forms of MS worldwide are within the age range of 18 to 65, the sponsor feels the age range specified in the inclusion criteria was appropriate. Given the similar MS diagnostic criteria, the age range and gender distribution between the trial population and the Australia MS population¹⁰, the sponsor believes the results of the trial are likely generalisable to Australia MS patients.

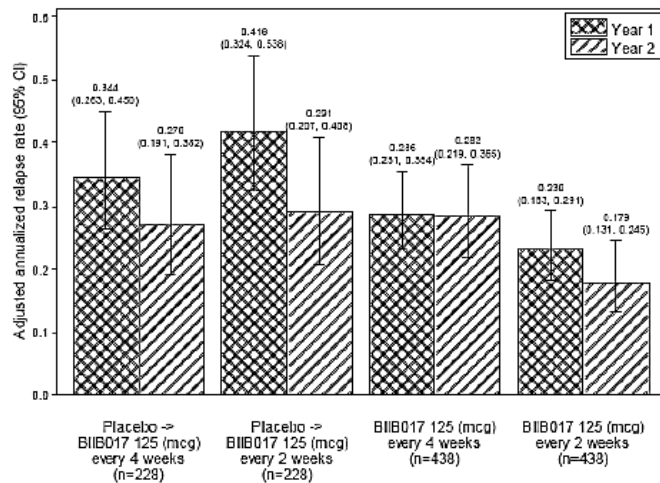
For the analyses over the complete two years of the study, those subjects exposed to active treatment throughout the entire study were compared to the subjects initially randomised to placebo. Because these placebo subjects switched to BIIB017 every 2 weeks (Q2W) or every 4 weeks (Q4W) after the first year, this represents a conservative analysis of the efficacy of BIIB017 over two years in which the treatment effect is underestimated. As described below, even with this conservative approach, the analyses over the interim two years of the study indicated that efficacy is maintained beyond the placebo-controlled first year of the study, particularly for the BIIB017 Q2W dosing regimen.

Acknowledging that the lack of a placebo comparator beyond Year 1 limits the ability to describe a specific treatment effect versus placebo for BIIB017 in Year 2, the observation that the efficacy estimates remain similar from Year 1 to Year 2 provides evidence of maintenance of efficacy beyond one year, as illustrated by the consistent observations on the annualised relapse rate (ARR) and the number of new and newly enlarging T2 lesions.

The ARR was consistent (every 4 weeks) or lower (every 2 weeks) from Year 1 to Year 2 for those subjects originally randomised to BIIB017 as illustrated Figure 5.

¹⁰ Table 3.4 of MSRA 2011: Economic Impact of Multiple Sclerosis in 2010 Australian MS Longitudinal Study. Report prepared for Multiple Sclerosis Research Australia by Covance Pty Ltd and Menzies Research Institute Tasmania

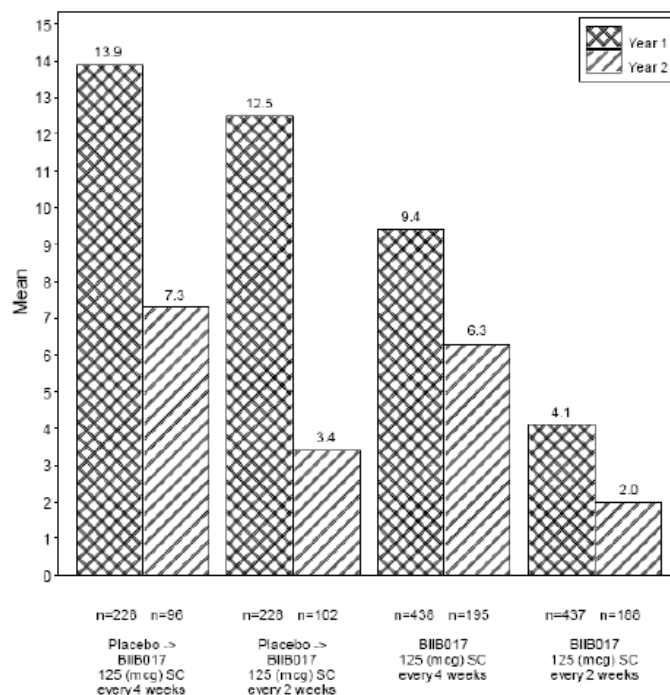
Figure 5: Summary of annualised relapse rate (INEC confirmed relapses) by study year-ITT population dosed in Year 2.



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 annualised relapse rate and 95% CI are based on negative binomial regression (if the model can not be converged, Poisson regression is used instead), adjusted for baseline EDSS (<4 vs. ≥4), baseline relapse rate and age (<40 vs. ≥40).

