28 January 2021
EMA/CHMP/102816/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tysabri

International non-proprietary name: natalizumab

Procedure No. EMEA/H/C/000603/X/0116

Note

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

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Table of contents

List of abbreviations

ADA	Antidrug antibodies
AEs	Adverse Events
AUC_{inf}	Area-Under-the-Concentration-Time-Curve from time zero to infinity
AUC_{last}	Area-Under-the-Concentration-Time-Curve from time zero to last time point
BLQ	Below the Limit of Quantitation
BW	Body Weight
C_{max}	Maximum Serum Concentration
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIPCs	Critical In-Process Controls
CIPTs	Critical In-Process Tests
CNS	Central Nervous System
CL	Clearance
CL/F	Apparent Clearance
CP	Controlled Parameters
C_{trough}	trough concentration
C_{trough_ss}	trough concentration at steady state
CUA	Combined Unique Active
DMT	Disease Modifying Therapy
DTI	Diffusion Tensor Imaging
EC_{50}	Concentration at 50% of maximum observed biologic effect
EDSS	Expanded Disability Status Scale
EC_{80}	Concentration at 80% of maximum observed biologic effect
ELISA	Enzyme-Linked ImmunoSorbent Assay
EID	Extended Interval Dosing
E_{max}	Maximum observed biologic Effect
F	Bioavailability
Gad+	Gadolinium enhancing
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
HCPs	Healthcare Professionals
IM	Intramuscular
IFN	Interferon
IPC	In-Process Controls

IPTs	In-Process Tests
IRIS	Immune Reconstitution Inflammatory Syndrome
ISRs	Injection Site Reactions
IV	Intravenous
IS	Immunosuppressant
JCV	John Cunningham Virus (human polyomavirus)
K_a	Absorption Rate Constant
LLOQ	Lower Limit Of Quantification
MAA	Marketing Authorisation Application
MAdCAM	Mucosal Addressin Cell Adhesion Molecule
MAH	Marketing Authorisation Holder
MFI	Mean Fluorescence Intensity
mITT	Modified Intention To Treat
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
MTR	Magnetization Transfer Ratio
PASS	Post-Authorisation Safety Study
PD	Pharmacodynamics
PFS	Pre-Filled Syringe
PK	Pharmacokinetics
PL	Patient Leaflet
PLEX	Plasma Exchange
PML	Progressive Multifocal Leukoencephalopathy
popPK	population Pharmacokinetics
PRAC	Pharmacovigilance Risk Assessment Committee
Q4W	Every 4 weeks
Q6W	Every 6 weeks
Q12W	Every 12 weeks
RMP	Risk Management Plan
RRMS	Relapsing Remitting Multiple Sclerosis
R_{min}	Observed minimum % saturation/nadir value
SAE	Serious Adverse Event
SC	Subcutaneous
SDMT	Symbol Digit Modalities Test
SmPC	Summary of Product Characteristics

SPMS	Secondary Progressive Multiple Sclerosis
sVCAM-1	Soluble Vascular Cell Adhesion Molecule-1
t½	Terminal half-life calculated as ln(2)/elimination rate constant (Kel)
TAMC	Total Aerobic Microbial Count
T_{max}	Time to reach maximum serum concentration values
TOP	Tysabri Observational Programme
TOUCH	TYSABRI Outreach: Unified Commitment to Health
TYMC	Total Yeast and Moulds Combined
ULOQ	Upper Limit Of Quantification
URTI	Upper Respiratory Tract Infection
UTI	Urinary Tract Infection
V_d	Volume of Distribution
V/F	Apparent Volume of Distribution
VAS	Visual Analogue Scale
VCAM-1	Vascular Cell Adhesion Molecule-1
VFT	Visual Function Test
WBC	White Blood Cells

1. Background information on the procedure

1.1. Submission of the dossier

Biogen Netherlands B.V. submitted on 9 March 2020 extensions of the marketing authorisation.

Extension application to introduce a new pharmaceutical form (solution for injection), associated with a new strength (150 mg) and a new route of administration (subcutaneous use). The Risk Management Plan (RMP) (version 26.1) is updated accordingly.

The Marketing Authorisation Holder (MAH) applied for an addition of a new strength, addition of a new pharmaceutical form and an addition of a new route of administration.

The MAH applied for the following indication for Tysabri 150mg solution for injection:

TYSABRI is indicated as single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups:

- Patients with highly active disease activity despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) (for exceptions and information about washout periods see sections 4.4 and 5.1)
  or
- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing (Gad+) lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

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) points (c) (d) (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 EMEA-P/0123/2020 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The Applicant 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: Jan Mueller-Berghaus Co-Rapporteur: N/A

The application was received by the EMA on	9 March 2020
The procedure started on	26 March 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	19 June 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	22 June 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	09 July 2020
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	23 July 2020
The MAH submitted the responses to the CHMP consolidated List of Questions on	09 September 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	13 October 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 October 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	12 November 2020
The MAH submitted the responses to the CHMP List of Outstanding Issues on	23 December 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	13 January 2021
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 Tysabri on	28 January 2021

2. Scientific discussion

2.1. Problem statement

Natalizumab is a recombinant, humanised, anti-α4 integrin antibody and belongs to the therapeutic class of monoclonal antibodies. Natalizumab 300 mg IV (Tysabri) is currently approved as a single DMT for the treatment of adult patients with highly active RRMS. The approved pharmaceutical form is a 300 mg concentrate for solution for infusion. The infusion is to be administered over approximately 1 hour and patients are to be observed during the infusion and for 1 hour after the completion of the infusion for signs and symptoms of hypersensitivity reactions.

An alternative subcutaneous (SC) route of administration for natalizumab could provide additional benefit to patients and physicians, since SC administration is considered a more convenient means of administration because it reduces the amount of time required at each treatment visit. The SC route may also be a cost-saving method of administration when compared with the IV route for patients, hospitals, and clinics, as reduced time and resources are required.

2.1.1. Disease or condition

Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disorder of the central nervous system (CNS) that is characterised by inflammation, demyelination, and oligodendrocyte and neuronal loss.

2.1.2. Epidemiology

MS is one of the most common progressive neurological diseases of adults worldwide [Collaborators 2019]. The disease usually begins between the ages of 20 and 40 and is twice as common in women as in men. There is increasing incidence and prevalence of MS in both developed and developing countries

2.1.3. Aetiology and pathogenesis

The cause of MS is unknown but the most striking pathogenic mechanism in MS is the immune system's attack and destruction of the body's own myelin sheath. Many cells and molecules of the immune system—likely unleashed by T-cell activation—participate in demyelination. The entire cascade of immune system events eventually culminates in myelin destruction. The key features of this cascade are not fully understood, including the precise ordering of events, the antigens targeted by T cells, and the contributions of B lymphocytes, or B cells, and other cells of the immune system.

2.1.4. Clinical presentation, diagnosis

The majority of MS patients (approximately 85%) present with subacute relapses or attacks, with symptoms and signs referable to the CNS.The relapse/attack is followed by a complete or partial remission/return to normal, only to be followed at a future date by another relapse usually in a different CNS location, thus presenting as RRMS. The first such attack is referred to as a clinically isolated syndrome. Some patients (approximately 15%) present with a gradually progressive course, without an initial well-defined attack. This is termed primary progressive MS. Most of these patients present with features of a spinal cord syndrome.

The diagnostic criteria for MS have been continuously evolved and include MRI with intravenous (IV) contrast agent containing gadolinium, lumbar puncture for cerebrospinal fluid examination, physical examinations, and electrophysiological tests.

2.1.5. Management

MS management includes treatment of acute relapses with high-dose steroids, DMTs, including injectables like interferons, glatiramer acetate, oral DMTs (teriflunomide, dimethyl fumarate, fingolimod, ozanimod, siponimod, cladribine), and infusions (e.g., natalizumab, alemtuzumab, ocrelizumab, mitoxantrone), as well as symptomatic treatments for managing MS symptoms (e.g., bladder problems, fatigue, spasticity).

About the product

Natalizumab (Tysabri) is a recombinant, humanised, anti-α4 integrin monoclonal antibody.

Natalizumab is a selective adhesion-molecule inhibitor and binds to the α4 subunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Specifically, natalizumab binds to the α4β1 integrin, blocking the interaction with its cognate receptor, vascular cell adhesion molecule-1 (VCAM-1), and ligands, osteopontin, and an alternatively spliced domain of fibronectin connecting segment 1. Natalizumab also blocks the interaction of α4β7 integrin with the mucosal addressin cell adhesion molecule 1 (MAdCAM). Disruption of these molecular interactions prevents transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue.

A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4-expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. As such, natalizumab may act to suppress inflammatory activity present at the disease site and inhibit further recruitment of immune cells into inflamed tissues.

Natalizumab IV received Marketing Authorisation in the EU on 27 June 2006.

A line extension is being submitted to add a new route of administration for Tysabri (natalizumab). Currently, Tysabri is supplied as 300 mg natalizumab in 15 mL glass vials for IV infusion. For patient convenience, the MAH seeks approval for an additional route of administration, SC injection. The SC presentation will also be used to administer 300 mg of natalizumab and will be supplied as two 150 mg/mL pre-filled syringes, each containing 1 mL. The excipient formulation for Tysabri by IV infusion and SC use is the same qualitatively and meets the same quality standards. The only difference being the amount of excipients.

Type of Application and aspects on development

In January 2020, a pre-submission meeting was held with PEI (Rapporteur) and the Applicant presented the available clinical and quality data package to support submission of the extension application.

No central scientific advice has been received for this procedure.

2.2. Quality aspects

2.2.1. Introduction

Tysabri is currently authorised as a 15 mL concentrate for solution for infusion in a vial, corresponding to a strength of 300 mg (concentration of 20 mg/mL) (EU/1/06/346/001). The purpose of this line extension application is to add:

- A new strength - 150 mg;

- A new pharmaceutical form - solution for injection in pre-filled syringe (PFS);

- A new route of administration - subcutaneous use (SC).

The pack size consists of two PFSs per carton, each containing 1 mL of solution. The qualitative composition in excipients in the SC formulation remains the same: sodium phosphate, monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, polysorbate 80 and water for injections.

2.2.2. Active Substance

Manufacture, process controls and characterisation

Description of the manufacturing process

The active substance, also referred to as Natalizumab-SC (solution for injection) or Natalizumab-IV (concentrate for solution for infusion), is manufactured at Biogen Inc, 5000 Davis Drive, Research Triangle Park (RTP), NC 27709-4627, USA and Biogen (Denmark) Manufacturing ApS, Biogen Allé 1, DK-3400 Hillerød (HIL), Denmark. The sites are EU GMP compliant.

Information regarding the manufacturing process and process controls for the shared portions of the natalizumab active substance manufacturing process is provided in the approved natalizumab-IV dossier. The new manufacturing steps including process hold times are described in the present submission.

The information provided is adequate.

Control of materials

With regards to raw materials, solution media and cell banks, the applicant refers to information registered for the natalizumab-IV process. In addition, information on the filters used is provided. This is acceptable.

Control of critical steps and intermediates

Critical in-process controls (CIPCs), critical in-process tests (CIPTs), in-process tests (IPTs), in-process controls (IPC) and controlled parameters (CP) along with their action limits or in-process specifications for the natalizumab-SC process are presented and considered acceptable.

Process validation

Process validation has been completed for the commercial manufacture of natalizumab-SC active substance. Specific studies supporting this validation included process consistency validation of and formulation/dispensing processes, hold time validation for process intermediates.

Process consistency validation was based on manufacture of 3 consecutive large-scale active substance batches. During the manufacture of the three consistency batches all acceptance criteria were met, indicating that the process performs consistently.

With regard to intermediates, hold times for feed, retentate and formulated active substance have been evaluated. For both the large-scale and the small-scale study, samples met their acceptance criteria at all time-points evaluated. Based on this study, hold times for the active substance intermediates introduced with the new process are considered sufficiently validated.

At large-scale, the controlled parameters and CIPCs and CIPTs were met. Furthermore, active substance from large scale and small scale met the active substance release specifications. Although use of more than 1 batch would have provided a broader database, the results show that the active substance meets all release specifications. This is considered sufficient.

Process validation was based on the successful manufacture of 3 consecutive process verification batches. Results provided for CP, CIPC, IPC, CIPT and IPT show that the 3 batches comply with the required action limits and/or specifications.

Qualification of active substance shipping is based on data from natalizumab-IV shipping qualification. This is acceptable, since the transport containers used for natalizumab-SC active substance are also used for

natalizumab-IV active substance and transport by refrigerated truck or air transport applies to both processes, natalizumab-IV and natalizumab-SC. In addition, adequate product quality prior to shipment (natalizumab-SC active substance) and after shipment (natalizumab-SC finished product) was demonstrated based on active substance and finished product batch release data, indicating that active substance transport has no impact on product quality. Furthermore, the applicant will test the active substance according to standard prior to launch of the product. This is acceptable.

Manufacturing process development

Throughout development, natalizumab-SC active substance had been manufactured according to different processes and different manufacturing sites.

Comparability of natalizumab-SC active substance manufactured was evaluated. The 3 process verification active substance batches manufactured were compared to natalizumab-SC batches from process manufactured at the RTP site, and commercial natalizumab-IV active substance. Based on release tests and additional characterisation studies, comparability of natalizumab-SC from process active substance is considered sufficiently demonstrated.

Characterisation

As the newly proposed active substance manufacturing process is an extension of the currently approved active substance manufacturing process, reference is made to the approved dossier regarding characterisation of the active substance and process-related impurities. This is acceptable.
Results for product-related impurities (for 3 active substance batches) were presented with the current submission and fall well within the range of batches from the commercial process. The impurity level in natalizumab-SC active substance batches is sufficiently low and within the range of commercial natalizumab-IV active substance.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications for natalizumab-SC active substance include control of identity, purity and impurities, biological activity and other general tests.

A complete set of specifications, analytical methods, method validation and batch analysis has been provided.

With regard to bioburden, the limit for TAMC (total aerobic microbial count) and TYMC (total yeast and moulds combined) is acceptable. Overall, the specifications for natalizumab-SC active substance are considered acceptable. Adequate justification for the specifications is provided.

Analytical methods

Analytical methods for testing of natalizumab-SC are briefly described. The methods used are the same as those used for commercial natalizumab-IV; where appropriate the SC active substance is diluted to 20 mg/mL (as the IV presentation). All methods are considered adequately validated.

Batch analysis

Batch release data are provided for 7 natalizumab-SC active substance batches manufactured at RTP (4 from process and 3 process consistency batches) and 3 process consistency batches manufactured. All batches comply well with the specifications.

Reference materials

Natalizumab-SC utilises the same reference standard as natalizumab-IV.

Container closure system

The natalizumab-SC active substance is stored in containers. The containers are the same as containers that were historically used for the natalizumab-IV active substance, specifically with the container closure referred to as "container closure #2" (CCL#2). Reference to the approved information for natalizumab-IV active substance is accepted.

Stability

A shelf life of 24 months when stored at (2°C - 8°C) is claimed for natalizumab-SC active substance.

Stability of natalizumab-SC active substance was evaluated in accordance with ICH Q5C. Primary stability data are provided for 3 batches (process verification batches for process manufactured at Biogen RTP) at long-term storage condition of 5±3°C. In addition, stability is being evaluated for the 3 process verification active substance batches manufactured. For these batches, data under accelerated conditions was provided.

Active substance stability was assessed based on analytical methods that are also used for active substance release testing, end-of-shelf-life acceptance criteria are the same as for release, with two exceptions. The justifications provided are acceptable.

The main change in natalizumab quality attributes that occurred upon storage under long-term condition is an increase in lower pI isoforms. This is well known from natalizumab IV. Nevertheless, at 24 months the release criterion for low pI isoform was still met. Under accelerated storage conditions, a faster increase in lower pI isoform was observed. This finding was consistent across the batches.

The available stability data adequately support the proposed shelf life for natalizumab-SC active substance of 24 months at (2°C - 8°C).

The applicant committed to place at least one representative production batch of active substance on stability per year, if manufactured. This commitment is acknowledged.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description and composition of the dosage form

Natalizumab-SC finished product is a sterile, aqueous formulation for SC administration in a PFS, with a pack size of two PFSs per carton.

The PFS contains 1 mL of solution and is made of glass (Type I) with a coated with and thermoplastic rigid needle shield. A 27-gauge needle is pre-affixed to the syringe. Each PFS has a needle guard system that will automatically cover the exposed needle when the plunger is fully depressed.

Natalizumab is formulated with the following excipients: sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, polysorbate 80 and water for injections.

There is no overage.

Pharmaceutical development

Formulation development

The formulation of natalizumab SC is similar to that of natalizumab IV. The SC formulation has a higher concentration of the active substance and contains the same excipients as the IV at the same concentrations, except for a higher concentration of one of the excipients.

Robustness of the chosen formulation was evaluated in design of experiments (DoEs) that varied protein concentration, content, and pH of the formulation and assessed natalizumab stability under long-term, accelerated and stress conditions. Based on the results of the robustness study, natalizumab when formulated at 150 mg/mL can be expected to be stable upon storage at 5°C.

Manufacturing process development

Process characterisation was performed through a combination of scale-down and at-scale studies. The studies are considered adequate.

Subsequently, a risk-based approach was used to define a final process control strategy, assigning criticality and acceptable ranges and limits for all process controls as described in section P.3.4.

Overall, the approach is considered adequate.

In accordance with ICH Q3D, risk assessment for elemental impurities was made. Based on the assessment, the limit of elemental impurities in the finished product is well below the permitted daily exposures and further controls are not required.

Furthermore, process I used clinical active substance while process II used active substance manufactured according to the proposed commercial process.

The comparability of finished product process I and process II was assessed based on release testing and additional characterisation for selected physicochemical attributes. For comparative stability reference is made to section 3.2.P.8 Stability. The extent of testing is considered adequate. Comparability criteria are adequately justified and accepted. Based on the data submitted, finished product process I and II are considered comparable.

Container closure system

The container closure system was discussed. An extractables study was performed on product-contacting materials and identified extractable compounds above the analytical evaluation threshold limits. Therefore, a subsequent leachables study was performed. This study did not identify leachables above the reporting limit at up to 60 months of storage at long-term and accelerated temperature. Based on a toxicological risk assessment, there are no concerns with regard to patients safety.

Container performance was evaluated for the finished product (PFS assembled with plunger rod, finger flange and needle guard) and for the naked PFS under long-term (5°C) and accelerated (25°C) storage conditions. Testing on the assembled PFS was more extensive. Testing on the naked syringe was performed. The data indicate that the PFS remains functional for a period of 24 months under long-term storage condition.

Manufacture of the product and process controls

Manufacturing process

Natalizumab-SC finished product manufacturers and the respective responsibilities have been listed. Assembly of the PFS with the needle safety device is performed. The finished product manufacturing process is a standard process. An overall process flow diagram has been provided. The information on the manufacturing process and process controls is satisfactory. Information on controls of critical steps is provided and considered adequate.

Process validation

Process validation at was performed based on process performance consistency for 4 finished product lots covering the anticipated range for batch size. This is endorsed. For each of the process performance consistency runs, all results for key and controlled parameters and (critical) in-process controls and tests conformed to the pre-defined acceptance criteria and were consistent across lots. Results from additional non-routine process characterisation met all requirements. Based on these data, it can be concluded that the natalizumab-SC finished product manufacturing process performs consistently.

Manufacturing process and hold times were adequately validated in challenge studies extending hold times beyond the maximum time.

Container closure integrity was demonstrated for a sufficient number of syringes from each consistency batch. The aseptic filling process was adequately validated by media fills using process parameters that encompass those used during normal production.

Filter validation studies were conducted to demonstrate that the sterilising filter performs acceptably under defined manufacturing process conditions. All results met their pre-defined acceptance criteria confirming that the sterilising filter is compatible with the product stream and produces a sterile filtrate.

Sterilisation of the primary container closure system (syringe and stopper) is performed by the supplier. Adequacy of the sterilisation process is supported by representative certificates of analysis for syringe and stopper.

Shipping validation was briefly summarised with regard to transport of natalizumab-SC PFS and transport of the finished goods. For temperature control of transport, reference is made to validation of temperature-controlled trucks and shipping containers used is for transport of natalizumab-IV. This is acceptable. In addition, evaluation according to standard will be performed. This is endorsed.

Product specification, analytical procedures, batch analysis

Specifications for natalizumab-SC finished product include control of identity, purity and impurities, biological activity and other general tests.

Testing is performed on the unlabelled, unassembled PFS. The final release testing of the natalizumab-SC finished product in the PFS assembled with plunger rod, finger flange and needle safety device must meet the test requirements of the visual inspection of functionality.

The panel of release tests is in line with ICH Q6B. However, measures for functionality of the PFS were missing and the applicant was asked to include them as part of the release and stability specification for natalizumab-SC finished product. In response to the request, the applicant provided a detailed justification as to why they consider that these tests are not necessary. Additional data were provided to support this justification. It is therefore considered acceptable not to include testing as part of the natalizumab-SC finished product specifications.

The submitted data for PFS functionality throughout finished product shelf-life is supportive, however, the overall base is rather limited (i.e. batch stored under long-term condition). This is acknowledged. Given that results from the batch indicate that PFS functionality will be maintained, it is currently acceptable not to include it as part of the natalizumab-SC finished product stability specifications.

The acceptance criteria for release and stability testing are considered adequate. However, the applicant was requested during the procedure to tighten the shelf-life specification for an acceptance criterion.

The information provided on characterisation of impurities is considered sufficient. No new impurities are formed during the finished product manufacture.

The justifications for the individual finished product specifications as provided are considered acceptable.

Analytical methods

Analytical procedures which are also used for the active substance are discussed in the relevant sections of the dossier (S.4.2 and S.4.3). Procedures that are specific for finished product are compendial and sufficiently described and verified. In addition, information on testing is provided.

Batch analysis

A list of natalizumab-SC finished product batches manufactured so far is provided. All natalizumab-SC finished product batches comply with the specifications in place at the time of testing and also comply with the proposed commercial specifications. Given that PFS functionality has not been tested routinely, information on these parameters is not presented here.

Reference materials

Natalizumab-SC utilises the same reference standard as natalizumab-IV.

Container closure system

The container closure system for finished product is adequately described for both the primary closure system, i.e. the naked PFS, and the non-drug contacting secondary containers (finger flange, plunger rod, needle guard). Representative certificates for both primary and secondary container closure system were provided from the vendor.

