15 October 2020
EMA/CHMP/594296/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Plegridy

International non-proprietary name: peginterferon beta-1a

Procedure No. EMEA/H/C/002827/X/0056

Note

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

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List of abbreviations

AE	Adverse Event
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve from hour 0 extrapolated to infinity
AUC_{0-336}	Area under the concentration-time curve from hour 0 to hour 336
AUC_{0-504}	Area under the concentration-time curve from hour 0 to hour 504
AUC_{0-last}	Area under the concentration-time curve from hour 0 to the last measurable concentration
AUC_{0-t}	Area under the concentration-time curve from hour 0 to the last observed concentration at time t
BD	Becton Dickinson
BLQ	Below the Limit of Quantification
bpm	Beats per minute
BL/GF	Break-Loose force and Glide Force
BMI	Body Mass Index
BIIB017	Peginterferon beta-1a
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL/F	Apparent total body clearance
C_{max}	Maximum observed concentration
CNS	Central Nervous System
CRU	Clinical Research Unit
CV	Coefficient Variation
DMD	Disease Modifying Drug
EDSS	Expanded Disability Status Scale
$EAUC_{0-336}$	Effect-time curve from time zero to 336 hours postdose
$EAUC_{0-504}$	Effect-time curve from time zero to 504 hours postdose
Ebaseline	Baseline concentration
EMA	European Medicines Agency
Epeak	Maximum effect
ET_{max}	Time to reach Maximum effect
GCP	Good Clinical Practice
cGMP	current Good Manufacturing Practice
IFN β	Beta interferon
IM	Intramuscular
ISRs	Injection site reaction
LL	Luer Lock
LLOQ	Lower Limit of Quantification
λZ	Terminal elimination rate constant
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MS	Multiple Sclerosis
Nabs	Neutralizing antibodies
%AUCextrap	Percentage extrapolation of AUC_{∞}
PD	Pharmacodynamics
PEG	Polyethylene Glycol
PFS	Pre-filled syringe
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics

PPQ	Process Performance Qualification
PRAC	Pharmacovigilance Risk Assessment Committee
QCs	Quality Control samples
RRMS	Relapsing-Remitting Multiple Sclerosis
SC	Subcutaneously
SD	Standard deviation
SmPC	Summary of Product Characteristics
TEAEs	Treatment-Emergent Adverse Events
T_{max}	Time to maximum observed concentration
$T_{1/2}$	Terminal elimination half-life
tQC	Trending quality control
Vd/F	Apparent volume of distribution during terminal elimination phase

1. Background information on the procedure

1.1. Submission of the dossier

Biogen Netherlands B.V. submitted on 10 February 2020 an extension of the marketing authorisation (MA).

Extension application to introduce a new route of administration (intramuscular use) for the 125 µg solution for injection.

The Marketing Authorisation Holder (MAH) applied for a change or addition of a new route of administration.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(e) - Extensions of marketing authorisations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0371/2019 on the agreement of a paediatric investigation plan (PIP)

At the time of submission of the application, the PIP P/0371/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: N/A

The application was received by the EMA on	10 February 2020
The procedure started on	27 February 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	25 May 2020

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	26 May 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 June 2020
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	26 June 2020
The MAH submitted the responses to the CHMP consolidated List of Questions on	17 July 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	18 August 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	04 September 2020
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	17 September 2020
The MAH submitted the responses to the CHMP List of Outstanding Issues on	18 September 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	01 October 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Plegridy on	15 October 2020

2. Scientific discussion

2.1. Problem statement

Plegridy is an interferon beta-1a with a prolonged response (due to Polyethylene Glycol [PEG] conjugation). It is indicated in adult patients for the treatment of relapsing-remitting multiple sclerosis (RRMS).

The recommended dose of Plegridy is 125 micrograms injected subcutaneously (SC) every 2 weeks. The product may be self-administered by patients.

The product is available as a 63, 94 and 125 micrograms strength, both in a pre-filled syringe and a pre-filled pen. The lower strengths are used for dose titration at the start of treatment, to prevent flu-like symptoms.

The current application concerns an extension application. The MAH proposes to add intramuscular injection (IM) to offer patients an alternative route of administration with fewer injection site reactions (ISRs) as compared to subcutaneous injection.

A new pre-filled syringe has been developed for this purpose. The syringe contains 125 micrograms of peginterferon beta-1a. The dose can be limited to 63 micrograms and 94 micrograms with the use of titration clips.

2.1.1. Disease or condition

Plegridy is indicated in adult patients for the treatment of RRMS.

2.1.2. Epidemiology and risk factors

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) with a worldwide prevalence estimated at 2 to 2.5 million patients. The disease is unevenly distributed throughout the world; its prevalence varies between <5 cases per 100,000 people in tropical areas and Asia and >100 to 200 cases per 100,000 in temperate areas, especially those with large populations of Northern European origin.

The worldwide incidence of MS is estimated to be 3.6 cases per 100,000 person-years in women (95% confidence interval [CI] 3.0-4.2) and 2.0 cases per 100,000 person-years in men (95% CI 1.5-2.4) [Alonso and Hernan 2008]. Therefore, MS is approximately twice as common in women as men and predominantly affects adults aged 20 to 60 years.

A genetic predisposition to MS exists, particularly variation involving the HLA-DRB1 locus [Lincoln 2005; Sawcer 2011]. Risk is elevated if a family member has MS [Ebers 2008]. Risk of MS increases with increasing geographic latitude. Vitamin D deficiency has been found to significantly increase the risk of developing MS, so reduced sunlight exposure during childhood at higher latitudes may be an explanation for the geographic phenomenon [Ascherio and Munger 2007].

2.1.3. Aetiology and pathogenesis

The aetiology of MS is unknown, the synergic effect of genetic and environmental factor leads to immune-mediated inflammatory activity of the CNS that lead to destruction of the myelin sheath and axonal injury.

2.1.4. Clinical presentation, diagnosis and prognosis

MS can present with a range of neurological symptoms depending on the category of disease and location of the lesions, but commonly reported symptoms in established, untreated MS are visual dysfunction, weakness, which is frequently lower limb, sensory symptoms, and bladder problems, and progressive ambulatory decline will affect a sizable proportion of patients with MS. Diagnosis of MS is based on clinical presentation together with the findings in the magnetic resonance imaging [Mc Donald 2001, 2010, 2017].

RRMS is the most common form of MS, representing approximately 85% of patients at diagnosis. The course of RRMS is unpredictable, with variable periods of disease activity interspersed with periods of stability. According to earlier natural history studies, approximately 40% and 25% of patients with RRMS will, within the first 15 years after diagnosis, need to use a walking aid and be wheelchair-dependent [Myhr 2001]. Recent findings from cohorts of patients mostly treated with disease modifying drugs (DMDs) from early onset have found lower transition rates to secondary progressive MS.

2.1.5. Management

There is no cure available for MS. Therapies for MS include treatment for relapses (e.g. steroids), symptomatic treatments (e.g. drugs for stabilization of nerve conduction, drugs for managing fatigue, depression, pain) and those that alter the course of the disease (DMDs).

There are several DMD for MS including beta interferons (IFN β) (Avonex, Betaferon and Rebif), glatiramer acetate (Copaxone), teriflunomide (Aubagio), dimethyl fumarate (Tecfidera), fingolimod (Gilenya), siponimod (Mayzent), ozanimod (Zeposia), alemtuzumab (Lemtrada), natalizumab (Tysabri), ocrelizumab (Ocrevus), cladribine (Mavenclad).

About the product

Plegridy is a PEG-modified interferon beta-1a (Company Code: BIIB017) that is approved for the treatment of RRMS.

BIIB017 binds to the type I interferon receptor on the surface of cells and elicits a cascade of intracellular events leading to the regulation of interferon-responsive gene expression. Biological effects that may be mediated by BIIB017 include up-regulation of anti-inflammatory cytokines (e.g. IL-4, IL-10, IL-27), down-regulation of pro-inflammatory cytokines (e.g. IL-2, IL-12, IFN-γ, TNF-α) and inhibiting the migration of activated T cells across the blood brain barrier. However, the full/definitive mechanism of action for BIIB017 is not known, as the pathophysiology of MS is only partially understood.

Type of Application and aspects on development

This dossier concerns a line extension application for Plegridy (peginterferon beta-1a) to add IM injection as an additional route of administration for the adult population. Peginterferon beta-1a is administered every 2 weeks via SC injection and is approved for RRMS in adults. The basis for this application is an open-label, multicentre, 2-period crossover study (105HV106) to assess the bioequivalence of BIIB017 administered by SC and IM injection in healthy volunteers.

Existing IFN β on the market are available for either SC or IM injection. The approval of BIIB017 for IM administration will provide patients with an alternative route of administration along with the convenience of less frequent IM dosing seen with a pegylated interferon compared with a non-pegylated interferon. In addition, data from the literature show that the IM administration of IFN β-1a resulted in fewer ISRs than the SC route [Balak 2012; Minagara 2008].

2.2. Quality aspects

2.2.1. Introduction

The current application concerns a line extension for Plegridy to be administered via the IM route as addition to the current MA for Plegridy, which is administered SC for RRMS. Besides the different route of administration, Plegridy for IM and SC administration share the same indication, posology, composition and formulation.

The active substance of Plegridy is peginterferon beta-1a, herein referred to as BIIB017. BIIB017 pre-filled syringe (PFS) for IM injection will only be manufactured in the administration dose strength of 125 µg (micrograms) per syringe.

The only differences between the BIIB017 PFS for IM injection and the approved BIIB017 PFS for SC injection are:

(1) the new finished product manufacturing site with slightly adapted manufacturing process,

(2) the container closure; a 1 mL Becton Dickinson (BD) Luer Lock (LL) syringe, instead of a 1 mL staked needle syringe

(3) the co-packaged needle (23G, 1.25" stainless steel), instead of staked needle (29G, 0.5”stainless steel)

(4) the method of titration utilising titration clip devices, which control the administered dose to ½ and ¾ of the administration dose syringe, instead of availability of administration dose strength of 63 and 94 µg.

2.2.2. Active Substance

There were no changes made to this section as the same active substance (BIIB017-B) is used to produce BIIB017 delivered IM or SC.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The BIIB017 finished product is a sterile, liquid formulation in a PFS for IM injection containing 125 µg of peginterferon beta-1a. Other excipients are: sodium acetate trihydrate; acetic acid, glacial; arginine hydrochloride; polysorbate 20 and water for injections. No novel excipients are used.

