European Union Risk Management Plan
Tyruko® 300 mg concentrate for solution for infusion
(Natalizumab (PB006))

Risk Management Plan (RMP) version to be assessed as part of this application	
RMP version number	2.0
Data lock point for this RMP	30 Nov 2025
Date of final sign off	05 Jan 2026
Rationale for submitting an updated RMP	This RMP has been updated to: Align with the reference product Tysabri® (natalizumab) RMP v34.0, dated 25 Sep 2025 (Biogen Netherlands B.V.), available on the European Medicines Agency (EMA) website, last updated on 14 Nov 2025.

Summary of Significant Changes in This RMP Version

RMP part/module	High level description of major changes
Part I Product overview	Pharmacotherapeutic group, invented name(s) in the European Economic Area (EEA), brief description of the product, dosage in the EEA and pharmaceutical form and strength have been updated.
Part II - Module SII Non-clinical part of the safety specification	None.
Part II - Module SIII Clinical trial exposure	None.
Part II - Module SIV Populations not studied in clinical trials	None.
Part II - Module SV Post-authorisation experience	Section revised to present data according to the Good Pharmacovigilance Practice (GVP) Module V Revision 2 RMP requirements.
Part II - Module SVI Additional EU requirements for the safety specification	Section revised to present data according to the GVP Module V Revision 2 RMP requirements.
Part II - Module SVII Identified and potential risks	Section revised to present data according to the GVP Module V Revision 2; RMP template requirements and the

RMP part/module	High level description of major changes
	safety concerns have been aligned with the reference product Tysabri® RMP v34.0, dated 25 Sep 2025.
Part II - Module SVIII Summary of the safety concerns	The summary of the safety concerns has been updated to align with the reference product Tysabri® RMP v34.0, dated 25 Sep 2025.
Part III Pharmacovigilance plan (including post-authorisation safety studies)	This section has been revised to align with the GVP module V revision 2 requirements. Malignancies targeted follow up questionnaire (TFUQ) has been removed to align with the reference product Tysabri®.
Part IV Plans for post-authorisation efficacy studies	Section revised to present data according to the GVP Module V Revision 2 RMP requirements.
Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	The summary of the safety concerns has been updated to align with the reference product Tysabri® RMP v34.0, dated 25 Sep 2025.
Part VI Summary of the risk management plan	This section revised to present data according to the GVP Module V Revision 2 RMP requirements and aligned with Part 1, Part II module SVIII.
Part VII Annexes	Annex 4: Progressive Multifocal Leukoencephalopathy (PML)' and 'Herpes infections' TFUQs have been updated and Malignancy TFUQ has been removed to align with the reference RMP Tysabri®. Annex 7: Updated references details. Annex 8: Summary of changes to the risk management plan over time has been updated.

Other RMP versions under evaluation: No other RMP versions are currently under evaluation.

Details of the currently approved RMP	
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Qualified person responsible for Pharmacovigilance (QPPV) Details	
QPPV name:	Dr. Mohamed Ali Kotal
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV/deputy.
QPPV/deputy signature:	I am approving this document as Deputy QPPV on behalf of the EU QPPV.

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List of Abbreviations

Acronym	Definition
AE	Adverse event
ARN	Acute retinal necrosis
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	Area under the curve
CD	Crohn's disease
CD19, CD34, CD4, CD8	cluster of differentiation markers
CHMP	Committee for Medicinal Products for Human Use
CNS	Central Nervous System
CSF	cerebrospinal fluid
CSR	clinical study report
DDD	Defined Daily Dose
DHPC	Direct healthcare professional communication
DMT	Disease Modifying Therapy
DNA	Deoxy ribonucleic acid
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
GVP	Good Pharmacovigilance Practice
HCPs	Healthcare Professionals
HHV	Human Herpesvirus
INN	International Non-Proprietary Name
IRIS	Immune Reconstitution Inflammatory Syndrome
IV	Intravenously

Acronym	Definition
IVIg	intravenous immunoglobulin
JCV	John-Cunningham virus
JCV GCN	John-Cunningham virus -granule cell neuronopathy
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MTR	Magnetisation Transfer Ratio
N	Number of patients in population/treatment group
n	number of patients/subjects
PCR	Polymerase chain reaction
PD	pharmacodynamic
PK	Pharmacokinetic
PL	Package Leaflet
PLEX	plasma exchange
PML	Progressive multifocal leukoencephalopathy
PSUR	Periodic Safety Update Report
PT	Preferred term
PTY	Patient Treatment Years
QPPV	Qualified person responsible for Pharmacovigilance
RMP	Risk Management Plan
RRMS	Relapsing Remitting Multiple Sclerosis
SAF	Safety

Acronym	Definition
SD	Single dose
SmPC	Summary of Product Characteristics
TFUQ	Targeted follow up questionnaire
US	United States
WBC	White Blood Cell

Part I: Product(s) Overview

Table 1 – Part I.1: Product Overview

Active substance (INN or common name)	Natalizumab
Pharmacotherapeutic group (ATC Code)	Immunosuppressants, monoclonal antibodies; Anatomical Therapeutic Chemical (Classification System) (ATC): L04AG03
Marketing Authorisation Holder	Sandoz GmbH
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	Tyruko® 300 mg concentrate for solution for infusion (Internal code name used throughout the document: PB006)
Marketing authorisation procedure	Centralized
Brief description of the product Chemical class Summary of mode of action Important information about its composition	Natalizumab is a recombinant humanised anti-α4- integrin antibody produced in a murine cell line by recombinant Deoxyribonucleic acid technology. 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, and ligands osteopontin, and an alternatively spliced domain of fibronectin, connecting segment. Natalizumab blocks the interaction of α4β7 integrin with the mucosal addressin cell adhesion molecule-1. 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.
Hyperlink to the Product Information	[Summary of Product Characteristics (SmPC) and Package leaflet (PL)]
Indication(s) in the EEA	Current: Tyruko® is indicated as single disease modifying therapy (DMT) in adults with highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups: • Patients with highly active disease despite a full and adequate course of treatment with at least one DMT. (for exceptions and information about washout periods see Sections 4.4 and 5.1 of the SmPC)

	or • Patients with rapidly evolving severe RRMS 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.
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current: Tyruko® 300 mg is administered by intravenous infusion once every 4 weeks. Method of administration: This medicinal product is for intravenous use. For detailed information on posology, re-administration, special populations-elderly, renal and hepatic impairment, paediatric population and method of administration, please refer to the current SmPC.
	Proposed: Not applicable.
Pharmaceutical form and strength	Current: Concentrate for solution for infusion; 300 mg
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II Safety specification

Part II: Module SII - Non-clinical part of the safety specification

PB006 is a biosimilar to Tysabri® (natalizumab), which is its reference medicinal product. The active ingredient of PB006 is a monoclonal antibody with the identical primary amino acid sequence as natalizumab. Both products are also considered as similar in all other relevant quality attributes. In such a case, several nonclinical safety assessments relevant for new drugs are not warranted, including developmental and reproductive toxicity, genotoxicity, carcinogenicity, as well as safety pharmacology and drug interaction studies. The preclinical data on Tysabri® is therefore considered relevant for PB006.

Despite the lack of residual uncertainties remaining from the analytical and in vitro functional similarity exercise a 4-week repeat-dose toxicity study was conducted in cynomolgus monkeys to compare the toxicity, pharmacokinetics (PK), and immunogenicity of PB006 with European Union (EU)-approved Tysabri®. This study was primarily performed to satisfy requirements laid out by other health authorities at that time to support entry into global clinical development. Based on the original Tysabri® studies, the animals were treated either with placebo formulation, the test item PB006 or the reference item Tysabri® at dose levels of 3 or 30 mg/kg by intravenous infusion every other day for 4 test weeks. The study, which was conducted in compliance with Organization for Economic Co-operation and Development Good Laboratory Practice, demonstrated comparability of PB006 and Tysabri® in terms of toxicity, PK, and immunogenicity.

Other toxicity studies of PB006 were not conducted.