The long-term stability studies and the container closure integrity studies demonstrate the compatibility of the finished product solution with the primary container closure system and the ability of the container closure system to protect the finished product solution from microbial contamination.

Stability of the product

The applicant proposes a shelf-life of 2 years for natalizumab-SC finished product when stored at (2˚C - 8˚C).

Considering the totality of the submitted finished product stability data and taking into account that formulation and container closure system is the same for the batches from the developmental and primary stability study, the proposed finished product shelf-life of 2 years at 5 ± 3°C in the outer carton can be accepted.

The PFS can be kept in the original packaging for up to 24 hours at room temperature (up to 25° C). The PFS must not be returned to refrigeration.

Adequate data demonstrating PFS functionality upon storage throughout the shelf-life was lacking. The only information provided on performance of the PFS is provided in section 3.2.P.2.4. In response to the concern

raised, the applicant has provided additional information. For this batch, PFS functionality was demonstrated for the entire finished product shelf-life period.

Post approval change management protocol (PACMP)

The scope of this PACMP is to enable approval of additional purification suites for the natalizumab-SC active substance manufacturing process in order to ensure supply chain continuity. The scope of this PACMP is limited to facilities that are currently approved to manufacture commercially licensed Tysabri IV infusion active substance.

The proposed strategy for process validation is similar to the validation performed at the manufacturing site, except for example hold-time validation for process intermediates. Omission of these validation activities can be accepted based on the data available from the process validation at the manufacturing site.

The proposed comparability test panel for release and additional characterisation testing is acceptable.

The PACMP is considered acceptable.

Adventitious agents

There are no changes to the adventitious agents safety evaluation.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The pharmaceutical development, manufacturing process and controls are based on the currently authorised 300 mg concentrate for solution for infusion in a vial.

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.

No major objection was identified, and the applicant has adequately addressed the issues raised during the procedure.

The overall quality documentation provided in this line extension application is considered adequate and complies with existing guidelines.

Two Recommendations have been agreed.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Tysabri 150 mg solution for injection is considered acceptable when used in accordance with the conditions defined in the SmPC.

From a quality point of view, this line extension application is considered acceptable.

2.2.6. Recommendation(s) for future quality development

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

2.3. Non-clinical aspects

2.3.1. Pharmacology

There were no non-clinical pharmacology studies conducted to support the SC administration of natalizumab.

2.3.2. Pharmacokinetics

The pharmacokinetics (PK) of different formulations of natalizumab upon SC administration were evaluated in the context of a nonclinical local tolerance study in non-human primates (see toxicology below).

2.3.3. Toxicology

Local tolerance

The non-clinical toxicology programme to support SC administration of natalizumab consisted of a single good laboratory practice (GLP) local tolerance study.

The objective of the study (P00002-05-01) was to evaluate PK profiles, bioavailability, anti-natalizumab antibody formation, and local tolerability following administration of natalizumab by IV, SC, or intramuscular (IM) injection in non-human primates.

Cynomolgus monkeys (3/sex/group) were administered test articles were as follows: natalizumab, 20 mg/ml commercial formulation (BG00002-B) administered as a single IV dose of 30 mg on day 1; natalizumab 150 mg/ml liquid formulation (BG00002-D) administered at 150 mg SC or IM on days 1 and 36; natalizumab 120 mg/ml lyophilised formulation, administered at 120 mg SC or IM on days 1 and 36.

The PK profiles of the high-concentration liquid and lyophilized test articles were assessed through Day 36 of the study. Injection site biopsies were performed on animals in the SC and IM dose groups on Day 39 of the study for histopathologic assessment of signs of local tolerability.

There were no test article-related effects on clinical signs, food consumption or bodyweight (BW) associated with commercial natalizumab administered by IV injection or high-concentration liquid or lyophilized natalizumab administered by SC and IM injection.

Increases in peripheral blood lymphocytes, and to a lesser extent eosinophils, basophils, and unclassified cells, compared to pre-study (baseline) values were noted in all groups; these increases were regarded as an expected pharmacodynamic (PD) effect of the test article. Duration of this effect was longer in animals receiving 120 or 150 mg compared to those receiving 30 mg.

Mean time to reach maximum serum concentration values (T_{max}) was achieved immediately after IV administration, and delayed, but more rapidly following IM than SC injection for the high-concentration test articles. Mean maximum serum concentration values (C_{max}) values were less than dose proportional across routes when compared to the commercial IV dose group but were consistent for the test articles administered extravascularly. The mean values for half-life ($t_{½}$) were comparable across all dose groups irrespective of the route of administration. Both mean area-under-the-concentration-time-curve from time zero to the last time point (AUC_{last}) and area-under-the-concentration-time-curve from time zero to infinity (AUC_{inf}) were greater than dose proportional in the SC and IM dose groups, indicating 100% relative bioavailability and consistency following extravascular administration.

Saturation of α4-integrin peaked on Day 1 and returned to predose levels by Day 22 IV injection; saturation peaked between Days 1 and 8 in the SC and IM dose groups and remained above predose levels through Day 36. Some dose-dependency was observed, given that mean α 4-integrin saturation was greater in the liquid high-concentration SC and IM dose groups compared to lyophilized SC and IM dose groups beginning on Day 15.

Immunogenicity was relatively consistent across all dose groups and did not appear to be greater following SC or IM dosing when compared to the IV route.

Local injection site reactions (ISRs) included slight to severe erythema consistent with procedure-related bruising, primarily in the IV dose group, and very slight to severe edema in individual animals after the second IM dose of either the high-concentration or lyophilized test article. Histopathological evaluation of biopsy samples from SC and IM injection sites 3 days after the second dose on Day 36 revealed minor changes, including focal degeneration and/or focal necrosis of the subcutaneous or muscular tissue. Animals that received the lyophilized test article via SC or IM injection had only slightly more severe local histopathological changes than those receiving the high-concentration test article. Overall, changes at the injection site following SC and IM administration of the high-concentration liquid and lyophilized formulations were not regarded as adverse.

In summary, the liquid high-concentration and lyophilized high-concentration natalizumab was well tolerated following SC or IM injection in cynomolgus monkeys; both produced anticipated increases in peripheral blood lymphocyte counts that were comparable to, but of slightly greater persistence than, those observed following a single 30 mg IV dose at the commercial formulation. Local ISR were limited to procedure-related erythema; edema typically followed the second IM dose of either the liquid or lyophilized test articles, with minor local histological focal changes being associated with both routes of extravascular administration.

2.3.4. Ecotoxicity/environmental risk assessment

Natalizumab is a humanised IgG4 antibody, a protein consisting of natural amino acids, the use of which will not alter the concentration or distribution of the substance in the environments. Therefore, natalizumab is not expected to pose a risk to the environment.

2.3.5. Discussion on non-clinical aspects

In order to support the SC route of administration the Applicant submitted a GLP local tolerance study in cynomolgus monkeys.

The study evaluated two different routes of extravascular injection (SC and IM) in comparison to IV administration. Natalizumab was well tolerated in all groups. Regardless of the route of administration, the main findings were related to the PD effect of natalizumab with a longer duration in animals treated with a high dose. Local ISR at the SC injection sites were limited to procedure-related erythema and edema and minor focal histological changes and are considered non-adverse.

The study assessed tolerability to two different natalizumab high-dose formulations (liquid and lyophilised) in comparison to the commercial IV formulation. It is noted that none of the high-dose formulations represents the currently proposed natalizumab-SC DP formulation. Given that the currently proposed natalizumab-SC formulation uses the same excipients as the commercial natalizumab-IV formulation, and there is already clinical experience with the current natalizumab-SC formulation, further non-clinical assessment of local tolerability of the natalizumab-SC presentation is not warranted.

2.3.6. Conclusion on the non-clinical aspects

Together with the non-clinical programme as reviewed at the time of marketing authorisation application (MAA), the non-clinical study submitted with the present application is considered adequate and sufficient to support SC administration of natalizumab.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with good clinical practices (GCP) as claimed by the Applicant.

The Applicant 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

In order to support the 300 mg every 4 weeks (Q4W) SC regimen as an alternative to the currently approved 300 mg Q4W IV route of administration, the Applicant presented efficacy data from 2 clinical studies:

- the phase I study **101MS102 (DELIVER)** Table 1
- the phase II study **101MS206 (REFINE)** Table 2

Table 1: Study 101MS102 (DELIVER) PK & PD variables & endpoints

Study Number (Status)	Study Population	Number of Participants	Study Phase Study Design	Total Dose	PK & PD Variables & Endpoints
101MS102 (completed)	<u>All participants:</u> Male or female; aged 18 to 65 years; natalizumab-naive <u>Groups A, B, C, & F:</u> Participants with **SPMS**; continuous clinical worsening over a period of at least 3 months; baseline EDSS between 2.5 and 6.5 (inclusive) <u>Groups D & E:</u> Participants with **RRMS**; baseline EDSS between 0.0 and 6.5 (inclusive)	**76 participants** randomised (52 SPMS, 24 RMS): SPMS 300 mg IV Q4W (N = 16) SPMS 300 mg SC Q4W (N = 14) SPMS 300 mg IM Q4W (N = 15) SPMS Reference treatment (N = 7) RRMS 300 mg IV Q4W (N = 12) RRMS 300 mg SC Q4W (N = 12)	Phase 1b Open-label, randomised, parallel-group design Evaluation of safety, PK, and PD properties following IV, SC, or IM administration	<u>Groups A, B, C, D, & E:</u> 8-week study period, 300 mg single-dose (Part I) 6-month study period, 300 mg repeat-dose Q4W (6 doses; Part II) <u>Group F:</u> Reference treatment, efficacy evaluation and AE monitoring for first 32 weeks <u>Groups A, B, C, & F:</u> Follow-up treatment extension phase: 300 mg SC Q4W starting at Month 8, 12, 15, or 18	**PK:** • Natalizumab serum concentration • C_{max} • T_{max} • $AUC_{0\text{-}672}$ and $AUC_{0\text{-}1344}$ • AUC_{inf} • V_d • V/F • CL/F • $t_{½}$ • F **PD:** • α4 integrin saturation • sVCAM serum concentration • lymphocyte count measurements • lymphocyte subsets

Table 2: Study design of 101MS206 (REFINE) PK & PD variables & endpoints

Study Number (Status)	Study Population	Number of Participants	Study Phase Study Design	Total Dose	PK & PD Variables & Endpoints
101MS206 (completed)	Male or female; aged 18 to 55 years; participants with **RRMS**; relapse-free for 12 months prior to randomisation; treated with natalizumab for 12 months prior to randomisation	**290 participants** randomised: 300 mg IV Q4W (N = 54) or Q12W (N = 52) 300 mg SC Q4W (N = 45) or Q12W (N = 54) 150 mg IV (N = 47) or SC (N = 38) Q12W 277 participants in efficacy population	Phase 2 Randomised, blinded, parallel-group design Evaluation of safety, tolerability, and efficacy of multiple regimens	**Six treatment arms:** 300 mg IV Q4W or Q12W 300 mg SC Q4W or Q12W 150 mg IV or SC Q12W Duration: Blinded regimen for 60 weeks, open-label regimen from Weeks 60 to 68 (300 mg IV Q4W)	**PK:** • Natalizumab serum concentration **PD:** • α4 integrin saturation • CD49d expression

2.4.2. Pharmacokinetics

Overview studies

The PK, PD, (α4 integrin saturation, sVCAM receptor measurement, lymphocyte count, and lymphocyte subsets), and immunogenicity of natalizumab following SC administration were evaluated in a completed Phase 1 study (Study 101MS102 [DELIVER]) in participants with RRMS or secondary progressive MS (SPMS). This study is two-parted, Part I accounts for a single dose intensive PK/PD phase, Part II for repeated-dose treatment (period of 6 months).

Trough natalizumab samples have been collected from a completed randomised, blinded Phase 2 study (Study 101MS206 [REFINE]), where safety, tolerability, and efficacy of IV and SC was explored in participants with RRMS over a 72-week period.

Study 101MS102

Approximately 60 natalizumab-treated subjects from Groups A, B, C, D, and E of Study 101MS102 were to participate in the lymphocyte subset sub study to assess the effect of natalizumab on blood levels of lymphocyte subsets, including CD34+ cells. Blood and urine samples were stored for possible future John Cunningham Virus(JCV)-related research.

Study 101MS206

Participants had previously received IV natalizumab for at least 12 months and were randomised to receive natalizumab 300 mg IV Q4W, IV Q12W (every 12 weeks), SC Q4W, or SC Q12W or natalizumab 150 mg IV or SC Q12W for up to 60 weeks.

Summary of PK data and data analysis

Study 101MS102

The PK profile of each dose of natalizumab was assessed by determining the serum concentration-time profiles of natalizumab given by the IV, SC, and IM routes of administration from serum samples taken prior to and

over the 56-day period during Part I. Samples were taken predose, at 4, 24, 48, 72, 96 hours postdose and 7, 14, 21, 28, 35, 42, and 56 days post dose. Additional sample collections during Part II allowed assessments of drug accumulation with each dose (weeks 12, 16, 20, 24, 28, and 32).

A total of 1229 samples were measured for natalizumab. The concentration of natalizumab in serum was to be determined using an enzyme-linked immunosorbent assay (ELISA). The ELISA assay is based upon the binding of natalizumab to an immobilized monoclonal antibody (12C4) that binds to the VLA-4 binding domain. This complex is then detected with labelled anti-human IgG4-AP. Samples with concentrations below the lower limit of quantification (LLOQ) (0.500 ug/mL) were reported as below the limit of quantitation (BLQ).

Of those, 159 (12.9%) samples were reported as BLQ. Sixty-six of these BLQ samples were collected pre-dose and were assigned a value of zero. An additional 25 BLQ samples were collected in some subjects during times when anti-natalizumab antibodies were positive. All remaining BLQ data were assigned as "missing" for the PK analyses.

Non-compartment analysis was used to determine C_{max}, T_{max}, $AUC_{0\text{-}last}$, AUC_{inf}, volume of distribution (V_d) or apparent volume of distribution (V/F), clearance (CL) or apparent clearance (CL/F), and t½, as appropriate.

Absolute bioavailability after SC administration was also calculated using the ratios of AUC corrected for dose by each route of administration.

Study 101MS206

A validated sandwich ELISA method was used for PK measurements. A total of 1311 PK human samples from 289 study subjects were analysed in a total of 70 assay runs for the determination of natalizumab concentration. Samples were collected at Day 3, 7, 14, 21, 28, 42, and Day 56 after the Week 48 dose of study treatment.

The working range of the assay was between 0.500 µg/mL (LLOQ), and 32.0 µg/mL (upper Limit of quantification (ULOQ)). Samples that returned values above this range were diluted into range with pooled normal human serum and retested in the assay. Samples in which levels of natalizumab could not be quantified were reported as BLQ.

Natalizumab concentrations from samples collected every 3 months were summarised by treatment arm with summary statistics (n, mean, standard deviation, median, and range). PK analyses were performed on the PK population. Of the 289 randomized subjects who received at least 1 dose of study treatment, 273 subjects were included in the PK population.

In total, 162 participants received at least 1 SC dose of natalizumab of different regimens in both studies. 26 participants were enrolled in Study 101MS102 (Cohorts B and D) and 136 participants in Study 101MS206. Of these 162 participants, 53 received a 300 mg dose (Q12W), and 38 received a 150 mg dose (Q12W) and 71 patients (n=26; 101MS102 and n=45; 101MS206) received 300 mg SC (Q4W).

Bioanalytics

An overview of the bioanalytical methods used throughout clinical development of natalizumab was provided.

Natalizumab concentration in human serum was assessed by ELISA. Based on the bioanalytical reports submitted, the assay performance can be considered acceptable for both studies. Incurred sample re-analysis was only performed for study 101MS206 and not for study 101MS102. This could be accepted, given that

incurred sample re-analysis was not a regulatory requisite in EU at the time when sample analysis for 101MS102 was performed.

Validation reports for the validation of PD assays were submitted for 2 analytical methods used in study 101MS206, i.e. the flow cytometry assay "*Alpha-4 Expression/Saturation and VCAM-1 binding Assay*" and the sandwich ELISA to measure soluble VCAM-1 (sVCAM-1) in human serum. Both methods were considered adequately validated. Upon request, information on the validation for the PD methods used in study 101MS102 was provided by the Applicant. The Alpha4 saturation assay was qualified; the sVCAM-1 assay was a commercially available assay. The provided performance reports demonstrate that the assays performed satisfactorily during analysis of samples from study 101MS102.

The presence of antibodies to natalizumab in human serum (ADA) was assessed using an ELISA. The test strategy was based on a screening assay and a subsequent confirmatory assay. The ADA method was validated for use by Focus Diagnostics in 2006. The assay could be considered validated with regard to intra- and inter-assay precision, robustness and inter-laboratory comparability. However, the validation approach is not fully in line with current recommendations on assessment of immunogenicity. E.g. information on assay sensitivity, drug tolerance, matrix effect or a possible impact of ADA on natalizumab efficacy were missing. Upon request, the Applicant clarified that the assay used for detection of ADA in studies 101MS102 and 101MS106 is a modified version of the ELISA method used to support MAA. The method had been developed at Biogen and validated at Focus. Sensitivity of the assay was 500 ng/ml, selectivity for matrix interference had been inferred from the original ADA assay, based on similarities between assay formats and critical reagents used. This could be accepted.

Absorption

Absorption is well captured due to dense sampling and allowed the estimation of bioavailability based on direct AUC comparison (50-70%). From population PK (popPK) updated with SC PK data, bioavailability was estimated to 82.1%, and an absorption rate constant was estimated to be 0.0111 1/hr. PopPK derived bioavailability of the SC formulation is supported by exposure simulations and comparison with PK observations. Mean C_{max} values after SC dosing were 33% to 36.7% of the values achieved following IV administration of 300 mg natalizumab. After the absorption phase, IV and SC PK profiles appear comparable.

Bioequivalence

Two bioequivalence studies have been completed (Study C-1805 and Study C-1806) indicating PK comparability of the manufactured products (BG00002-A, BG00002-B). In the clinical studies to support the filing of natalizumab SC, formulations BG00002-E, BG00002-D, and BG00002-H have been used.

Distribution

Mean V_d in Study 101MS102 was calculated to 3.456 ± 1.4041 L following 300 mg SC Q4W. Mean volume slightly exceeds the one following IV route of administration in this study (mean: 2.327 ± 0.9598 L). Median steady-state V_d was estimated to 5.58L 95% Confidence Interval (CI) (5.27-5.92 L).

Elimination

Natalizumab is catabolized by general protein degradation processes. It is eliminated by catabolism into amino acids in the lysosomal system; typical small-molecule metabolic pathways are not expected to contribute to its clearance indicating a reduced potential for direct drug-drug interactions via Cytochromes P450 enzymes.

The Phase 1 study (Study 101MS102) indicated that the elimination t½ is similar between both routes of administrations in patient group RRMS: 300 mg IV 272.5 ± 84.7h; 300 mg SC 291.4 ± 72.9h. Data was limited to 672h. In SPMS patients, t½ was observed to be slightly higher: 386.08 ± 91.805h. The estimated median t½ by popPK was 26.8 days. Variability of t½ in terms of the 2.5th and the 97.5th percentile based on popPK ranges from 11.6 to 46.2 days.

Mean CL/F was calculated to be 12.1± 3.90 ml/h after SC 300mg in SPMS patients and 16.4 ± 7.03 ml/h after SC 300 mg in RRMS patients. After IV 300mg, mean CL were calculated to be 10.2 ml/h in SPMS patients and 9.3 ml/h in RRMS patients. Population median estimate for linear CL was 6.21 mL/h with 95%CI (5.60-6.70 mL/h).

Dose proportionality and time dependencies

Dose proportionality

In Study 101MS206, doses of 300 mg and 150 mg have been tested following Q4W and Q12W dosing regimens. Due to the high percentage of BLQ samples following Q12W dosing intervals, no conclusion on dose proportionality could be drawn based on the available data set.

Simulations of mean trough levels at steady state based on the updated popPK model indicated an overall dose-proportional increase in exposure (trough level) with dose over the range from 300 mg to 450 mg SC.

Time dependency

101MS102

After SC administration of 300 mg natalizumab, C_{max} values reached by approximately 1 week. The mean C_{max} after 300 mg SC administration in SPMS participants was 41.2 µg/mL (range 22.0 to 66.4 µg/mL); in RRMS participants at the same dose, the C_{max} was 35.4 µg/mL (range 22.0 to 47.8 µg/mL).
The mean C_{max} following SC administration in both populations was lower than that for the 300 mg IV arm in the corresponding populations. For SPMS patients, mean C_{max} after IV dosing was 112.1 µg/mL (range 59.2 to 156.0 µg/mL, and for RRMS patients mean C_{max} after IV dosing was 107.1 µg/mL (range 78.9 to 164.0 µg/mL). Mean C_{max} values after SC dosing were 33% to 36.7% of the values achieved following IV administration of 300 mg natalizumab.

The mean AUC_{inf} after a single 300 mg SC dose in observed in SPMS participants was 27,431.9 µg*h/mL (range 15,009 to 45,904 µg*h/mL). In RRMS participants, mean AUC_{inf} was 21,449.7 µg*h/mL (range 9,893 to 36,836 µg*h/mL).

Mean natalizumab trough concentrations collected prior to each dose during Part II show accumulation occurring with each successive dose, which was comparable between the routes of administration. Steady state is indicated to be reached within 16-32 weeks post dose.

Study 101MS206

Trough levels collected every three months showed that SC level is continuously below the IV trough levels of natalizumab following 300 mg Q4W but overall at the level of steady state from pre-treatment (300 mg Q4W IV). The achieved exposure ranges in terms of steady-state trough concentration (C_{trough_ss}) of both routes of administration are highly overlapping.

Intra- and inter-individual variability

Inter-individual variability (IIV) of PK parameter (Cl, Vd, absorption rate constant K_a) was assessed using popPK modelling. IIV was moderate to high for K_a.
Bioavailability varied between non-compartmental analysis (50%-70%) and popPK analysis (82%)

Overall, variability for PK parameters after SC administration did not appear any greater than IV dosing. PK profiles after IV and SC administration of natalizumab (Study 101MS102) indicated no major deviation of natalizumab disposition in participants with different patient population RRMS and SPMS.

Special populations

No further analysis with respect to PK in special populations has been conducted in the context of this procedure. Covariates on PK were tested during the model update of popPK including IV and SC data.