BIIB017 PFS for IM injection is supplied in a sterile 1 mL Type I borosilicate glass syringe with a bromobutyl rubber plunger stopper and OVS tamper-evident seal. BIIB017 is filled into the PFS at a nominal volume of 0.5 mL. The intended dosage form for use by the patient consists of the PFS with 125 µg strength for titration and administration dosing. Titration of the dose during the first month of treatment is controlled with titration clip devices.

Pharmaceutical Development

Composition of the PFS finished product for IM use is identical to the already approved PFS for SC use. The same active substance (BIIB017-B) and the same excipients are used to produce BIIB017 delivered IM or SC.

Development of BIIB017 finished product for IM injection included transfer of the BIIB017 manufacturing process to with a slightly adapted manufacturing process. Minor changes are introduced in the filtration step, the finished product filling and the component preparation step:

- A filter flush was implemented prior to filtration as process improvement in the bioburden reduction filtration on bulk finished product.
- Due to differences in hold up volume between SC and IM needles, a slightly higher target fill volume is utilised in the IM process. This is to ensure that the target dose is delivered with the larger IM needle and Luer Lock syringe hold-up volume.
- Closure of LL syringe is required (tamper-evident seal - OVS).

The differences between the manufacturing processes at the current manufacturer for SC syringes and new manufacturer for IM syringes are well described.

Comparability between the manufacturing process for PFS for IM injection and the manufacturing process for PFS for SC injection has been shown by comparing the release data and additional characterisation of subvisible particulate matter of three process performance qualification (PPQ) batches PFS for IM injection with historical ranges of 76 PFS batches for SC injection.

Results show that the IM finished product is comparable with the SC finished product, with the exception of extractable volume. Extractable volume is slightly higher for IM batches due to the higher fill volume target. Due to differences in hold up volume between SC and IM needles, a slightly higher target fill volume is utilised in the IM process. This is to ensure that the target dose is delivered with the larger IM needle and Luer Lock syringe hold-up volume.

The differences between the container closure system for the PFS for IM injection and the PFS for SC injection are differences in the needle (difference in length and gauge required for IM presentation) and differences in the closure. The Luer Lock syringe requires tamper evident seal and LL connection and tip cap. Suitability of the container closure system has been shown by container closure integrity testing, extractables and leachables studies and functionality testing.

Container closure integrity testing was performed during process validation, shipping qualification and long-term storage.

Data of extractables and leachables studies for the materials in contact with the finished product were submitted. The presented results do not raise any safety concerns.

The results of functional testing were provided. Functionality studies at stability conditions up to 48 months (at 5°C); up to 9 months (at 25°C) and up to 6 months (at 40°C) are ongoing.

The low doses (63 and 94 µg) will be administered by the use of titration clip devices. The CE-marked medical devices are supplied as Titration Kit in a separate package. Information on design and performance of these titration clip devices has been provided. The administration of the correct doses, as mentioned in the Summary of product characteristics (SmPC), using these titration clip devices has been shown in dose accuracy studies.

The MAH did not perform a traditional human factor study, however a comparative usability assessment was performed against the AVOSTARTGRIP® device, i.e. an already available titration clip device for administration of IFN β.

The MAH has changed the artwork for the carton exterior, packaging and package leaflet to clearly distinguish between the SC and IM formulation. Furthermore, the physical presentations of the products differ. Therefore, the probability of occurrence of administration of incorrect medication in the titration phase (confusion between the IM and SC formulation) is assessed as "low".

Manufacture of the product and process controls

Plegridy IM PFS finished product is manufactured, released, stored, labelled, and packaged in accordance with current Good Manufacturing Practice (cGMP). The manufacturing of BIIB017 finished product consists of the following steps:

– Step 1: Compounding of Formulation Buffer

– Step 2: Thawing of the Bulk Drug Substance

– Step 3: Pooling and Mixing

– Step 4: Addition of Formulation Buffer to Achieve Target Protein Concentration and Formulation

– Step 5: Filtration into Dispensing Vessel

– Step 6: Sterile Filtration to the Filling Line

– Step 7: Aseptic Syringe Filling and Plunger Placement

– Step 8: 100% Visual Inspection

– Step 9: Finished product storage

The manufacturing process has been well described. The process controls and control of critical steps and intermediates are the same as for the SC manufacturing process and are acceptable.

Process evaluation consisted of the production of three PPQ batches in which several hold times were challenged. Finished product release assays were performed on the filled LL syringes, and the results were compared to the release specification and historic database for the licensed BIIB017 finished product administered SC.

The results confirm that the finished product manufacturing process for BIIB017 finished product for IM injection at is validated.

Product specification, analytical procedures, batch analysis

The finished product specification includes tests for identity, quantity, potency (by antiviral cytopathic effect assay), purity and safety.

The specifications for BIIB017 PFS for IM injection specifications are identical to or tighter than the specifications for BIIB017 PFS for SC injection. The specifications for protein concentration, oxidation and biantennary sialylation are tightened as a result of re-evaluation of the specifications for BIIB017 PFS for SC injection. The information provided in this section is sufficient and acceptable.

Analytical procedures

Except for container closure integrity testing as sufficiently detailed in the dossier, all analytical methods are the same as for the BIIB017 finished product for SC injection. The method validations have been adequately summarized.

Batch analysis

The release test results for the PPQ lots of BIIB017 finished product for IM injection have been provided. A summary of the lots, their manufacturing history, and purpose of use have been presented.

All results met the release specifications, demonstrating the quality and consistency of the commercial manufacturing process.

Stability of the product

A shelf life of 36 months when stored at 2 °C to 8 °C is claimed for the finished product.

Based on the stability data presented the same shelf-life (36 months at 5°C with an allowance of storage for up to 30 days at room temperature (not to exceed 25 °C) within the 36-month shelf life) has been claimed for BIIB017 finished product for IM injection as is currently approved for BIIB017 finished product for SC injection.

The applicant has submitted a comparative stability evaluation of IM and SC presentations demonstrating that both presentations behave similar upon storage and therefore the same shelf-life is considered acceptable for commercial lots BIIB017 PFS for IM injection as is currently approved for BIIB017 PFS for SC injection.

A shelf life of 36 months when stored at 2 °C to 8 °C is acceptable for the finished product. Plegridy for SC or IM administration can be stored at room temperature (up to 25 °C) for up to 30 days protected from light, after this period it should be discarded.

Post approval change management protocol(s)

Not applicable.

Adventitious agents

Plegridy active substance is the same for Plegridy SC and IM. There are no process changes/differences in the active substance, hence Virology testing is the same as what is currently registered in section 3.2.A Adventitious Agents Safety Evaluation for Plegridy SC MAA.

No changes were made to this section.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The current application concerns a line extension for Plegridy to be administered via the IM route as addition to the current MA for Plegridy, which is administered SC for RRMS.

Besides the different route of administration, Plegridy for IM and SC administration share the same indication, posology and formulation. BIIB017 PFS for IM injection will only be manufactured in the administration dose strength of 125 µg per syringe.

The differences between the BIIB017 PFS for IM injection and the approved BIIB017 PFS for SC injection were justified and adequately discussed.

Composition of the PFS finished product for IM use is identical to the already approved PFS for SC use. The same active substance (peginterferon beta-1a, BIIB017-B) is used to produce BIIB017 delivered IM or SC.

Comparability between the manufacturing process for PFS for IM injection and the manufacturing process for PFS for SC injection has been shown by comparing the release data and additional characterisation of subvisible particulate matter of three PPQ batches PFS for IM injection with historical ranges of 76 PFS batches for SC injection. Results show that the IM finished product is comparable with the SC finished product, with the exception of extractable volume. Extractable volume is slightly higher for IM batches due to the higher fill volume target. Due to differences in hold up volume between SC and IM needles, a slightly higher target fill volume is utilised in the IM process. This is to ensure the target dose is delivered with the larger IM needle and Luer Lock syringe hold-up volume.

The differences between the container closure system for the PFS for IM injection and the PFS for SC injection are differences in the needle (difference in length and gauge required for IM presentation) and differences in the closure. The Luer Lock syringe requires tamper evident seal and LL connection and tip cap. Suitability of the container closure system has been shown by container closure integrity testing, extractables and leachables studies and functionality testing.

LL syringes for IM use are washed, siliconised, and sterilised, while the approved syringes for SC use are siliconised and sterilised by the supplier.

The manufacturing process has been well described. Process evaluation consisted of the production of three PPQ batches in which several hold times were challenged. It has been shown that the

manufacturing process is well controlled. The specifications for BIIB017 PFS for IM injection specifications are identical to or tighter than specifications for BIIB017 PFS for SC injection.

The adventitious agents safety is sufficiently assured, and no changes were made to this section.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of this line extension for Plegridy is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

In conclusion, based on the review of the quality data provided, this line extension application for Plegridy to add the IM route of administration is considered approvable from the quality point of view.

2.2.6. Recommendations for future quality development

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

2.3. Non-clinical aspects

No new non-clinical studies have been submitted to support this extension application.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with Good Clinical Practice (GCP) as claimed by the MAH.

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

- Tabular overview of clinical studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Participants (current)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Bioequivalence (BE)	105HV106	Evaluate the PK of BIIB017 administered via intramuscular (IM) and subcutaneous (SC) routes of administration	Phase 1, single dose, randomized, open-label, crossover	BIIB017; One dose each of BIIB017 125 mcg SC, administered IM and SC	136 enrolled; 130 completed	Healthy subjects	Subjects dosed on Day 1 and Day 29	Complete; Full

2.4.2. Pharmacokinetics

Peginterferon beta-1a (or BIIB017) currently approved administration is via SC injection using a single-use pre-filled pen or pre-filled syringe (available at 3 different concentrations - 64, 94 and 125 µg/0.5 ml). IM administration using a single use pre-filled syringe is being proposed as an alternative route of administration. IM injection will only be manufactured in the dose strength of 125 µg per syringe but with titration clips to deliver the lower doses of 63 and 94 µg.

Study 105HV106 was submitted to support the application with a primary objective of assessing the bioequivalence of BIIB017 administered by SC and IM injection in healthy volunteers. Secondary objectives of this study were to evaluate the safety, tolerability, and additional pharmacokinetics (PK) parameters of SC administration as compared with IM administration of BIIB017 in healthy volunteers. In addition, as exploratory objectives, pharmacodynamics (PD) parameters such as neopterin and titre of binding antibodies to the pegylated and IFN β-1a components of BIIB01 were planned to be evaluated. The latter was not carried out since there were no unusual PK or safety results.

Pharmacokinetics of BIIB017 were characterized previously in the original MAA. During that time a small study (Study 105HV101) in healthy volunteers evaluated PK and PD of BIIB017 following SC and IM administration of a dose of 125 µg BIIB017. Although the findings from that study suggested similar bioavailability following SC and IM administration, no conclusion could be drawn because the sample size was too low (N= 8 subjects per administration). In this report, the PK and PD results of Study105HV106 were described and discussed.

