Unit: Technical Assessment Unit

Public assessment report for biological products

Tyruko

Administrative information:

Trade name of the medicinal product:	Tyruko
INN (or common name) of the active substance(s):	Natalizumab
Manufacturer of the finished product	Patheon Italia S.p.A., Italy.
Marketing Authorization holder	Sandoz GmbH, Austria.
Applied Indication(s):	Treatment of adult patients with highly active relapsing-remitting multiple sclerosis (RRMS).
Pharmaceutical form(s) and strength(s):	Concentrate for solution for Infusion, 300 mg/15 ml (20 mg/mL)
Route of administration	Intravenous (IV)
Type of registration (EMA/FDA – Local)	EMA&FDA

List of abbreviations

%RS	Relative α4-integrin receptor saturation
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular phagocytosis
ADCP	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of variance
ARR	Annualized relapse rate
AUC_{0-inf}	Area under the concentration time curve from time zero to infinity
AUC_{0-t}	Area under the effect curve from zero to last timepoint
$AUEC_{0-12w}$	Area under the effect time curve from time zero to 12 weeks
$AUEC_{4-12w}$	Area under the effect curve from four to 12 weeks
C1q	Complement factor 1q
CD19+	Cluster of differentiation 19 activation
CDC	Complement-mediated cytotoxicity
CI	Confidence interval
CL	Clearance
C_{max}	Maximum concentration

COVID-19	Coronavirus disease 2019
CTCAE	Common terminology criteria for adverse events
C_{trough}	Trough concentration
CV	Arithmetic Coefficient of variation
ECGs	Electrocardiogram
ECLIA	Electrochemiluminescence immunoassay
EDSS	Expanded disability status scale
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
E_{max}	Maximum effect
EU	European Union
EU	European union
FAS	Full analysis set
Fc	Fragment crystallizable
FcRn	Fc gamma neonatal receptor
Fcγ	Fc gamma
GCP	Good clinical practice
GdE	Gadolinium-enhancing
IgG	Immunoglobulin G
ISR	Injection site reaction
IV	Intravenous
JCV	John cunningham virus
k_{el}	Terminal elimination rate constant
LLOQ	Lower Limit of Quantification
MAA	Marketing authorization application
MAdCAM-1	ucosal vascular address in cell adhesion molecule 1
MedDRA	Medical dictionary for regulatory activities
MRIs	Magnetic Resonance Imaging
Nab	Neutralizing antibody
PD	Pharmacodynamics
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PP	Per protocol
PT	Preferred term
PY	Patient year
RRMS	Relapsing-remitting multiple sclerosis
SAE	Serious adverse event
SAF	Safety population
SD	Standard Deviation
SE	Standard error
SmPC	Summary of product characteristics
SMQ	Standardized meddra query
SOC	System Organ Class
SSW	Safety switch population

$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to Cmax
US	United states
VAS	Visual analog scale
VCAM-1	Vascular cell adhesion molecule-1
Vz	Volume of distribution
α4β integrin	Alpha-4 Beta integrin

Table of contents

1. General introduction about the product including brief description of the AI, its mode of action and indications……..……..……...3

2. Quality aspects……...……...3

2.2 Drug Substance (Active ingredient)……...……. 3

2.3 Drug product……3

3. Non-clinical aspects…….……..5

4. Clinical aspect……..…….…….7

5. Benefit/risk conclusion……...……...……...…….8

6. General Conclusion and Recommendations if any……..……..8

1. Introduction

The file evaluated according to EDA Reliance Model & the company submitted data which are the following:

1. Quality module-3 from the CTD file.
2. EMA Unredacted Assessment.

2. Quality aspects:

Manufacturer(s):

• Drug Substance

- The Active substance is manufactured at Polpharma Biologics S.A., Ul. Trzy Lipy 3 , 80-172 Gdansk - POLAND ;

• Drug product

- The Finished product is manufactured at Patheon Italia S.p.A. , Via Morolense 5 , Ferentino FR , 03013 - Italy - ITALY ;

Stability

Approved Shelf Life

Active product: 2 years.
Finished product: 3 years.