Overall, no new risks or potential risks were identified during the non-clinical development of PB006. The toxicity study conducted with PB006, together with the analytical similarity of PB006 critical quality attributes to the reference product and established knowledge available for the reference product, indicated that the non-clinical safety profile of PB006 is comparable to that of Tysabri®. Important identified and potential risks reported on the reference product Tysabri® will be addressed by the Sandoz pharmacovigilance program on PB006.

Key safety findings from non-clinical studies for natalizumab (PB006 and Tysabri®) are presented in Table 2.

Table 2 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings from Non-clinical Studies	Relevance to human usage
Toxicity	
• Key issues identified from the repeat-dose intravenous cynomolgus PB006 comparative toxicity study:	The same safety profile is expected for Tysabri® and PB006, due to their high similarity and the data from a comparative cynomolgus toxicity study. Consistent with the pharmacological activity of natalizumab, altered trafficking of lymphocytes was

Treatment with PB006 or EU-approved Tysabri® at the high dose level led to an increase in the absolute number of the total and differential leucocyte count, in the number of reticulocytes and in all lymphocyte subtypes compared to the placebo control at the end of the treatment period on test day 31. The relative distribution of the differential White Blood Cell (WBC) count and the relative distribution of the differential lymphocyte count remained generally unchanged. The myeloid:erythroid ratio of the male and female animals treated with PB006 or EU-approved Tysabri® at dose levels of 3 or 30 mg/kg was dose-dependently increased on test day 32 compared to the control group. No test item-related influence was noted on behaviour and external appearance, body weight and body weight gain, food and drinking water consumption, Electrocardiography parameters, circulatory functions, clinical biochemistry parameters, urinary parameters, the eyes or optic region, auditory acuity, relative and absolute organ weights, macroscopic organ appearance at necropsy and histopathological examination at any dose level of the PB006- or EU-approved Tysabri®-treated groups. There was no noteworthy difference between the animals treated with PB006 and the animals treated with EU-approved Tysabri®. All findings were considered to be anticipated pharmacodynamic (PD) effects of natalizumab being a monoclonal antibody binding to α4 integrin. • Originator data with Tysabri®: In a 6-month multiple dose study in juvenile cynomolgus monkeys Tysabri® was administered intravenously (IV) weekly and compared with a vehicle control group. Expected increases in total WBCs, resulting primarily from increases in lymphocytes, were seen in Tysabri® treated animals and consisted of increases in both T and B cells. Higher spleen weights and spleen weight ratios were observed in the natalizumab-treated groups. Histologically, the higher spleen weights correlated to an increased frequency and severity of splenic follicular hypertrophy and hyperplasia (graded as minimal to mild). There were no gross necropsy findings, effects on organ weights, or spleen findings in the 17-week recovery animals indicating reversibility of these findings.	apparent as WBC increases as well as increased spleen weights in most in vivo studies. Although some dose-dependency was observed in both parameters in terms of the incidence of the observation per group, the extent of changes when observed was generally unchanged with dose. These changes do not appear to have any adverse toxicological consequences and can be expected to occur at the clinical dose level. Hypereosinophilia without symptoms has been observed in patients treated with natalizumab in the post-marketing setting.

In a 6-month multiple dose study in cynomolgus monkeys, Tysabri® was administered IV weekly and compared with a vehicle control group. Dose-related increases in WBC counts were observed in this study, primarily due to increases in circulating lymphocyte counts at high dose levels.	
• Originator data concerning reproductive/developmental toxicity: The effect of Tysabri® on reproduction was evaluated by the originator in 5 studies, 3 in guinea pigs and 2 in cynomolgus monkeys. These studies showed no evidence of teratogenic effects or relevant effects on growth of offspring. A study in pregnant cynomolgus monkeys demonstrated Tysabri®-related changes in the fetus that included mild anemia, reduced platelet counts, increased spleen weights and reduced liver and thymus weights. These changes were associated with increased splenic extramedullary hematopoiesis, thymic atrophy and decreased hepatic hematopoiesis. Platelet counts were also reduced in offspring born to mothers treated with Tysabri® until parturition, however there was no evidence of anemia in these offspring. All changes were observed at doses in excess of the human dose and were reversed upon clearance of Tysabri®. In cynomolgus monkeys treated with Tysabri® until parturition, low levels of natalizumab were detected in the breast milk of some animals.	Data from clinical trials, a prospective pregnancy registry, post-marketing cases and available literature do not suggest an effect of natalizumab exposure on pregnancy outcomes. The completed prospective natalizumab pregnancy registry contained 355 pregnancies with available outcomes. There were 316 live births, 29 of which were reported to have birth defects. Sixteen of the 29 were classified as major defects. The rate of defects corresponds to the defect rates reported in other pregnancy registries involving multiple sclerosis (MS) patients. There is no evidence of a specific pattern of birth defects with natalizumab. There are no adequate and well-controlled studies of natalizumab therapy in pregnant women. Cases of thrombocytopenia in infants born to women exposed to natalizumab during pregnancy were reported in the postmarketing setting. Monitoring of platelet counts is recommended in neonates born to women exposed to natalizumab during pregnancy. Natalizumab should be used during pregnancy only if clearly needed. If a woman becomes pregnant while taking natalizumab, discontinuation of natalizumab should be considered. A benefit-risk evaluation of the use of natalizumab during pregnancy should take into account the patient's clinical condition and the possible return of disease activity after stopping the medicinal product. Natalizumab is excreted in human milk. The effect of natalizumab on newborns/infants is unknown. Breast-feeding should be discontinued during treatment with natalizumab (Section 4.6, [Tyruko® SmPC]).
• Originator data concerning genotoxicity and carcinogenicity: In studies conducted in mice, growth and metastasis of melanoma and lymphoblastic leukemia tumor cells was not increased by the administration of natalizumab. No clastogenic or mutagenic effects of natalizumab were observed in the Ames or human chromosomal aberration assays. Natalizumab	These observations suggest that natalizumab treatment is unlikely to increase the risk of cancer in humans.

showed no effects on in vitro assays of α4-integrin-positive tumor line proliferation or cytotoxicity.	
• Originator data concerning fertility: Fertility studies in guinea pigs demonstrated no treatment-related effects on male fertility at doses up to 30 mg/kg every other day, which results in 38-fold greater exposure (based on cumulative area under the curve [AUC]) than the anticipated human exposure. Female guinea pigs showed a reduction in fertility in 1 of 2 studies at a dose of 30 mg/kg every other day, which results in 40-fold greater exposure (based on cumulative AUC) than the anticipated human exposure. Doses below 30 mg/kg did not result in a reduction in female fertility.	It is considered unlikely that natalizumab will affect fertility performance in humans following the maximum recommended dose (Section 4.6, [Tyruko® SmPC]).
• Originator data concerning cardiovascular safety: Decreases in mean arterial blood pressure, left ventricular systolic pressure, and cardiac output, and increases in heart rate and total peripheral resistance were observed in some animals when administered to beagle dogs by intravenous infusion.	Potential treatment-related changes were observed only in the dog study, where doses of 3 mg/kg were associated with transient decreases in systemic and left ventricular pressure in 1 dog. The finding that these were transient effects, together with the lack of development of any significant cardiovascular changes following 6 months of dosing in primates, indicates that natalizumab is unlikely to have cardiovascular effects in humans. Furthermore, the lack of effect in 2 monkey species and also absence of α4 integrins on cardiac tissue make it unlikely that this single finding is of relevance to humans.

Part II: Module SIII - Clinical trial exposure

PB006 has been developed as a biosimilar to Tysabri®, a DMT indicated in adults with highly active RRMS that has been authorized in the European Union since 2006.

Clinical data obtained by the Applicant to support the marketing authorization application are from three clinical pharmacology studies, PB006-01-01 (Tysabri® only), PB006-01-02, and PB006-01-03, and one confirmatory safety and efficacy study, PB006-03-01 (see Table 3).