Methods

Study design

Study 105HV106 was an open-label, multi-center, 2-period, crossover study to assess the bioequivalence and tolerability of BIIB017 administered by SC and IM injection in healthy volunteers.

According to the MAH, the Investigators obtained institutional review board (IRB, Midlands Independent Review Board, Kansas, USA) approval for the study protocol and all amendments.

The clinical study was conducted in 2 sites of Covance Clinical Research Unit Inc. in the USA (i.e. Daytona Beach, Florida and Dallas, Texas). The date of 1st treatment was on 3 December 2018 and the end of study was on 24 May 2019. The PK-samples were analysed at the BioAgilitix Labs (Durham, NC, USA) on 5 March – 2 July 2019. The PD-samples were analysed at Charles River Laboratories (Quebec, Canada) on 4 April - 29 May 2019. The study report is dated 31 October 2019.

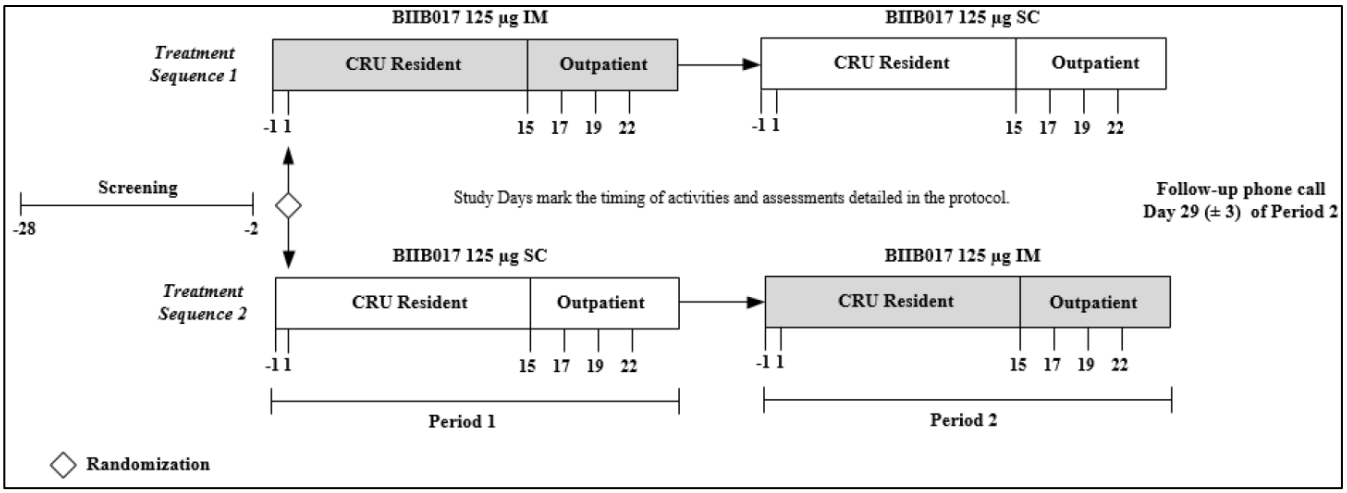
After a screening period of up to 28 days, volunteers reported to the Clinical Research Unit (CRU) on Day -1 of Period 1 (Check-in) and on Day 1 of Period 1, volunteers were randomized 1:1 to treatment sequence 1 or 2. Volunteers were dosed on Day 1 of Period 1 and discharged from the CRU on Day 15 of Period 1. Volunteers returned for outpatient visits on Days 17, 19, and 22 of Period 1. After a washout period of a minimum of 27 days following Day 1 of Period 1, volunteers returned to the CRU on Day -1 of Period 2 (Check-in). Volunteers were dosed on Day 1 of Period 2 and discharged from the CRU on Day 15 of Period 2. Volunteers returned for outpatient visits on Days 17, 19, and 22 of Period 2.

Each volunteer received both of the following treatments administered to the anterolateral thigh:

- Treatment A (test): A single IM dose of 125 µg BIIB017.
- Treatment B (reference): A single SC dose of 125 µg BIIB017.

The study scheme is depicted in Figure 1

Figure 1: Study Schematic of Crossover Design



CRU = Clinical Research Unit; IM = intramuscular; SC = subcutaneous.
Day -1 of Period 2 was to occur 27 (+3) days after Day 1 of Period 1 (dosing) in order that dose administrations occurred 28 (+3) days apart.

Pharmacokinetics

A total of 23 blood samples were collected for determining the concentrations of BIIB017 at the following time points relative to dosing on Day 1 of each period: within 2 hours prior to dosing and 3, 6, 12, 24, 32, 40, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 384, 432 and 504 hours post-dose.

Pharmacodynamics

The same number and time points of blood samples as in the PK part were collected for determining neopterin serum levels.

Immunogenicity

Samples to test for the presence and titre of binding antibodies to PEG and IFN ß-1a were collected prior to dosing in each period and at the last outpatient visit on Day 22 of Period 2. These samples were stored to be analysed only in the event of an unexpected PK or safety finding. Since there were no unusual PK or safety results, antibody status was not tested, and no immunogenicity data are available for this study.

Safety

Clinical assessments were performed to evaluate the safety profile of BIIB017.

Investigated medicinal product for test and reference for treatment

BIIB017 (20kDa mPEG-O-2-methylpropionaldehyde-modified human IFN β-1a) was provided as a solution in 20 mM acetic acid/sodium acetate buffer (pH 4.8), 150 mM arginine hydrochloride, and 0.005% Polysorbate 20 in volunteer-specific, labeled, prefilled syringe to deliver 0.5 mL of 0.25 mg/mL BIIB017 (125-µg dose).

Population studied

A total of 136 healthy subjects (61 females and 75 males), aged 21-55 years with a body mass index (BMI) of 19 – 30 kg/m^2 were enrolled and dosed in period 1. Six subjects did not receive BIIB017 in period 2 due to AEs (n=3), non-compliance (n=2) and physician decision (n=1). Thus, 130 subjects (SC=66 and IM=64) were dosed in period 2 and available for PK analysis. In addition, 5 other subjects

were discontinued from the study due to lost to follow-up (n=1) and subject withdrawal (n=4). Hence, a total of 125 volunteers completed the study according to protocol.

Analytical methods

ELISA for measuring BIIB017 levels in serum

For the study samples analysis, the system suitability and performance requirements were met. Global run accuracy and precision ranged from 94.2 to 100% and 8.5 to 10.3%, respectively.

A total of 6,085 samples were analysed. A total of 241 runs were performed, of which 23 (9.5%) failed to meet the acceptance criteria (i.e. incorrect calibrator volume, 3/6 Control Samples (QCs) failed, contamination of curve), and the samples were re-assayed on subsequent runs. Twelve additional runs were conducted to evaluate incurred sample re-analysis; of these 12 runs, 2 failed to meet acceptance criteria. These 2 runs were repeated, for a total of 14 sample re-analysis runs.

A total of 274 samples (0.05 % of total samples analysed) was re-analysed due to the following reasons: concentration above upper limit of quantification = 190 samples, concentration measured for a pre-dose sample/repeated due to below the limit of quantification (BLQ) for second re-assay value = 3 samples, BLQ at dilution = 74 samples and others = 9 samples.

For ISR, approximately 10% of the first 1000 samples, then 5% of the samples that exceed the initial 1000 were tested. Individual incurred samples from multiple subjects between the maximum observed concentration (C_{max}) and the elimination phase were selected and a total of 372 samples (5%) were analyzed, of which 332 samples (88%) were within 30% of their mean.

ELISA for measuring neopterin concentration in serum

The serum concentration of neopterin following administration of BIIB017 125 µg IM and SC was measured for PD analysis. Neopterin is a protein that is synthesized by IFN-β activated monocytes and macrophages and is a well-established marker of IFN-β activity [Casoni 2004].

Based on the positive performance of the standards and QCs during sample analysis, the neopterin concentration values reported for the study samples from the ELISA assay were valid.

The actual study samples were analysed in duplicate and sample analysis was repeated if the percentage of coefficient variation (CV) between duplicate drug concentrations was >25%. Mean results were reported and expressed as nmol/l. All study samples were analysed within the validated temperature, freeze/thaw cycles, and long-term storage stabilities.

Immunogenicity Assessments

Antibody status was not tested as no unusual PK or safety findings were observed.

Pharmacokinetic data analysis

The following PK parameters were calculated using non-compartmental methods using Phoenix WinNonlin (Certara, USA, Inc., version 8.1): (primary) C_{max} and area under the concentration-time curve from hour 0 extrapolated to infinity ($AUC_{0-\infty}$), and (secondary), time to maximum observed concentration (t_{max}), Area under the concentration-time curve from hour 0 to hour 336 (AUC_{0-336}), hour 504 (AUC_{0-504}), and the last measurable concentration (AUC_{0-last}), percentage extrapolation of AUC_{∞} (%AUCextrap), terminal elimination rate constant (λZ), terminal elimination half-life ($t_{1/2}$), apparent total body clearance (CL/F), and apparent volume of distribution during terminal elimination phase (Vd/F).

All AUCs in PK analysis were calculated using the linear trapezoidal rule and the minimum requirement for the calculation of AUC is the inclusion of at least three consecutive serum concentrations above the

Lower Limit of Quantification (LLOQ), with at least one of these concentrations following C_{max}. Percentage extrapolation greater than 20% were excluded from descriptive and formal statistics.

Evaluation pharmacodynamic endpoints

Neopterin levels were summarized by treatment group and nominal time point using descriptive statistics for the PD Population. Derived PD parameters including baseline concentration (Ebaseline), area under the effect-time curve from time zero to 336 hours postdose ($EAUC_{0-336}$), area under the effect-time curve from time zero to 504 hours postdose ($EAUC_{0-504}$), maximum effect (Epeak), and time to reach maximum effect (ET_{max}) were summarized using arithmetic mean, standard deviation (SD), CV%, geometric mean and geometric CV%, median, minimum, and maximum by treatment group for the PD Population.

Evaluation of immunogenicity

No evaluation was done since immunogenicity testing was not performed.

Statistical methods

The statistical analysis was performed using the software package SAS® 9.4 (SAS Institute Inc., Cary, NC, USA).