This is in agreement with our expectation of the known concordant effect between the ARR at one and two years shown in previous studies of interferons [Avonex PLA 95-0979 Summary of Basis of Approval 1995; PRISMS Study Group 1998; Rebif BLA 98-0261 Medical Review 1999; Rebif BLA 103780/0 S 2002; The IFNB Multiple Sclerosis Study Group 1993] which had informed the study design which was outlined above. Maintenance of efficacy is also demonstrated by the mean number of new or newly enlarging T2 lesions which are lower in Year 2 compared to Year 1 (Figure 6).

Figure 6: Number of new and newly enlarging T2 lesions by study year-ITT population dosed in Year 2.



NOTE: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications up to week 48 are imputed based on previous visit data assuming the constant rate of lesion development or group mean at same visit.

Further, subjects originally randomised to placebo who switched to BIIB017 in the second year provide a comparator group (placebo→BIIB017) against which to assess the effects of

BIIB017 over two years. In such analyses by original randomization group for time to first relapse (Figure 7) and time to sustained progression of disability (Figure 8), consistent efficacy across the 2 year study period was also demonstrated. Importantly, this analysis, which is consistent with the guidance for studies involving placebo in the first year only [Committee for Medicinal Products for Human Use (CHMP) 2006], is conservative as it results further support the maintenance of efficacy beyond 1 year.

Figure 7: Time to first relapse (INEC confirmed relapse) over 2 years-ITT population

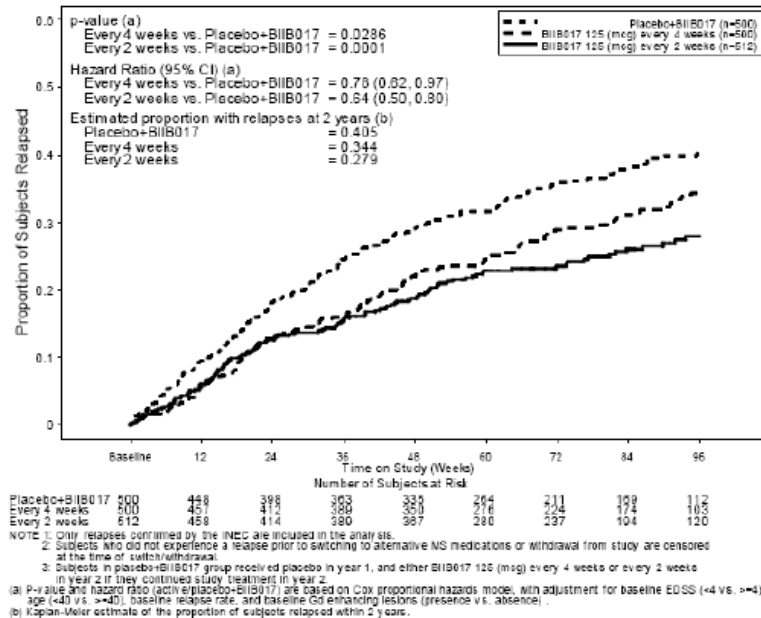
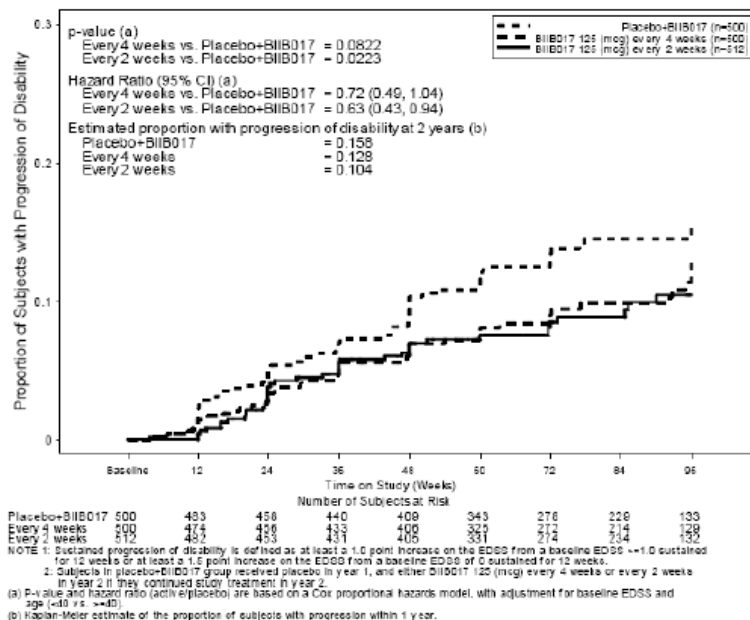


Figure 8: Time to sustained progression of disability as measured by increase in EDSS over 2 years-ITT population.



In summary, maintenance of efficacy for peginterferon beta-1a 125 µg was shown across multiple clinical and MRI endpoints in Study 301. The use of a conservative comparator and efficacy estimates that are consistent from Year 1 to Year 2 and over two years lend reassurance that the study, as designed, is able to provide information on the maintenance of efficacy. The results are especially convincing as the findings at one year and over two

years are observed across multiple endpoints in different domains relevant to the assessment of efficacy in MS and support the indication sought.