Table 3- Tabulated overview of all clinical studies completed as part of the PB006 clinical development program

Study/ Phase	Design	Treatment	Subjects (treated)
Tysabri® Pilot-01-01 Phase 1	Randomized, double-blind, 3-arm, parallel-group, PK/PD study with EU-Tysabri®	Single-dose, IV infusion of EU-Tysabri®, at 1, 3 and 6 mg/kg	36 healthy subjects Number of subjects (n)=12 per dose
PB006-01-02 Phase 1	Open-label, single-arm, safety study with PB006	Single-dose, IV infusion of PB006, at 300 mg	10 healthy subjects
PB006-01-03 Phase 1	Randomized, double-blind, 3-arm, parallel-group, single-dose PK/PD study with PB006 versus US-Tysabri® and EU-Tysabri®	Single-dose, IV infusion of PB006, US-Tysabri® or EU-Tysabri®, at 3 mg/kg	450 healthy subjects PB006: n=149 EU-Tysabri®: n=151 US-Tysabri®: n=150
PB006-03-01 Phase 3	Randomized, double-blind, 2-arm, parallel-group, confirmatory efficacy and safety study with PB006 versus EU-Tysabri®	Multiple-dose, IV infusions of 300 mg PB006 or EU-Tysabri®, every 4 weeks, for a total of 48 weeks (12 infusions)	264 RRMS patients PB006: n=131 EU-Tysabri®: n=133*

* A subset of 30 patients enrolled in the EU-Tysabri® group was switched after 24 weeks from treatment with EU-Tysabri® to treatment with PB006 for the remaining period. Thus, a total of 161 patients were treated with PB006.

Exposure data are additionally provided for the two larger studies in the tables below. An overview of exposure in PB006-03-01 is provided in Table 4 and broken-down by age and gender in Table 5. An overview of exposure in PB006-01-03 is provided in Table 6 and broken-down by age and gender and ethnicity in Table 7 and Table 8, respectively.

Table 4 - Duration of exposure in PB006-03-01 (Safety (SAF) population)

Duration	PB006 N = 161 n (%)	EU-Tysabri® N = 134 n (%)
Less than 1 month	161 (100.0)	134 (100.0)
At least 1 month	159 (98.8)	132 (98.5)
At least 3 months	156 (96.9)	129 (96.3)
At least 6 months	123 (76.4)	96 (71.6)

Duration	PB006 N = 161 n (%)	EU-Tysabri® N = 134 n (%)
At least 9 months	120 (74.5)	94 (70.1)
At least 12 months	0 (0.0)	0 (0.0)
Subject-time (years)	127.53	103.71

Subject-time is the sum of each subject's treatment exposure in years.
Source: Derived from [clinical study report (CSR) PB006-03-01, Tables 14.4.1.1 and 14.4.2.1]

Table 5 - Duration of exposure in PB006-03-01 by age group and gender (SAF population)

		PB006 N = 161		EU-Tysabri® N = 134	
Age	Sex	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)
Total	Total	161 (100.0)	127.53	134 (100.0)	103.71
	Male	60 (37.3)	48.89	55 (41.0)	42.67
	Female	101 (62.7)	78.64	79 (59.0)	61.03
18 to 25 years	Total	16 (9.9)	13.35	21 (15.7)	17.51
	Male	6 (3.7)	5.06	11 (8.2)	9.71
	Female	10 (6.2)	8.29	10 (7.5)	7.80
>25 to 35 years	Total	65 (40.4)	51.40	39 (29.1)	28.64
	Male	25 (15.5)	20.71	13 (9.7)	10.21
	Female	40 (24.8)	30.69	26 (19.4)	18.43
>35 to 45 years	Total	55 (34.2)	42.83	48 (35.8)	37.45
	Male	21 (13.0)	16.65	22 (16.4)	16.95
	Female	34 (21.1)	26.18	26 (19.4)	20.50
>45 to 60 years	Total	25 (15.5)	19.95	26 (19.4)	20.10
	Male	8 (5.0)	6.47	9 (6.7)	5.80
	Female	17 (10.6)	13.48	17 (12.7)	14.30

Subject-time is the sum of each subject's treatment exposure in years.
Source: Derived from [CSR PB006-03-01, Tables 14.4.1.2 and 14.4.2.2]

Table 6 - Duration of exposure in PB006-01-03 (safety set)

	PB006 N = 450	
Treatment group	Subjects n (%)	Subject time (days)
Total	450 (100.0)	12600

3 mg/kg sd IV PB006	149 (33.1)	4172
3 mg/kg sd IV EU-Tysabri®	151 (33.6)	4228
3 mg/kg sd IV US-Tysabri®	150 (33.3)	4200

Subject-time is the sum of each subject's treatment exposure in days. Subject-time in this single dose study was planned to be 28 days for each subject.
Source: Derived from [CSR PB006-01-03, Table 15.5.3]

Table 7 - Duration of exposure by age group and gender in PB006-01-03 (safety set)

		PB006 N = 450	
Age	**Sex**	**Subjects n (%)**	**Subject-time (days)**
Total	Total	450 (100.0)	12600
	Male	220 (48.9)	6160
	Female	230 (51.1)	6440
18 to 54 years	Total	437 (97.1)	12236
	Male	210 (46.7)	5880
	Female	227 (50.4)	6356
55 to 61 years	Total	13 (2.9)	364
	Male	10 (2.2)	280
	Female	3 (0.7)	84

Subject-time is the sum of each subject's treatment exposure in days. Subject-time in this single dose study was planned to be 28 days for each subject.
Source: Derived from [CSR PB006-01-03, Table 15.5.2]

Table 8 - Duration of exposure by ethnic origin in PB006-01-03 (safety set)

	PB006 N = 450	
Race	**Subjects n (%)**	**Subject-time (days)**
Hispanic or Latino	50 (11.1)	1400
Not Hispanic or Latino	400 (88.9)	11200

Subject-time is the sum of each subject's treatment exposure in days. Subject-time in this single dose study was planned to be 28 days for each subject.
Source: Derived from [CSR PB006-01-03, Table 15.5.4]

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Important exclusion criteria from the Phase 3 trial PB006-03-01, investigating the efficacy and safety of PB006 in patients with RRMS, are presented in Table 9.

Table 9 - Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Manifestation of MS other than RRMS.	Natalizumab is indicated for patients with RRMS.	No	Other types of MS fall outside of the indication.
Relapse within the 30 days prior Screening and until administration of the first dose of study drug.	To avoid confounding factors affecting efficacy and safety assessments.	No	This exclusion criterion was to avoid confounding factors affecting efficacy and safety assessments and not due to a particular concern.
Prior treatment with natalizumab, alemtuzumab, ocrelizumab, daclizumab, rituximab, cladribine, or other B- and T-cell targeting therapies.	Patients with a treatment history of DMTs with immunosuppressant effect may be at increased risk of progressive multifocal leukoencephalopathy (PML).	Yes. PML risk following switch from disease modifying therapies with immunosuppressant effect is included as missing information.	Not applicable.
Prior total lymphoid irradiation or bone marrow or organ transplantation.	Patients with prior total lymphoid irradiation or bone marrow or organ transplantation are thought to be at increased risk of PML, most probably due to their immunosuppressive treatment.	No	PML is included as an important identified risk
Any prior treatment with immunosuppressant or immunomodulatory effect within the defined time periods prior to Screening (please refer to [CSR PB006-03-01, Section 9.3.2]).	Patients with prior use of an immunosuppressive or immunomodulatory therapy before starting natalizumab within the stated timelines may be at increased risk of PML.	Yes. PML risk following switch from disease modifying therapies with immunosuppressant effect is included as missing information.	Not applicable

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Increased risk of opportunistic or other active infections within 2 weeks prior to Screening.	Natalizumab is contraindicated in patients at increased risk for opportunistic infections (Section 4.3, [Tyruko® SmPC]).	No	An increased risk for opportunistic infections is a contraindication for use (Section 4.3, [Tyruko® SmPC]) and warnings and appropriate measures to reduce the risk of opportunistic infections are included in the SmPC (Section 4.4, [Tyruko® SmPC]). In addition, PML and serious herpes infections are important identified risks. This is considered sufficient.
Patients with John Cunningham virus (JCV) index >1.5 at Screening.	A JCV index >1.5 is associated with an increased risk of PML.	No	PML is included as an important identified risk.
Past or current PML diagnosis.	PML is a contraindication for use (Section 4.3, [Tyruko® SmPC]).	No	PML is included as an important identified risk.
Clinically relevant, severe cardiac or pulmonary diseases, uncontrolled hypertension, poorly controlled diabetes, or renal or hepatic impairment (please refer to [CSR PB006-03-01, Section 9.3.2]).	To avoid confounding factors affecting safety and efficacy assessments.	No	This broad exclusion criterion was to avoid confounding factors affecting safety and efficacy assessments. The decision to treat with natalizumab will be made by the healthcare provider after consideration of the patient's medical history/present medical condition and the product information for PB006.

SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

However, since PB006 showed a similar PK, PD, and safety profile to that of reference natalizumab in non-clinical studies and a similar PK and safety profile in the clinical trials, it is justified to build also on the extensive clinical trial experience that has accumulated for the reference product, Tysabri®, as described above.

SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Exposure of special populations included or not included in the clinical trial development program for PB006 is outlined in Table 10.

Table 10 - Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women Breastfeeding women	Pregnant and breastfeeding women were excluded from clinical trials with natalizumab.
Patients with relevant comorbidities:	• Patients with hepatic impairment: Studies have not been conducted to examine the effects of hepatic impairment. • The mechanism for elimination and results from population PK suggest that dose adjustment would not be necessary in patients with hepatic impairment. • Patients with renal impairment: Studies have not been conducted to examine the effects of renal impairment. • The mechanism for elimination and results from population PK suggest that dose adjustment would not be necessary in patients with renal impairment. • Patients with cardiovascular impairment: Patients with clinically relevant, severe cardiovascular impairment were excluded from the clinical development program. • Immunocompromised patients: Not applicable. Immunocompromised patients are excluded from use. • Patients with a disease severity different from inclusion criteria in clinical trials: Not applicable. Natalizumab is only indicated for patients with highly active RRMS.
Population with relevant different ethnic origin	Although the majority of subjects included in the completed clinical trials for natalizumab were Caucasian, there are no data to suggest that there are important differences in the PK of natalizumab for patients with different racial or ethnic origins.

Type of special population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Other	Elderly and paediatric patients were excluded from the clinical development program.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorization exposure

SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume in milligrams of active substance sold during the reporting interval and the Defined Daily Dose (DDD) provided by the World Health Organization Collaborating Centre for Drug Statistics Methodology in Oslo.

Patient exposure (patient-treatment years) = Quantity of natalizumab sold (mg)/DDD (mg)×365

The DDD for parental natalizumab is 10 mg.

The estimated post-marketing exposure is provided in Section SV.1.2.

SV.1.2 Exposure

During the reporting interval and cumulatively, worldwide patient exposure was estimated to be 10,368 patient treatment years (PTY) for Tyruko®, see Table 11.

Table 11 SV.1: Cumulative and Interval Patient Exposure from Marketing Experience (Presented in PTY)

Country	Cumulative Exposure till data lock point (30 Nov 2025)	
	Amount sold (mg)	Estimated exposure (PTY)*
EEA	31539300	8641
Japan	-	-
Rest of the World	6154500	1686
US and Canada	149100	41
Total	37,842,900	10,368

Source of data: Worldwide sales volume. The values in above tables are calculated by using formulas in excel.

*The sum up values may not match with the total as the figures are rounded off to nearest digit.

The patient exposure based on demographics (i.e., gender, age, race, ethnicity, and indication) could not be estimated, as the data based on demographics is not available.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

The clinical development program for PB006 did not identify any additional risks of PB006 over the reference medicinal product, Tysabri®.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Table 12 - Important identified risks

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
Progressive Multifocal Leukoencephalopathy (PML)	PML has been classified as an important identified risk for PB006, consistent with the reference product, Tysabri®. Use of natalizumab has been associated with the uncommon event of PML, which may be fatal or result in severe disability. The recommendations in the label and additional risk minimization measures are considered to be adequate to mitigate the risk of PML, and therefore, the risk-benefit balance remains favourable.
Serious herpes infections	Serious herpes infections have been classified as an important identified risk for PB006, consistent with the reference product, Tysabri®. Natalizumab treatment increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster viruses. Serious, life-threatening and sometimes fatal cases have been reported in the post-marketing setting in multiple sclerosis patients receiving the treatment. Acute retinal necrosis (ARN) has been observed in patients with natalizumab therapy. Some cases have occurred in patients with central nervous system (CNS) herpes infections (e.g. herpes meningitis and encephalitis). Serious cases can lead to blindness.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

‘Malignancies’ which was previously classified as important potential risk is removed from the list of safety concerns.

‘PML risk following switch from disease modifying therapies with immunosuppressant’ which was previously classified as missing information is removed from the list of safety concerns.

Reason for the removal of the list of safety concerns:

These important identified risks and missing information have been removed to align with the reference product Tysabri® (natalizumab) RMP v34.0, dated 25 Sep 2025.

SVII.3 Details of important identified risks, important potential risk, and missing information

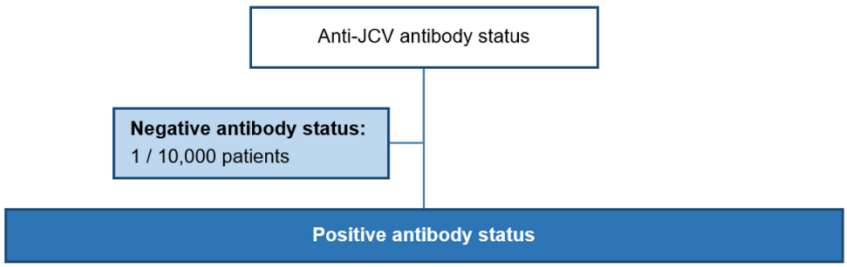
SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Progressive multifocal leukoencephalopathy (PML)

During the clinical development of PB006, no cases of PML were reported.

Table 13 - Important identified risk: Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML)	**Details** Preferred Terms (PTs): JC virus granule cell neuronopathy, Leukoencephalopathy, Progressive multifocal leukoencephalopathy, JC polyomavirus test positive, Human polyomavirus infection, JC virus CSF test positive, JC virus infection (Medical Dictionary for Regulatory Activities [MedDRA] v.28.1). Furthermore, cases were manually evaluated for PML evidence using the relevant laboratory findings and were considered relevant only if laboratory findings were suggestive of PML
Potential mechanisms:	Progressive multifocal leukoencephalopathy is an opportunistic infection caused by the John-Cunningham virus (JCV). Two general mechanisms have been suggested to explain the association between natalizumab treatment and PML. The first is that blocking alpha 4 integrin decreases lymphocyte trafficking, and the subsequent reduction in immune surveillance allows for the activation of a latent infection in the nervous system. The second suggested mechanism is associated with the finding that deletion of alpha4 integrin is associated with increased numbers of B cells and immature progenitor cells released from the bone marrow. Both of these cell populations may be reservoirs of latent JCV. Besides oligodendrocytes, JCV can also infect cerebellar granule cell neurons resulting in JCV GCN.
Evidence source(s) and strength of evidence	Use of natalizumab has been associated with the uncommon event of PML, which may be fatal or result in severe disability (Section 4.4, [Tyruko® SmPC]). PML has been classified as an important identified risk for PB006, consistent with the reference product, Tysabri®.
Characterization of the risk:	The global incidence of PML in natalizumab treated patients has been estimated at 4.08/1000 patients (Vivekanandan et al. 2021). The PML incidence for anti-JCV antibody negative patients has been estimated to be 0.1 in 1,000. In anti-JC virus antibody positive patients, the incidence depends on antibody levels, duration of treatment with natalizumab, and prior use of immunosuppressants (EMA/137488/2016). Progressive multifocal leukoencephalopathy may be fatal or result in severe disability. The mortality rate of MS patients who received natalizumab has been estimated at 20%. About 40% of survivors will have serious disability (Karnofsky scale 10–40) (Sørensen et al. 2012). In both the pivotal Phase 1 PK/PD study PB006-01-03 and the Phase 3 study PB006-03-01 for PB006, no cases of PML occurred during the studies or in the 6-month PML follow-up. **Estimated US incidence of PML stratified by risk factor:**



Natalizumab Exposure	No Prior Immunosuppressant Use	Prior Immunosuppressant Use
1-24 months	< 1/1,000	1/1,000
25-48 months	2/1,000	6/1,000
49-72 months	4/1,000	7/1,000
73-96 months	2/1,000	6/1,000

Source: (Biogen, 2021)

As of 31-Oct-2025, there have been 06 cases of Progressive multifocal leukoencephalopathy received by the MAH in the post-marketing dataset with an estimated cumulative worldwide post-marketing exposure to natalizumab of 10,368 PTYs.