A 2-treatment, 2-period crossover analysis of variance (ANOVA) model was used to estimate the geometric mean ratios and their CIs. For each primary endpoint (AUC_{∞} or C_{max}), the model included the endpoint on a log-transformed scale as the dependent variable, with treatment, period, and treatment sequence as fixed effects, and volunteer as the random effect. The estimation was based on restricted maximum likelihood approach. The estimated ratio between treatment groups and the associated 90% CI on the original scale were presented and used to establish bioequivalence. The primary analysis model assumed that volunteers drop out at random, conditional on the fixed and random effects and was based on the PK Population (volunteers who received both doses of study treatment with sufficient PK measurements to allow calculation of PK parameters).

As a sensitivity analysis, the above ANOVA analysis was repeated in the Full Analysis (Safety) Population (subjects who received at least 1 dose of study treatment and had at least 1 post-baseline PK measurement) for Cmax, $AUC_{0-\infty}$ and AUC_{0-last}. In addition, results of $AUC_{0-\infty}$ or C_{max} from all study volunteers were summarized by treatment group using descriptive statistics.

The primary parameters $AUC_{0-\infty}$ and C_{max} were used to establish bioequivalence of the test treatment to the reference treatment. The 90% CIs for the ratios of geometric means between test and reference were calculated for $AUC_{0-\infty}$ and C_{max} using log-transformed data. The bioequivalence was established if the 90% CIs for $AUC_{0-\infty}$ and C_{max} were within the range of 80% to 125%.
The PK parameters including tmax, AUC_{0-336}, AUC_{0-504}, AUC_{0-last}, %AUCextrap, λZ, $t_{1/2}$, CL/F, and Vd/F were summarized using arithmetic mean, SD, CV%, geometric mean and geometric CV%, median, minimum, and maximum by treatment group for the PK Population.

Absorption

Bioequivalence

The serum concentration of BIIB017 following singles doses of 125 µg BIIB017 SC or 125 µg BIIB017 IM were summarised in Table 1 and Table 2 and illustrated in Figure 2.

The serum concentration versus time profiles after single doses of 125 µg BIIB017 SC and 125 µg BIIB017 IM were similar, with maximal concentrations reached at a median t_{max} of 40 hours post-dose for SC (range: 11.9 to 312 hours) and 40 hours post-dose for IM (range: 6 to 144 hours) (Table 1). After

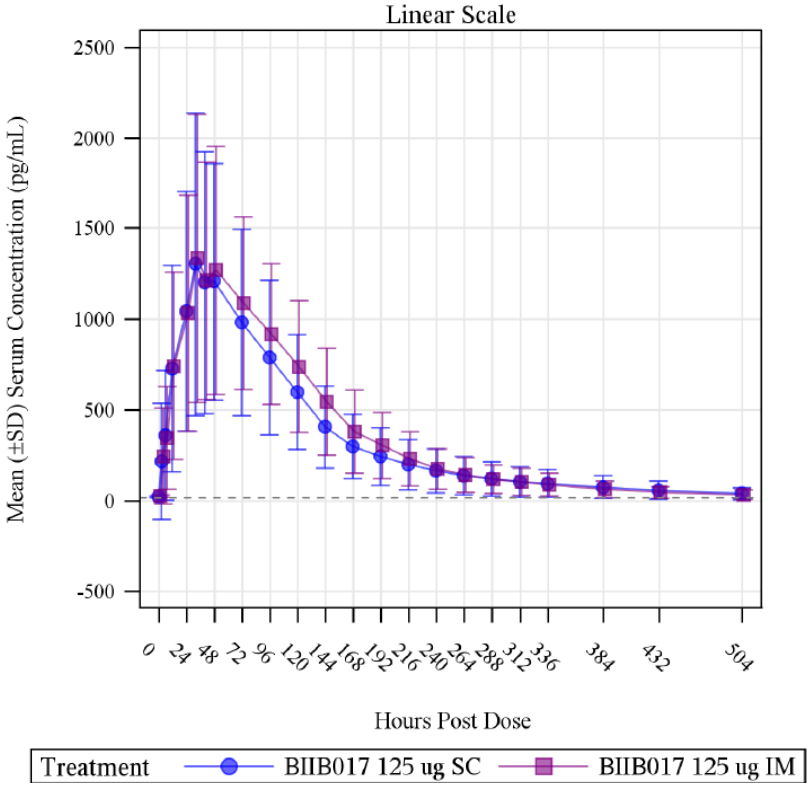
reaching C_{max}, the serum concentrations of BIIB017 declined monophasically, with mean $t_{1/2}$ values of 97.1 hours (29.1 to 239.9 hours) for SC and 79.1 hours (26.3 to 233.3 hours) for IM.

In general, moderate to high between-subject variability was noted for the PK parameters ($AUC_{0-\infty}$, C_{max}, and AUC_{0-last}) for both routes of administration, with CV% values ranging from 41% to 57% for SC and 40% to 54% for IM (Table 1).

Geometric mean values for C_{max} and $AUC_{0-\infty}$ seemed slightly higher for IM than SC. However, statistical analysis showed that 125 µg BIIB017 SC and 125 µg BIIB017 IM were bioequivalent. Geometric least squares mean ratio (90% CI) of IM versus SC was 1.08 (0.98 to 1.20) for C_{max} and 1.09 (1.02 to 1.16) for $AUC_{0-\infty}$ all contained within the 0.80 to 1.25 equivalence range.

The additional sensitivity analysis for $AUC_{0-\infty}$, AUC_{0-last} and C_{max}, based on the Safety Population also showed that all 90% CIs of geometric least squares mean ratio (IM versus SC) were contained within the 0.80 to 1.25 equivalence range (Table 2).

Figure 2: Arithmetic Mean (±SD) serum concentration-time profiles for BIIB017 (pg/mL) following a single SC and IM dose of 125 µg BIIB017–PK Population (n = 130)



NOTE: Lower limit of quantification=15.6pg/mL. BLQ is treated as 0 for linear scale and missing for semi-logarithmic scale
Non-determinable is set to missing
Abbreviations: SC= subcutaneous; IM=intramuscular
Run date: 14OCT2019

Table 1: PK parameters of BIIB017 following a single SC and IM dose of 125 µg BIIB017 (non-transformed values; arithmetic mean ± SD, t_{max} median, range) – PK Population

Treatment	$AUC_{0-\infty}$ pg/ml/ (N = 124 for SC and 129 for IM)	AUC_{0-t} pg/ml/h (N = 130 for both SC and IM)	C_{max} pg/ml (N = 130 for both SC and IM)	t_{max} hour (N = 124 for SC and 129 for IM)	t1/2 hour (N = 127 for SC and 130 for IM)
BIIB017 SC (125 µg)	173512 ± 70565	163228 ± 71765	1461 ± 835	40 (12 - 312)	97 ± 33
BIIB017 IM (125 µg)	184729 ± 74022	179851 ± 73676	1502 ± 804	40 (6 –144)	79 ± 26
***Ratio (90% CI)**	1.09 (1.02 - 1.16)	1.13 (1.06 - 1.21)	1.08 (0.98 - 1.20)	NA	NA
Between subject CV %	41 (SC); 40 (IM)	44 (SC); 41 (IM)	57 (SC); 54 (IM)		

$AUC_{0-\infty}$: Area under the concentration-time curve from hour 0 extrapolated to infinity
AUC_{0-t}: Area under the concentration-time curve from hour 0 to the last observed concentration at time t
C_{max}: Maximum observed concentration
T_{max}: Time to maximum observed concentration
$T_{½}$: Terminal elimination half-life
SC: Subcutaneous; IM: Intramuscular; CI: Confidence Interval; CV: Coefficient variation
*ln-transformed values geometric mean ratio

Table 2: Sensitivity analysis for primary PK parameters – Safety population

Treatment	$AUC_{0-\infty}$ pg/ml/ (N = 128 for SC and 131 for IM)	AUC_{0-t} pg/ml/h (N = 134 for SC and 132 for IM)	C_{max} pg/ml (N = 134 for SC and 132 for IM)
BIIB017 SC (125 µg)	173695 ± 69684	163615 ± 70925	1459± 827
BIIB017 IM (125 µg)	185645 ± 75087	180798 ± 74759	1517 ± 814
***Ratio (90% CI)**	1.09 (1.02 - 1.16)	1.13 (1.06 - 1.21)	1.08 (0.98 - 1.20)
Between subject CV%	40 (SC); 40 (IM)	43 (SC); 41 (IM)	57 (SC); 54 (IM)

$AUC_{0-\infty}$: Area under the concentration-time curve from hour 0 extrapolated to infinity
AUC_{0-t}: Area under the concentration-time curve from hour 0 to the last observed concentration at time t
C_{max}: Maximum observed concentration
SC: Subcutaneous; IM: Intramuscular; CI: Confidence Interval; CV: Coefficient variation
*ln-transformed values geometric mean ratio

Distribution

N/A

Elimination

N/A

Dose proportionality and time dependencies

N/A

Intra- and inter-individual variability

In general, moderate to high between-subject variability was noted for the PK parameters ($AUC_{0-\infty}$, C_{max} and AUC_{0-last}) for both routes of administration, with CV% values ranging from 41% to 57% for SC and 40% to 54% for IM.

Special populations

N/A

Pharmacokinetic interaction studies

N/A

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

Methods

The bioequivalence study described above also had the following exploratory objectives:

- To evaluate PD of SC and IM administration of BIIB017 in healthy volunteers
- To evaluate the immune response to BIIB017

The serum concentration of neopterin following administration of BIIB017 125 µg IM and SC was measured for PD analysis. Derived PD parameters included Ebaseline, $EAUC_{0-336}$, $EAUC_{0-504}$, Epeak, and ET_{max}.

The presence of binding antibodies to PEG and the presence and titre of binding antibodies to IFN ß-1a. These samples were collected with the intention of analysing them only in the event of unexpected PK or safety findings.

The PD Population was defined as all randomized volunteers who received at least 1 dose of study treatment with at least 1 PD measurement after baseline. All 136 volunteers were included in the PD Population.

Results

Demographics

Seventy-five volunteers were male and 61 were female, all aged between 21 and 55 years. The mean weight and BMI of volunteers was similar for each randomized treatment sequence group with a mean weight (SD) of 77.3 kg (11.93) and 78.7 kg (12.82), and mean BMI (SD) of 26.9 kg/m2 (2.51) and 26.2 kg/m2 (2.80) for treatment sequence of IM/SC and SC/IM, respectively.