The final popPK model of natalizumab included 3 effects that were statistically significant in the covariate selection: Formulation on CL (Phase II formulations used in earlier IV studies LNZRSH-A and LNZRSH-B versus all other formulation), BW effect on CL, BW effect of V2. The effect of ADA on CL was added to the base model before covariate selection. CL increased by approximately 2.17-fold for the Phase 2 formulations. CL and V2 increased as BW increased. CL was 2.54-fold higher for participants who were positive for ADA compared with those who were not.

Exposure simulation results showed - regardless of pre-treatment to steady state following 300 mg Q4W IV - a decrease in C_{trough_ss} values with BW (from 30 mg/l to about 18 mg/l) that is expected due to the fix dose regimens.

Pharmacokinetic interaction studies

No PK interaction studies were provided by the Applicant.

Pharmacokinetics using human biomaterials

No studies using human biomaterial were provided by the Applicant.

2.4.3. Pharmacodynamics

Mechanism of action

Natalizumab is a recombinant, humanised, anti-α4 integrin antibody derived from a monoclonal antibody raised against human α4 integrin. The α4 subunit of human integrins is highly expressed on the surface of all

leukocytes, with the exception of neutrophils. Specifically, natalizumab binds to the α4β1 integrin, blocking the interaction with its cognate receptor, VCAM-1, and ligands, osteopontin, and an alternatively spliced domain of fibronectin connecting segment 1.

Natalizumab also blocks the interaction of α4β7 integrin with the mucosal addressin cell adhesion molecule 1. This prevents transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4-expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. This way, natalizumab may act to suppress inflammatory activity present at the disease site leading to the inhibition of further recruitment of immune cells into inflamed tissues.

PK and PD simulations based on a natalizumab population PK/PD model connecting serum natalizumab levels with α4-Integrin Saturation support the rationale for the SC dose of 300 mg Q4W.

Primary and Secondary pharmacology

Primary pharmacology

Natalizumab binds specifically to the α4 integrins being expressed on the surface of certain peripheral blood leukocytes, thereby disrupting the interaction of integrins with endogenous receptors like VCAM-1 and MAdCAM on endothelial cells. The blockade leads in turn to increased peripheral cell counts of those leukocytes that express α4 integrins.

In Study 101MS02, α4-integrin saturation, sVCAM serum concentration, lymphocyte count measurements and lymphocyte subsets have been measured as PD marker/endpoints.
In Study 101MS266, PD endpoints measured were α4-integrin saturation and CD49d expression.

The choice of PD marker were deemed reasonable to compare PD effects from IV and SC formulation and dosing.

Study 101MS102

Overall, data from 101MS102 indicated no major deviations between IV and SC profiles with respect to the here presented PD endpoints. Of note, although PK C_{trough} levels from 84 day and later were lower following SC administration of natalizumab, integrin saturation is observed to be higher (Day 84 – Day 168) or equal (> Day 168) compared to mean IV observations.

Mean integrin saturation was 90.0% or greater within 24 hours after the administration of either IV or SC doses and remained elevated, with mean values at or above 80.0%, for up to 4 weeks (672.0 h) after dosing. Saturation began to decline at about 6 weeks, with the mean saturation between 30.0% and 60.0% by 8 weeks following natalizumab administration for all treatment arms.

Mean sVCAM observed minimum % saturation/nadir value (R_{min}) was 220.4 ng/mL (range 143 to 333 ng/mL) for SPMS participants and 205.6 ng/mL (range 157 to 300 ng/mL) for RRMS patients, respectively, following SC administration of natalizumab. This translated into -59.81% (range -66.7% to -49.2%) and -58.36% (range -66.0% to -46.0%) change from baseline for SPMS and RRMS participants, respectively. The mean time to reach the nadir after SC administration was 20.2 days (range 3.9 to 57.0 days) for SPMS and 12.6 (range 7.0 to 28.0 days) for RRMS. Mean sVCAM R_{min} was 232.1 ng/mL (range 129 to 386 ng/mL) for SPMS participants and 209.6 ng/mL (range 113 to 336 ng/mL) for RRMS participants following IV administration of natalizumab. This translates into -55.77% (range -65.5% to -35.3%) and -57.29% (range -62.6% to -47.7%) change from

baseline for both patient subgroups, respectively. The mean time to reach the nadir after IV administration was 15.6 days (range 3.0 to 42.1 days) and 7.7 days (range 3.0 to 14.1 days) for SPMS and RRMS participants, respectively reflecting a reduction in sVCAM as a feedback response to the reduced number of α4-integrin receptors available to interact with sVCAM.

Lymphocyte subsets evaluation after a single dose and at Week 32 after multiple dosing of natalizumab showed an increase in absolute cell counts was observed in total leukocytes , monocytes, and dendritic cells, as well as all lymphocyte subsets examined (CD4+ T, CD8+ T, NK cells, B cells, and CD34+ HPCs), for both the IV and SC groups, however characterized with a high inter-patient variability.

A slight effect of route of natalizumab administration could be observed for monocytes count over time. Mean % change from baseline was 20-30% higher in the IV subgroup.

Study 101MS206

Predose α4-integrin saturation measurements at Baseline were in the range of 78.2% to 81.8% for all treatment arms of Study 101MS206. Throughout the randomised treatment period, a high mean trough α4- integrin saturation was maintained for all participants in the 300 mg SC or IV Q4W treatment arms, ranging from 76.8% to 83.1%. This indicated that difference in mean C_{trough} values following 300 mg Q4W IV and SC were not translated into differences in integrin saturation levels.

Similarly, the measurement of CD49d expression (based on measurement of mean fluorescence intensity [MFI]) was similar at baseline but increased by the week 12 Visit and remained elevated during the randomised treatment period for all Q12W treatment arms. In contrast, measurement of CD49d expression was consistent with baseline through the week 60 Visit for the IV and SC Q4W treatment arms (median range 300 mg IV Q4W, 220.0 to 231.0 MFI; 300 mg SC Q4W, 211.0 to 241.5 MFI).

Lymphocyte subsets including CD3+ T cells, CD4+ T cells, CD8+ T cells, total B cells [CD19+], memory B cells [CD19+/CD38-/CD27+(CD19+)], and natural killer cells [NK; CD3- /CD16+CD56+] were evaluated over time. During the randomised treatment period, results from the 300 mg Q4W SC arm indicated no significant changes in absolute numbers and percentage of lymphocyte subsets in comparison with the 300 mg IV Q4W arm.

Immunogenicity

Study 101MS102

The percentage of patients who transiently developed ADA was slightly higher in the SC group (23%) compared to the IV treatment group (15%). Of note, one participant in the SC treatment arm who was persistently positive for ADA development was withdrawn from the study.

Study 101MS206

None of the participants was tested positive for ADA in the natalizumab 300 mg IV Q4W or 300 mg SC Q4W arms during the randomised treatment period.

The influence of ADAs on the PK of IV natalizumab was evaluated during a parallel type II variation for updating popPK analysis. The influence was substantial (persistent ADAs lead to a 2.5 fold increase in CL) and is adequately described in the Summary of Product Characteristics (SmPC) of both the IV and SC formulation. Of note, ADA influence on CL (IV formulation) was originally estimated to a 2.9 fold increase, which is deemed comparable, although non-linear clearance has been newly integrated in the popPK model by update.

The Applicant tried to investigate the influence of ADAs on PK/PD and efficacy in participants of SC studies. Given the small sample sizes involved, firm conclusions regarding the impact of transient or persistent ADA

development on the PK/PD and efficacy of SC natalizumab could not be drawn. This was endorsed. Besides, frequency of ADAs appeared not be higher after SC vs. IV administration. Thus, it could be agreed that guidance and recommendations regarding ADA vigilance provided in the SmPC for the SC formulation are appropriate.

Secondary pharmacology

In anti-JCV antibody positive patients, extended interval dosing (EID) of natalizumab (average dosing interval of approximately 6 weeks [Q6W]) was suggested to be associated with a lower Progressive Multifocal Leukoencephalopathy (PML) risk compared to approved dosing interval of 4 weeks (SmPC, Section 4.4).

For the SC route of administration, the association between risk of PML and the dosing interval is unknown.

Population PK/PD

A popPK/α4 integrin model was developed using IV and SC clinical data, describing the relationship between natalizumab binding and α4-integrin saturation using a model exhibiting sigmoidal behaviour of the maximum observed biologic effect (E_{max}). Based on this model, the concentration at 50% of maximum observed biologic effect (EC_{50}) is estimated to be 2.51 mg/L, the concentration at 80% of maximum observed biologic effect (EC_{80}) is estimated to 10 mg/L. In terms of PD parameters, formulation effect on E_{max} and Hill coefficient was estimated for 2 formulation groupings, 1. LNZRSH-B, BG00002-D, BG00002-H and 2. LNZRSH-A, BG00002-A, BG00002-B, relative to the commercial formulation, BG00002-E.
The final PD model indicated that the binding of natalizumab to α4 integrin was affected by age and natalizumab formulation (phase II formulations used in earlier IV studies LNZRSH-A and LNZRSH-B versus all other formulation). Younger participants tended to have different binding characteristics relative to older participants, expressed by the model-estimated parameters E_{max} and Hill coefficient. These simulations indicated that the impact of age on α4-integrin saturation is expected to be minimal. No dose adjustment is recommended based on age for natalizumab.

Relationship between plasma concentration and effect

PK results from Study 101MS102 and Study 101MS206 indicated that, due to the absorption process, exposure after 300 mg Q4W SC was markedly lower than after 300 mg Q4W IV in terms of C_{max}, AUC and slightly but consistently reduced in terms of mean C_{trough} levels whereas comparable integrin saturation and PD effects were observed in both groups. In contrast, PD results following the SC route of administration of natalizumab showed similar target engagement level and subsequent PD response, as measured by α4-integrin binding, CD49d expression, sVCAM levels, and lymphocyte counts. This suggested that the high peaks in natalizumab concentration following IV dosing might not be required for certain PD effects.

Simulations based on natalizumab PK/α4 integrin model with a different dosing regimen ranging from 300 mg to 450 mg SC Q4W indicated that administering natalizumab 300 mg Q4W SC will result comparable C_{trough} (slightly below the exposure range following 300 mg Q4W IV). Given the established PK/PD relationship, the highly overlapping PK exposure range will result in comparable α4 integrin levels to those of the clinically approved 300 mg Q4W IV administration. Large increases in serum concentrations >10 mg/L (= EC_{80} level) will result in only marginal changes in α4-integrin binding. Thus, a reduction in C_{max} by 70% following SC administration compared with IV did not result in a proportional drop in α4-integrin binding. In addition, the lowest observed C_{max} (22 mg/L) after the 300 mg SC dose of natalizumab is still more than twice the EC_{80}.

Exposure simulations using the updated popPK model indicated that overall, 83% - 93% of participants in each BW category (<59 kg, 60-79 kg, 80-99 kg, >100 kg) are predicted to reach C_{trough_ss} above the EC_{80} level of 10 mg/L.

2.4.4. Discussion on clinical pharmacology

With respect to bioanalytical methods used, data on qualification/validation of the PD methods used in studies 101MS102 and 101MS206 were considered acceptable. The validation approach for the ADA assay is not fully in line with current recommendations on assessment of immunogenicity. Nevertheless, based on the additional information provided, the assay could be considered suitable.

Discrepancies between non-compartmental analysis and popPK analysis were detected, especially with respect to bioavailability after SC administration. PopPK derived bioavailability (82%) of the SC formulation was supported by exposure simulations and comparison with PK observations.

Although visual predictive checks stratified by route of administration were of acceptable quality, covariate effects such as ADA formation on PK, impact of BW or formulation on PK (including F) could not be fully assessed due to the limited amount and time scale of SC data and imbalanced data resulting from the respective routes of administration. However, a thorough description of C_{trough} levels is deemed necessary to liaise PK with PD (integrin saturation) and probable safety concerns.

The influence of ADAs on the PK of IV natalizumab was evaluated during a parallel type II variation for updating popPK analysis. The influence was substantial (persistent ADAs lead to a 2.5 fold increase in CL) and is adequately described in the SmPC of both the IV and SC formulation. Of note, ADA influence on CL (IV formulation) was originally estimated to a 2.9 fold increase, which is deemed comparable, although non-linear clearance has been newly integrated in the popPK model by update.

The Applicant tried to investigate the influence of ADAs on PK/PD and efficacy in participants of SC studies. Given the small sample sizes involved, firm conclusions regarding the impact of transient or persistent ADA development on the PK/PD and efficacy of SC natalizumab could not be drawn. This was endorsed. Besides, frequency of ADAs appeared not be higher after SC vs. IV administration. Thus, it could be agreed that guidance and recommendations regarding ADA vigilance provided in the SmPC for the SC formulation are appropriate.

Given the uncertainty in PK after SC administration of 300 mg natalizumab and known PK characteristics (non-linear CL, BW effect on PK) some other concerns have been raised and supporting simulations were requested with respect to PK and PK/PD of natalizumab. Summary statistics and simulation results indicated overall comparable C_{trough_ss} values after 300 mg Q4W dosing IV and SC, respectively, regardless of pre-treatment to steady state following 300 mg Q4W IV.

Exposure simulations based on the updated popPK model assuming the 300 mg Q4W SC regimen showed a decrease in C_{trough_ss} values with BW (from 30 mg/l to about 18 mg/l) that is expected due to the fix dose regimens. Differences between the BW categories in achieved steady state level did not translate into major differences in α4-integrin level saturation (overall 82%-85%). This is plausible as given the expected level of C_{trough_ss}, overall, 83-93% of participants in each BW category (<59 kg, 60-79 kg, 80-99 kg, >100 kg) were predicted to have C_{trough} above the EC_{80} level of 10 mg/L.

Simulated C_{trough_ss} reached following an EID of Q6W were however significantly lower (median C_{trough_ss} ~ 6 mg/l) compared to Q4W dosing which were about 3- to 4 fold higher. PK/PD predictions indicated that this translates into lower percentage in median integrin saturation (~70-73%) compared to Q4W dosing. Overall, SC exposure and response following 300 mg Q6W SC was predicted to be slightly lower comparted to IV administration of 300 mg natalizumab Q6W at steady state but highly overlapping. Stratification by BW groups indicated a decrease in C_{trough_ss} from about 10 mg/l to 5 mg/l. Accordingly, this translated into lower integrin saturation levels (median: 65-75%). More explicitly, the majority of patients of all BW groups were expected not to reach the EC_{80} level of 10 mg/l, even at the lowest BW category (60%) but increasing with BW (up to

88%). Based on the current data, no conclusion on reduced or maintained efficacy following EID (Q6W) could be drawn. Clinical relevance is investigated in Study 101MS329.

The provided simulation results however showed an increase in C_{trough} with BW (>100 kg) compared to the BW group 80-99kg which is not plausible due to the fix dosing regimen. The Appliant was asked to discuss this finding, taking the characteristics of the simulated patient population and identified covariates on PK into account. In response, the Applicant clarified that the former virtual population for simulations consisted of a non-uniform distribution of sample size across weight categories causing the finding of concern. PK simulations were adapted assuming a uniform distribution (1000 patients for each BW group <59 kg, 60-79 kg, 80-99 kg, >100 kg). In comparison to the former analysis (day 120 simulations following an adjustment to sample size) a clear influence of BW on exposure reached at steady state became apparent. The percentages of participants with C_{trough_ss} < 10 mg/L for each BW group after SC and IV administration were provided and resulted in comparable values. In patients weighing 80 to 99 kg, the predicted percentage of patients with C_{trough_ss} < 10 mg/L is 14.5% and 14.4% following SC and IV administration, respectively. As expected, due to the impact of BW on PK, the predicted percentages increase in patients at BW >100 kg (SC: 26.4%; IV: 25.5%) again regardless of the mode of administration.

Predicted degree of corresponding α4-integrin saturation assuming a uniform distribution (1000 patients for each BW group <59 kg, 60-79 kg, 80-99 kg, >100 kg), again, was overall comparable between weight groups. Median saturation at C_{trough} [%] ranged from 80 to about 85 %, indicating that differences in C_{trough} levels at steady state have no pivotal effect on saturation levels achieved.

Some other concerns have been raised for clarification with respect to the formulations used, immunogenicity data and presentation of PK and PD data. From this, an adequate presentation of PD data over time with a measure of variability was requested (Studies 101MS102 and 101MS206). The respective graphical representations provided showing PD results over time following SC and IV treatment indicate overall comparability between modes of administration

2.4.5. Conclusions on clinical pharmacology

The PK data package is deemed overall sufficient to describe single dose and multiple dose PK after SC administration of 300 mg natalizumab.

PK and several PD markers were measured in SC and IV arms of 101MS102 and 101MS206 to directly compare the PD following 300 mg Q4W IV or SC. Overall, PD and PK/PD results following 300 mg Q4W showed comparability of the SC and IV route of administration. PopPK and PK/PD modelling support the selected dose of 300 mg for SC administration using the Q4W dosing regimen.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

NA

2.5.2. Main study(ies)

Methods

In order to support the 300 mg Q4W SC regimen as an alternative to the currently approved 300 mg Q4W IV route of administration, the Applicant presented efficacy data from 2 clinical studies:

- the phase I study **101MS102 (DELIVER)** Table 3
- the phase II study **101MS206 (REFINE)** Table 4

In these studies, a total of 71 patients were exposed to the 300 mg natalizumab Q4W SC regimen. In addition, 53 were exposed to 300 mg Q12W SC, and 38 were exposed to 150 mg Q12W SC. A total of 81 patients were exposed to the standard dosing regimen of 300 mg Q4W IV. 52 patients received 300 mg Q12W IV, and 47 received 150 mg Q12W IV.

Study 101MS102

This was a randomized, open-label, dose-ranging study to evaluate the PK and initial safety of SC and IM natalizumab in subjects with MS. The study was conducted at twelve investigational sites in the US.

The Applicant stated that study 101MS102 was primarily designed to evaluate the safety, PK, and PD properties of natalizumab and was not powered to detect any differences between the IV and SC routes of administration in either the SPMS or RRMS population or within the study populations over time. Therefore, no definitive conclusions could be drawn regarding efficacy; however, some general inferences were made.

Table 3: Study 101MS102 (DELIVER) Efficacy variables & endpoints

Study Number (Status)	Study Population	Number of Participants	Study Phase Study Design	Total Dose	Efficacy Variables and Endpoints
101MS102 (completed)	**All participants:** Male or female; aged 18 to 65 years; natalizumab-naïve **Groups A, B, C & F:** Participants with SPMS; continuous clinical worsening over a period of at least 3 months; baseline EDSS between 2.5 and 6.5 (inclusive) **Groups D & E:** Participants with RMS; baseline EDSS between 0.0 and 6.5 (inclusive)	76 participants randomised (52 SPMS, 24 RMS): SPMS 300 mg IV Q4W (N=16) SPMS 300 mg SC Q4W (N=14) SPMS 300 mg IM Q4W (N=15) SPMS reference treatment (N=7) MS 300 mg IV Q4W (N=12) RMS 300 mg SC Q4W (N=12)	Phase 1b Open-label, randomised, parallel-group design Evaluation of safety, PK, and PD properties following IV, SC, or IM administration	**Groups A, B, C, D & E:** 8-week study period duration, 300 mg single-dose (Part I) 300 mg repeat-dose, Q4W for 6 months (6 doses; Part II) **Group F:** Reference treatment, efficacy evaluation, and AE monitoring for first 32 weeks **Groups A, B, C & F:** Follow-up treatment extension phase. 300 mg SC (Q4W) at Month 8, 12, 15, or 18.	**Clinical endpoints:** • EDSS • MSFC (T25FW, 9-HPT, and PASAT-3) • SDMT • VAS • VFT **Radiological endpoints:** • Gd+ lesion counts • T2 and FLAIR sequences • T1 sequences with/without Gd • Whole brain measurements of T2 relaxation and atrophy • MTR in whole brain and NABT • DTI sequences

Study 101MS206

This study was a phase 2, multicenter, randomized, blinded, prospective, parallel-group study evaluating the safety, tolerability, and efficacy of multiple regimens of natalizumab over a 72-week period in patients with RRMS who had previously received IV natalizumab for at least 12 months. The primary endpoint for this study

was the cumulative number of combined unique active (CUA) MRI lesions (detectable new Gd+ lesions and new or newly enlarging T2 hyperintense lesions).

Table 4: Study 101MS206 (REFINE) Efficacy variables & endpoints

Study Number (Status)	Study Population	Number of Participants	Study Phase Study Design	Total Dose	Efficacy Variables and Endpoints
101MS206 (completed)	Male or female; aged 18 to 55 years; participants with **RRMS**; relapse-free for 12 months prior to randomisation; treated with natalizumab for 12 months prior to randomisation	**290 participants** randomised: 300 mg IV Q4W (N=54) or Q12W (N=52) 300 mg SC Q4W (N=45) or Q12W (N=54) 150 mg IV (N=47) or SC (N=38) Q12W 277 participants in efficacy population	Phase 2 Randomised, blinded, parallel-group design Evaluation of safety, tolerability, and efficacy of multiple regimens	**Six treatment arms:** 300 mg IV Q4W or Q12W 300 mg SC Q4W or Q12W 150 mg IV or SC Q12W Duration: Blinded regimen for 60 weeks, open-label regimen from Weeks 60 to 68 (300 mg IV Q4W)	**Clinical endpoints:** • Clinical relapses • ARR • EDSS • SDMT • VAS **Radiological endpoints:** • CAL • Gd+ lesion counts • T1 sequences with/without Gd • T2 sequences with/without Gd

Study Participants

Study 101MS102

Patients with SPMS and RRMS, aged 18 to 65 years who were natalizumab naïve were eligible to participate. In addition, the following criteria had to be met:

- Patients for Groups A, B, C, and F must have had a diagnosis of SPMS, as defined by Lublin and Reingold [Lublin and Reingold 1996], but without superimposed relapses. This condition required the presence of continuous clinical disease worsening over a period of at least 3 months. Must have had a baseline EDSS score between 2.5 and 6.5, inclusive.
- For Groups D and E Must have had a diagnosis of a relapsing form of MS and fall within the therapeutic indication stated in the locally approved label for Tysabri. Must have a baseline EDSS score between 0.0 and 6.5, inclusive.