Approved Storage Conditions:

Active Substance: 5 ± 3ºC

Finished product: -Store in a refrigerator (2 ˚C to 8 ˚C).
-Keep the vial in the outer carton in order to protect from light.
-Do not freeze.

3. Non –clinical aspect:

- **Pharmacodynamic** similarity of Tyruko to both US- and EU-Tysabri was tested using in-vitro studies that assessed their binding affinity to α4β1 and α4β7 integrin as well as their ability to inhibit interaction between α4-integrin and VCAM-1 or MAdCAM-1. Comparability studies also assessed Fc-related effector functions (ADCC, CDC & ADCP), binding to Fcγ receptors, interactions with FcRn receptor, as well as binding to C1q. Similarity was demonstrated between Tyruko and both US- and EU-Tysabri.
- Further studies, including in vivo primary PD studies, secondary PD, safety pharmacology, Pharmacodynamic drug interactions or PK studies of Tyruko, have not been performed. This is accepted in biosimilar products nonclinical development program as per the guidelines.
- Studies regarding **toxicology**, including developmental and reproductive toxicity studies, are not required for non-clinical testing of biosimilars according to the EMEA/CHMP/BMWP/42832/2005 Rev1 guideline. Neither are studies regarding safety pharmacology, carcinogenicity and local tolerance.

  In **4-week repeated dose** study, the design is regarded as appropriate in terms of species selection, used dosages, frequency and route of administration. The lack of a recovery period is accepted, because reported findings of Natalizumab are already known for Tysabri and related to its pharmacological activity as a monoclonal antibody binding to α4 integrin. Blocking of the α4 integrin also allows migration of the immature red blood cells from the bone marrow and, consequently, the increase in progenitor cell circulation.

Observed findings, such as *increased hematological parameters* (lymphocytes, reticulocytes; myeloid: erythroid ratio), were seen in all animals treated with either Tyruko or Tysabri. *Altered trafficking of lymphocytes*, characterized by an increase in white blood cells, has already been reported for Tysabri and was described as reversible, ***without any adverse toxicological changes***.

- A main issue remains *the limited number of animals per treatment group* (3/sex/group), which does not allow reliable distinguishing between differences in findings of Tyruko and Tysabri® treated animals and *individual data variability*. **Based on** the results of the study and **taking into consideration** the intrinsic variability of the model, the limited sample size and the absence of adverse histopathological findings in any of the animals, there ***was no noteworthy difference between the animals treated with Tyruko and the animals treated with Tysabri® from a toxicity and TK point of view***.

No new unexpected toxicities were identified for Tyruko. The marginal differences observed are considered to be within the biological variability. The toxicological similarity assessment raised no concerns. Therefore, **data obtained from this repeat-dose toxicology study can be regarded as supportive information**.

Discussion for possible ***reasons for ADA detection prior to first infusion on day 1*** for female animal number 30 of the 30mg/kg Tysabri treatment group revealed that **a non-ADA mechanism (**such as **the** existence of pre-existing drug-reactive antibodies as well as other non-antibody interferences in the ELISA assay**) seems to be more likely.** As it was confirmed that, according to the protocol, only treatment naive animals were used in the study, consistent discrepancy at both pre- dose and on day 30 makes contamination of the serum samples unlikely, as well as no ADAs developed in other animals in the high dose group due to interference with high Tysabri levels. Furthermore, serum natalizumab levels of this female animal were similar to the serum natalizumab concentrations in other animals of this dose group and ADA detection at pre-dose in female number 30 had no influence on data interpretation in this study.

4. Clinical aspect:

➢ Clinical Overview

The development program comprises four clinical studies, **one pivotal PK/ PD** study with PB006, US-Tysabri, and EU-Tysabri in healthy subjects, **one pivotal Phase III** study with PB006 versus EU-Tysabri in patients with **RRMS**, **one pilot PK/PD** study with EU-Tysabri in **healthy subjects**, and **one supportive safety** study with PB006 in **healthy subjects**.