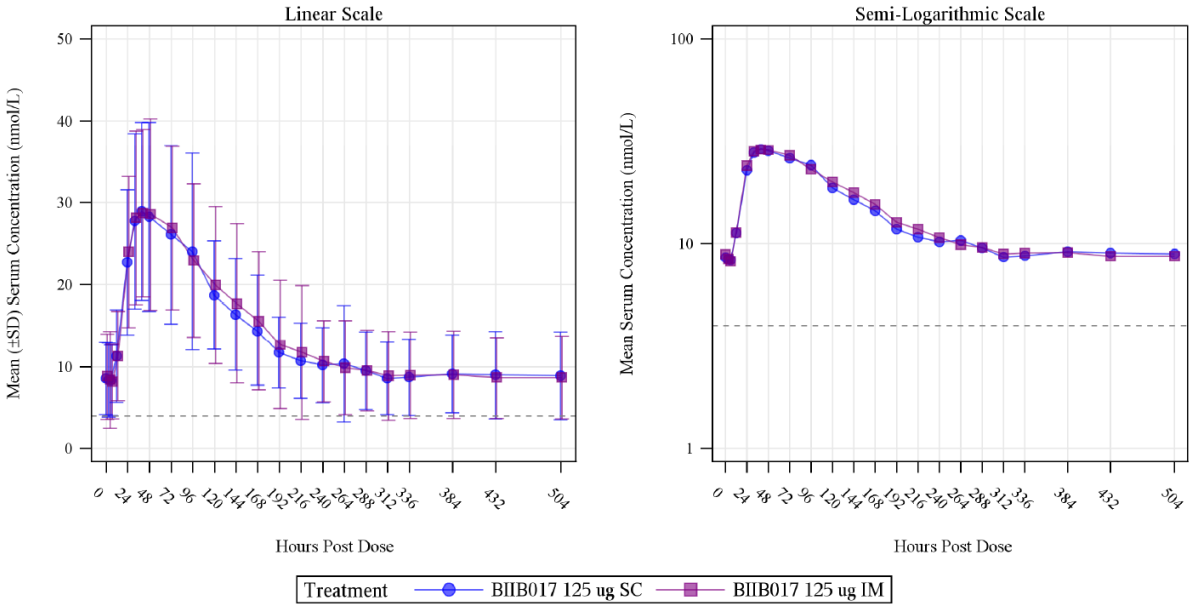
Neopterin

Serum concentrations for neopterin following singles doses of 125 µg BIIB017 SC or 125 µg BIIB017 IM are illustrated in Figure 3. A summary of neopterin parameters is presented in Table 3.

The serum neopterin concentration versus time profiles following single doses of 125 µg BIIB017 SC or 125 µg BIIB017 IM were similar, with maximal concentrations (Epeak) reached at a median ET_{max} of 40.1 hours and 44.0 hours, respectively. Geometric mean neopterin levels increased from baseline to maximum concentration similarly between the 2 injection routes, with the increase from 8.0 to 22.6 nmol/L for SC, and from 8.1 to 23.2 nmol/L for IM. The overall systemic exposure to neopterin ($E_{AUC0-336}$ and $E_{AUC0-504}$) were also similar between the 2 routes of administration.

In general, moderate to high between-subject variability was noted for the PD parameters ($E_{AUC0-336}$, $E_{AUC0-504}$, and E_{peak}) for both routes of administration, with CV% values ranging from 40% to 43% for SC and 34% to 41% for IM.

Figure 3: Arithmetic mean (+/-SD) serum concentration profiles for neopterin (nmol/L) following a single subcutaneous and intramuscular dose of 125 ug BIIB017 - PD population



NOTE: Lower limit of quantification=4nmol/L. BLQ is treated as 0 for linear scale and missing for semi-logarithmic scale. Non-determinable is set to missing
Abbreviations: SC= subcutaneous; IM=intramuscular
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Table 3: Summary statistics for PD parameters - PD Population

		BIIB017 125 ug SC (N=134)		**BIIB017 125 ug IM (N=132)**
$E_{baseline}$ (nmol/L)				
	n	134		132
	Geometric mean	8.0	8.1	
	Geometric CV (%)	33.8		37.4
	Arithmetic mean (SD)	8.6 (4.4)		8.8 (5.3)
	CV%	51.3		60.3
	Median	7.4		7.9
	Min, Max	4.4,43.3		0.0,53.9
$E_{AUC0-336h}$ (h*nmol/L)				
	n	131		131
	Geometric mean	2294.2	2398.7	
	Geometric CV (%)	44.0		39.7
	Arithmetic mean (SD)	2495.1 (1030.0)		2580.4 (1069.2)
	CV%	41.3		41.4
	Median	2388.8		2455.6
	Min, Max	683.2,6812.5		708.2,9284.6
$E_{AUC0-504h}$ (h*nmol/L)				
	n	130		131
	Geometric mean	2459.0	2558.0	
	Geometric CV (%)	44.2		40.5
	Arithmetic mean (SD)	2679.1 (1140.0)		2756.9 (1137.7)
	CV%	42.6		41.3
	Median	2546.3		2613.5
	Min, Max	683.2,8418.1		722.3,9294.2
E_{peak} (nmol/L)				
	n	134		132
	Geometric mean	22.6	23.2	
	Geometric CV (%)	41.1		34.1
	Arithmetic mean (SD)	24.3 (9.7)		24.5 (8.3)
	CV%	39.7		33.8

	Median		23.6	23.4
	Min, Max		8.7,64.7	9.0,54.1
ET_{max} (h)				
	n		134	132
	Geometric mean	45.9	45.0	
	Geometric CV (%)		36.9	35.1
	Arithmetic mean (SD)		49.4 (23.3)	47.9 (18.9)
	CV%		47.2	39.5
	Median		40.1	44.0
	Min, Max		24.0,215.0	24.0,144.0

PD: Pharmacodynamics; SC: Subcutaneous; IM: Intramuscular; SD: Standard Deviation; CV: Coefficient variation
Ebaseline: Baseline concentration
$EAUC_{0-336}$: Effect-time curve from time zero to 336 hours postdose
$EAUC_{0-504}$ Effect-time curve from time zero to 504 hours postdose
Epeak: Maximum effect
ET_{max}: Time to reach maximum effect
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2.4.4. Discussion on clinical pharmacology

Analytical methods

A statement on the application of appropriate GCP standards in the submitted study was provided by the MAH. Upon request, the MAH provided copies of the approval letter from the Midlands Independent Review Board.

During the procedure, the MAH was requested to further clarify the handling and processing of blood samples to obtain the serum. This information was provided and according to standard laboratory procedures.

The MAH was requested to provide the reports for the ELISA used for measuring BIIB017 and neopterin levels in serum to confirm the acceptability of the methods. The method validation reports for the ELISA used for measuring BIIB017 levels in serum was provided confirming the acceptability of the method. The method validation report for the determination of neopterin was also provided. A minor deviation from the Guideline on bioanalytical method validation was found but no longer pursued as the analysis was done for exploratory purpose only.

For the ELISA to measure serum BIIB017 levels, stability data until 549 days was provided during the procedure and met the required criteria. Hence, the storage period of 212 days of the samples before processing was covered by the tested stability data.

The MAH was requested to clarify the reasons of the 9 samples labelled as "others" that were re-analysed. The MAH clarified as follows: the LLOQ was not included in the standard curve in these samples due to a %CV or %RE greater than 25%. As a consequence, these samples had a new "LLOQ" which was the next upper concentration on the standard curve. In the re-analysis, the samples were analysed using the full standard curve in line with the SOP. The clarification is agreed.

Pharmacokinetics

Based on the results, the exposure of BIIB017 in serum has been demonstrated to be bioequivalent after a single dose administration of 125 μg BIIB017 either via SC or IM. The point estimate ratio and the 90% CI for $AUC_{0-\infty}$, AUC_{0-t} and C_{max} between SC and IM were 1.09, (1.02 – 1.16); 1.13, (1.06 – 1.21); and 1.08, (0.98 – 1.20), respectively and were within the acceptance range of 0.80 – 1.25.

According to the protocol, for the SC injection, 6 subjects were not included in the statistical analysis for $AUC_{0-\infty}$ due to poor regression of the elimination phase (n=2) and >20% extrapolation in $AUC_{0-\infty}$ (n=4); and 1 subject for the IM injection due to >20% extrapolation in $AUC_{0-\infty}$. Exclusion if AUC_{0-t} covers less than 80% of $AUC_{0-\infty}$ is not according to the Guideline on the investigation of bioequivalence, section 4.1.8. All subjects should be included. In the sensitivity analysis all subjects were included; hence the

sensitivity analysis already solved this issue. Moreover, as this application concerns a procedure to include a new route of administration, $AUC_{0\text{-last}}$ was considered a valid parameter to conclude comparable bioavailability between SC and IM route of administration.

Information about PK profiles of Plegridy following IM vs SC administration was included in a dedicated subheading in section 5.2 of the SmPC.

Pharmacodynamic

Neopterin peak concentrations (Epeak) reached a level of 22.6nmol/L for SC and 23.2nmol/L for IM administration. The T_{max} was 40.1hours for SC administration and 44.0hours for IM administration. The overall systemic exposures to neopterin were also similar between the 2 routes of administration; $EAUC_{0\text{-}336}$ geometric mean was 2294h*nmol/L for SC administration and 2399h*nmol/L for IM administration. The $EAUC_{0\text{-}504}$ geometrical mean was 2459h*nmol/L and 2558h*nmol/L following SC and IM administration, respectively. Therefore, the serum concentration profile of neopterin were comparable between the two routes of administration. Bioequivalence between the SC and IM route of administration could be concluded from a PD perspective.

Results on ET_{max}, $EAUC_{0\text{-}336h}$ and $EAUC_{0\text{-}504h}$ from the PD analysis following the SC and the IM injections were included a dedicated subheading in section 5.2 of the SmPC.

Immunogenicity

There were no immunogenicity tests conducted. Considering the limited exposure time, cross over between route of administration and the low immunogenicity of BIIB017, this is understood. However, the route of administration may impact the immunogenicity. A discussion on the impact of the route of administration on immunogenicity was provided and included in clinical safety section (see 2.6.1 section).

2.4.5. Conclusions on clinical pharmacology

The 90% CI for $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}t}$ and C_{max} between SC and IM were within the acceptance range of 0.80 - 1.25. Overall, bioequivalence was shown between SC and IM administration.

The neopterin peak concentration (Epeak), time to neopterin peak concentrations (T_{max}) and overall systemic exposures to neopterin were comparable between the two routes of administration. Thus, the serum concentration profile of neopterin were comparable between the two routes of administration and bioequivalence between the SC and IM route of administration could be concluded from a PD perspective.

2.5. Clinical efficacy

Plegridy received approval in the European Union on the 18th of July 2014. Hence, efficacy of BIIB017 administered SC is considered established. Bioequivalence of IM and SC administration of BIIB017 was assessed in Study 105HV106 (see clinical pharmacology section above). No new clinical efficacy studies were conducted to support this extension application.