Study 101MS206

Patients with RRMS, aged 18 to 55 years, who were pre-treated with natalizumab for a minimum of 12 months were eligible to participate. In addition, the following criteria had to be met:

- Free of MS relapse, as determined by the enrolling Investigator, for 12 months prior to randomization.
- In the 12 months prior to the initiation of natalizumab, subject must have experienced a minimal level of disease activity as defined by: ≥2 documented clinical relapses OR 1 relapse and documented MRI activity, defined by the presence of at least 1 Gd+ lesion on MRI, unrelated to the relapse.

Treatments

Study 101MS102

The study evaluated five treatment groups. Each group received 300 mg per dose, either IV or SC. The groups were treated in part I at baseline (day 0) and then every 4 weeks from weeks 8 to 28.

Table 5: Natalizumab Treatment Groups in Study 101MS102

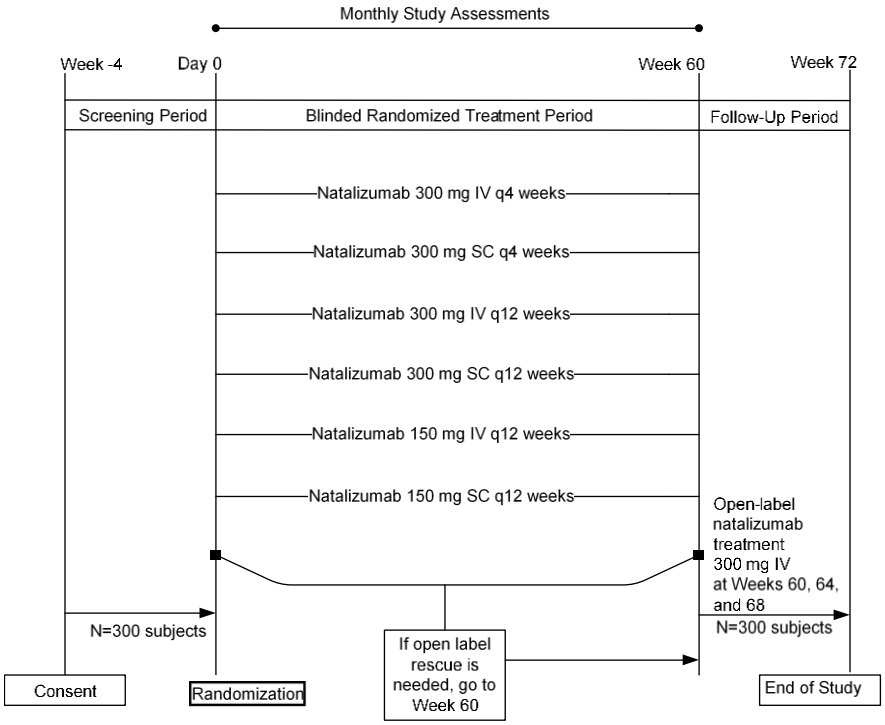
Study Group	Formulation and Route of Administration	MS Patient Population
A	2 × 1 mL BG00002-D diluted into 100 mL saline for IV infusion over 60 minutes	SPMS
B	2 × 1 mL BG00002-D SC injections	SPMS
C	2 × 1 mL BG00002-D IM injections	SPMS
D	2 × 1 mL BG00002-H SC injections	Relapsing MS
E	15 mL BG00002-E diluted into 100 mL saline for IV infusion over 60 minutes	Relapsing MS

For subjects in the natalizumab treatment groups (Groups A, B, C, D, and E), the study period between Screening and Week 32 was divided into 2 parts: an 8 week, Single Dose, Intensive PK/PD Phase (Part I), followed by a Repeated-Dose Treatment Extension phase in which subjects received natalizumab once per month for 6 months (Part II). During Part II, subjects were to continue to receive the same natalizumab dose and route that was assigned to them in Part I of the study. Natalizumab was to be administered monthly (at weeks 8, 12, 16, 20, 24, and 28) for 6 months.

Study 101MS206

The study explored dosing with natalizumab by SC and IV routes. Subjects were screened at a regularly scheduled natalizumab dose visit and enrolled at their next monthly visit if they met all inclusion criteria. Within 1 month after receiving their most recent infusion of natalizumab, eligible subjects were randomly assigned to 1 of 6 dosing regimens and initiated the first dose of study treatment.

Figure 1: Study design and natalizumab treatment groups in Study 101MS206



Objectives

Both studies were not primarily designed and powered for a direct comparison of the 300 mg Q4W SC vs. the 300 mg Q4W IV regimen.

Study 101MS102

The primary objective of the study was to compare the PK and PD of single SC and IM doses of 300 mg natalizumab to IV administration of 300 mg natalizumab in MS subjects.

Secondary objectives included the following:

- To investigate the safety, tolerability, and PK of repeated natalizumab doses administered SC and IM.
- To investigate the immunogenicity of repeated natalizumab doses administered SC and IM.
- To explore proof of concept within the SPMS population using change from baseline in: Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC) Scale, Symbol Digit Modalities Test (SDMT), Visual Analogue Scale (VAS) to measure quality of life, and Visual Function Test (VFT); and brain MRI measures including: number of new or newly enlarging T2 hyperintense lesions, number of new T1 hypointense lesions, number of new Gd+ lesions, whole-brain atrophy, magnetization transfer ratio (MTR), and diffusion tensor imaging (DTI).
- To observe the effect of natalizumab administered IV and SC on brain MRI measures in subjects with relapsing forms of MS.

Study 101MS206

The primary objective of this study was to explore the effects of multiple regimens of natalizumab on disease activity and safety in subjects with RRMS.

Additional objectives of this study were as follows:

- To characterize and compare PK/PD profiles across multiple dose regimens of natalizumab.
- To characterize effects on secondary brain MRI measures.
- To evaluate potential laboratory markers of immune function and trafficking across the treatment regimens.
- To assess the safety and tolerability across multiple dose regimens.

Outcomes/endpoints

Study 101MS102

The primary endpoints of this PK study did not include an efficacy measure.

Efficacy data were evaluated as exploratory endpoints only. Analyses were conducted to assess potential benefits of natalizumab therapy by various routes (IV, IM, SC) of administration in patients with SPMS and RMS. These efficacy measures included EDSS, MSFC, SDMT, VAS, VFT, and brain MRI measures (Table 6).

Study 101MS206

The primary efficacy endpoint was the cumulative number of CUA lesions.

Additional/exploratory clinical efficacy endpoints included the following:

- Number and Volume of Gd+ Lesions
- Number of New or Newly Enlarging T2 Hyperintense
- Proportion of Subjects Relapsing and ARR Over 60-Week Treatment Period
- Time to First Protocol-Defined Relapse by Week 60
- Proportion of Subjects Requiring Rescue Treatment
- Time to First MRI That Met Rescue Criteria by Week 60
- Change in EDSS From Baseline Through Week 60
- Sustained EDSS Progression at Week 60
- Change in Subject Assessed Well-Being (VAS) From Baseline Through Week 60
- Change in SDMT From Baseline Through Week 60

Table 6: Comparison of Efficacy endpoints across studies 101MS102 and 101MS206

Efficacy Endpoint	Study 101MS102	Study 101MS206
Clinical Endpoints		
EDSS	X	X
Sustained disability progression by EDSS		X
MSFC	X	
SDMT	X	X
VAS	X	X
VFT	X	
Assessment of relapse	X	X
MRI Endpoints		
Gad+ lesion counts	X	X

T1 sequences with and without Gadolinium	X	X
T2 sequences and FLAIR	X	
T2 sequences with and without Gadolinium		X
MTR in whole brain and normal appearing brain tissue	X	

EDSS: Expanded disability Status Scale; MSFC: Multiple Sclerosis Functional Composite; VAS: Visual Analogue Scale; VFT: Visual Function Test; MRI: Magnetic Resonance Imaging; Gad+: Gadolinium-enhancing: FLAIR: Fluid-attenuated inversion recovery; MTR: Magnetization Transfer Ratio.

Sample size

Study 101MS102

No formal sample size calculation was carried out for this study. A sample of 12 subjects per dosing group was considered sufficient to characterize the PK profile of the different natalizumab routes.

Study 101MS206

This study was exploratory in nature, and sample size was not based on statistical considerations. Based on MRI data from previous studies with natalizumab and simulations, and assuming a 10% dropout rate, a sample size of 50 subjects per group was anticipated to provide an approximately 80% power to detect a trend for difference between the standard regimen and an alternative regimen with 50% loss-of efficacy as compared with the standard regimen at a 1-sided 0.1 level of significance.

Randomisation and blinding (masking)

Study 101MS102

A total of 52 SPMS subjects were randomized at an approximate ratio of 2:2:2:1 to receive a single IV, SC, or IM dose of 300 mg natalizumab (Groups A [16 subjects], B [14 subjects], and C [15 subjects], respectively), or to receive a reference treatment (Group F [7 subjects]).

Once enrollment for Groups A, B, C, and F was completed, 24 subjects with relapsing MS were to be randomized at a ratio of 1:1 into Group D (300 mg SC [12 subjects]) or Group E (300 mg IV [12 subjects]).

Study 101MS102 was an open-label study.

Study 101MS206

This was a randomized, blinded study. All study staff (with the exception of the unblinded site pharmacist for IV infusions), subjects, and the sponsor were blinded to natalizumab dose but not to route of administration. In order to minimize the risk of unblinding, the examining neurologist was required to be blinded to both, dose and route of administration.

Statistical methods

Study 101MS102

Efficacy analyses were performed to explore different routes of administration (IV, IM, and SC) in participants with SPMS and RRMS. Efficacy endpoints were summarised over time using descriptive statistics. All the statistical analyses in this study were descriptive. There was no imputation used for missing data.

Study 101MS206

The modified intention to treat (mITT) population, defined by the Applicant as all randomised participants who received at least 1 dose of study treatment and had at least 1 efficacy assessment used for all efficacy analyses. Subjects who had statistical protocol deviations as listed below were excluded from the mITT population.

Efficacy endpoints were summarised by presenting summary statistics for continuous and count variables, or frequency distributions for categorical variables. All statistical analyses for efficacy in this study were descriptive in nature; therefore, no formal comparisons and no adjustments for multiple comparisons/multiplicity were made. No interim analysis was conducted for the study.

Statistical protocol deviations were deviations that could lead to biased endpoint measurements. Subjects incurring any of the following statistical protocol deviations could be excluded from the efficacy and PD analyses. Statistical protocol deviations included the following:

- Positive results for anti-natalizumab antibodies at screening
- Administration of an incorrect investigational product during the study
- Diagnosis of PML
- Lack of compliance with treatment (defined as not receiving 2 or more consecutive doses)

The primary efficacy endpoint was the cumulative number of CUA lesions. Missing data were imputed using the mean number of new active lesions by treatment arm and visit except data from treatment arms that were closed prematurely. Data from arms that were closed prematurely were not included, since a large proportion of the data would have had to be imputed. In addition, data were summarised by treatment arm without imputation.

The number and change from baseline in the number and the volume of Gd+ lesions, new or enlarging T2 hyperintense lesions, and new, nonenhancing T1 hypointense lesions were summarized by treatment group and timepoint.

Only protocol-defined relapses (as identified by the Investigator) during the randomized treatment period were included. In this regard, clinical relapses were defined by new or recurrent neurological symptoms not associated with fever or infection, having a minimum duration of 24 hours and including the following:

- An increase of ≥ 1 grade in ≥ 2 functional scales of the EDSS, or
- An increase of ≥ 2 grades in ≥ 1 functional scale of the EDSS, or
- An increase ≥ 1 EDSS if the previous EDSS was ≤ 5.5, or an increase of ≥ 0.5 if the previous EDSS was ≥ 6 (an increase of ≥ 1.5 in the EDSS if previous EDSS was equal to 0).

The AAR for each treatment group was calculated as the total number of relapses experienced in the group divided by the total number of days in the randomized period for the group, and the ratio was multiplied by 365.25. In addition, the subject level ARR was calculated as the number of relapses for that subject divided by the number of days the subject participated in the randomized period, and the ratio was multiplied by 365.25.

Sustained disability progression was defined as follows: at least a 1.5-point increase on the EDSS from baseline (Day 0) EDSS = 0 that was sustained for 12 weeks (± 5 days), at least a 1.0-point increase on the EDSS from a baseline EDSS score of ≥1.0 and ≤5.5 that was sustained for 12 weeks (± 5 days), and at least a 0.5-point increase on the EDSS from a baseline EDSS score of ≥6 that was sustained for 12 weeks (± 5 days).

The proportion of subjects who had a relapse, who had disability progression, who met MRI rescue criteria, and who received rescue therapy were estimated using the Kaplan-Meier method.

The EDSS, SDMT and VAS scores and change from baseline in EDSS, SDMT and VAS scores were summarized by treatment group and timepoint.

Results

Participant flow

Study 101MS102

A total of 76 natalizumab-naïve participants were randomized, hereof 52 patients with SPMS and 24 with RMS as displayed in Figure 2.

Figure 2: Overview of subject disposition in Study 101MS102

Treatment	Population	Route	Randomized	Completed Part I	Completed Part II
A	SPMS	IV	16	16	12
B	SPMS	SC	14	14	13
C	SPMS	IM	15	14	11
D	RRMS	SC	12	11	9
E	RRMS	IV	12	11	10
Total subjects evaluable			69	66	55

SPMS: Secondary progressive multiple sclerosis; RRMS: Relapsing Remitting; IV: intravenous; SC: Subcutaneous

Study 101MS206

A total of 290 RMS participants were enrolled and randomly assigned to the 6 treatment arms. A total of 289 participants received at least 1 dose of study treatment, and the efficacy analyses were performed in 277 randomized participants. Of the 290 participants, 54 were randomized to the 300 mg IV Q4W, and 45 were randomized to the 300 mg SC Q4W.

Of 290 subjects, 117 (40%) discontinued randomized treatment due to the premature closure of the 4 Q12W treatment arms: 300 mg IV Q12W: 20 of 52 subjects (38%); 300 mg SC Q12W: 36 of 54 subjects (67%); 150 mg IV Q12W: 33 of 47 subjects (70%); 150 mg SC Q12W: 28 of 38 subjects (74%) (Figure 3). A majority of the 117 subjects who discontinued the randomized treatment due to arm closures did not withdraw from the study and entered the open-label natalizumab treatment period. Thirty-nine of 191 subjects (20.4%) in the 4 closed treatment arms received rescue therapy with open-label natalizumab treatment: 13 subjects in the 300 mg IV Q12W arm, 10 subjects in the 300 mg SC Q12W arm, 8 subjects in the 150 mg IV Q12W arm, and 8 subjects in the 150 mg SC Q12W arm.

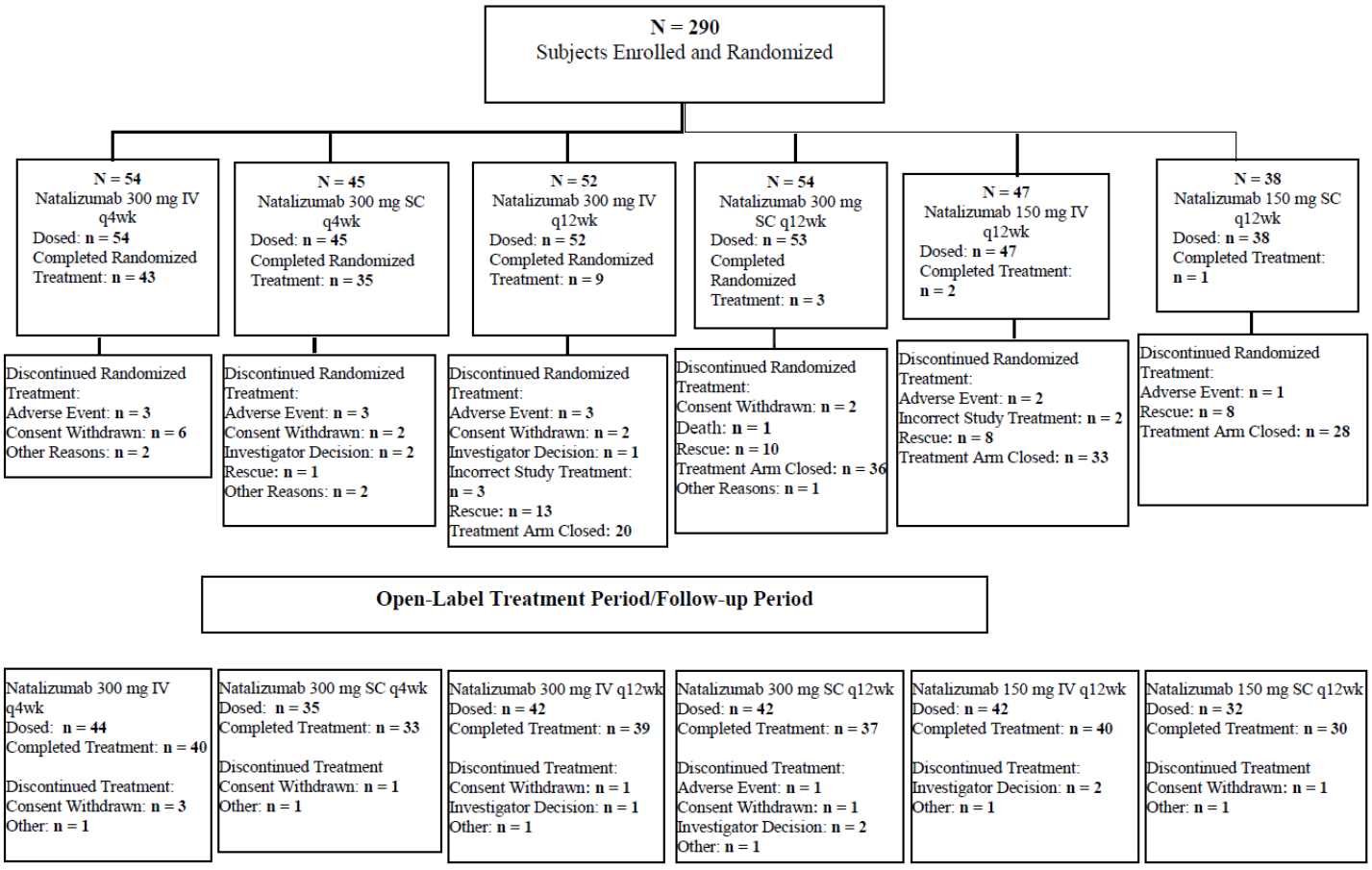
Across all 6 treatment arms, 12 of 290 subjects (4%) withdrew consent, and 3 of 290 subjects (1%) discontinued the study due to the Investigator's decision (Figure 3). There was 1 death in the 300 mg SC Q12W arm (Figure 3). 5 of 290 subjects (2%) were administered incorrect study treatment and discontinued the

study (Figure 3); however, an additional 6 subjects were identified to have received at least 1 dose of incorrect study treatment during data reconciliation phase of the study. Overall, 11 of 290 subjects (3.8%) were administered incorrect study treatment and were excluded from the efficacy analyses.

Overall, 237 randomized subjects (82%) from across the 6 treatment arms entered the open-label follow-up period and were administered 300 mg IV Q4W. The subjects who entered the open-label natalizumab treatment included those who discontinued randomized treatment period because of closure of the four Q12W treatment arms and chose to receive open-label natalizumab rather than withdraw from the study.

Nineteen subjects (6%) discontinued the open-label natalizumab treatment: 7 subjects withdrew consent, 6 subjects discontinued because of other reasons, 5 subjects were discontinued by the Investigator, and 1 subject discontinued due to an AE (Figure 3).

Figure 3: Overview of subject disposition in Study 101MS206



Recruitment

Study 101MS102

Date of first treatment: 22 October 2007

Last subject completed the final study visit: 16 November 2011.

End of Study Date: 13 January 2012

Study 101MS206

Date of First Treatment: 04 August 2011

End of Study Date: 03 October 2014

Conduct of the study

Study 101MS102

Protocol 101MS102 was amended 5 times (21 Aug 2007; 17 Sept 2007; 10 Jun 2008; 13 Nov 2009; 09 Apr 2010). Here, we provide an overview of main changes including the amendments:

- Amendments in the clinical and MRI endpoints including the addition of SDMT and VAS to the protocol (No 1 and 3).
- Revision of the patient population for Groups D and E from subjects with SPMS to subjects with relapsing forms of MS because relapsing patients are an anticipated patient population for use of natalizumab administered by SC injection (No 4).
- Update the protocol to reflect that SC administration has been selected for use in the extension phase of the study based on the review of the preliminary data and that only 300 mg doses of natalizumab were to be compared (No 4).
- Revision of the requirements for anti-natalizumab antibody testing (No 4).

The most common major protocol deviations were study drug administration (12 subjects), missed assessments (6 subjects), and ICF/PHI issues (5 subjects).

Study 101MS206

Protocol 101MS206 was amended 3 times (03 Mar 2011, 28 Feb 2012 and 16 Nov 2012) to add a pharmacogenomic analysis to evaluate individual susceptibility or resistance to develop PML (No 1), align safety information (No.2) and frequency of anti-JCV antibody testing (No.3) to the current recommendations for Tysabri.

As per protocol deviation, twelve participants were excluded from the efficacy set due to an administration of an incorrect investigational product during the study (n=11) or PML diagnosis (n=1).

Baseline data

Study 101MS102

Treatment groups were balanced within subject populations with respect to age and height. Gender and race reflected the MS population, which is primarily female (35 [67%] subjects for SPMS subjects [Groups A, B, C, and F] and 16 [70%] subjects for relapsing MS subjects [Groups D and E]); and predominantly white (49 [94%] subjects for SPMS subjects and 21 [91%] subjects for relapsing MS subjects).

With regard to relapse history, there were notable differences between the 2 subject populations. For the SPMS population (Groups A, B, C, and F) the mean number of relapses within the 3 years prior to study entry was 0.7 with 29 (56%) subjects having no relapses and 15 (29%) having 1 relapse. The occurrence of relapses across the SPMS treatment groups within 3 years and 12 months prior to study entry was variable with Group B having the greatest number of subjects with no relapses (11 [79%] subjects) and Group F the fewest (3 [43%] subjects) during the past 3 years. The mean time since the most recent relapse was 69.45 months with a median of 55.45 months (range 2.8 months to 348.0 months). The longest mean time since the most recent relapse was for Group B (93.40 months) and the shortest was Group A (56.71 months).

For the relapsing MS population (Groups D and E) the mean number of relapses within the 3 years prior to study entry was 1.9 with 6 (26%) subjects having 1 relapse, 7 (30%) having 2 relapses and 5 (22%) having 3 relapses. The occurrence of relapses across the Groups D and E within 3 years and 12 months prior to study entry was similar. The mean time since the most recent relapse was 21.0 months, much shorter than that for the SPMS population.