The **3-arm PK/PD** study in healthy subjects (PB006-01-03) was **one** of the **two pivotal** studies in the clinical program demonstrating similarity of **PB006** versus **US-Tysabri** and **EU-Tysabri**. This PK/PD study demonstrated **PK similarity** and included **sensitive PD** endpoints which support the demonstration of **similar efficacy**. In addition, the **clinical pharmacology** data generated for **EU-Tysabri** and **US-Tysabri** in this study established the scientific bridge between both products.

The **Phase III** study in **RRMS** patients **(PB006-03-01)** was the **second pivotal** study in the clinical program. The study showed that there were **no clinically meaningful differences** with regard to **efficacy**, **immunogenicity** and **safety** between **PB006** and **EU-Tysabri** in the target population.

Pilot study Tysabri Pilot-01-01 in healthy subjects. The purpose of this **pilot study** was to **collect PK/PD** data with **three** different doses of **EU-Tysabri** in order to establish appropriately sensitive study design features, including the dose selection and **primary endpoints**, for the **pivotal PK/PD** study **(PB006-01-03)**.

➢ **Clinical Efficacy**

- The **primary objective**, to demonstrate the **similarity** in cumulative number of **new active lesions** over **24 weeks** for **PB006** versus **EU-Tysabri**, was met. **Similarity** was demonstrated, as the **95% CI** for the difference **EU-Tysabri versus PB006** was well within the specified **similarity** margins **(-2.1; 2.1)**. The **95% CI** was **-0.613; 0.944**.
- Results from the **primary analysis** were confirmed in **all sensitivity analyses** (based on the **FAS population**, analysis with **corrected stratification** factors and analysis using **multiple imputation**). In the sensitivity analysis of the primary endpoint excluding patients from site 7002, the **95% CI** for the **difference EU-Tysabri** versus **PB006** was still well within the specified **similarity** margins **(-2.1; 2.1)**, confirming that the **data integrity** issue **did not** impact the outcome of the **primary efficacy analysis**.
- The **secondary** endpoint **cumulative number of new active lesions** over **48 weeks** was (mean [SD]) **1.5 (3.72)** in the **PB006** group and **2.3 (5.68)** lesions in the **EU-Tysabri** group. **Numerical differences** observed between groups were considered to be **not clinically meaningful**.
- The **secondary endpoint cumulative** number of **new GdE T1-weighted lesions** over **24 weeks** and **48 weeks** was **similar** in the **2 groups**, with (mean [SD]) **0.3 (1.01)** lesions with **PB006** versus **0.4 (1.25)** lesions with **EU-Tysabri** over **24 weeks**, and **0.3 (1.02)** lesions with **PB006** versus **0.4 (1.39)** lesions with **EU-Tysabri over 48 weeks**.
- The **secondary** endpoint **percentage** of patients **without new GdE T1-weighted lesions** was **similar** in the **PB006** and **EU-Tysabri** groups over **24 weeks (83.2%** and **78.9%** patients in the **PB006** and **EU-Tysabri** groups, respectively) and over **48 weeks** (**80.2%** and **77.7%** patients in the **PB006** and **EU-Tysabri** groups, respectively).
- Regarding the secondary endpoint **cumulative number of new/enlarging T2-weighted lesions** over **24 weeks**, mean (SD) of **1.5 (3.79)** lesions were reported with **PB006**, compared to **2.0 (4.12)** lesions with **EU-Tysabri**. Over **48 weeks**, mean (SD) of **1.6 (3.90)** lesions were reported with **PB006** compared to **2.4 (5.79)** lesions with **EU-Tysabri**. **Numerical differences** observed between groups were considered to **be not clinically meaningful**.
- The **secondary** endpoint **percentage of patients without new/enlarging T2-weighted lesions** was **similar** in the **PB006** and **EU-Tysabri** groups over **24 weeks** (**57.3%** of patients with **PB006** and

54.1% of patients with **EU-Tysabri**) and over **48 weeks** (**54.2%** patients with **PB006** and **50.5%** patients with **EU-Tysabri**).