2.5.1. Discussion on clinical efficacy

As SC and IM administration was shown to be bioequivalent with regard to PK and PD parameters and profiles, the efficacy results obtained for SC administration can be extrapolated to IM administration.

2.5.2. Conclusions on the clinical efficacy

Efficacy of IM injection of Plegridy was considered demonstrated.

2.6. Clinical safety

Patient exposure

The safety population is defined as all volunteers who were randomized and received at least 1 dose of study treatment. All 136 volunteers enrolled in Study 105HV106 were included in the safety population. ISRs were specifically analysed because of the anticipated decrease of these events in the IM route of administration.

Adverse events

Throughout the course of the study, every effort was to be made to remain alert to possible adverse event (AEs). If an AE occurred, the first concern was to be the safety of the volunteer. If necessary, appropriate medical intervention was to be provided.

At the signing of the informed consent form, each volunteer was to have been given the names and telephone numbers of study site staff for reporting AEs and medical emergencies. Activities (Version 21.1) and classified as either pre-treatment AEs or treatment-emergent AEs (TEAEs) as follows:

- Pre-treatment AEs were events that started prior to the initial dosing of study treatment in the study.
- TEAEs were events that increased in severity or that were newly developed during Treatment Period 1 or Treatment Period 2. If an AE started (or increases in severity) during a specific Treatment Period, this AE was attributed to the treatment the volunteer was receiving during the Treatment Period.

All analyses of AEs included only TEAEs.

Overall, there were 92 volunteers that reported at least 1 AE after receiving 125 µg BIIB017 SC and 87 volunteers that reported at least 1 AE after receiving 125 µg BIIB017 IM (Table 4). All AEs were considered resolved prior to the end of study. There were no SAEs reported. Three volunteers discontinued study treatment and were withdrawn from the study due to AEs (Table 4).

Table 4: Overall summary of Adverse events - safety population

	BIIB017 125 ug SC (N=134) n (%)	BIIB017 125 ug IM (N=132) n (%)
Number of subjects with		
Any event	92 (68.7)	87 (65.9)
Severity (a)		
Mild	87 (64.9)	83 (62.9)
Moderate	5 (3.7)	4 (3.0)
Severe	0	0
Related event (b)	89 (66.4)	81 (61.4)
Serious event	0	0
Related serious event (b)	0	0
Events leading to drug withdrawal	1 (0.7)	2 (1.5)
Events leading to study withdrawal	1 (0.7)	2 (1.5)
Fatal event	0	0

NOTE 1: A subject can appear in more than one category.
(a) Each subject counted once at maximum severity.
(b) Related as assessed by the investigator.
Run Date:14OCT2019

The most commonly reported AEs across both treatment periods were headache, chills, pain, injection site pain, injection site erythema, and pyrexia. The most frequently reported AE in volunteers that received BIIB017 SC was headache, which was reported by 55 volunteers.

Similarly, 47 volunteers experienced at least 1 AE of headache after receiving BIIB017 IM. The most frequently reported AEs in volunteers that received BIIB017 IM were headache and chills, which were each reported by 47 volunteers. Comparably, 36 volunteers that received BIIB017 SC reported chills. Generalized pain was experienced by more volunteers that received BIIB017 IM, with 29 volunteers reporting at least 1 instance of pain after BIIB017 IM compared to 19 volunteers reporting pain after BIIB017 SC. Injection site erythema was experienced by more volunteers that received BIIB017 SC, with 34 volunteers experiencing at least 1 instance of injection site erythema after BIIB017 SC compared to 3 volunteers experiencing injection site erythema after BIIB017 IM. A similar number of volunteers experienced injection site pain across both groups, with 19 volunteers experiencing at least 1 instance after BIIB017 SC and 15 volunteers experiencing after BIIB017 IM. A similar number of volunteers reported pyrexia across both groups, with 12 volunteers reporting at least 1 instance after BIIB017 SC and 13 volunteers reporting at least 1 instance after BIIB017 IM.

Analysis by severity

The Investigator assessed the severity of each AE as mild, moderate, or severe.

The majority of volunteers experienced AEs that were mild in severity; however, moderate AEs were recorded for 5 volunteers following administration of 125 µg BIIB017 SC and 4 volunteers following administration of 125 µg BIIB017 IM (Table 4). The moderate AEs included headache, injection site erythema, otitis externa, and presyncope. No severe AEs were reported.

Analysis by relationship to Study Treatment

The Investigator assessed the relationship of each AE to study treatment as either related or not related. The number of volunteers reporting study treatment-related AEs were similar between treatments. Of the 92 volunteers that had at least 1 AE following administration of BIIB017 SC, 89 were considered related to the study treatment, and of the 87 volunteers that had at least 1 AE following administration of BIIB017 IM, 81 were considered related to the study treatment (Table 5).

The study-drug related AE with the highest incidence was headache, with a similar number of volunteers reporting the AE after each treatment. Chills was the second highest study drug-related AE, with 36 volunteers reporting at least 1 instance after administration of BIIB017 SC and 46 volunteers reporting at least 1 instance after administration of BIIB017 IM. With the exception of 1 AE of injection site pain, all ISRs were considered related to the study treatment and there was a higher incidence of volunteers reporting ISRs following administration of BIIB017 SC (Table 5).

With the exception of the AEs of presyncope and otitis externa, all other moderate AEs were considered related to the study treatment

Table 5: Adverse Events Related to Study Treatment by System Organ Class and Preferred Term - Safety Population

	BIIB017 125 ug SC (N=134) n (%)	**BIIB017 125 ug IM (N=132) n (%)**
Subjects with any TEAEs related to study treatment	89 (66.4)	81 (61.4)
General disorders and administration site conditions	75 (56.0)	71 (53.8)
Chills	36 (26.9)	46 (34.8)
Pain	19 (14.2)	29 (22.0)
Injection site pain	19 (14.2)	15 (11.4)

Pyrexia	11 (8.2)	13 (9.8)
Feeling hot	7 (5.2)	8 (6.1)
Influenza like illness	3 (2.2)	3 (2.3)
Injection site erythema	34 (25.4)	3 (2.3)
Asthenia	0	2 (1.5)
Injection site reaction	0	2 (1.5)
Feeling cold	1 (0.7)	1 (0.8)
Feeling of body temperature change	2 (1.5)	1 (0.8)
Injection site induration	4 (3.0)	1 (0.8)
Injection site pruritus	11 (8.2)	1 (0.8)
Fatigue	4 (3.0)	0
Injection site bruising	2 (1.5)	0
Injection site extravasation	1 (0.7)	0
Injection site haematoma	1 (0.7)	0
Injection site oedema	1 (0.7)	0
Injection site rash	2 (1.5)	0
General disorders and administration site conditions		
Injection site warmth	5 (3.7)	0
Nervous system disorders	52 (38.8)	54 (40.9)
Headache	52 (38.8)	46 (34.8)
Dizziness	3 (2.2)	8 (6.1)
Somnolence	1 (0.7)	4 (3.0)
Paraesthesia	1 (0.7)	2 (1.5)
Dysgeusia	1 (0.7)	0
Musculoskeletal and connective tissue disorders	20 (14.9)	20 (15.2)
Pain in extremity	1 (0.7)	6 (4.5)
Myalgia	5 (3.7)	4 (3.0)
Arthralgia	5 (3.7)	3 (2.3)
Back pain	11 (8.2)	3 (2.3)
Joint stiffness	0	1 (0.8)
Limb discomfort	0	1 (0.8)
Muscle spasms	0	1 (0.8)
Musculoskeletal pain	0	1 (0.8)
Musculoskeletal stiffness	0	1 (0.8)
Groin pain	1 (0.7)	0
Neck pain	2 (1.5)	0
Gastrointestinal disorders	9 (6.7)	10 (7.6)
Nausea	7 (5.2)	8 (6.1)
Vomiting	2 (1.5)	3 (2.3)
Diarrhoea	0	1 (0.8)
Abdominal pain	1 (0.7)	0
Faeces soft	1 (0.7)	0
Flatulence	1 (0.7)	0
Eye disorders	4 (3.0)	6 (4.5)
Eye irritation	3 (2.2)	2 (1.5)
Photophobia	0	2 (1.5)
Eye pain	1 (0.7)	1 (0.8)
Vision blurred	0	1 (0.8)
Metabolism and nutrition disorders	4 (3.0)	6 (4.5)
Decreased appetite	4 (3.0)	6 (4.5)
Respiratory, thoracic and mediastinal disorders	7 (5.2)	3 (2.3)
Nasal congestion	3 (2.2)	2 (1.5)
Cough	1 (0.7)	1 (0.8)
Oropharyngeal pain	1 (0.7)	0
Rhinorrhoea	2 (1.5)	0
Sneezing	2 (1.5)	0
Skin and subcutaneous tissue disorders	5 (3.7)	2 (1.5)
Rash	0	1 (0.8)
Sensitive skin	1 (0.7)	1 (0.8)
Dermatitis	2 (1.5)	0
Erythema	2 (1.5)	0

Pruritus	2 (1.5)	0
Vascular disorders	0	2 (1.5)
Flushing	0	2 (1.5)
Cardiac disorders	1 (0.7)	1 (0.8)
Palpitations	1 (0.7)	1 (0.8)
Renal and urinary disorders	1 (0.7)	0
Pollakiuria	1 (0.7)	0

NOTEs
1: Events were coded using MedDRA version 22.0.
2: A subject was counted only once within each system organ class, preferred term and treatment-emergent period.
3: System organ class and preferred term are presented in decreasing frequency in the group of BIIB017 125 ug IM.
4: Included in this table are treatment-emergent adverse events.
Run Date:17OCT2019

Serious adverse event and deaths

There were no deaths, serious AE, or other significant events recorded in this study (Table 4).

Laboratory findings

Blood chemistry, haematology, and urinalysis samples were collected throughout the study.

Data for haematology, blood chemistry, and urinalysis received from the central laboratory. Out-of-range values were flagged in the listings as high (H) or low (L) for haematology and blood chemistry, and as 'abnormal' for urinalysis. For haematology and blood chemistry, shift tables presenting movement in and out of reference range from period baseline to each scheduled post-baseline visit were provided for each treatment group. Corresponding shift tables (normal versus abnormal) were produced for urinalysis. For post-baseline, only data from scheduled visits were included in the summary tables.

There were no apparent trends in the haematology data for either treatment group. One volunteer was withdrawn from the study due to anaemia (Table 6).