All six cases were reported in the switch group (Tysabri to Tyruko) reflecting long natalizumab exposure. In two patients PML was fatal and in 2 other patients, PML was life-threatening..

Risk factors and risk groups

The following risk factors are associated with an increased risk of PML:

- The presence of anti-JCV antibodies.
- Treatment duration, especially beyond 2 years. After 2 years all patients should be re-informed about the risk of PML with the medicinal product.
- Immunosuppressant use prior to receiving the medicinal product.

Patients who are anti-JCV antibody positive are at an increased risk of developing PML compared to patients who are anti-JCV antibody negative. Patients who have all three risk factors for PML (i.e., are anti-JCV antibody positive and have received more than 2 years of therapy with this medicinal product and have received prior immunosuppressant therapy) have a significantly higher risk of PML.

In anti-JCV antibody positive natalizumab treated patients who have not used prior immunosuppressants the level of anti-JCV antibody response is associated with the level of risk for PML (Section 4.4, [Tyruko® SmPC]).

Anti- John Cunningham virus antibody negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status or a false negative test result (Section 4.4, [Tyruko® SmPC]).

Patients who test as positive for anti-JCV antibodies at any time should be considered to be at an increased risk for developing PML, independent from any prior or subsequent antibody test results (Tysabri® RMP).

Preventability

Progressive multifocal leukoencephalopathy is not preventable, however early detection and stopping of natalizumab treatment may improve outcome.

	Due to this increased risk of developing PML, the benefits and risks of treatment should be individually reconsidered by the specialist physician and the patient; patients must be monitored at regular intervals throughout and should be instructed together with their caregivers on early signs and symptoms of PML (Section 4.4, [Tyruko® SmPC]). *Extended interval dosing* In anti-JCV antibody positive patients, extended interval dosing of natalizumab (average dosing interval of approximately 6 weeks) is suggested to be associated with a lower PML risk compared to approved dosing. If utilising extended interval dosing, caution is required because the efficacy of extended interval dosing has not been established and the associated benefit risk balance is currently unknown (Section 4.4, [Tyruko® SmPC]). *Anti- John Cunningham virus antibody testing* Anti- John Cunningham virus antibody testing provides supportive information for risk stratification of treatment with this medicinal product. Testing for serum anti-JCV antibody prior to initiating therapy or in patients receiving the medicinal product with an unknown antibody status is recommended. Anti- John Cunningham virus antibody negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status or a false negative test result. Re-testing of anti-JCV antibody negative patients every 6 months is recommended. Retesting low index patients who have no history of prior immunosuppressant use every 6 months once they reach the 2-year treatment point is recommended. The anti- John Cunningham virus antibody assay (Enzyme-Linked Immunosorbent Assay) should not be used to diagnose PML. Use of plasmapheresis/plasma exchange (PLEX) or intravenous immunoglobulin (IVIg) can affect meaningful interpretation of serum anti-JCV antibody testing. Patients should not be tested for anti-JCV antibodies within 2 weeks of PLEX due to removal of antibodies from the serum, or within 6 months of IVIg (i.e. 6 months = 5x half-life for immunoglobulins) (Section 4.4, [Tyruko® SmPC]). *Magnetic Resonance Imaging screening for PML* Before initiation of treatment with this medicinal product, a recent (usually within 3 months) MRI should be available as a reference and be repeated at least on a yearly basis. More frequent MRIs (e.g. on a 3 to 6 monthly basis) using an abbreviated protocol should be considered for patients at higher risk of PML (Section 4.4, [Tyruko® SmPC]). No studies have been performed to evaluate the efficacy and safety of natalizumab when switching patients from DMTs with an immunosuppressant effect. It is unknown if patients switching from these therapies to this treatment have an increased risk of PML, therefore these patients should be monitored more frequently (i.e. similarly to patients switching from immunosuppressants to natalizumab) (Section 4.4, [Tyruko® SmPC]). Progressive multifocal leukoencephalopathy should be considered as a differential diagnosis in any MS patient taking Tyruko® presenting with neurological symptoms and/or new brain lesions in MRI. Cases of asymptomatic PML based on MRI and positive JCV Deoxy ribonucleic acid (DNA) in the cerebrospinal fluid have been reported (Section 4.4, [Tyruko® SmPC]).

	Physicians should refer to the Physician Information and Management Guidelines for further information on managing the risk of PML in natalizumab-treated patients (Section 4.4, [Tyruko® SmPC]). **If Progressive multifocal leukoencephalopathy or JCV-granule cell neuronopathy (JCV GCN) is suspected, further dosing must be suspended until PML has been excluded.** The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction and, if so, whether these symptoms are typical of MS or possibly suggestive of PML or JCV GCN. If any doubt exists, further evaluation, including MRI scan preferably with contrast (compared with pre-treatment baseline MRI), cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered as described in the Physician Information and Management Guidelines. Once the clinician has excluded PML and/or JCV GCN (if necessary, by repeating clinical, imaging and/or laboratory investigations if clinical suspicion remains), dosing may resume. The physician should be particularly alert to symptoms suggestive of PML or JCV GCN that the patient may not notice (e.g. cognitive, psychiatric symptoms or cerebellar syndrome). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of. Progressive multifocal leukoencephalopathy has been reported following discontinuation of this medicinal product in patients who did not have findings suggestive of PML at the time of discontinuation. Patients and physicians should continue to follow the same monitoring protocol and be alert for any new signs or symptoms that may be suggestive of PML for approximately 6 months following discontinuation of natalizumab. *If a patient develops PML the dosing of natalizumab must be permanently discontinued (Section 4.4, [Tyruko® SmPC]).* Educational tools for healthcare professionals (HCPs) (Physician Information and Management Guideline) and educational tools for patients/carers (patient alert card, treatment initiation form, treatment continuation form, and treatment discontinuation form) to inform on the important risk of PML are described in Part V.2.
Impact on the benefit-risk balance of the product	Use of natalizumab has been associated with an increased risk of PML, which may be fatal or result in severe disability (Section 4.4, [Tyruko® SmPC]). The recommendations in the label and additional risk minimization measures are considered to be adequate to mitigate the risk of PML, and, therefore, the risk-benefit balance remains favorable. The totality of evidence established similarity of PB006 to the reference product Tysabri® in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise as required by CHMP/437/04 Rev 1. Overall, the results of the global development program confirm that PB006 is biosimilar to the reference product Tysabri® and has a similar and positive benefit-risk ratio.
Public health impact	PML is not considered to have a major impact on public health.

Important Identified Risk: Serious herpes infections

During the clinical development of PB006, no cases of serious herpes infection were reported.