Study 101MS206

Of 290 enrolled subjects, 204 (70%) were female, ranging 63% (24 of 38 subjects in the 150 mg SC Q12W arm) to 76% (41 of 54 subjects in the 300 mg SC Q12W arm).

The overall median (min, max) age was 38.0 years (19 years, 56 years); 1 subject (<1%) was in the age range of 18 to 19 years; 48 subjects (17%) were in the age range of 20 to 29 years; 117 subjects (40%) were in the age range of 30 to 39 years; 95 subjects (33%) were in the age range of 40 to 49 years; and 29 subjects (10%) were in the age range of 50 to 56 years. The median (min, max) BW was 66.70 kg (45.0 kg, 142.0 kg). The predominant race represented in the study was White (233 subjects [80.0%]). Twenty percent of subjects (57) did not report their race. All geographic areas represented were in Europe.

The baseline mean EDSS scores ranged from 2.54 to 2.99 across the 6 natalizumab treatment arms. The baseline individual EDSS scores ranged from 0.0 to 6.5: 0.0 (3% of subjects), 1.0 (9% of subjects), 1.5 (14% of subjects), 2.0 (17% of subjects), 2.5 (12% of subjects), 3.0 (7% of subjects), 3.5 (12% of subjects), 4.0 (11% of subjects), 4.5 (3% of subjects), 5.0 (3% of subjects), 5.5 (4% of subjects), 6.0 (3% of subjects), and 6.5 (<1% of subjects).

Baseline MRI parameters, Gd+ lesion count and volume, T2 lesion volume, and non-Gd+ T1 lesion volume (mean, median) were similar across the 6 treatment arms in the 288 out of 290 enrolled subjects. The screening MRI data indicated that none of the subjects in any of the 6 treatment arms had Gd+ lesions. The total mean (median) T2 lesion volume was 11.3 (7.7), while the total mean (median) Gd- T1 lesion volume was 4.4 (2.4).

The mean number of relapses in the 12 to 24 months prior to natalizumab initiation was similar, ranging from 0.9 to 1.5 across the 6 treatment arms. Of 290 subjects, 49 (17%) had ≥3 relapses, 46 (16%) had 2 relapses, and 94 (32%) had 1 relapse 12 to 24 months prior to natalizumab initiation. The mean number of relapses since initiation of natalizumab was similar, ranging from 0.2 to 0.7 across the 6 treatment arms. Nine of 290 subjects (3%) had ≥3 relapses. Four of 290 subjects (1%) experienced their most recent relapse ≤1 year prior to enrollment: 2 subjects in the 300 mg IV Q4W arm, 1 subject in the 300 mg SC Q12W arm, and 1 subject in the 150 mg IV Q12W arm. The mean number of years since the most recent relapse after natalizumab initiation

was similar across all the treatment arms, ranging from 1.02 years in the 300 mg SC Q4W arm to 1.88 years in the 150 mg IV Q12W arm. The total mean number of Gd+ lesions on MRI scan in the year prior to natalizumab initiation was 2.3 for the entire study population; the mean numbers across all the treatment arms was similar (the mean number for 300 mg IV Q4W arm was 1.5; other mean numbers ranged from 2.2 to 3.0). The median number of Gd+ lesions was similar, ranging from 1.0 to 1.5 across the 6 treatment arms.

The mean EDSS score prior to natalizumab initiation was similar across all the treatment arms, ranging from 2.72 to 3.16 (median scores ranged from 2.5 to 3.0). The mean baseline value was similar across all the treatment arms, ranging from 2.54 to 2.99 (median scores ranged from 2.5 to 3.0).

Prior MS therapy in subjects randomized to the 6 treatment arms was generally representative of the overall population of patients with RRMS and was generally well balanced among the treatment groups. Prior to study entry, mean duration of natalizumab use across all the treatment arms was 3.0 years, ranging from 2.7 to 3.2 years. The median number of prior natalizumab infusions across the treatment groups ranged from 25.0 to 36.0 infusions.

Numbers analysed

Study 101MS102

For Parts I and II (from baseline through Week 32), the efficacy population was defined as all subjects who had at least 1 post-baseline assessment of the efficacy parameters to be analysed. Additionally, if subjects received less than 5 doses of natalizumab or were persistently ADA positive then they were excluded from the efficacy population.

A total of 76 natalizumab-naïve participants were randomized, hereof 52 patients with SPMS and 24 with RMS Based on above criteria, 9 subjects were excluded from the efficacy analyses (2 from group A; 1 from group B; 2 from group C; 3 from group D and 1 from group E). Then, efficacy evaluable population included 14 participants in group A, 13 participants in group B, 9 participants in group D and 10 participants in group E.

During the procedure, the Applicant clarified that the primary efficacy analysis set was the per protocol set

Study 101MS206

As presented in above section, mITT population as defined by the Applicant included all randomised participants without protocol deviations listed in statistical methods who received at least 1 dose of study treatment, had at least 1 efficacy assessment

Out of the 290 randomised participants, 289 received at least 1 dose of study treatment. Twelve participants were excluded from the efficacy set due to an administration of an incorrect investigational product during the study (n=11) or PML diagnosis (n=1). Therefore, 277 participants were included in the efficacy population.

Outcomes and estimation

Study 101MS102

Overall, both SPMS and RRMS participants were mostly stable during the study and no clear differences in During Study 101MS102, 3 SPMS participants in the IV treatment arm and 2 RRMS participants in the SC treatment arm had an MS relapse in Parts I and II. There were no MS relapses in SPMS participants in the SC

treatment arm or in RRMS participants in the IV treatment arm. One participant had an MS relapse in the Follow-Up Treatment Extension Phase with participants with MS.

EDSS scores were observed between participants treated with the IV and SC formulations (Table 7).

Except for an increase in T25FW in the SPMS IV group, no difference in MSFC scores was observed between participants receiving natalizumab by the SC or IV route of administration for the SPMS and RRMS populations over the time periods (Table 8).

The performance of SMDT and VAS at baseline was better for RRMS than for SPMS groups. With the exception of a deterioration for VAS performance reported for group A over the study period, a trend towards an improvement was observed for both tests for RRMS and SPMS IV and SC groups. For VFTs, no substantial changes were observed over time for groups A, B, D and E.

No new Gd+ lesions were identified over time irrespective of route of administration. The number of patients with new or newly enlarging T2 hyperintense lesions was low (2 in group A, 3 in groups B, D and E), and no clear differences were found between the IV or SC treatment arms in patients with RRMS and SPMP.

Table 7: Mean EDSS Scores Over Time – Study 101MS102 (Efficacy Evaluable Population)

	SPMS IV	SPMS SC	RRMS IV	RRMS SC
n	14	13	10	9
Baseline	5.57	5.46	4.00	3.22
Day 56	5.68	5.35	3.75	2.61
Week 20	5.27	5.62	3.90	2.72
Week 32	4.96	5.65	4.11	2.56

Only mean values are presented in this table.
SPMS: Secondary progressive multiple sclerosis; RRMS: Relapsing Remitting; IV: intravenous; SC: Subcutaneous

Table 8: Mean MSFC Scale Values Over Time – Study 101MS102 (Efficacy Evaluable Population)

	SPMS IV	SPMS SC	RRMS IV	RRMS SC
n	14	13	10	9
Z-score BL	-0.295	-0.096	0.384	0.470
Week 32	-0.517	0.019	0.368	0.472
9-HP BL	38.33	31.93	24.29	21.94
Week 32	43.03	32.08	24.08	21.83
PASAT3 BL	42.7	41.8	47.6	45.1
Week 32	44.5	45.1	46.6	44.4
25FW BL	15.09	11.70	6.75	5.86
Week 32	24.19	12.33	6.92	5.12

Only mean values are presented in this table.
SPMS: Secondary progressive multiple sclerosis; RRMS: Relapsing Remitting; IV: intravenous; SC: Subcutaneous; BL: baseline; 9-HP: nine hole peg test; PASAT3: The Paced Auditory Serial Addition Test (3 seconds); 25FW: 25-foot walking test

Study 101MS206

Primary MRI-endpoint

Cumulative Number of CUA Lesions

The primary efficacy endpoint was the cumulative number of new CUA lesions since baseline based on brain MRI scans at Weeks 12, 24, 36, 48, and 60.

During the randomized treatment period, CUA lesions were detected by the Week 12 Visit (Table 9) in the four Q12W treatment arms. The increase in MRI activity in a large proportion of subjects in the four Q12W treatment arms led to premature closure of these arms by the Data and Safety Monitoring Committee.

The total mean number of combined unique active lesions since baseline during the randomized period in the natalizumab 300 mg SC Q4W treatment arm (0.02) was comparable to that in the 300 mg IV Q4W arm (0.23) (Table 9).

Table 9: Summary Statistics of Number of CUA Lesions Since Baseline by Visit During the Randomized Treatment Period for All Treatment Arms (efficacy population set).

	Natalizumab 300 mg IV q4wk	Natalizumab 300 mg SC q4wk	Natalizumab 300 mg IV q12wk	Natalizumab 300 mg SC q12wk	Natalizumab 150 mg IV q12wk	Natalizumab 150 mg SC q12wk
Number of subjects in the mITT population	53	45	46	52	43	38
Week 12						
n	51	43	45	50	35	32
Mean	0.00	0.00	0.07	0.64	0.54	0.75
SD	0.000	0.000	0.447	2.783	2.049	1.723
Median	0.00	0.00	0.00	0.00	0.00	0.00
Min, Max	0.0,0.0	0.0,0.0	0.0,3.0	0.0,17.0	0.0,10.0	0.0,7.0
Week 24						
n	51	39	45	41	28	20
Mean	0.20	0.00	1.53	0.85	4.79	7.80
SD	1.265	0.000	5.806	1.636	13.953	12.340
Median	0.00	0.00	0.00	0.00	0.00	4.00
Min, Max	0.0,9.0	0.0,0.0	0.0,38.0	0.0,7.0	0.0,68.0	0.0,52.0
Week 36						
n	47	37	33	24	17	9
Mean	0.00	0.00	1.36	3.21	2.65	2.67
SD	0.000	0.000	4.547	9.117	8.177	3.742
Median	0.00	0.00	0.00	0.00	0.00	1.00
Min, Max	0.0,0.0	0.0,0.0	0.0,26.0	0.0,41.0	0.0,34.0	0.0,12.0
Week 48						
n	44	36	20	13	7	3
Mean	0.02	0.00	1.75	0.38	2.14	0.67
SD	0.151	0.000	4.940	0.961	5.242	0.577
Median	0.00	0.00	0.00	0.00	0.00	1.00
Min, Max	0.0,1.0	0.0,0.0	0.0,22.0	0.0,3.0	0.0,14.0	0.0,1.0
Week 60						
n	39	30	11	6	2	1
Mean	0.03	0.03	1.91	0.83	0.00	0.00
SD	0.160	0.183	3.270	1.169	0.000	
Median	0.00	0.00	0.00	0.50	0.00	0.00
Min, Max	0.0,1.0	0.0,1.0	0.0,10.0	0.0,3.0	0.0,0.0	0.0,0.0
Total						
n	52	44	45	50	35	32
Mean	0.23	0.02	3.84	3.08	6.09	6.44
SD	1.262	0.151	8.054	8.216	15.424	11.285
Median	0.00	0.00	1.00	0.00	0.00	2.00
Min, Max	0.0,9.0	0.0,1.0	0.0,38.0	0.0,46.0	0.0,68.0	0.0,52.0

IV: intravenous; SC: Subcutaneous; q4W : every 4 weeks; q12w: every 12 weeks, mITT: modified intention to treat.

Additional efficacy analyses

Number and Volume of Gd+ Lesions

The MRI data indicated that all subjects were free of Gd+ lesions at Screening.

The change from baseline in the number and volume of Gd+ lesions during the 60-week randomized treatment period was comparable in the two Q4W treatment arms: 300 mg IV Q4W arm: mean number of Gd+ lesions 0.00, mean volume of Gd+ lesions 0.0000; and 300 mg SC Q4W: mean number of Gd+ lesions: 0.03; mean volume of Gd+ lesions: 0.0018.

However, during the randomized treatment period, new Gd+ lesions was detected in some subjects by Week 12 in the four Q12W treatment arms, with the mean number of Gd+ lesions ranging from 0.07 to 0.59. The number of Gd+ lesions detected increased through study visits at Week 24 (mean number ranging from 0.66 to 6.00) and Week 36 (mean number ranging from 0.91 to 5.56). The number of subjects analysed in the four Q12W treatment arms decreased over time because of the number of subjects requiring rescue therapy and eventually because of closure of the 4 treatment arms. An increase in the volume of Gd+ lesions was also detected by Week 12 in the 4 closed treatment arms.

Number and Volume of New or Newly Enlarging T2 Hyperintense

The mean numbers of new or newly enlarging T2 hyperintense lesions detected in the two Q4W treatment arms were comparable at each visit during the randomized treatment period; the mean number of lesions by Week 60 in both arms was 0.03. The mean T2 hyperintense lesion volume across the 2 open treatment arms did not vary from baseline.

New or newly enlarging T2 hyperintense lesions were detected by Week 12 in all four Q12W treatment arms, with the mean number of lesions ranging from 0.07 to 0.61. The number of detected lesions increased through Week 24 and Week 36. The number of evaluable subjects in these 4 treatment arms decreased as they met rescue criteria, subsequently leading to closure of these arms.

Proportion of Subjects Relapsing and ARR Over 60- Week Treatment Period

During the randomized treatment period, approximately 14% of subjects in the mITT population had at least 1 protocol-defined relapse, as identified by the Investigator.

In total there were 40 relapses across all 6 treatment arms: 300 mg IV Q4W: 4 relapses (1 per subject); 300 mg SC Q4W: 4 relapses (1 per subject); 300 mg IV Q12W: 8 relapses (1 per subject); 300 mg SC Q12W: 10 relapses (1 per subject); 150 mg IV Q12W: 11 relapses (9 subjects with 1 relapse each, 1 subject with 2 relapses); 150 mg SC Q12W: 3 relapses (1 per subject).

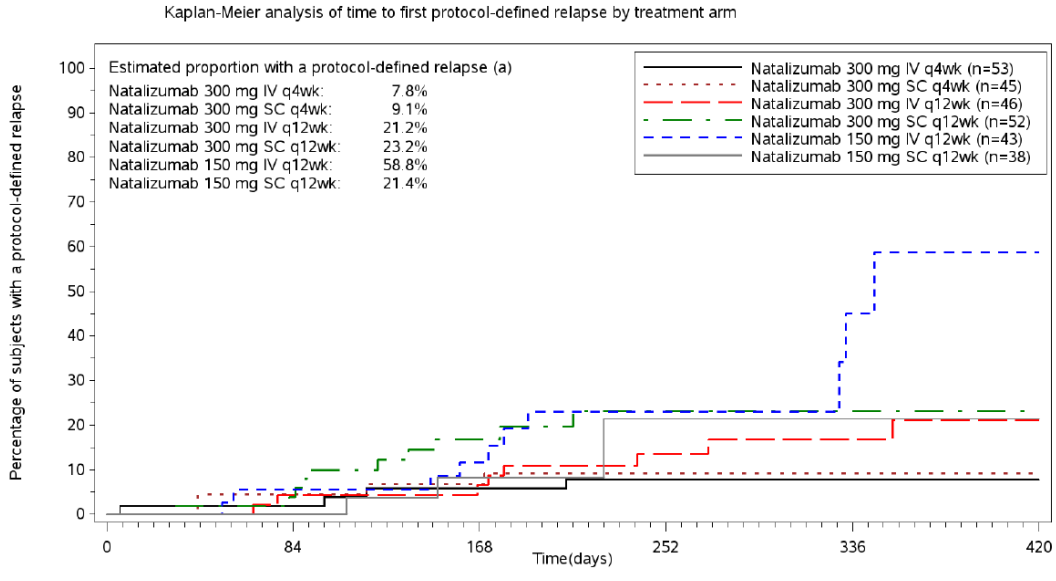
The unadjusted ARR in the two Q4W arms was comparable: 300 mg IV Q4W arm: 0.07; 300 mg SC Q4W: 0.08. The subject-level mean ARR in the two Q4W arms were as follows: 300 mg IV Q4W arm: 0.07 and 300 mg SC Q4W arm: 0.24. Although each of the Q4W arms had 4 relapses (1 relapse per subject), 1 subject in the 300 mg SC Q4W arm had a relapse by Day 42 followed by rescue on Day 57 of the randomized treatment period, which led to a higher subject-level mean relapse rate than in the 300 mg IV Q4W treatment arm.

Time to First Protocol-Defined Relapse by Week 60

Based on the Kaplan-Meier estimate of the time to first protocol-defined relapse by treatment arm (Figure 4), the proportions of subjects with protocol-defined relapses at the Week 60 Visit in the two Q4W arms was comparable: 300 mg IV Q4W arm: 7.8%; and 300 mg SC Q4W: 9.1%.

The proportions of subjects with protocol-defined relapses at the Week 60 Visit in the four Q12W treatment arms were as follows: 300 mg IV Q12W: 21.2%; 300 mg SC Q12W: 23.2%; 150 mg IV Q12W: 58.8%; and 150 mg SC Q12W: 21.4%.

Figure 4: Kaplan-Meier analysis of time to first protocol-defined relapse by treatment arm.



Number of subjects at risk(b)

Natalizumab 300 mg IV q4wk	53	51	48	46	43	37
Natalizumab 300 mg SC q4wk	45	41	40	38	38	31
Natalizumab 300 mg IV q12wk	46	44	43	30	22	9
Natalizumab 300 mg SC q12wk	52	48	34	18	10	3
Natalizumab 150 mg IV q12wk	43	33	26	13	5	2
Natalizumab 150 mg SC q12wk	38	32	18	4	3	1

(a) Kaplan-Meier estimate of the proportion of subjects with a protocol-defined relapse at 420 days.
(b) On days other than Day 420, the number at risk is the number of subjects who were still in the study and did not have the event at the end of the specified time. On Day 420, the number at risk is the number of subjects who were censored on Day 420.

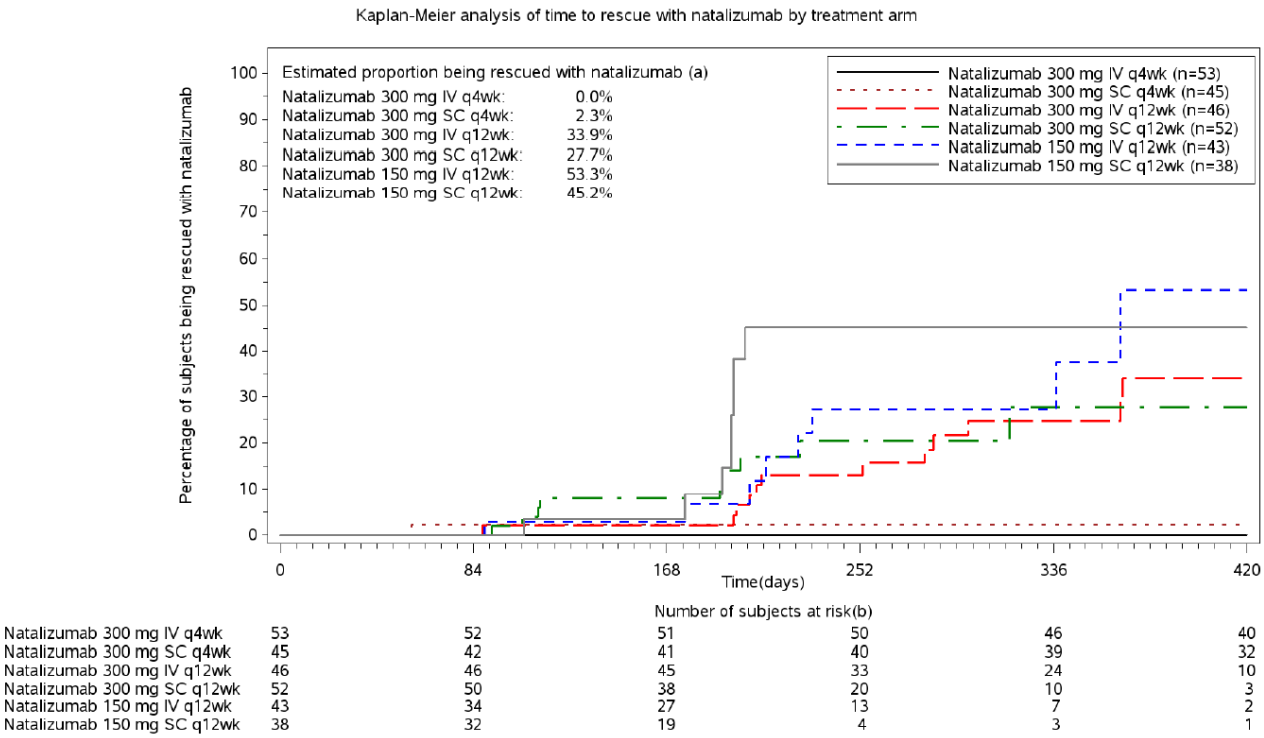
Proportion of Subjects Requiring Rescue Treatment

Overall, 90 of 277 subjects (32%) in the mITT population met the rescue criteria during the randomized period. Of 277 subjects, 39 (14%) had a protocol-defined relapse, 41 (15%) had an MRI meeting Gd+ rescue criteria, 23 (8%) had an MRI meeting T2 hyperintense lesion rescue criteria, and 9 (3%) had a sustained EDSS progression that met rescue criteria. Note: participants can meet more than one criterion.

The Kaplan-Meier estimate of the proportion of subjects requiring rescue with natalizumab by the Week 60 Visit in the 300 mg SC Q4W arm was 2.3% (Figure 5). No subjects were rescued in the 300 mg IV Q4W arm.

The Kaplan-Meier estimates of the proportion of subjects requiring rescue treatment with open-label natalizumab by the Week 60 Visit in the four Q12W treatment arms were: 300 mg IV Q12W arm: 33.9 %; 300 mg SC Q12W: 27.7%; 150 mg IV Q12W: 53.3%: and 150 mg SC Q12W: 45.2%.

Figure 5: Kaplan-Meier Analysis of time to rescue with Natalizumab by treatment arm.