Table 6: Haematology Shift from Baseline - Safety Population

	BIIB017 125 ug SC (N=134)	BIIB017 125 ug IM (N=132)
Shift to Low (a)		
Hematology: Leukocytes	5/130 (3.8)	3/129 (2.3)
Hematology: Neutrophils	5/128 (3.9)	3/129 (2.3)
Hematology: Erythrocytes	1/127 (0.8)	1/124 (0.8)
Hematology: Hemoglobin	6/118 (5.1)	3/117 (2.6)
Hematology: Hematocrit	4/122 (3.3)	0/123
Hematology: Platelets	0/131	1/130 (0.8)
Hematology: Ery. Mean Corpuscular Hemoglobin	2/112 (1.8)	2/110 (1.8)
Hematology: Ery. Mean Corpuscular HGB Concentration	2/129 (1.6)	4/128 (3.1)
Hematology: Ery. Mean Corpuscular Volume	1/119 (0.8)	1/118 (0.8)
Shift to High (b)		
Hematology: Leukocytes	1/131 (0.8)	0/131
Hematology: Lymphocytes	8/128 (6.3)	4/126 (3.2)
Hematology: Neutrophils	1/131 (0.8)	0/131
Hematology: Monocytes	2/130 (1.5)	2/129 (1.6)
Hematology: Eosinophils	0/130	1/129 (0.8)
Hematology: Erythrocytes	0/128	1/130 (0.8)
Hematology: Platelets	16/124 (12.9)	17/122 (13.9)
Hematology: Ery. Mean Corpuscular Volume	1/127 (0.8)	1/129 (0.8)

NOTE 1: Entries are number post-baseline shifts/number at risk (percentage).
(a) Shift to low includes normal to low, high to low, and unknown to low.
(b) Shift to high includes normal to high, low to high, and unknown to high.
Run Date:14OCT2019

There were no trends in the mean blood chemistry data for either treatment group. One volunteer was withdrawn from the study due to physician decision after elevated liver function tests, creatine phosphokinase, and creatine. A second volunteer was withdrawn for blood creatine phosphokinase increased (Table 7).

Table 7: Blood Chemistry Shift from Baseline – Safety population

	BIIB017 125 ug SC (N=134)	BIIB017 125 ug IM (N=132)
Shift to Low (a)		
Chemistry: Creatinine	0/123	3/124 (2.4)
Chemistry: Carbon Dioxide	0/124	1/125 (0.8)
Chemistry: Calcium	1/130 (0.8)	0/130
Chemistry: Urate	1/128 (0.8)	1/128 (0.8)
Shift to High (b)		
Chemistry: Alanine Aminotransferase	6/128 (4.7)	6/124 (4.8)
Chemistry: Aspartate Aminotransferase	1/129 (0.8)	0/130
Chemistry: Alkaline Phosphatase	3/128 (2.3)	2/129 (1.6)
Chemistry: Bilirubin	4/131 (3.1)	2/131 (1.5)
Chemistry: Gamma Glutamyl Transferase	3/128 (2.3)	1/126 (0.8)
Chemistry: Creatinine	5/131 (3.8)	2/131 (1.5)
Chemistry: Sodium	7/127 (5.5)	10/129 (7.8)
Chemistry: Potassium	2/121 (1.7)	0/121
Chemistry: Chloride	0/127	3/127 (2.4)
Chemistry: Carbon Dioxide	3/128 (2.3)	1/127 (0.8)
Chemistry: Glucose	3/ 97 (3.1)	1/101 (1.0)
Chemistry: Calcium	3/127 (2.4)	3/127 (2.4)
Chemistry: Phosphate	9/124 (7.3)	12/122 (9.8)
Chemistry: Protein	2/130 (1.5)	2/131 (1.5)

NOTE 1: Entries are number post-baseline shifts/number at risk (percentage).
(a) Shift to low includes normal to low, high to low, and unknown to low.
(b) Shift to high includes normal to high, low to high, and unknown to high.
Run Date:14OCT2019

A summary of shifts from baseline in urinalyses data is presented in Table 8.

Table 8: Urinalysis shift from baseline – Safety population

	BIIB017 125 ug SC (N=134)	BIIB017 125 ug IM (N=132)
Shift to Abnormal (c)		
Urinalysis: Occult Blood	3/123 (2.4)	4/126 (3.2)
Urinalysis: Protein	1/130 (0.8)	4/131 (3.1)
Urinalysis: Nitrite	2/130 (1.5)	2/129 (1.6)
Urinalysis: Leukocyte Esterase	7/126 (5.6)	11/129 (8.5)

NOTE 1: Entries are number post-baseline shifts/number at risk (percentage).
(a) Shift to low includes normal to low, high to low, and unknown to low.
(b) Shift to high includes normal to high, low to high, and unknown to high.
Run Date:14OCT2019

Vital Sign Measurement, Physical Examination Findings, and Other Observations Related to Safety

Vital Sign Measurements

For each treatment group, observed measurements of vital signs (temperature, respiratory rate, pulse, systolic blood pressure, and diastolic blood pressure) and change from period baseline were summarized by visit using descriptive statistics. The abnormalities were consistent between treatment groups. There were no abnormal vital signs data that were associated with any clinical symptoms. There were no apparent trends in the mean vital signs data for either treatment group.

Physical Examination Findings & Patients Health Questionnaire (depression module)

Any clinically significant physical examination findings were reported as AEs and presented in above section.

The majority of volunteers responded "Not at all" to the PHQ-9 questions at all timepoints. Sporadic responses other than "Not at all" were recorded, none of which were considered clinically relevant.

Electrocardiograms

One volunteer had an abnormal electrocardiogram that was considered a clinically significant AE and resulted in study treatment withdrawal and withdrawal from the study.

Immunological events

Antibody status was not tested as no unusual PK or safety findings were observed.

Safety in special populations

N/A

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

One volunteer discontinued study treatment and was withdrawn from the study after receiving 125 µg BIIB017 SC (blood creatinine phosphokinase increased), and 2 volunteers discontinued study treatment and were withdrawn from the study after receiving 125 µg BIIB017 IM (anaemia and tachycardia).

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

Generally, the reported adverse events was comparable between the two routes of administration. The SC administration has a higher frequency of the following ISR; induration, pruritus, bruising, extravasation, haematoma, oedema and rash, compared to the IM group. However, pain in extremity, limb discomfort, muscle spasms, musculoskeletal pain and musculoskeletal stiffness were reported with a higher frequency in the IM group compared to the SC group. This is not unexpected, as these AEs are all related to the route of administration. Information about commonly reported AEs across both treatment periods together with AEs reported for the SC arm only and the IM arm only were presented in section 4.8 of the SmPC.

The laboratory test also showed a comparable frequency of shift between the two routes of administration. However, urinalysis shows a higher frequency in shift to abnormal values for protein and leukocyte esterase following IM administration compared to SC administration. The MAH's position was that differences in urine analysis were not statistically significant and may be chance finding or related to the first or midstream catch as the results did not lead to renal adverse events. This rationale is not fully agreed as it should be noted that the shift to abnormal is 3 times higher occurred after a single administration. Longer exposure may have resulted in the occurrence of renal adverse events. As it cannot be excluded whether the findings were chance finding, related to the first or midstream catch or indeed related to the route of administration, the higher incidence of shift to abnormal was included in the section 4.8 of the SmPC as follows: "Abnormal urine protein was reported in 1/130 (0.8%) for the SC route of administration and 4/131 (3.1%) in the IM group without any associated adverse drug reactions".

The shift in vital signs occurred with comparable frequency in both routes of administration.

No immunological tests were performed; however, the route of administration may have an impact on the immunogenicity. Therefore, the MAH was requested to discuss the potential impact of the route of administration on immunogenicity. The MAH submitted comparative data on immunogenicity following SC and IM administration from Minagar *et al* 2008, Perini *et al* 2001, Ross *et al* 2000 and White *et al* 2016. As these studies also included immunogenicity as an outcome measure, the duration is much longer (6 months - 3 years) as compared to the bioequivalence study with a range of 27 days. This allows a valid conclusion on immunogenicity.

The data from Minagar *et al* concerned the studies with INF-beta-1a (without PEG) and showed that 19% of the patients on SC IFN-beta-1a 44 µg three times per week tested positive for Nabs (Neutralizing antibodies) at both Month 0 and Month 6, whereas none of those on IM IFN-beta-1a 30 µg once weekly were NAbs positive. Perini *et al* examined the role of dosage, route and frequency of administration of clinical grade interferon-beta preparations on immunogenicity. The findings from this study suggest that treatment with IFN-beta-1a IM was the least immunogenic treatment, i.e. INF-beta-1a was less immunogenic as compared to IFN -beta-1b, and IM administration was less immunogenic compared to SC administration. In patients treated with SC IFN-beta-1b, NAbs levels peaked 3 to 9 months after therapy initiation, and declined to pre-therapy levels in some patients after 3 years. Similar results were reported by Ross *et al* 2000. Data from White *et al* 2016 included an analysis of anti-PEG anti body formation following SC administration at 2 and 4 week interval, to characterise the immunogenic profile of the IFN portion and the PEG moiety of PEG-IFN. There was no difference between the PEG antibody formation following a 2 week or 4 week treatment interval. The authors concluded that the low incidence of immunogenicity, including extremely low frequency of anti-peginterferon NAbs developing at high titre levels, means that few patients are at risk of experiencing impaired efficacy during treatment with peginterferon beta-1a due to immunogenicity.

These data concern data from other INF-beta-1a products and were therefore considered circumstantial. However, it may be concluded that the immunogenicity following the route of administration is the same or lower as compared to the SC administration i.e. less than 1%.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile appears to be comparable between the two routes of administration. Some adverse events occur more frequently in one group compared to the other, however, these adverse events are generally related to the IM route of administration.