Table 14 - Important identified risk: Serious herpes infections

Serious herpes infections	**Details** High level term: Herpes viral infections; PTs: Herpes simplex test positive, Herpes virus test abnormal, Human herpes virus 6 serology positive, Human herpes virus 8 test positive, Post herpetic neuralgia (MedDRA v.28.1) - Filter for *serious* herpes infections. Of retrieved cases, only those wherein herpes infection coded as serious were considered as relevant.
Potential mechanisms	Herpes viruses lie dormant in the neuronal tissue in a large majority of the population. Natalizumab reduces leukocyte trafficking by blocking the interaction of α4-integrin with adhesion molecules on the vascular endothelium and may also inhibit the interaction of α4-expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells, thereby inhibiting further recruitment and inflammatory activity of activated immune cells. The resulting impaired local immunosurveillance due to local depletion of lymphocytes may lead to a greater risk of severe local herpes or systemic spread in patients treated with natalizumab.
Evidence source(s) and strength of evidence	Serious herpes infection has been classified as an important identified risk for PB006, consistent with the reference product, Tysabri®.
Characterization of the risk:	PB006 There were few non-serious herpes infections in the development program of PB006. However, no serious herpes infections were observed. There were no cases of encephalitis, meningitis, or ARN in the development program for PB006. Tysabri ® In clinical trials for the initial marketing application for the originator, Tysabri®, herpes infections (Varicella-Zoster virus, Herpes simplex virus) occurred slightly more frequently in natalizumab-treated patients than in placebo-treated patients. An analysis of herpes infections, both simplex and zoster, was conducted to assess a potential risk for these infections for Tysabri®. In the placebo-controlled MS and Crohn's disease (CD) studies, the incidence of herpes-like symptoms was slightly higher in natalizumab-treated subjects than placebo-treated subjects (natalizumab vs. placebo: 7.1% vs. 6.0% for MS and 1.6% vs. 1.0% for CD). Four subjects receiving natalizumab experienced serious infections, with 3 subjects receiving intravenous acyclovir for varicella infection (European Medicines Agency, 2007). In post-marketing experience, serious, life-threatening, and sometimes fatal cases of encephalitis and meningitis caused by herpes simplex or varicella zoster have been reported in multiple sclerosis patients receiving natalizumab (Section 4.8, Tysabri® SmPC). In post-marketing experience, rare cases of ARN have been observed in patients receiving natalizumab. Some cases have occurred in patients with CNS herpes infections (e.g. herpes meningitis and encephalitis). Serious cases of ARN, either affecting one or both eyes, led to blindness in some patients (Section 4.8, Tysabri® SmPC).

	As of 31-Oct-2025, there have been two cases of herpes infections received by the MAH in the post-marketing dataset with an estimated cumulative worldwide post-marketing exposure to natalizumab of 10,368 PTYs. These two cases reported the events of herpes zoster cutaneous disseminated and ophthalmic herpes zoster (n=1, each). Of the two cases, one case was reported in a patient who switched from Tysabri to Tyruko. The overall analysis did not reveal any significant new safety related information that could impact the known safety profile of natalizumab.
Risk factors and risk groups	None identified for natalizumab.
Preventability	If herpes encephalitis or meningitis occurs, the medicinal product should be discontinued, and appropriate treatment for herpes encephalitis or meningitis should be administered (Section 4.4, [Tyruko® SmPC]). Patients presenting with eye symptoms such as decreased visual acuity, redness and painful eye should be referred for retinal screening for ARN. Following clinical diagnosis of ARN, discontinuation of this medicinal product should be considered in these patients (Section 4.4, [Tyruko® SmPC]).
Impact on the benefit-risk balance of the product	Natalizumab treatment increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster viruses. Serious, life-threatening, and sometimes fatal cases have been reported in the post-marketing setting in multiple sclerosis patients receiving the treatment (Section 4.4, Tyruko® SmPC). Serious ARN has been observed in patients administered natalizumab and can lead to blindness (Section 4.8, Tyruko® SmPC). The totality of evidence established similarity of PB006 to the reference product Tysabri® in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise as required by CHMP/437/04 Rev 1. Overall, the results of the global development program confirm that PB006 is biosimilar to the reference product Tysabri® and has a similar and positive benefit-risk ratio.
Public health impact	Serious herpes infections are not considered to have a major impact on public health.

Important Potential Risk: None.

Missing Information: None

Part II: Module SVIII - Summary of the safety concerns

Table 15 - – Part II: SVIII - Summary of safety concerns

Summary of safety concerns*	
Important identified risks	Progressive multifocal leukoencephalopathy (PML) Serious herpes infections
Important potential risks	None
Missing information	None

* The summary of safety concerns has been aligned to the latest list of safety concerns of "Tysabri®" RMP v.34.0 dated 25 Sep 2025 (Marketing Authorisation Holder (MAH): Biogen Netherlands B.V.).

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

The Global Pharmacovigilance System ensures the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

9.1.1 Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for Progressive multifocal leukoencephalopathy and Serious herpes infections:

Specific adverse event follow-up questionnaire will be used to collect further data to help further characterize and/or closely monitor each of the respective safety concerns specified below:

- Progressive multifocal leukoencephalopathy (PML)
- Serious herpes infections

These forms are provided in Annex 4.

Specific adverse reaction follow-up questionnaires are provided to the reporters in order to obtain structured information on reported suspected adverse reactions of special interest to further characterize the nature of events, demographics of patients at risk, and the presence of risk factors and confounding factors.

Follow up of case reports: The minimum desired case information for natalizumab includes the brand name and batch number of the suspect product. Additional efforts must be made to collect this information in accordance with GVP Module VI.

Other forms of routine pharmacovigilance activities for all included risks and missing information

None

III.2 Additional pharmacovigilance activities

There are no planned, ongoing or completed additional pharmacovigilance activities.

III.3 Summary table of additional pharmacovigilance activities

There are no ongoing or planned categories 1-3 safety studies.

Part IV: Plans for post-authorisation efficacy studies

There are no planned post-authorization efficacy studies.

Part V: Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)

Risk minimisation plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1 Routine risk minimisation measures

Table 16 - – Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Progressive multifocal leukoencephalopathy (PML)	**Routine risk communication:** - SmPC Sections 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 5.1 Pharmacodynamic properties - Package Leaflet (PL) Sections 2 What you need to know before you receive Tyruko® and 4 Possible side effects**Routine risk minimisation activities recommending specific clinical measures to address the risk:** • A contraindication for use in patients with pre-existing PML is included in SmPC Section 4.3 and PL Section 2 • Information regarding the clinical presentation of PML and risk factors for its development are included in SmPC Section 4.4 and PL Section 2 • Recommendations regarding the detection and management of PML are included in SmPC Section 4.4. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Restricted medical prescription – PB006 is prescribed and continuously supervised by specialized physicians experienced in the diagnosis and treatment of neurological conditions with timely access to MRI.
Serious herpes infections	**Routine risk communication:** - SmPC Sections 4.3 Contraindications, 4.4 Special warnings and precautions for use and 4.8 Undesirable effects - PL Sections 2 What you need to know before you receive Tyruko® and 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:**

Safety concern	Routine risk minimisation activities
	• A contraindication for use in patients with increased risk for opportunistic infections is included in the SmPC Section 4.3 and PL Section 2 • Information on the increased risk and clinical presentation of serious herpes infections are included in SmPC Section 4.4 and PL Section 2 • Recommendations on the detection and management of serious herpes infections are included in SmPC Section 4.4. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription – PB006 is prescribed and continuously supervised by specialized physicians experienced in the diagnosis and treatment of neurological conditions with timely access to MRI.
Important potential risks	
None.	
Missing information	
None.	

V.2 Additional risk minimisation measures

The proposed additional risk minimization measures have been aligned with those for the reference product, Tysabri®.

Educational materials:

Health care professionals will be educated on the important identified risk of PML via a 'Physician Information and Management Guideline' (see Annex 6) and via the distribution of a Direct healthcare professional communication (DHPC) if/when new information becomes available.

Objective:

To inform physicians on the risk and the nature of PML, risk factors for development of PML, its diagnosis and treatment, specific steps to be taken to minimize this risk and the identification and management of possible sequelae (e.g. immune reconstitution inflammatory syndrome [IRIS]).

Rationale for the additional risk minimisation activity:

The Physician Information and Management Guideline provides detailed information on PML, including practical advice to physicians that is not available through the SmPC.