- The **secondary** endpoint **cumulative number of persistent lesions** was **similar** in the **PB006** and **EU-Tysabri** groups over **24 weeks** (mean [SD] of **0.5 [2.46]** with **PB006** and **0.4 [2.92]** with **EU-Tysabri**) and over **48 weeks** (mean [SD] of **0.5 [2.55]** with **PB006** and **0.6 [3.35]** with **EU-Tysabri**).
- The **secondary** endpoint **annualized relapse rate over 24 weeks** was **0.206** with **PB006** versus **0.152** with **EU-Tysabri**. Over **48 weeks**, the **rate was 0.174** with **PB006** versus **0.133** with **EU-Tysabri**. Generally, **annualized relapse rates** were **low** in **both** groups. **Numerical differences observed** between groups were considered to be **not clinically meaningful**.
- From the presented data on **efficacy**, **biosimilarity** between the **PB006** and **EU-Tysabri** can be concluded.

➢ **Clinical Safety and Immunogenicity**

- In the **single-dose healthy** subject study, **PB006-01-03**, the percentage of patients with **TEAEs** was **similar** for **PB006, US-Tysabri and EU-Tysabri.** On the **PT level**, most commonly reported was **headache**, followed by **AEs related to the injection/infusion**. While on the **level of individual PTs** the **frequencies** may have **numerically differed between** the **PB006, the EU-Tysabri and US-Tysabri** groups, the **AE** profile was overall **considered** to be **similar** between the **3 groups**. There were **2 subjects with SAEs**, **both** in the **US-Tysabri** group. **All SAEs** were **unlikely related to study drug**. **No TEAEs** leading to **discontinuation** occurred in the study. Overall, the **safety** profile was **similar** across the **3 groups**.
- In the **multiple-dose study in RRMS** patients, **PB006-03-01**, the percentage of patients with **TEAEs** was **similar** in the **PB006** and the **EU-Tysabri** group. **Most** commonly reported were **headache and nasopharyngitis**. While on the **level of individual PTs** the frequencies may have **numerically differed** between the **PB006** and **EU-Tysabri** groups, sometimes favoring **EU-Tysabri** and sometimes favoring **PB006**, the AE profile was overall considered to be **similar** between the **2 groups**. There were **5 patients** with **SAEs** (balanced across groups), with all **SAEs except** for the event of **hypotension** being **not or unlikely related** to study drug. **TEAEs** leading to **discontinuation** occurred in **8 patients** in the **PB006** group and **4 in the EU-Tysabri** group. **Most** common **TEAEs** leading to **discontinuation** were **pruritus and urticaria**, which are known and common adverse drug reactions of natalizumab. **AESIs** were generally balanced across groups. **Most** commonly reported **AESIs** were events of herpes. **No** subjects had any **signs suggestive** of **PML** during the study or in the **6-month PML** follow-up. **Comparative results** from the group switching treatment with **EU-Tysabri** to **PB006** after 24 weeks versus the **EU-Tysabri** continuing group **did not** reveal any clinically meaningful differences in the **AE or immunogenicity** profile.

Overall, the **safety profile** was similar across the **2 groups**. The safety data from this study were consistent with data as presented in the **Tysabri SmPC**.

- In summary, the results from the clinical studies confirmed similar **safety and immunogenicity** for **PB006** and the **reference** product. **No increased immunogenicity or hypersensitivity** reactions were observed in the **Phase 3** study after the switch from EU-Tysabri to PB006.

➢ **Benefit-Risk Assessment**

- **Based on clinical data**, **biosimilarity of PB006 and Tysabri** was shown, and therefore the same **benefit-risk ratio** applies for the **biosimilar as** for the **reference product**.
- **PB006** will be administered with the same dosing and **administration route** for the **same indications as Tysabri**, and the same label is proposed as for the **reference product**.
- The **difference** in formulation between **PB006 and Tysabri** did **not** result in any **clinically meaningful differences in safety**.

➢ **Clinical Conclusion**

In conclusion, the totality of the **clinical data** confirmed that there are **no clinically meaningful differences** between the **biosimilar and the reference** product. Overall, the results of the global development program confirmed that **PB006** is **biosimilar** to the reference product **Tysabri**.

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.

https://www.ema.europa.eu/en/documents/overview/tyruko-epar-medicine-overview_en.pdf