While the primary and secondary endpoints demonstrating efficacy of peginterferon beta-1a 125 µg against placebo were assessed at the end of Year 1, interim data supporting maintenance of efficacy over two years were provided in the original Marketing Authorisation Application (MAA) submission. For this reason, the text proposed by the Delegate specifying that efficacy has only been assessed over 12 months could be misleading. The Product Information (PI) guidelines also stipulate that information concerning therapeutic applications including target disease and treatment indication should be stated in a clear and concise manner. However, the sponsor recognises the importance of accurately describing the study design and data supporting the efficacy of peginterferon beta-1a; therefore, the sponsor proposes modifications to the Clinical Trials section to ensure it is very clear to prescribers that the efficacy results were derived from the placebo-controlled first year of the study.

As per the Australian PI guidelines, the sponsor accepts the Delegate's suggestion to remove mention of relapses or delay to disability progression from the indication statement and include these data in the Clinical Trials section at this time. As mentioned by the Delegate, the sponsor may choose to submit the complete 2 year data and propose an update to the label as a postapproval variation. The indication proposed by the sponsor is as follows:

Plegridy is indicated for the treatment of relapsing forms of Multiple Sclerosis (MS).

Long term safety data

In the Delegate's overview, it is noted that Biogen Idec has committed to longer term safety assessment in an extension study.

Study 105MS302 titled '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' is ongoing. This study was extended to September 2015 to obtain additional safety data and is considered sufficient to monitor long-term safety. The safety of peginterferon beta-1a will also continue to be monitored through routine pharmacovigilance activities.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Plegridy solution for injection, pre-filled syringe or pre-filled pen, containing 125 µg/0.5 mL, 94 µg /0.5 mL and 63 µg /0.5 mL of peginterferon beta-1a to have an overall positive benefit-risk profile for the amended indication;

PLEGRIDY is indicated for the treatment of relapsing remitting forms of multiple sclerosis (See CLINICAL TRIALS).

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate on the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- The sponsor's position on the statement in the PI with regards to carcinogenicity is considered acceptable.
- The sponsor's position on the statement in the PI with regards to exclusion criteria in the Clinical trials is also considered acceptable.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. The final study report of the pivotal efficacy and safety study that will provide efficacy and safety data to two years was not completed at the time of submission. No patients aged under 18 years or over 65 years have been assessed for efficacy or safety. The study was not designed to provide a comparison with placebo in disability progression over two years. Given the similarity of peginterferon beta-1a to interferon beta-1a the Delegate was inclined to accept this reduced level of evidence to support an indication similar to that of Avonex but with a specific statement that efficacy beyond 12 months have not been adequately assessed. The Delegate requested the committee's advice on whether the indication proposed is acceptable or whether the statistically significant differences in relapse rate and/ or in disability progression over 12 months are sufficient to support the indication proposed by the sponsor.

The ACPM advised the evidence submitted demonstrated adequate efficacy and a very manageable safety profile and supported an indication similar to Avonex, as proposed by Delegate.

The ACPM also advised that while reduction in relapses and disability has been demonstrated over 1 year, the relevant TGA-adopted EMA guideline recommends; 'Two years is considered the minimum duration to demonstrate efficacy'. In a long term illness such as multiple sclerosis two years of data to support on-going treatment is strongly preferred. A PI statement should be added that efficacy beyond 12 months has not been adequately assessed.

While good evidence that peginterferon 125 µg every 2 weeks (the proposed dose) provides a broadly similar pharmacodynamic (PD) effect as Avonex 30 µg weekly (the approved dose) and safety is not an issue, concern was expressed that the optimum dose has not been effectively explored.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Plegridy peginterferon beta-1a (rch) 125 microgram/0.5 mL solution for injection pre-filled pen; 63 microgram/0.5 mL and 94 microgram/0.5 mL solution for injection prefilled syringe Titration Pack; 125 microgram/0.5 mL solution for injection prefilled syringe; 63 microgram/0.5 mL and 94 microgram/0.5 mL solution for injection pre-filled pen Titration Pack, indicated for:

*Plegridy is indicated for the treatment of relapsing forms of Multiple Sclerosis (MS)
(see Clinical Trials)*

Specific conditions of registration applying to these goods

Implementation in Australia of the Plegridy peginterferon beta-1a (rch) Risk Management Plan (AUS-RMP), version 2.0, dated 23 May 2014 (data lock point October 2012), included with submission 2013-024-25-1-1, and any future updates, as agreed with the TGA's Office of Product Review.

Attachment 1. Product Information

The Product Information approved for main Plegridy at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 2. Extract from the Clinical Evaluation Report

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