Target audience and planned distribution path:

The Physician Information and Management Guideline has been developed for physicians initiating and supervising treatment with Tyruko®, and for radiologists involved in the differential diagnosis of PML.

The guidelines (and any relevant DHPC) will be provided to target HCPs, and in addition, MRI learning material on the differentiation of MS relapse from PML will also be available.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Adverse event (AE) reports are reviewed on an on-going basis and appropriate action taken as needed.

Frequency and severity of AEs due to PML are the primary indicator. The post-marketing AE profile is compared with the expected AE profile.

An evaluation of the effectiveness of risk minimization measures is done in Periodic Safety Update Reports (PSURs) on the basis of all collected safety information. A conclusion of the appropriateness of the current safety profile and a possible need for changes to risk minimization is presented therein.

Educational tools targeting patients and/or carers

Patients will be educated on the important identified risk of PML via a Patient alert card, a Treatment initiation form, a Treatment continuation form, and a Treatment discontinuation form.

Objective:

To educate patients and carers on the risk of PML whilst on natalizumab treatment and for up to 6 months afterwards, on the nature of PML and to ensure they exercise vigilance regarding its development.

Rationale for the additional risk minimisation activity:

The treatment initiation form provides detailed information to patients on the risk of PML to ensure patients are fully informed of the risk of PML and consent to treatment prior to starting Tyruko®.

The treatment continuation form provides additional information to patients on the increased risk of PML development after 24 months of Tyruko® treatment, to further promote patient understanding of the risk of treatment continuation and to ensure they consent to this risk.

The treatment discontinuation form provides information to patients on when MRI imaging may be warranted, informs patients that PML has been reported up to 6 months after stopping Tyruko®, reminds patients of PML symptoms, reporting side effects and to keep alert card with them after discontinuation.

The patient alert card provides targeted information on risk of PML to educate both patients and/or carers on the need for vigilance regarding this risk by providing information on early signs and

symptoms, latency, and reinforcement of the importance of seeking Healthcare Professional (HCP) advice in a timely manner.

Target audience and planned distribution path:

The patient alert card, treatment initiation form, continuation form, and discontinuation form are intended for use by patients and/or carers. These will be distributed by the patient's HCP at the time of treatment initiation, after 24 months of Tyruko® treatment, and at discontinuation, respectively.

Plans to evaluate the effectiveness of the interventions and criteria for success:

AE reports are reviewed on an on-going basis and appropriate action taken as needed.

Frequency and severity of AEs due to PML are the primary indicator. The post-marketing AE profile is compared with the expected AE profile.

An evaluation of the effectiveness of risk minimization measures is done in PSURs on the basis of all collected safety information. A conclusion of the appropriateness of the current safety profile and a possible need for changes to risk minimization is presented therein.

V.3 Summary of risk minimisation measures

Table 17 - – Part V.3: 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 communication:** SmPC Sections 4.2, 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, treatment initiation form, treatment continuation form, and treatment discontinuation form)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire **Additional pharmacovigilance activities:** None.
Serious herpes infections	**Routine risk communication:** SmPC Sections 4.3, 4.4 and 4.8; and PL Sections 2 and 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Legal status: Restricted medical prescription Additional risk minimization measures: None	Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None
Important potential risks		
None.		
Missing information		
None.		

Part VI: Summary of the risk management plan

Summary of risk management plan for Tyruko® 300 mg concentrate for solution for infusion (natalizumab)

This is a summary of the risk management plan (RMP) for Tyruko®. The RMP details important risks of Tyruko®, how these risks can be minimised, and how more information will be obtained about Tyruko®'s risks and uncertainties (missing information).

Tyruko®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Tyruko® should be used.

Important new concerns or changes to the current ones will be included in updates of Tyruko®'s RMP.

I. The medicine and what it is used for

Tyruko® is authorised for use as a single disease modifying therapy (DMT) in adult patients with highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups:

• Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT).

or

• Patients with rapidly evolving severe RRMS 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.

It contains natalizumab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Tyruko®'s benefits can be found in Tyruko®'s European Public Assessment Report, including in its plain-language summary, available on the EMA website, under the medicine's webpage: Tyruko | European Medicines Agency (EMA).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Tyruko®, together with measures to minimise such risks and the proposed studies for learning more about Tyruko®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Tyruko®, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Tyruko® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tyruko®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Progressive multifocal leukoencephalopathy (PML) Serious herpes infections
Important potential risks	None
Missing information	None

II.B Summary of important risks

The safety information in the proposed product information is aligned to the reference medicinal product.

Important identified risk: Progressive multifocal leukoencephalopathy (PML)

Evidence for linking the risk to the medicine	Use of natalizumab has been associated with the uncommon event of PML, which may be fatal or result in severe disability (Section 4.4, [Tyruko® SmPC]). PML has been classified as an important identified risk for Tyruko®, consistent with the reference product, Tysabri®.
Risk factors and risk groups	The following risk factors are associated with an increased risk of PML: • The presence of anti-JCV antibodies. • Treatment duration, especially beyond 2 years. After 2 years all patients should be re-informed about the risk of PML with the medicinal product. • Immunosuppressant use prior to receiving the medicinal product.

	Patients who are anti-JCV antibody positive are at an increased risk of developing PML compared to patients who are anti-JCV antibody negative. Patients who have all three risk factors for PML (i.e., are anti-JCV antibody positive and have received more than 2 years of therapy with this medicinal product and have received prior immunosuppressant therapy) have a significantly higher risk of PML. In anti-JCV antibody positive natalizumab treated patients who have not used prior immunosuppressants the level of anti-JCV antibody response is associated with the level of risk for PML (Section 4.4, [Tyruko® SmPC]). Anti-JCV antibody negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status or a false negative test result (Section 4.4, [Tyruko® SmPC]). Patients who test as positive for anti-JCV antibodies at any time should be considered to be at an increased risk for developing PML, independent from any prior or subsequent antibody test results (Tysabri® RMP).
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2, 4.3, 4.4, 4.8, and 5.1; and PL Sections 2 and 4 Legal status: Restricted medical prescription Additional risk minimization measures: • Educational tools for HCPs (Physician Information and Management Guideline) • Educational tools for patients/carers (patient alert card, treatment initiation form, treatment continuation form, and treatment discontinuation form)

Important identified risk: Serious herpes infections

Evidence for linking the risk to the medicine	Serious herpes infections has been classified as an important identified risk for Tyruko®, consistent with the reference product, Tysabri®.
Risk factors and risk groups	None identified for natalizumab.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.3, 4.4, 4.8; and PL Sections 2 and 4 Legal status: Restricted medical prescription

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Tyruko®.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Tyruko®.

Annex 4 - Specific adverse drug reaction follow-up forms

Progressive multifocal leukoencephalopathy

Targeted Follow-up Checklist "Progressive Multifocal Leukoencephalopathy" (version 2.0)

Serious herpes infections

Targeted Follow-up Checklist "Serious Herpes Infections" (version 2.0)

Annex 4.1 Progressive multifocal leukoencephalopathy (PML)

Manufacturer Receipt Date (dd/mm/yyyy): ___/_____/_____ **Argus case ID: _____**

Batch number: _____

Targeted Follow-up Checklist (V 2.0)
Progressive Multifocal Leukoencephalopathy

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Primary Suspect Product

Provide additional details on the dosing and frequency of the Primary Suspect Product, including information on the use of multiple regimens:

Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)	Dose	Route	Frequency of Dosing	Number of Administered Doses (Tyruko®)	Lot/ Batch #

Did the patient present with any of the following signs or symptoms? Check all that apply.