(a) Kaplan-Meier estimate of the proportion of subjects being rescued with natalizumab at 420 days.
(b) On days other than Day 420, the number at risk is the number of subjects who were still in the study and did not have the event at the end of the specified time. On Day 420, the number at risk is the number of subjects who were censored on Day 420.

Time to First MRI That Met Rescue Criteria by Week 60

The Kaplan-Meier estimate of the proportion of subjects who met the MRI rescue criteria at the Week 60 Visit was 2.0% in the 300 mg IV Q4W arm; no subjects in the 300 mg SC Q4W arm had an MRI that met the rescue criterion during the randomized treatment period.

Based on the Kaplan-Meier estimate, the proportions of subjects that met the MRI rescue criteria by the Week 60 Visit in the four Q12W treatment arms were as follows: 300 mg IV Q12W: 43.5%; 300 mg SC Q12W: 48.6%; 150 mg IV Q12W: 52.8%; and 150 mg SC Q12W: 70.3%. The 150 mg SC Q12W arm was the first one to be closed because of a clinically meaningful number of subjects who met the MRI rescue criteria as compared with the standard natalizumab dosing arm (300 mg IV Q4W).

Change in EDSS From Baseline Through Week 60

The mean change in the EDSS score from baseline through Week 60 was stable and comparable in the two Q4W treatment arms: -0.16 for the 300 mg IV Q4W arm and -0.04 for the 300 mg SC Q4W arm.

There was little change in the mean EDSS score over time during the randomized period for the subjects remaining in the four Q12W treatment arms.

Sustained EDSS Progression at Week 60

The small proportion of subjects who showed sustained EDSS progression by Week 60 was comparable in the two Q4W arms: 5.9% in the 300 mg IV Q4W arm and 4.8% in the 300 mg SC Q4W arm.

In the four Q12W treatment arms, the number of evaluable subjects decreased over time. As a result, of the small number of subjects remaining in these arms through Week 60, no subject demonstrated sustained EDSS progression.

Change in Subject Assessed Well-Being (VAS) From Baseline Through Week 60

The mean VAS scores ranged from 69.1 to 77.8 across all 6 treatment arms during the randomized treatment period; in general, mean VAS scores were lower (lower quality of life) than the baseline value across all treatment arms.

The mean (median) change from baseline in the VAS score at Week 60 was comparable in the two Q4W treatment arms: 300 mg IV Q4W: -4.1 (-3.0); 300 mg SC Q4W: -4.5 (-3.0).

Change in SDMT From Baseline Through Week 60

During the randomized treatment period, the mean SDMT scores at baseline across all treatment arms ranged from 42.9 to 47.4.

In the two Q4W treatment arms, the mean change in the SDMT score from baseline to the Week 60 Visit was comparable and indicated a higher score on the SDMT: +6.3 in the 300 mg IV Q4W arm and +6.8 in the 300 mg SC Q4W arm.

The SDMT scores for the four Q12W treatment arms varied because as the treatment arms closed prematurely and the number of evaluable subjects in these arms decreased through Week 60.

Ancillary analyses

NA

Summary of main study(ies)

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

Table 10: Summary of Efficacy for trial 101MS206 (REFINE)

Title: REFINE		
Study identifier	101MS206	
Design	Phase 2, multicenter, randomized, blinded, prospective, parallel-group study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	60 weeks not applicable 12 weeks
Hypothesis	Exploratory: safety efficacy and tolerability	
Treatments groups	300mg SC Q4W	Tysabri 300mg Q4W SC n=45
	300mg IV Q4W	Tysabri 300mg Q4W IV n=54

Endpoints and definitions	Primary endpoint	CUA lesions	Cumulative number of CUA (detectable new Gad+ lesions and new or newly enlarging T2 hyperintense) MRI lesions	
	Secondary endpoint	ARR	ARR over the 60-week duration	
	Secondary endpoint	Proportion of subjects Relapsing	Participants with protocol-defined relapses at the week 60 Visit	
	Secondary endpoint	Sustained EDSS worsening	Participants with sustained EDSS worsening	
Database lock	21 October 2014			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat defined by the Applicant as all randomised participants who received at least 1 dose of study treatment, had at least 1 efficacy assessment used for all efficacy analyses and no major protocol deviations.			
Descriptive statistics and estimate variability	Treatment group		300mg SC Q4W	300mg IV Q4W
	Number of subject		45	54
	Cumulative number of CUA		0.02 (SD=0.151)	0.23 (SD=1.262)
	ARR		0.08	0.07
	Proportion of subjects Relapsing		9.1	7.8
	Sustained EDSS worsening		4.8%	5.9%
Effect estimate per comparison	Primary endpoint		No formal comparisons were done	
	Secondary endpoints		No formal comparisons were done	

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

NA

Clinical studies in special populations

NA

Supportive study(ies)

NA

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In order to support the SC route of administration the Applicant presented data from two clinical studies: 101MS102 and 101MS2016.

The population analysed in the two studies included RRMS and SPMS patients. Regarding RRMS patients, patients included in Study 101MS102 had a diagnosis of a relapsing form of MS and fall within the therapeutic indication stated in the locally approved label for Tysabri with a baseline EDSS score between 0.0 and 6.5,

inclusive. Regarding RRMS patients, patients included in Study 101MS2016 had received previously IV natalizumab for at least 12 months and were free from relapse for 12 months prior to randomization. This information was specified in section 5.1 of SmPC. Overall, based on the patient selection criteria, the analysed populations were considered sufficiently sensitive and representative for the target population.

The choice of endpoints (e.g. EDSS, ARR, MRI lesions) was in line with Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev. 2).

Study 101MS102 was an open-label study, which was primarily designed to evaluate the safety, PK, and PD properties of natalizumab. It was not powered to detect any differences between the IV and SC routes of administration in either the SPMS or RRMS population or within the study populations over time. Moreover, efficacy endpoints in study 101MS102 were only exploratory. This limitation has been reflected in section 5.1 of the SmPC.

Study 101MS206 was a phase 2, multicenter, randomized, blinded, prospective, parallel-group study evaluating the safety, tolerability, and efficacy of multiple regimens of natalizumab over a 72-week period in patients with RRMS who had previously received IV natalizumab for at least 12 months and who were free of MS relapse for 12 months prior to randomization. The rational for Study 101MS206 was to explore whether the efficacy of natalizumab treatment could be maintained with longer treatment intervals. The dosing intervals were chosen based on the observation that efficacy was maintained for 12 weeks despite treatment interruption in patients who previously were stable on natalizumab 300 mg IV Q4W. In order to provide information on the potential utility of dosing regimens associated with lower overall natalizumab exposure levels, this study explored the safety, tolerability, and clinical effects of 2 lower-dose regimens administered Q12W that were predicted to provide a range of α4 integrin binding metrics throughout the dosing interval. The study explored both SC and IV routes of administration, but it was also not primarily designed to compare the efficacy of IV vs SC administration. The primary endpoint for this study was the cumulative number of CUA MRI lesions (detectable new Gad+ lesions and new or newly enlarging T2 hyperintense lesions). Although both studies included SC formulation arms, they were originally not designed to demonstrate equivalence in clinical efficacy of the 300 mg SC Q4W regimen compared to the approved 300 mg IV Q4W regimen and were hence not powered for such comparison. This resulted in relatively low number of patients exposed to the target 300 mg SC regimen that could compromise the overall evidence for the non-inferiority of the SC regimen. This limitation has been reflected in the section 5.1 of the SmPC

Study 101MS102 was an open-label study. In the light of the original trial objectives this could be acceptable. However, given the role the study on the comparison of IV and SC administration in this MA extension, this could not be considered optimal. A blinded approach would have been highly preferable to minimize bias. Study 101MS206 was blinded for treatment but not for route of administration. In the light of minimizing bias in the comparison of IV and SC, blinding patients and study site staff also to the route of administration might have been preferable. However, double-injections (IV+SC) in order to maintain blinding to the route of administration would have increased patient burden. This must be weighed against the possible advantages of complete blinding. Since the examining neurologist was required to be blinded to both, dose and route of administration, the influence on efficacy assessments may be considered negligible for efficacy analyses.

With regard to statistics, it must be noted that all analyses were defined *post-hoc*. This was considered problematic. Additionally, only mean values according to administration were provided. No differences in means were given and the uncertainty of estimates as e.g. given by CIs was also not provided. This was not endorsed. Moreover, the primary analyses were conducted in a mITT set excluding protocol deviations which might affect statistical analyses.

Efficacy data and additional analyses

Efficacy results were highly comparable between the Q4W IV and SC groups of both studies. Only few new active Gad+ lesions and new or enlarging T2-hyperintense lesions occurred in Q4W IV and SC patients. The absolute numbers of lesions was also highly similar. A highly similar efficacy was also found for all secondary efficacy measures, including time-to-first relapse, change in EDSS, and change in SDMT.

However, as discussed before, these findings have to be handled with caution, given that the analyses were not powered for such direct comparison of the two alternative (IV vs. SC) 300 mg Q4W regimens and may therefore not be sufficiently sensitive to conclude on the efficacy of the alternative SC treatment regimen.

Additional information was requested with regard to specific differences of the data of the mITT set provided, compared to a proper PP population, which would be considered most sensitive to observe differences of the routes of administration. The Applicant provided additional data on the two analyses sets. However, it was not completely clarified whether additional patients to the one who experienced PML might have deviated from the protocol and should have been excluded from the per protocol set. Albeit some remaining uncertainties regarding differences of the mITT and the PP population, this issue was not pursuit further, given the general trend of improved efficacy in the SC group.

Additional analyses were also requested with regard to means and CIs per route of administration and differences between routes of administration including confidence intervals. The question was only incompletely answered by the MAH as data for study 101MS102 were only provided as tabular listings of descriptive statistics, and since data on key secondary endpoints were not provided for study 101MS206. However, given the trend to superior efficacy in SC as compared to IV, the provided data provides sufficient reassurance of a non-inferior efficacy for SC. In this light, further discussions would be overall beneficial but were suspended. The issue was therefore not further pursued, and it was concluded that the overall clinical database, especially if read in conjunction with the PK/PD analyses, argues for a non-inferior efficacy of the natalizumab 300 mg SC Q4W regimen compared to the 300 mg IV Q4W regimen.

2.5.4. Conclusions on the clinical efficacy

The lack of prospectively planned phase III studies and respective efficacy analyses as well as the only small patient number treated with the target dose and regimen of 300 mg SC Q4SW could compromise the overall evidence for the non-inferiority of the SC regimen.

Upon request, the Applicant provided additional data and analyses on the two analyses sets as well as additional data including means and CI per route of administration and differences between routes of administration including CI. The responses were critically assessed. Overall, albeit some shortcomings of the additional data presented, it is concluded that the overall clinical database argues for a non-inferior efficacy of the natalizumab 300 mg SC Q4W regimen compared to the 300 mg IV Q4W regimen.

2.6. Clinical safety

Patient exposure

The safety data package for the SC formulation of natalizumab includes the same 2 completed studies (101MS102 and 102MS206) that were used to demonstrate the PK/PD characteristics and efficacy of the SC formulation (Table 11 and Table 12).

Table 11: Exposure by Treatment Group (Study 101MS102)

Treatment Group (n)	Disease Category	Treatments
Group A (n = 16)	SPMS	Natalizumab 300 mg IV Q4W
Group B (n = 14)	SPMS	Natalizumab 300 mg SC Q4W
Group C (n = 15)	SPMS	Natalizumab 300 mg IM Q4W
Group D (n = 12)	RRMS	Natalizumab 300 mg SC Q4W
Group E (n = 11)	RRMS	Natalizumab 300 mg IV Q4W
Group F (n = 7)	SPMS	Reference group: standard of care in Parts I and II, then natalizumab 300 mg SC Q4W in the follow-up phase

SPMS: Secondary progressive multiple sclerosis; RRMS: Relapsing Remitting; IV: intravenous; SC: Subcutaneous; IM: Intramuscular; Q4W: every four weeks.

Although the study was originally designed to compare the IV, SC, and IM routes of administration for natalizumab, the SC route was selected for continued development and for comparison with the IV route based on a review of the preliminary data, which indicated that accumulation following SC administration was comparable to that observed following IV

Table 12: Exposure by Treatment Group (Study 101MS206)

Treatment Group	n	Treatments
IV Groups	54	Natalizumab 300 mg Q4W for 60 weeks
	52	Natalizumab 300 mg Q12W for 60 weeks
	47	Natalizumab 150 mg Q12W for 60 weeks
SC Groups	45	Natalizumab 300 mg Q4W for 60 weeks

	53	Natalizumab 300 mg Q12W for 60 weeks
	38	Natalizumab 150 mg Q12W for 60 weeks

IV: intravenous; SC: Subcutaneous; Q4W: every four weeks; Q12W: every twelve weeks.

Participants in the treatment groups receiving natalizumab 300 mg or 150 mg at a dosing interval of Q12W had clinically relevant increases in MS disease activity that met the predefined rescue criteria compared with the standard natalizumab dosing group (300 mg IV Q4W). Hence, per DSMC advice, the four Q12W treatment groups were prematurely discontinued during the randomised treatment period.

Adverse events

Common AEs by severity

The incidence of AEs was similar in the SC and IV and most AEs were mild or moderate (Table 13, Table 14 and Table 15).

Table 13: Incidence of AEs (PTs) Occurring in ≥ 10% of Participants by Severity in the SC and IV Groups (Study 101MS102)

	SC Group	**IV Group**
Incidence of mild AEs (all)	**11 (42%)**	**11 (40.7%)**
Mild AEs with incidence ≥ 10%	UTI (5 [19%]) Headache (4 [15%])	UTI (4 [15%]) Headache (3 [11%]) Contusion (3 [11%]) Fall (3 [11%])
Incidence of moderate AEs (all)	**12 (46%)**	**11 (40.7%)**
Moderate AEs with incidence ≥ 10%	Fatigue (4 [15%])	0
Incidence of severe AEs (all)	**1 (4%)**	**4 (15%)**
Severe AEs with incidence ≥ 10%	0	0
Severe AEs (all, < 10%)	Diverticulitis, lumbar radiculopathy, and fatigue	Eye infection, SC abscess, suicide attempt, Holmes tremor, vertigo, asthma, heat exhaustion, neuralgia, and gastroesophageal reflux disease

A participant was counted only once within each PT under highest severity. PTs are presented by decreasing incidence.
AEs: Adverse events IV: intravenous; SC: Subcutaneous.

Table 14: Summary of the Severity of AEs Across the Treatment Groups During the Randomised Treatment Period (Study 101MS206)

Severity	**300 mg IV Q4W**	**300 mg SC Q4W**	**300 mg IV Q12W**	**300 mg SC Q12W**	**150 mg IV Q12W**	**150 mg SC Q12W**	**Total**

N. of participants	54	45	52	53	47	38	289
Mild	23 (43)	16 (36)	22 (42)	23 (43)	18 (38)	9 (24)	111 (38)
Moderate	21 (39)	18 (40)	18 (35)	15 (28)	15 (32)	12 (32)	99 (34)
Severe	4 (7)	3 (7)	1 (2)	3 (6)	1 (2)	1 (3)	13 (4)
Total	48 (89)	37 (82)	41 (79)	41 (77)	34 (72)	22 (58)	223 (77)

Numbers in parentheses are percentages. The safety population is defined as all participants who received at least 1 dose of study drug in the randomised treatment period and have at least 1 postbaseline assessment of any safety parameter.
AEs: Adverse events IV: intravenous; SC: Subcutaneous. Q4W: every four weeks; Q12W: every twelve weeks.

The 13 participants (4%) with severe AEs during the randomised treatment period presented with the following:

- 300 mg IV Q4W group - 4 participants (7%): PML and immune reconstitution inflammatory syndrome (IRIS), depression, neuralgia, and epilepsy.
- 300 mg SC Q4W group - 3 participants (7%): headache, MS relapse, and coma.
- 300 mg IV Q12W group - 1 participant (2%) had several severe AEs during a hospitalisation. 300 mg SC Q12W group - 3 participants (6%): lung adenocarcinoma metastatic and anxiety, MS relapse, and fall and radius fracture.
- 150 mg IV Q12W group - 1 participant (2%): epilepsy.
- 150 mg SC Q12W group - 1 participant (3%): urosepsis.

Table 15: AEs that occurred in ≥ 5% of participants in the two Q4W treatment groups in Study 101MS206

300 mg SC Q4W	**300 mg IV Q4W**
MS relapse, nasopharyngitis, headache, UTI, fatigue, diarrhoea, pain in extremity, arthralgia, nausea, bronchitis, gastroenteritis, vomiting, depression, abdominal pain, and pain	MS relapse, nasopharyngitis, headache, UTI, fatigue, influenza, diarrhoea, back pain, arthralgia, nausea, pharyngitis, toothache, oral herpes, and cough

AEs: Adverse events; IV: intravenous; SC: Subcutaneous; Q4W: every four weeks; UTI: Urinary Tract Infection.

Infections

Infections that are known to have a causal association with natalizumab are PML and herpes infections.

Study 101MS102

Overall, infections were reported in 12 participants (46%) in the SC group and in 14 participants (52%) in the IV group during Parts I and II (Table 16). There were no reports of PML or herpes infections.

There was no specific pattern in the events in reference to a particular infection in the body. Urinary tract infections (UTIs) were the most commonly reported events (11 participants [20.8%] overall; 6 participants [23%] and 5 participants [18.5%] in the SC and IV groups, respectively). The other infections reported in more

than 1 participant overall were nasopharyngitis (5 participants [9%]), influenza (3 participants [6%]), and candidiasis, upper respiratory tract infection (URTI), gastroenteritis, laryngitis, pharyngitis, and vulvovaginal mycotic infection (2 participants [4%] each). In Parts I and II, 2 participants in the reference treatment group had infections: 1 participant had influenza, and 1 participant had an URTI. None of the infections were serious (SAE) in any treatment group (Table 16).

In the Follow-Up Treatment Extension Phase, 20 participants (53%) overall reported infections. The incidence of infections was slightly higher in the Follow-Up Treatment Extension Phase, although the reported AEs were similar to those in Parts I and II. Infections occurring in more than 2 participants overall were URTI (5 participants [13%]), UTI (5 participants [13%]), herpes zoster (3 participants [8%]), and sinusitis (3 participants [8%]) (Table 16).

Table 16: Infections Reported During Parts I and II (Study 101MS102)

	SC Group	**IV Group**
Number of participants	26	27
Number of participants with AE	12	14
Number of participants with SAE infection	0	0
Reported PTs	UTI (6) Gastroenteritis (2) Nasopharyngitis (2) Vulvovaginal mycotic infection (2) Bronchitis (1) Candidiasis (1) Diverticulitis (1) Influenza (1) Laryngitis (1) Pharyngitis (1) URTI (1)	UTI (5) Nasopharyngitis (3) Influenza (2) Abscess limb (1) Candidiasis (1) Eye infection (1) Laryngitis (1) Pharyngitis (1) Sinusitis (1) SC abscess (1) URTI (1)

Numbers in parentheses are the number of participants. A participant was counted only once within each PT.
AE: Adverse Event; SAE: Serious Adverse event; PT: Preferred Terms; UTI: Urinary tract infection; URTI: upper respiratory tract infection; IV: intravenous; SC: Subcutaneous

Study 101MS206

A total of 131 participants (45%) had infections during the study. The most commonly reported infections (≥ 5% of participants) were nasopharyngitis (17%), UTI (9%), and influenza (6%). The other AEs included pharyngitis, bronchitis, herpes zoster, and herpes virus infection.

- There were 5 participants who reported 5 SAEs of infections including one natalizumab-associated PML case in a patient with anti-JCV antibody positive who already received Natalizumab for more than 24 months.

Immunogenicity and Incidence of Anti-Natalizumab Antibody Formation

In accordance with the Agency's guidance, Studies 101MS102 and 101MS206 evaluated immunogenic responsiveness using semi-quantitative ELISA testing in natalizumab-naïve participants and participants who had received previous natalizumab treatment, respectively.

In the clinical studies, in all indications, approximately 10% of those tested had a positive anti-natalizumab antibody (ADA) titre at least once: approximately 6% of participants had persistently positive titres and the remaining 4% had transient ADA. Persistent ADA are associated with a decrease in the effectiveness of natalizumab and an increased incidence of hypersensitivity reactions and infusion-related reactions.

Study 101MS102

Table 17: Incidence of Anti-Natalizumab Antibodies by Individual Groups (101MS102)

	SPMS IV	SPMS SC	RRMS IV	RRMS SC
Number of subjects dosed	16	14	11	12
Number of subjects evaluated (a)	16 (100)	14 (100)	11 (100)	12 (100)
Number of subjects negative (b)	14 (88)	11 (79)	9 (82)	9 (75)
Number of subjects positive at any time	2 (13)	3 (21)	2 (18)	3 (25)
Number of subjects positive at final evaluation	1 (6)	1 (7)	1 (9)	0
Time of first positive evaluation (weeks) (c)				
0-8	2 (13)	2 (14)	1 (9)	3 (25)
8-32	0	0	1 (9)	0
>32	0	1 (7)	0	0
Mean	5.0	8.0	12.0	8.0
Min, Max	4, 6	6,33	8,16	6,8
Persistently positive (d)	0	1 (7)	0	0

Numbers in parentheses are percentages. Additionally, 5 subjects in SPMS reference group (Group F) received Tysabri SC during the follow-up treatment extension phase. 3 dosed subjects had at least 2 ADA results after the initiation of Tysabri SC and no positive results were observed at any timepoint in this group. (a) Subjects with one or more post natalizumab infusion antibody result. (b) Negative at all post dose results. (c)The percentages are based on the number evaluated. (d) Persistent positive is defined as 2 positive results separated by at least 6 to 12 weeks, with one of the positive results occurring when the subject has received at least 24 weeks of treatment.

Study 101MS206

Immunogenic responsiveness was assessed in this study with a larger randomised and blinded sample size (290 enrolled participants). This study was conducted over a 72-week period to collect data for the comparison of the effect of immunogenicity following IV and SC administration of natalizumab. The occurrence of serum ADA was analysed at Screening and immediately prior to natalizumab infusion at Weeks 12, 24, 36, and 48 and at the Week 60 Visit.

None of the 288 participants tested were positive for ADA at screening. No participants tested positive for ADAs in the 300 mg IV Q4W or 300 mg SC Q4W groups throughout the randomised treatment period. Two participants (1 in the 300 mg IV Q12W group and 1 in the 150 mg IV Q12W group) tested positive results for ADA at Week 12 and Week 24, respectively, and were later confirmed to be persistently positive through Week 60 and through Week 36 (and an unscheduled visit), respectively. Neither of these participants had documented hypersensitivity or efficacy-related AEs relating to ADA (**Table *18***).