2.7. Risk Management Plan

Safety concerns

Table 9: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	• Use during second and third trimester of pregnancy

Pharmacovigilance plan

Table 10: Ongoing and planned additional pharmacovigilance activities

Study name and description **Study Status**	**Summary of objectives**	**Safety concern(s) addressed**	**Milestones**	**Due dates**
<u>Category 1</u> – ***Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation***				
None				
<u>Category 2</u> – ***Imposed mandatory additional pharmacovigilance activities that are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances***				
None				
<u>Category 3</u> – ***Required additional pharmacovigilance activities***				
Drug utilization study in pregnancy (exposure in second and third trimester) • **<u>Status:</u>** Planned	***<u>First stage:</u>*** • Evaluate interferon-beta utilization among pregnant women in MS in Sweden and Finland at 3 and, if needed, 5 years following label implementation using aggregate level data • Evaluate trends in DU patterns in the target population (second and third trimester) before and after label implementation. • Evaluate the feasibility of conducting a pregnancy outcomes study ***<u>Second stage:</u>*** • If feasible, conduct a pregnancy outcomes study on patients exposed during second and third trimester using individual level data.	• Use during second and third trimester of pregnancy	***<u>First stage:</u>*** • Drug utilisation study report 3 years after label implementation • If needed, Drug utilisation study report 5 years after label implementation	

Risk minimisation measures

Table 11: Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important identified risks		
None		
Important potential risks		
None		
Areas of missing information		
• Use during second and third trimester of pregnancy	***<u>Routine risk minimisation measures:</u>*** • Information in Section 4.6 of the SmPC describing the paucity of data in relation to drug exposure during the second and third trimester of pregnancy ***<u>Other routine risk minimisation measures beyond the Product Information:</u>*** Legal status: Prescription only medicine. Use restricted to physicians experienced in the treatment of MS ***<u>Additional risk minimisation measures:</u>*** • No additional risk minimisation measures are proposed.	***<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u>*** • None ***<u>Additional pharmacovigilance activities:</u>*** • Drug utilization study in pregnancy (exposure in second and third trimester)

Conclusion

The CHMP and PRAC considered that the risk management plan version 5.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Plegridy solution for subcutaneous injection in pre-filled syringe. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Plegridy is an interferon beta-1a with a prolonged response (due to PEG conjugation) indicated in adult patients for the treatment of RRMS, the most common phenotype of MS. In MS, an immune-mediated inflammatory activity of the CNS leads to destruction of the myelin sheath and axonal injury.

3.1.2. Available therapies and unmet medical need

There is no cure available for MS. Therapies for MS include treatment for relapses, symptomatic treatments and DMD. There are several DMD for MS including other beta interferons (IFN β) (Avonex, Betaferon and Rebif) which are available for either SC or IM injection.

Plegridy is an interferon beta-1a with a prolonged response (due to PEG conjugation). It is indicated in adult patients for the treatment of relapsing-remitting multiple sclerosis. The recommended dose of Plegridy is 125 micrograms injected SC every 2 weeks. The product may be self-administered by patients. The product is available as a 63, 94 and 125 micrograms strength, both in a pre-filled syringe

and a pre-filled pen. The lower strengths are used for dose titration at the start of treatment, to prevent flu-like symptoms.

The current application concerns an extension application. The MAH proposes to add IM injection to offer patients an alternative route of administration with fewer injection site reactions as compared to subcutaneous injection.

A new pre-filled syringe has been developed for this purpose. The syringe contains 125 micrograms of peginterferon beta-1a. The dose can be limited to 63 micrograms and 94 micrograms with the use of titration clips.

3.1.3. Main clinical study

The development program consisted of 1 open-label, multicentre, 2-period crossover study with a primary objective of assessing the bioequivalence of BIIB017 administered by SC and IM injection in 136 healthy volunteers. Bioequivalence was examined using PK parameters and assessing the safety and tolerability of SC administration as compared with IM administration of BIIB017 in healthy volunteers. Exploratory objectives were to evaluate the PD parameters, i.e. neopterin serum concentration, of SC administration as compared with IM administration in healthy volunteers. The presence and titre of binding antibodies to the pegylated and IFN β-1a components of BIIB017 was also to be evaluated in case of unusual PK or safety findings.

The low doses (63 and 94 µg) will be administered by the use of titration clip devices. These titration clip devices can administer the required dose (1/2 and 3/4 dose) and are similar to titration clips already available for other products.

3.2. Favourable effects

$AUC_{0-\infty}$, AUC_{0-t} and C_{max} were 173695 pg/ml/h, 163615 pg/ml/h and 1459 pg/ml for the SC route of administration, and 185645pg/ml/h and 180798pg/h and 1517pg/ml for the IM route of administration. The point estimate ratio and the 90% CI for $AUC_{0-\infty}$, AUC_{0-t} and C_{max} between SC and IM were 1.09 (1.02-1.16); 1.13 (1.06-1.21); and 1.08 (0.98-1.20), respectively.

The time to neopterin peak concentrations (T_{max}) was 40.1hours and 44.0hrs following SC and IM administration, respectively. The neopterin peak concentration (Epeak) were 22.6nmol/L for SC and 23.2nmol/L for IM administration. The median overall systemic exposures ($EAUC_{0-504h}$) to neopterin were 2546h*nmol/L and 2613h*nmol/L for SC and IM administration, respectively.

3.3. Uncertainties and limitations about favourable effects

There are no relevant uncertainties and limitations related to favourable effects.

3.4. Unfavourable effects

The following TEAEs were reported with >2% difference between the two routes of administration for the SC vs IM respectively: Chills (26.9% vs 34.8%), pain (14.2% vs 22.0%), injection site pain (14.2% vs 11.4%), injection sit erythema (25.4% vs 2.3%), headache (38.8% vs 34.8%), dizziness (2.2% vs 6.1%), backpain (8.2% vs 2.3%).

The following AEs were reported in the SC treatment arm only: injection site bruising (1.5%), injection sit extravasation (0.7%), injection site haematoma (0.7%), injection site oedema (0.7%) and injection site rash (1.5%)

The following AEs were reported in the IM treatment arm only: joint stiffness limb discomfort, muscle spasms, musculoskeletal pain, musculoskeletal stiffness. All with a frequency of 0.8%.

Urinalysis shows a shift to abnormal values for protein for 4/131 (3.1%) following IM administration compared to 1/130 (0.8%) following SC administration.

3.5. Uncertainties and limitations about unfavourable effects

The bioequivalence study was not appropriate to study immunogenicity as it was too short. However, circumstantial evidence submitted by the MAH, i.e. data from other INF beta-1a products, shows that the immunogenicity following IM administration is lower than that following the SC route.

It is unclear if the shift to abnormal values for protein is a chance finding, related to the first or midstream collection or indeed related to the route of administration.

3.6. Effects Table

Table 12 Effects Table for Plegridy IM

Effect	Short Description	Unit	SC	IM	Uncertainties/ Strength of evidence	Ref.
Favourable Effects						
$AUC_{0-\infty}$	AUC from hr 0 extrapolated to infinity	pg/ml/h	173695	185645	**SoE**: ratio (90% CI) 1.09 (1.2-1.16) **Unc**: six subjects excluded	105HV106
AUC_{0-t}	AUC from administration to last observer concentration at time t	pg/ml/h	163615	180798	**SoE:** ratio (90% CI) 1.13 (1.06-1.21)	105HV106
C_{max}	Maximum plasma concentration	pg/ml	1459	1517	**SoE:** ratio (90% CI) 1.08 (0.98-1.2)	105HV106
T_{max}	Time to maximum effect (median)	h	40.1	44		105HV106
Epeak	Peak concentration (median)	nmol/L	23.6	23.4		105HV106
$E_{AUC0-504h}$	Overall exposure (median)	h*nmol/L	2546	2613		105HV106
Unfavourable Effects						
TEAEs with >2% difference	Chills Pain ISR pain ISR erythema Headache Dizziness Backpain	n (%)	36(26.9) 19(14.2) 16(14.2) 34(25.4) 52(38.8) 3(2.2) 11(8.2)	46(34.8) 29(22.0) 15(11.4) 3(2.3) 46(34.8) 8(6.1) 3(2.3)		105HV106
TEAEs in SC only	ISR bruising ISR extravasation ISR haematoma ISR oedema ISR rash (1.5%)	n (%	2 (1.5%) 1 (0.7%) 1 (0.7%) 1 (0.7%) 2 (1.5%)			105HV106
TEAEs in MI only	Joint stiffness Limb discomfort Muscle spasms Musculoskeletal pain Musculoskeletal stiffness	n (%)		1(0.8) 1(0.8) 1(0.8) 1(0.8) 1(0.8)		105HV106
Immunogenicity			low	unknown	**Unc**: not examined. Circumstantial evidence indicates lower frequency following SC	105HV106

Effect	Short Description	Unit	SC	IM	Uncertainties/ Strength of evidence	Ref.
					administration	
Urinalysis	Protein shift to abnormal Leukocyte esterase shift to abnormal	Shift/number at risk (%)	1/130 (0.8%) 7/126 (5.6%)	4/141 (3.1%) 11/129 (8.5%)	**Unc**: could be chance finding or related to route of administration	105HV106

ISR: Injection site reaction; TEAEs: Treatment-related adverse event; IM: Intramuscular; SC: Subcutaneous; Unc: uncertainties; SoE: strength of evidence.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The active substance is the same for both the IM and SC formulation. The main difference is the route of administration. The MAH showed that the point estimates and 90% CI of the PK parameters ($AUC_{0-\infty}$, AUC_{0-t} and C_{max}) for between SC and IM were within the acceptance range of 0.80 - 1.25. Neopterin levels, a well-known PD marker for INF-B, were comparable in SC and IM administration, thus bioequivalence between the SC and IM route of administration could be concluded from a PK and PD perspective.

The dose of 125µg used in the study was the most appropriate dose to examine the bioequivalence as this is the dose required for therapy.

The frequency and reported type of AE were generally comparable between the two routes of administration. There was a higher frequency of ISR reported for the SC administration. IM administration let to occurrences of pain in extremity, limb discomfort, muscle spasms, musculoskeletal pain and musculoskeletal stiffness. These findings were not unexpected as they are all related to the route of administration. Although immunogenicity was not evaluated in the bioequivalence study, the MAH provided a literature review supporting that immunogenicity following IM administration is expected to be lower than that following the SC route. The higher incidence of proteinuria required an SmPC amendment i.e. "Abnormal urine protein was reported in 1/130 (0.8%) for the SC route of administration and 4/131 (3.1%) in the IM administration."

3.7.2. Balance of benefits and risks

In the present procedure, the MAH has shown PK and PD bioequivalence between Plegridy IM and SC administration. Efficacy of IM injection of Plegridy was considered demonstrated.

No new safety signals were raised. AEs were considered clinically manageable and generally comparable between the two routes of administration with fewer ISR as compared to SC injection, which is considered a benefit for the patients.

Therefore, the favourable effects of Plegridy IM outweigh the risks

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

Based on the review of the submitted data, the IM administration of Plegridy is considered bioequivalent

to SC administration of Plegridy. Therefore, a benefit/risk balance comparable to the SC administration of Plegridy can be concluded. The overall B/R is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, clinical pharmacology and safety, the CHMP considers by consensus that the benefit-risk balance of, Plegridy 125 micrograms solution for injection in pre-filled syringe for intramuscular use, is favourable in the following indication:

Plegridy is indicated in adult patients for the treatment of relapsing remitting multiple sclerosis.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Plegridy subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.