☐ Hemiparesis ☐ Cognitive impairment ☐ Weakness ☐ Headaches
☐ Hemianopia ☐ Personality changes ☐ Aphasia ☐ None of the above

☐ Brainstem deficits ☐ Dysarthria ☐ Visual impairment ☐ Others (*please specify*)
☐ Clumsiness/ Cerebellar deficits ☐ Sensory deficits ☐ Fever
_____

Was brain MRI/ Magnetic Resonance Angiography performed? ☐ **Yes** *(provide report and/or summarize below)* ☐ **No** ☐ **Unknown**

Results:_____
_____
_____
_____

CSF JCV analysis ☐ **Yes** *(provide results below)* ☐ **No** ☐ **Unknown**

Type of test (polymerase chain reaction (PCR), JCV antibody)	**Test date**	**Result**

Please include results of other relevant tests

Type of test	**Test date**	**Result**
JCV (serum or urine)		
Anti JCV antibody index		
Absolute lymphocyte count		
WBC – including lymphocyte subsets (e.g., CD4, CD8)		
Brain biopsy		
Other		

Patient History:
Does the patient have a history of any immunosuppressive disorders prior to the start of the suspect drug (eg, Human immunodeficiency virus infection; malignancy, e.g., leukemia, lymphoma, myeloproliferative diseases; sarcoidosis; other disturbances of the immune system, e.g., history of low CD4/CD8 ratio; other)?

☐ Yes *(summarize below)* ☐ No ☐ Unknown

Immune disorder	**Date of onset**	**Status (active, inactive)**	**Other details**

Concomitant / Co-suspect / historical medication:
Is the patient currently taking or has the patient taken in the past any of the following immunosuppressive medications*? Check all that apply and include in sequential order the starting and completion dates and indication for the medication in the space below.

☐ Chemotherapy/ Cytoreductive therapy *please specify*
☐ Other immunosuppressant drugs *please specify*
☐ None of the above
☐ Corticosteroids *specify dose and duration*
☐ Radiation therapy

* See "Examples of immunosuppressants, antineoplastics, and immunomodulators" on next page

_____

Treatment and response:
List patient treatment regimen and outcome of the event below. Include dates of treatment, response to treatment, and hospitalization dates if relevant.

_____
_____

What was the **outcome** of the event?

☐ Resolved; Date:
☐ Ongoing
☐ Resolved with sequelae; Which?
☐ Death; Date:

Additional details:

_____
_____
_____

*** Examples of immunosuppressants, antineoplastics, and immunomodulators**

(Please consider that this list does not include all drugs that can suppress the immune system.)

Adalimumab, Alefacept, Alemtuzumab, Anakinra, Azathioprine, Cladribine, Cyclophosphamide, Cyclosporine, Daclizumab, Dimethyl fumarate, Diroximel fumarate, Efalizumab, Etanercept, Fingolimod, Fludarabine, Glatiramer acetate, Infliximab, Interferons, Intravenous immunoglobulin, Leflunomide, Mercaptopurine, Methotrexate, Methylprednisolone, Mitoxantrone, Monomethyl fumarate, Mycophenolate mofetil, Ocrelizumab, Ofatumumab, Ozanimod, Pemetrexed, Ponesimod, Prednisolone, Rituximab, Siponimod, Teriflunomide, Trastuzumab and Ublituximab

Targeted follow-up questionnaire for PML v.2.0

Annex 4.2 Serious Herpes Infections

Manufacturer Receipt Date (dd/mm/yyyy): ___/_____/_____ **Argus case ID: _____**

Batch number: _____

Targeted Follow-up Checklist (V2.0)
Serious Herpes Infections

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Event Description

1. Confirm the type of herpes virus infection:

☐ Varizella zoster virus (Human Herpesvirus (HHV)-3) ☐ Herpes simplex virus 1 or 2 (HHV-1/-2)
☐ Other

☐ Primary infection ☐ Reactivation ☐ Unknown/undetermined

2. Specify diagnosis (including complications, if any), the date the diagnosis was made and current clinical status.

3. For this adverse event, did the patient present with any of the following signs or symptoms? **Check all that apply.**

Skin: ☐ Skin infection (provide clinical description and specify the involved dermatome(s):
☐ Cutaneous dissemination

Central nervous system: ☐ CNS dissemination ☐ Meningitis
☐ Encephalitis ☐ Myelitis ☐ Confusion
☐ Psychotic symptoms ☐ Impaired consciousness ☐ Aphasia
☐ Seizures ☐ Sensitivity to light ☐ Neck stiffness

Ocular involvement: ☐ Retinal necrosis ☐ Decreased visual acuity
☐ Eye redness ☐ Eye pain
☐ Blindness one/both eye(s)

Others: ☐ Visceral dissemination ☐ Vasculitis ☐ Fever
☐ Headache ☐ Others (please specify)

Diagnostic tests

Were any of the following diagnostic tests performed for this adverse event? **Check all that apply.**

(Please specify tests, dates and results)

☐ CSF diagnostics ☐ HHV 1/2/3 PCR ☐ HHV 1/2/3 Immunoglobulin M/ Immunoglobulin

☐ Brain CT ☐ Brain MRI ☐ EEG

☐ Ocular diagnostics ☐ Other (specify)

Treatment for the adverse event

List the relevant treatments for the adverse event

Natalizumab Therapy Treatment					
Start date	Stop date	Dose & Frequency	Batch/lot	Route of administration	Number of infusions/injections

Other Treatment drugs					
Start date	Stop date	Dose & Frequency	Batch/lot	Route of administration	Number of infusions/injections

Patient History

Does the patient have any of the following current or past medical conditions? **Check all that apply.**

(Please specify medical condition, date of and patient age at onset)

☐ HHV 1/2 exposure (infection); Onset Date and patient age: _____

☐ HHV 3 exposure (varicella, shingles and/or vaccination); Onset Date and patient age: _____

Concomitant medications

Has the patient recently (i.e. within the past 6 months) taken any immunosuppressive therapies? **Check all that apply.**

(Please specify date, route, dose, duration, and indication)

☐ Corticosteroids Indication: _____Duration:_____ Dose & Route: _____

☐ Other immunosuppressive or immunomodulator therapies

Indication: _____ Duration:_____ Dose & Route: _____

☐ Cytotoxics Indication: _____Duration:_____ Dose & Route: _____

☐ Other (specify) Indication: _____Duration:_____ Dose & Route: _____

☐ None

Provide outcome for herpes meningitis/encephalitis and date of resolution if applicable:

☐ Recovered/ Recovering ☐ Recovered with sequelae ☐ unknown: _____

☐ Hospitalization ☐ Medically significant ☐ Other: _____

Further information

Would you be willing to provide further information? ☐ Yes ☐ No

Targeted follow-up questionnaire for Serious Herpes Infections v.2.0

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

<Draft/approved> key messages of the additional risk minimization measures

The Marketing Authorization Holder, according to agreement with the National Competent Authorities in each Member State where Tyruko® is marketed, will ensure that all physicians who intend to prescribe Tyruko® are provided with a physician pack containing the following elements:

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

Physician Information and Management Guidelines:

These educational materials shall contain the following key elements:

- Background information on the increased risk of atypical/opportunistic infections, in particular PML, which may occur with Tyruko® therapy, including a detailed discussion of data (including epidemiology, aetiology, and pathology) pertaining to the development of PML in Tyruko®-treated patients.
- Information relating to the identification of risk factors for Tyruko®-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.
- Information on extending the dosing interval for PML risk mitigation, including a reminder of the approved dosing schedule.
- 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 effectiveness of PLEX treatment and the management of associated 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 Tyruko® and for 6 months following discontinuation of therapy.
- A reminder on the need to discuss the benefit-risk profile of Tyruko® treatment with the patient, and the requirement to provide the patient information pack.

Patient alert card:

The patient alert card shall contain the following key elements:

- 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 Tyruko® treatment.
- Reminder to patients to read the package leaflet carefully before starting Tyruko®, and not to start Tyruko® 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 Tyruko®.
- 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 Tyruko® was started.

Treatment Initiation and Treatment Continuation Forms:

The treatment initiation and treatment continuation forms should contain the following elements:

- Information on PML and IRIS, including the risk of developing PML during Tyruko® 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:

The treatment discontinuation form should contain the following key elements:

- Information for the patient that PML has been reported up to 6 months after stopping Tyruko®, 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.