Table 18: Percentage of Participants With Anti-Natalizumab Antibodies (Study 101MS206)

	300mg IV Q4W	300mg SC Q4W	300mg IV Q12W	300mg SC Q12W	150mg IV Q12W	150mg SC Q12W
Number of subjects in the safety population	54 (100)	45 (100)	52 (100)	53 (100)	47 (100)	38 (100)
Positive for ADA (a)						
Screening	0/54	0/45	0/52	0/52[1]	0/47	0/38
Week 12	0/51	0/41	1/47	0/48	0/32	0/27
Week 24	0/50	0/39	1/44	0/29	1/23	0/15
Week 36	0/44	0/39	1/28	0/15	1/12	0/3
Week 48	0/43	0/36	1/17	0/8	0/5	0/2
Week 60	0/42	0/35	1/39	0/41	0/37	0/30
Early Term	0/11	0/7	0/8	0/7	0/6	0/6
Unscheduled relapse	0/6	0/7	0/8	0/13	1/11	0/2
Always negative (b)	54/54	45/45	51/52	53/53[1]	46/47	38/38
Persistent positive (c)	0/54	0/45	1/52	0/53	1/47	0/38

(a) Subjects with one or more post natalizumab infusion antibody result. (b) Negative at all post dose results. (c) Persistent positive is defined as 2 positive results separated by at least 6 to 12 weeks, with one of the positive results occurring when the subject has received at least 24 weeks of treatment

[1] One subject did not have a screening anti-natalizumab result (0/52) but tested negative at all subsequent timepoints (always negative 53/53).

Hypersensitivity Reactions

Based on safety data from clinical studies and postmarketing exposure the incidence of hypersensitivity reactions in patients treated with natalizumab monotherapy is approximately 4%, with reactions classified as serious and systemic (e.g., anaphylaxis) occurring at an incidence of < 1%.

Study 101MS102

Only 1 participant (4%) (IV group) had a hypersensitivity reaction (urticaria of moderate severity) in Parts I and II (Table 19). During the Follow-Up Treatment Extension Phase, another participant had an AE that was determined to be a drug hypersensitivity reaction, which was moderate in severity and considered not related to study treatment. This participant had received natalizumab IV during Parts I and II and received 1 further dose of natalizumab without incident.

Study 101MS206

Hypersensitivity reactions occurred in 3 participants including a case of mild urticaria (300mg SC Q4W), a case of moderate dermatitis and mild hypersensitivity (300mg SC Q4W) and another participant with drug hypersensitivity (allergic drug to another medical product) (300mg IV Q4W) (Table 19). Only the moderate dermatitis was considered related to study treatment. Upon analysis of the reported hypersensitivity reactions, the events occurred within the same day of receiving natalizumab and within the first 5 infusions. However, there was insufficient information regarding the time to onset of the events after receiving natalizumab to enable further comment.

Injection and Infusion Reactions Assessments

Study 101MS102

Infusion reactions were defined as AEs occurring within 2 hours after the start of a natalizumab IV infusion. Injection reactions were defined as AEs occurring within 1 hour after a natalizumab SC injection.

Infusion reactions (IV)

In Parts I and II, 7 participants (26%) in the IV group reported events occurring within 2 hours after the start of a natalizumab infusion. These events were ataxia, contusion, infusion site erythema (moderate), infusion site pain (moderate), infusion site pruritus (moderate), headache, loss of proprioception, and urticaria (moderate) (Table 19). No AEs occurred in more than 1 participant. None of these events were severe or serious or resulted in the discontinuation of study treatment, with the exception of the AE of urticaria, which was assessed as moderate in severity but resulted in the participant being withdrawn from the study. No infusion reactions were reported during the Follow-Up Treatment Extension Phase.

Injection reactions (SC)

In Parts I and II, for the SC group, the AEs that occurred within 1 hour of the SC injection in 4 participants (15%) were injection site pain, decreased blood potassium, headache, and menorrhagia (Table 19). In the Follow-Up Treatment Extension Phase, injection site reactions occurred in 6 participants (16%) and included dystonia, folliculitis, gait disturbance, hypertonic bladder, irritability, muscle spasticity, tachycardia, and UTI. None of the AEs that occurred in the Follow-Up Treatment Extension Phase were recurrences of the AEs reported in Parts I and II. None of these events were serious or resulted in the discontinuation of study treatment.

Study 101MS206

Treatment administration reactions were defined as AEs that occurred within 2 hours after natalizumab administration (either IV or SC) or on the same day as an AE for which the start time was missing.

Infusion reaction (IV)

In 3 IV treatment groups, 8 participants (15%) in the 300 mg Q4W group, 8 participants (15%) in the 300 mg Q12W group, and 8 participants (17%) in the 150 mg Q12W group had infusion reactions. The majority were mild in severity and considered not related to study treatment (Table 19). Only 1 severe infusion reaction was reported but was considered not related to study treatment.

Injection reaction (SC)

In 3 SC treatment groups, 11 participants (24%) in the 300 mg Q4W group, 11 participants (21%) in the 300 mg Q12W group, and 8 participants (21%) in the 150 mg Q12W group had injection reactions (Table 19). The majority were mild in severity and considered related to study treatment.

Table 19: Incidence of Infusion Reactions and Hypersensitivity Reaction by Preferred Term During the Randomised Treatment Period (Studies 101MS102 and 101MS206, Safety Population

	Study 101MS102				**Study 101MS206**	
	SPMS IV	**SPMS SC**	**RRMS IV**	**RRMS SC**	**Q4W IV**	**Q4W SC**
N. of subjects	16 (100)	14 (100)	11 (100)	12 (100)	54 (100)	45 (100)
Hypersensitivity	0	0	1 (9)	0	1 (2)	2 (4)
Dermatitis allergic	0	0	0	0	0	1 (2)
Drug hypersensitivity	0	0	0	0	1 (2)	0
Hypersensitivity	0	0	0	0	0	1 (2)

Urticaria	0	0	1 (9)	0	0	1 (2)
Infusion and injection site reactions	4 (25)	3 (21)	3 (27)	1 (8)	8 (15)	11 (24)
Administration site pain	0	0	0	0	0	1 (2)
Anxiety	0	0	0	0	0	1 (2)
Asthenia	0	0	0	0	1 (2)	1 (2)
Ataxia	1 (6)	0	0	0	0	0
Blood potassium decreased	0	1 (7)	0	0	0	0
Constipation	0	0	0	0	1 (2)	0
Contusion	1 (6)	0	0	0	0	0
Depression	0	0	0	0	1 (2)	1 (2)
Fatigue	0	0	0	0	2 (4)	1 (2)
Headache	0	1 (7)	1 (9)	0	2 (4)	2 (4)
Hypersensitivity	0	0	0	0	0	1 (2)
Infusion site erythema	1 (6)	0	0	0	0	0
Infusion site pain	1 (6)	0	0	0	0	0
Infusion site pruritus	1 (6)	0	0	0	0	0
Injection site pain	0	1 (7)	0	0	0	1 (2)
Irritability	0	0	0	0	0	1 (2)
Loss of proprioception	0	0	1 (9)	0	0	0
Melanocytic naevus	0	0	0	0	0	1 (2)
Menorrhagia	0	0	0	1 (8)	0	0
Migraine	0	0	0	0	1 (2)	0
Mood altered	0	0	0	0	0	1 (2)
Multiple sclerosis relapse	0	0	0	0	1 (2)	0
Nasopharyngitis	0	0	0	0	0	1 (2)
Nausea	0	0	0	0	0	1 (2)
Paraesthesia	0	0	0	0	0	1 (2)
Sleep disorder	0	0	0	0	1 (2)	0
Somnolence	0	0	0	0	0	1 (2)

Urinary incontinence	0	0	0	0	0	1 (2)
Urinary tract infection	0	0	0	0	0	2 (4)
Urticaria	0	0	1 (9)	0	0	0
Weight increased	0	0	0	0	1 (2)	0
Antinatalizumab Antibodies persistent positive	0	1(7)	0	0	0	0

NOTE 1: Numbers in parentheses are percentages. 2: A subject was counted only once within each system organ class/preferred term. 3: The safety population is defined as all subjects who received at least 1 dose of study drug in the randomized treatment period and have at least 1 post-baseline assessment of any safety parameter. 4: For Study 101MS102, data are from Part I and II only. For Study 101MS206 data are from the randomized treatment period only.

MS relapse

In studies 101MS102 and 101MS206, MS relapses reported as AEs were either protocol-defined or nonprotocol-defined (see definition on protocol-defined on Clinical efficacy statistical methods section).

Study 101MS102

In this study, five participants out of the 54 participants in the safety set had a relapse (all protocol-defined) (one relapse per participant) including 2 relapses in the SC group (time to first relapse 0-8 weeks and 8-16 weeks) and 3 relapses om the IV group (time to first relapse: 0-8 weeks, 8-16 weeks and 16-24 weeks). In the Follow-Up Treatment Extension Phase, one participant out of the 38 who entered the extension phase had a relapse.

Study 101MS206

During the randomised treatment period, a total of 63 participants (22%) across all treatment groups had at least 1 AE of MS relapse (protocol-defined and nonprotocol-defined):

- 8 participants (15%) in the 300 mg IV Q4W group [4 with protocol-defined relapses]
- 7 participants (16%) in the 300 mg SC Q4W group [4 with protocol-defined relapses]
- 13 participants (25%) in the 300 mg IV Q12W group [8 with protocol-defined relapses]
- 17 participants (32%) in the 300 mg SC Q12W group [10 with protocol-defined relapses]
- 13 participants (28%) in the 150 mg IV Q12W group [10 with protocol-defined relapses]
- 5 participants (13%) in the 150 mg SC Q12W group [3 with protocol-defined relapses]

Based on severity/intensity:

- 26 participants (9%) had a mild MS relapse
- 35 participants (12%) had a moderate MS relapse
- 2 participants (< 1%) had a severe MS relapse

A total of 22 participants prematurely discontinued randomised treatment because they had a MS relapse; 18 of these participants were rescued with open-label natalizumab. Seven of the 22 events of MS relapse remained unresolved.

Serious adverse event/deaths/other significant events

Deaths

There were 2 deaths reported in Studies 101MS102 and 101MS206 (one per study), both assessed as not related to study treatment by the Investigators.

Other serious adverse events

Study 101MS102

No SAEs were reported for any participant in the SC group during Parts I and II. SAEs were reported for 2 participants (7%) in the IV group; neither SAE was considered treatment-related.

In the Follow-Up Treatment Extension Phase, SAEs were reported for 6 participants (16%) overall: 3 participants (11%) who were in the IV group and 3 participants (12%) who were in the SC group in Parts I and II. None of the SAEs were considered treatment-related.

Study 101MS206

During the randomised treatment period, 23 of 289 participants (8%) had an SAE. The 23 participants reported 27 SAEs. Most SAEs (19 of 27 SAEs [70%]) were considered not related to natalizumab. A total of 6 serious MS relapse events were reported. These SAEs were reported more frequently in the 300 mg IV Q4W group compared with the 300 mg SC Q4W group, although the majority of SAEs (79%) in the IV group were considered not related to natalizumab.

Laboratory findings

Study 101MS102

Haematology Results

Overall, all treatment groups had shifts to either high or low values for a number of haematology parameters. However, there were few clinically significant changes. The majority of participants who had shifts to high or low values had normal values at baseline.

Shifts to high values were recorded for white blood cells (WBC) and lymphocyte counts. However, only 1 participant in the SC group had a change of sufficient clinical significance to be regarded as an AE: increased lymphocyte count that was assessed as mild in severity.

Blood Chemistry Results

Overall, all treatment groups had shifts to either high or low values for a number of blood chemistry parameters. Although there were few clinically significant changes, 2 participants in the IV group and 1 participant in the SC group had changes of sufficient clinical significance to be regarded as AEs. The 2 participants in the IV group had AEs of decreased blood sodium (1 mild and 1 moderate in severity). One participant in the SC group had an AE of decreased blood potassium (mild in severity).

Urinalysis Results

Few abnormalities were noted, but none of them were considered clinically significant by the Investigator.

Study 101MS206

Haematology Results

Since the participants in this study were on a 300 mg Q4W dosing regimen of natalizumab for the 12 months prior to enrolling in the study, the mean and median values for each haematology parameter at baseline were similar across the treatment groups.

During the randomised treatment period, the shift in WBC counts to high values was similar in the two Q4W treatment groups: 5 of 44 participants (11%) in the 300 mg IV Q4W group and 3 of 38 participants (8%) in the 300 mg SC Q4W group. The lymphocyte count and percent shift from baseline to high values were also similar in the 300 mg IV Q4W and 300 mg SC Q4W groups. For the red blood counts, 9% of participants in the 300 mg IV Q4W group and 6% of participants in the 300 mg SC Q4W group had a shift from baseline to low values. For haemoglobin count, 8% of participants in the 300 mg IV Q4W group and 3% of participants in the 300 mg SC Q4W group had a shift from baseline to low values.

A few clinically significant haematology changes were reported as AEs (SOC: Blood and lymphatic system disorders):

- Anaemia (4% of participants in the 150 mg IV Q12W group)
- Iron deficiency anaemia (2% of participants in the 300 mg IV Q4W group)
- Leucocytosis (3% of participants in the 150 mg SC Q12W group)
- Thrombocytopenia (2% of participants in the 300 mg IV Q12W group)

One participant in the 150 mg IV Q12W group had a moderate AE of abnormal laboratory test.

Blood Chemistry Results

The mean and median values for each parameter at the Baseline and Week 60 Visits were similar and within the normal range across the treatment groups. Shifts to low or high blood chemistry values were observed for most of the parameters; however, no abnormal pattern was observed for any of the blood chemistry parameters.

During the randomised treatment period, the shift from baseline for the liver enzymes (aspartate transaminase and alanine transaminase) was towards high values; however, these shifts were not considered AEs. The shifts to high blood glucose values were observed across all treatment arms, and the number of participants with shifts to high glucose values was similar in the 2 Q4W groups: 7 of 47 participants (15%) in the 300 mg IV Q4W group and 6 of 37 participants (16%) in the 300 mg SC Q4W group. Prolonged exposure to corticosteroids (used for the treatment of MS symptoms) is known to increase blood glucose levels [Liu 2013]. A shift to low blood glucose values was also reported across all treatment groups.

Urinalysis Results

Urinalysis was not done in this study.

Safety in special populations

NA

Safety related to drug-drug interactions and other interactions

NA

Discontinuation due to adverse events

Study 101MS102

In Parts I and II, no participants were discontinued from the SC groups due to AEs. In the IV group, 1 participant discontinued and later withdrew from the study due to an AE of urticaria that was considered related to study treatment. One participant in the SC group became pregnant and was no longer permitted to participate in the study.

In the SC group, one participant was withdrawn from the study after 6 doses of study treatment for being persistently positive for ADA. Similarly, another participant in the IV group was withdrawn from the study after 4 doses of study treatment for being positive for ADA; however, this participant did not meet the criteria for being persistently positive for ADA.

In the Follow-Up Treatment Extension Phase, 1 participant in the IV group was withdrawn from the study due to healthy issues unrelated with the study and finally died.

Study 101MS206

The most common reasons for discontinuation in the 300 mg IV Q4W treatment group were withdrawal of consent (6 participants), AEs (3 participants), and other reasons (2 participants). Among the 10 of 45 participants (22%) who prematurely discontinued randomised treatment in the 300 mg SC Q4W treatment group, the most common reasons for discontinuation were AEs (3 participants), withdrawal of consent (2 participants), Investigator decision (2 participants), rescue with open-label natalizumab infusion (1 participant), and other reasons (2 participants). The proportion of participants who discontinued the randomised treatment period in the 300 mg SC Q4W treatment group (22%) was similar to the proportion of participants who discontinued the randomised treatment period in the 300 mg IV Q4W treatment group (20%).

During the randomised treatment period, 32 participants discontinued study treatment due to AEs. Of these, 22 participants discontinued from the randomised treatment period prematurely because they had an MS relapse, and 18 of these were rescued with open-label natalizumab. Seven of the 22 events of MS relapse remained unresolved.

Ten participants had events other than MS relapse that led to the discontinuation of randomised treatment. The reasons included PML, gait disturbance, MRI inflammatory activity, neoplasia, intestinal perforation, epileptic seizures/epilepsy and coma. With the exception of case of PML (300mg IV Q4W) and the case of coma (300 mg SC Q4W) all other events were considered not related to study treatment. Except for the case of coma and epilepsy (150 mg IV Q12W), all events were resolved.

Post marketing experience

Based on the marketing data, the estimated worldwide patient exposure to natalizumab IV is 88,168 PY of treatment in the current reporting interval (8 August 2018 to 7 August 2019) and 752,162 PY cumulatively since launch. An evaluation of the postmarketing experience for natalizumab IV is provided in the PSUR (PSUR 34, data cut-off 7 August 2019).

2.6.1. Discussion on clinical safety

The most obvious shortcoming of the two studies is the only small number of patients who were treated with the target dose and regimen of 300 mg natalizumab SC Q4W. This leads to limitations in the validity of data.

However, both administration regimens were tolerated and no relevant differences in the type and incidence of AEs and SAEs between the SC and IV route of administration were found. The most commonly reported disorders were infections and infestations (nasopharyngitis, UTI, and influence), nervous system disorders (MS relapse, headache, and paraesthesia), gastrointestinal disorders (diarrhoea, nausea, and vomiting), musculoskeletal disorders (back pain, pain in extremity, and arthralgia), general disorders and administration site conditions (fatigue, injections site pain, pyrexia), and psychiatric disorders (depression, insomnia, and anxiety). Overall, AEs reported were consistent with AEs commonly reported in natalizumab trials and in the post-marketing setting.

There were no specific patterns in the occurrence of SAEs that would suggest a difference between the SC and IV routes of natalizumab administration.

There was no clinically meaningful increase in potentially immune-mediated AEs, such as hypersensitivity reactions and, for the SC route of administration compared with the IV route. There were few hypersensitivity reactions. Most events were of mild to moderate severity and were localized (e.g., urticaria, dermatitis). The incidence was not increased with SC administration and was in the range what was seen in natalizumab phase III studies exploring the 300 mg IV Q4W regimen. Nevertheless, this was based on few number of patients so the following statement has been added to section 4.8 of the SmPC "*Hypersensitivity reactions usually occurred within one hour after completion of the subcutaneous injections*. *The number of patients analysed in the DELIVER and REFINE studies was low (see sections 5.2 and 5.1, respectively*)".

The number of ADA was slightly higher in patients in the SC groups. Upon request, the frequencies and absolute numbers of patients with ADA for the SC route of administration were included in section 4.8 of the SmPC for subjects persistently positive and for subjects in whom antibodies were detected only on one occasion. Also, with regard to infusion/injection reactions, the number of events was slighter higher in the SC group in study 101MS206. During the procedure, section 4.2 of the SmPC was updated to reflect that "*patients are to be observed during the subcutaneous injections and for at least 1 hour after for signs and symptoms of injection reactions including hypersensitivity. For the first 6 doses, patients should be observed during the injection and for 1 hour after for signs and symptoms of injection reactions including hypersensitivity. After that, regardless of the route of administration, the 1-hour post-injection observation time may be reduced or removed according to clinical judgement if the patients have not experienced any injection reactions".* However, the types of reactions classified as injection reactions were quite variable and not in all cases the reported AEs could plausibly be related to the administration of natalizumab. Moreover, in study 101MS102 the incidence of injection reactions after SC administration was lower than the incidence of infusion reactions following IV administration. Hence, across trials, the incidence of infusion/injection reactions following the IV vs. the SC route was highly similar. However, due to the only small numbers analysed, the immunogenicity potential of subcutaneously administered Tysabri (anti-natalizumab antibody formation resulting in a potential adverse clinical consequence of serious hypersensitivity reactions, including anaphylaxis) is currently incompletely characterized and hence added as missing information in the RMP. In this regard, the Applicant committed to evaluate this aspect through a new post-authorisation safety study (PASS) category 3 (see section 2.7).

There was one case of PML in the 300 mg IV Q4W treatment group in study 101MS206, and no case of PML in the SC groups. However, patient numbers were too small to draw any conclusion about the PML risk with SC administration of natalizumab. EID that have been identified as effective in mitigating the PML risk associated

with IV administration of natalizumab have not been evaluated for the SC route. In this respect, the Applicant was requested to provide additional modelling and simulations. These analyses demonstrated that EID C_{trough_ss} and α4-integrin saturation are unlikely to differ significantly between the IV and SC routes of administration. Based on these analyses, the Applicant concluded that the effects of EID, irrespective of the route of administration, would be similar for established PML risk factors. However, as long as the absolute risk of PML with the SC route has not been established, it is not possible to draw clear conclusions whether this risk would be lowered through an extension of the SC dosing interval. The question could therefore not finally be answered, and additional data need to be collected. This should be done through patient registries. No recommendation regarding EID could yet be made for patients treated via the SC route. Upon request, the Applicant agreed to include clear information to the SmPC and to the educational materials in order to state that the information on EID and the decrease in PML risk is currently based on IV data only and may not be extrapolated to the SC route. The inclusion of a clear statement in both, SmPC and educational materials, was found deemed necessary since the potential of EID for lowering the risk of PML has not been established yet, while on the other hand, the efficacy of EID has also not been established. Without specific language on this lack of information for the SC treatment regimen, treating physicians may tend to treat patients with an SC EID regimen, although the benefit of such an extension is questionable while on the other hand there still is some risk for a reduced efficacy with EID. Consequently, the following warning is added to section 4.4 in the SmPC "*The decrease in PML risk is based on data from intravenous route of administration. No clinical data are available on either the safety or efficacy of this extended interval dosing with subcutaneous route of administration*" while the following statement can be found in section 5.1 of the SmPC: "*No clinical data are available on either the safety or efficacy of this extended interval dosing with the subcutaneous route of administration".*

During the procedure, the Applicant agrees to amend the NOVA study protocol in order to further study safety and efficacy of an EID SC treatment regimen. The SC and IV periods of the crossover will each be of 24-week duration, and trough PK/PD will be collected prior to each dose in the cross-over period in order to allow for direct observations of steady state PK/PD following IV an d SC doses administered Q6W with comparisons between routes of administration utilising within patient controls. This approach was endorsed.

During the procedure, the Applicant proposed to amend the section 4.2 of the Tysabri (subcutaneous use) SmPC as follows "*Therapy is to be initiated and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions, ~~in centres~~ with timely access to MRI. Administration is to be performed by a healthcare professional and patients monitored for early signs and symptoms of PML".* Interpreted as that this proposal allows flexibility to administer Tysabri not only in specialized centers but also in other medical settings, this proposal was agreed by the CHMP. Indeed, the key aspect is that patients treated with Tysabri are very closely monitored and examined for signs and symptoms of PML by a neurologist who is experienced in this field (e.g in a specialized center or in another medical setting as for example in an infusion center), at least prior to each infusion/injection, in order to detect such signs as early as possible and be able to introduce effective therapy.

The section 4.2 of the Tysabri subcutaneous SmPC was amended to include the statement that "home treatment is not recommended" At-home treatment would considerably reduce the number of contacts between a patient and his/her treating neurologist. Close monitoring through a neurologist experienced in the treatment of MS is considered key in reducing the risk of PML. This can be accepted.

There were no apparent clinically meaningful differences observed in laboratory parameters and in vital signs between the SC and IV routes of administration.

2.6.2. Conclusions on the clinical safety

In studies 101MS102 and 101MS206, both administration regimens have been well tolerated and no relevant differences in the type and incidence of AEs and SAEs have been found.

Although immune-mediated AEs may be a potential concern with SC administration, there was no meaningful increase in hypersensitivity events and the occurrence of persistent ADA, for the SC route of administration compared with the IV route. However, due to the only small numbers analysed, the immunogenicity potential of subcutaneously administered Tysabri is currently incompletely characterized and hence added as missing information in the RMP.

As discussed above, information on EID and the decrease in PML risk is currently based on IV data only and may not be extrapolated to the SC route and therefore, no recommendation regarding EID can be made for patients treated via the SC route. This information was clearly stated in the SmPC (sections 4.4 and 5.1) and in the educational material.

Despite the lack on data on EID and immunogenicity potential of subcutaneously administered Tysabri, the overall safety data derived from 101MS102 and 101MS206 argued for an acceptable safety and tolerability profile of the new formulation.

Note: With regard to the additional monitoring list, the EMA proposed the removal of Tysabri from the additional monitoring list. The current ongoing PASS, as well as the new PASS proposed in this extension of MA, are category 3 studies and the criteria concerning the mandatory inclusion in the list is for imposed PASS. No criterion for additional monitoring (mandatory scope) applies to Tysabri. Therefore, the PRAC agreed to the proposal to remove Tysabri from the additional monitoring list. The MAH has implemented the requested change, see PI.

2.7. Risk Management Plan

Safety concerns

Table 20: Summary of Safety concerns

Important identified risks	• Progressive multifocal leukoencephalopathy (PML) • Serious herpes infections
Important potential risks	• Malignancies
Missing information	• PML risk following switch from disease modifying therapies with immunosuppressant effect • Immunogenicity potential of subcutaneously administered Tysabri (anti-natalizumab antibody formation resulting in a potential adverse clinical consequence of serious hypersensitivity reactions, including anaphylaxis)

PML: Progressive multifocal leukoencephalopathy

Pharmacovigilance plan

Table 21: On-going and planned additional pharmacovigilance activities

Study name and description Study Status	Summary of objectives	Safety concerns 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				
Study IMA-06-02 Tysabri Observational Programme This is an observational study that will use real world data to assess the long-term safety of natalizumab • **<u>Status:</u>** Ongoing	*<u>Study Objectives:</u>* To assess the long-term safety and impact on disease activity and progression of Tysabri (natalizumab) in patients with RRMS in a clinical practice setting	• PML • Serious herpes infection • Malignancies	Annual reporting in the Periodic Safety Update Report	October
			Final report	2024
Study 101MS411 **An observational cohort study utilising data from the US natalizumab TOUCH prescribing program and select EU MS Registries** This study uses multiple registries to assess the risk of PML and OI patients switching from established DMTs • **<u>Status:</u>** Ongoing	*<u>Primary Objective:</u>* To estimate the risk of PML among patients on Tysabri switching from the newer DMTs (including fingolimod, DMF, teriflunomide) and from established DMTs (IFN beta and glatiramer acetate) To estimate the incidence of serious adverse events of other serious opportunistic infections among patients who switch to Tysabri from newer DMTs (including fingolimod, DMF and teriflunomide) and the established DMTs (IFN beta and glatiramer acetate)	• Risk of PML and other serious opportunistic infections in patients switching from DMTs with immunosuppressant effect	Feasibility of including data from the EU utilising existing registries	December 2016
			Annual reporting in the Periodic Safety Update Report	October
			Final report:	Q2 2024

Study name and description Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
PASS to investigate immunogenic potential of SC administration (following approval) An observational study utilizing data from EU national MS registries to estimate the incidence of anti-natalizumab antibody among patients who receive subcutaneous administration of natalizumab for treatment of relapsing remitting multiple sclerosis • **Status:** Planned	*Primary Objective (draft):* • To estimate the incidence of ADA in natalizumab naïve patients who start natalizumab treatment with SC injections *Secondary objectives (draft):* • To estimate the incidence of ADA among patients who switch from natalizumab IV infusion to SC injection • to evaluate serious adverse events including injection reactions and hypersensitivity reactions in association with positive ADA • To assess the incidence of MS relapse in association with positive ADA • To evaluate the difference of the incidence of ADA in patients who receive natalizumab SC Q4W vs Q6W	• Immunogenicity potential of subcutaneously administered Tysabri (anti-natalizumab antibody formation resulting in a potential adverse clinical consequence of serious hypersensitivity reactions, including anaphylaxis)	Study feasibility assessment	Q3 2021

DMF: dimethyl fumarate; DMT: disease modifying therapy; PML: Progressive multifocal leukoencephalopathy; RRMS: relapsing-remitting multiple sclerosis; TOP: Tysabri Observational Programme; IFN: Interferon; TOUCH: TYSABRI Outreach: Unified Commitment to Health: ADA: Antidrug antibodies; SC: Subcutaneous; IV: Intravenous; Q4W: every four weeks; Q6W: every six weeks PASS: Post-Authorisation Safety Study

Risk minimisation measures

Table 22: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Progressive multifocal leukoencephalopathy (PML)	***Routine risk minimisation measures:*** • Information in SmPC Sections 4.3, 4.4, 4.8, and 5.1; and PL Sections 2 and 4. • Legal status: Restricted medical prescription ***Additional risk minimisation measures:*** • Educational tools for HCPs (Physician Information and Management Guideline) • Educational tools for patients/carers (Patient alert card, Tysabri treatment initiation form, Tysabri treatment continuation form and Tysabri discontinuation form)	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • Specific adverse reaction follow-up questionnaire ***Additional pharmacovigilance activities:*** • Study IMA-06-02
Serious herpes infections	***Routine risk minimisation measures:*** • Information in SmPC Sections 4.3, 4.4 and 4.8; and PL Sections 2 and 4. • Legal status: Restricted medical prescription.	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • Specific adverse reaction follow-up questionnaire

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: • None	***Additional pharmacovigilance activities:*** • Study IMA-06-02
Important potential risks		
Malignancies	***Routine risk minimisation measures:*** • Information in SmPC Sections 4.3 and 4.8; and PL Section 2. • Legal status: Restricted medical prescription. ***Additional risk minimisation measures:*** • None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • Specific adverse reaction follow-up questionnaire ***Additional pharmacovigilance activities:*** • Study IMA-06-02
Areas of missing information		
PML risk in patients switching from DMTs with immuno-suppressant effect	***Routine risk minimisation measures:*** • Information in SmPC Section 4.4. • Legal status: Restricted medical prescription. ***Additional risk minimisation measures:*** • None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • None ***Additional pharmacovigilance activities:*** • Study 101MS411
Immunogenicity potential of subcutaneously administered Tysabri (anti-natalizumab antibody formation resulting in a potential adverse clinical consequence of serious hypersensitivity reactions, including anaphylaxis)	***Routine risk minimisation measures:*** • Information in SmPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2 • Legal status: Restricted medical prescription. ***Additional risk minimisation measures:*** • None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** • None ***Additional pharmacovigilance activities:*** • PASS to investigate immunogenic potential of SC administration (following approval)

DMT: Disease modifying therapy; HCPs: Healthcare Professionals; SmPC: Summary of Product Characteristics; PL: Patient Leaflet; PML: Progressive multifocal leukoencephalopathy: PASS: Post-Authorisation Safety Study

Conclusion

The CHMP and PRAC considered that the risk management plan version 27.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the Applicant 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

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

2.9.2. Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Tysabri (natalizumab) is removed from the additional monitoring list as a it does not fulfil any of the criterion for additional monitoring (mandatory scope).

Therefore, the statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, is removed from the SmPC and the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

MS is a chronic autoimmune and neurodegenerative disorder of the CNS that is characterised by inflammation, demyelination, and oligodendrocyte and neuronal loss.

3.1.2. Available therapies and unmet medical need

Natalizumab IV received Marketing Authorisation in the EU on 27 June 2006 as a DMT for treatment of RRMS. From its original approval in the US in 2004 through 31 July 2019, 198,646 individuals have been treated with natalizumab worldwide, with a cumulative exposure of 752,162 person-years.

The Applicant states that an alternative SC route of administration for natalizumab will provide additional benefit to patients and physicians. The SC route represents a more convenient means of administration because it reduces the amount of time required at each treatment visit. There is evidence from other medical conditions and indications that patients prefer SC to IV administration based on convenience [Falanga 2019; Pivot 2013; Santus 2019] and quality of life measures [Syrios 2018]. The SC route is also identified as a cost-saving method of administration when compared with the IV route for patients, hospitals, and clinics, as reduced time and resources are required [Farolfi 2017; Lopez-Vivanco 2017; Olsen 2018].

3.1.3. Main clinical studies

In order to support the 300 mg Q4W SC regimen as an alternative to the currently approved 300 mg Q4W IV route of administration, the Applicant presented efficacy data from 2 clinical studies:

- Study 101MS102 (DELIVER) was a phase 1, randomized, open-label, dose-ranging study to evaluate the PK, PD and safety of single SC and IM doses of 300 mg natalizumab to IV administration of 300 mg natalizumab in subjects with RRMS and SPMS. Efficacy was only a secondary aim for this study. Patients with RRMS had a baseline EDSS score between 0.0 and 6.5, inclusive and had to fall within the therapeutic indication stated in the locally approved label for Tysabri.
- Study 101MS206 (REFINE) was a phase 2, multicenter, randomized, blinded, prospective, parallel-group study evaluating the safety, tolerability, and efficacy of multiple regimens of natalizumab over a 72-week period in patients with RRMS who had previously received IV natalizumab for at least 12 months and were free of MS relapse for 12 months prior to randomization.

3.2. Favourable effects

Since its initial approval in 2006, Tysabri IV has become a well-established treatment option for patients with highly active MS.

Efficacy as monotherapy has been evaluated in one randomised, double-blind, placebo-controlled study lasting 2 years (AFFIRM study) in RRMS patients who had experienced at least 1 clinical relapse during the year prior to entry and had an EDSS score between 0 and 5. Median age was 37 years, with a median disease duration of 5 years. The patients were randomised with a 2:1 ratio to receive Tysabri 300 mg (n=627) or placebo (n=315) Q4W for up to 30 infusions. Neurological evaluations were performed every 12 weeks and at times of suspected relapse. MRI evaluations for T1-weighted Gad+ lesions and T2-hyperintense lesions were performed annually.

In the sub-group of patients indicated for treatment of rapidly evolving RRMS (patients with 2 or more relapses and 1 or more Gad+ lesion), the ARR was 0.282 in the Tysabri treated group (n=148) and 1.455 in the placebo group (n=61) ($p < 0.001$). Hazard ratio for disability progression was 0.36 (95% CI: 0.17, 0.76) p=0.008. These results were obtained from a *post hoc* analysis and should be interpreted cautiously. No information on the severity of the relapses before inclusion of patients in the study is available.

Interim analysis of results (as of May 2015) from the ongoing TOP, a phase 4, multicentre, single-arm study (n=5,770) demonstrated that patients switching from beta interferon (n=3,255) or glatiramer acetate (n=1,384) to Tysabri showed a sustained, significant decrease in ARR ($p<0.0001$). Mean EDSS scores remained stable over 5 years. Consistent with efficacy results observed for patients switching from beta interferon or glatiramer acetate to Tysabri, for patients switching from fingolimod (n=147) to Tysabri, a significant decrease in ARR was observed, which remained stable over 2 years, and mean EDSS scores remained similar from baseline to Year 2. The limited sample size and shorter duration of Tysabri exposure for this subgroup of patients should be considered when interpreting these data.

The efficacy and safety of Tysabri for SC administration was assessed in a randomised, blinded, parallel-group, phase 2 study (Study 101MS206 (REFINE)) exploring the safety, tolerability, and efficacy of multiple regimens of natalizumab (300 mg IV Q4W, 300 mg SC Q4W, 300 mg IV Q12W, 300 mg SC Q12W, 150 mg IV Q12W and 150 mg SC Q12W) in adult subjects (n=290) with RMS conducted over a 60 week period. The primary endpoint of this study was the cumulative number of CUA MRI lesions (sum of new Gad+ lesions on brain MRI and new

or newly enlarging T2 hyperintense lesions not associated with Gad+ on T1 weighted scans). The mean CUA for the 300 mg SC Q4W k arm was low (0.02) and comparable to the 300 mg IV Q4W arm (0.23). The CUA in the Q12W treatment arms was significantly higher than the Q4W treatment arms resulting in the early discontinuation of the Q12W arms.

3.3. Uncertainties and limitations about favourable effects

The application is based on data from the two clinical studies 101MS102 and 101MS2016. These studies were not prospectively planned as comparability studies for the 300 mg SC vs the 300 mg IV treatment regimen and were hence not powered for that direct comparison. This results in a relatively small RRMS population treated with the target dose of 300 mg Tysabri SC.

3.4. Unfavourable effects

Overall, AEs reported were consistent with AEs commonly reported in natalizumab trials and in the post-marketing setting. There were no specific patterns in the occurrence of SAEs that would suggest a difference between the SC and IV routes of natalizumab administration. With regard to infusion/injection reactions, the number of events was slighter higher in the SC group in study 101MS206 and ISR of mild/moderate severity were observed and would be a known risk.

3.5. Uncertainties and limitations about unfavourable effects

Some level of uncertainty results from the relatively low number of patients treated with the target dose of 300 mg SC. While it is not expected that adverse events related to Tysabri's mode of action (most importantly PML) will be increased with a SC treatment regimen, the risk for immunogenicity could potentially be increased by administration via the SC route.No clear signal on an increased risk for immunogenicity has been detected so far but clinical data on the development of ADA is limited.

3.6. Effects Table

Table 23: Effects Table for 300 mg Tysabri SC Q4W for RRMS

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Radiologic efficacy	Cumulative number of CUA MRI lesions	No.	0.02	0.23	Sufficient strength of evidence	101MS206
Clinical efficacy	ARR	No.	0.08	0.07	Sufficient strength of evidence	101MS206
	Participants with protocol-defined relapses at the Week 60 Visit	%	9.1	7.8	Sufficient strength of evidence	101MS206
	Participants with sustained EDSS progression	%	4.8	5.9	Sufficient strength of evidence	101MS206

Unfavourable Effects						
Total AE		%	82	89	Sufficient strength of evidence	101MS206
ISR	101MS102 101MS206	%	15 24	26 15		101MS102 101MS206
PML		No.	0	1	Unc: To be evaluated further	101MS206
ADA	101MS102 101MS206	% %	23 0	15 0	Unc: To be evaluated further	101MS102 101MS206
Hypersensitivity	101MS102 101MS206	%	0 4	9 2	Unc: To be evaluated further	101MS102 101MS206

Abbreviations: CUA: Cumulative Unique Active; ARR : Annualised Relapse Rate; EDSS : Expanded Disability Status Scale; AE: Adverse Effects; ISR: Infusion/Injection Site Reactions; PML: Progressive Multifocal Leukoencephalopathy; ADA: Antidrug Antibodies

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Based on results from studies 101MS102 and 101MS206 the clinical efficacy of subcutaneously administered Tysabri 300 mg given every 4 weeks is highly comparable to the approved IV regimen. The beneficial effects observed (reduction in newly active MR lesions, reduction in progression of disability, reduction in ARR) are considered highly relevant.

The adverse effects observed are comparable with what is known for the established IV regimen. Due to the number of cases, no conclusions about the PML risk with SC administration could be draw. EID that have been identified as effective in mitigating the PML risk associated with IV administration of natalizumab have not been evaluated for the SC route so no recommendation for EID SC could be provided. The incidence of ADA with SC injection is considered not sufficiently characterized yet and should therefore be subject to further investigations.

3.7.2. Balance of benefits and risks

Tysabri IV has been established as a highly efficacious treatment for RRMS. Based on currently available data, and considering PK/PD analyses, the efficacy of 300 mg Tysabri SC Q4W is considered highly comparable to the approved IV regimen.

The most important risk with Tysabri treatment is the occurrence of PML. Due to the rarity of the disease, no cases have been observed in patients treated via the SC route. More importantly, no recommendation regarding EID could be made for patients treated via the SC route. Specific statements were included in the SmPC and educational material to clearly communicate that the information on EID and the decrease in PML risk is currently based on IV data only and may not be extrapolated to the SC route. Due to the only small numbers analysed, the immunogenicity potential of SC administered Tysabri including ADA formation and hypersensibility AEs was incompletely characterized and hence added as missing information in the RMP and will be further characterised in a PASS category 3 study.

Based on these data, the benefit-risk of 300 mg Tysabri SC Q4W is considered positive.

3.8. Conclusions

The overall B/R of Tysabri 150 mg/ml solution for injection for SC administration is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, efficacy and safety, the CHMP considers by consensus that the benefit-risk balance of, Tysabri 150mg, solution for injection in pre-filled syringe, subcutaneous use is favourable in the following indication:

TYSABRI is indicated as single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups:

- Patients with highly active disease activity despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) (for exceptions and information about washout periods see sections 4.4 and 5.1)
  or
- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Tysabri 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 Applicant 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.

Additional risk minimisation measures

Based on how patients treated with Tysabri are currently monitored at national level, the MAH shall discuss and agree with the National Competent Authorities measures to enhance further this monitoring (e.g. registries, post-marketing surveillance studies) as appropriate. The MAH shall implement agreed measures for monitoring within a time frame agreed with the National Competent Authorities.

The educational programme is aimed at educating healthcare professionals and patients/carers of the potential and risk factors for the development of PML, its diagnosis and treatment, and the identification and management of possible sequelae.

The MAH shall ensure that in each Member State where Tysabri is marketed, all healthcare professionals and patients/carers who are expected to prescribe/use Tysabri have access to/are provided with the following educational materials:

- Physician educational materials:
  - Summary of Product Characteristics
  - Physician Information and Management Guidelines
- Patient information pack:
  - Package Leaflet
  - Patient Alert Card
  - Treatment initiation and treatment continuation forms
  - Treatment discontinuation form

These educational materials shall contain the following key elements:

Physician Information and Management Guidelines:

- Background information on the increased risk of atypical/opportunistic infections, in particular PML, which may occur with Tysabri therapy, including a detailed discussion of data (including **epidemiology, aetiology, and pathology**) pertaining to the development of PML in Tysabri-treated patients.
- Information relating to the **identification of risk factors** for Tysabri-associated PML, including details of the PML risk estimates algorithm summarising PML risk by risk factor (anti-John Cunningham virus [JCV] antibody status, prior IS use, and duration of treatment [by year of treatment]), and stratification of this risk by index value when applicable.
- **Information on extending the dosing interval for PML risk mitigation**, including a reminder of the approved dosing schedule. The decrease in PML risk is based on data from IV route of administration. No clinical data are available on either the safety or efficacy of dosing every 6 weeks with SC route of administration.
- Inclusion of **monitoring guidance** for MRI and anti-JCV antibody based on PML risk, including recommended timing, protocols, and interpretation of results.
- Detail regarding the **diagnosis of PML**, including principals, clinical assessment (including MRI and laboratory testing), and differentiation between PML and MS.
- **Management** recommendations in the event of cases of suspected PML, including considerations on the the effectiveness of Plasma Exchange (PLEX) treatment and the management of associated Immune-reconstitution inflammatory syndrome (IRIS).
- Detail on the **prognosis** on PML, including information on improved outcomes observed in asymptomatic PML cases.
- A reminder that irrespective of the presence or absence of PML risk factors, heightened clinical vigilance for PML should be maintained in all patients treated with Tysabri and for 6 months following **discontinuation of therapy**.
- A statement that all data available to characterise PML risk are from the IV route of administration. Considering the similar PD profiles, the same PML risk and relevant risk factors are assumed for different routes of administration.
- A reminder on the need to discuss the benefit-risk profile of Tysabri treatment with the patient, and the requirement to provide the patient information pack.

Patient alert card:

- Reminder to patients to show the card to any doctor and/or caregiver involved with their treatment, and to keep the card with them for 6 months after the last dose of Tysabri treatment.
- Reminder to patients to read the package leaflet carefully before starting Tysabri, and not to start Tysabri if there is a serious problem with their immune system.
- Reminder to patients no to take any other long-term medicines for MS while receiving Tysabri.
- A description of PML, potential symptoms and management of PML.
- A reminder of where to report side effects.
- Details of the patient, treating doctor and date Tysabri was started.

Treatment initiation and treatment continuation forms:

- Information on PML and IRIS, including the risk of developing PML during Tysabri treatment stratified by prior treatment with immunosuppressants and JCV infection.
- Confirmation that the doctor has discussed the risks of PML and the risk of IRIS if treatment is discontinued following suspicion of PML, and confirmation of patient understanding of the risks of PML and that they have received a copy of the treatment initiation form and a patient alert card.
- Patient details and prescriber name.

The treatment continuation form should contain the elements of the treatment initiation form and, in addition, a statement that the risks of PML increase with duration of treatment and that treatment beyond 24 months carries additional risk.

Treatment discontinuation form

- Information for the patient that PML has been reported up to 6 months after stopping Tysabri, and to therefore keep the patient alert card with them after treatment discontinuation.
- Reminder of PML symptoms, and when MRI imaging may be warranted.
- Reporting of side effects.