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ADIS BIOSIMILAR BRIEF

PB006: A Natalizumab Biosimilar

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Abstract
PB006 (Tyruko®) is the first biosimilar of the reference monoclonal anti-α4-integrin antibody natalizumab. It is approved for use in the same indications for which reference natalizumab is approved, as a single disease-modifying therapy in adults with highly active relapsing-remitting multiple sclerosis (RRMS). PB006 has similar physicochemical and pharmacodynamic properties to those of reference natalizumab, and the pharmacokinetic similarity of the agents has been demonstrated in a study in healthy subjects. PB006 demonstrated clinical efficacy similar to that of reference natalizumab in patients with RRMS, and was generally well tolerated in this population. The tolerability, safety and immunogenicity profiles of PB006 were similar to those of reference natalizumab, and switching from reference natalizumab to PB006 appeared to have no impact on tolerability or immunogenicity. The role of reference natalizumab in the management of RRMS is well established and PB006 provides an effective biosimilar alternative for patients requiring natalizumab therapy.

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PB006: Key Points

Biosimilar to reference natalizumab
Similar efficacy, tolerability and immunogenicity to reference natalizumab in patients with RRMS
Switching from reference natalizumab appears to have no impact on tolerability or immunogenicity
Approved for the same indications for which reference natalizumab is approved

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1 Introduction

PB006 (Tyruko®) is the first biosimilar of the reference monoclonal anti-α4-integrin antibody natalizumab and is approved in the EU for the same indications as the reference drug (Table 1) [1]. PB006 has similar physicochemical characteristics [2] and pharmacodynamic properties [3] to those of reference natalizumab, and pharmacokinetic similarity of the agents has also been demonstrated [3]. This article summarises, from an EU perspective, the key features of PB006 and its clinical use in the treatment of relapsing-remitting multiple sclerosis (RRMS).

2 Clinical Pharmacology

PB006 displays similar pharmacokinetic and pharmacodynamic behaviour to reference natalizumab, based on the findings of a randomized, double-blind, single-dose study in 453 healthy subjects. Participants in the study were randomized (1 : 1 : 1) to receive a single intravenous infusion of PB006, EU-sourced reference natalizumab or US-sourced reference natalizumab, each at a dose of 3 mg/kg [3].

Pharmacokinetic similarity between PB006 and EU- and US-sourced reference natalizumab (as well as between the two reference drugs) was demonstrated in the study [3]. Similar serum concentration kinetics for total natalizumab were displayed for all three drugs throughout the post-dose evaluation period. In the primary pharmacokinetic endpoint analysis, the 90% confidence interval (CI) for the area under the curve from

Table 1 PB006 (Tyruko®) prescribing summary in the EU [1][a]

Approved indications	
RRMS[b]	In patients with highly active disease despite a full and adequate course of treatment with ≥ 1 DMT[c]
	In patients with rapidly evolving severe RRMS defined by ≥ 2 disabling relapses in 1 year, and with ≥ 1 gadolinium enhancing lesion on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI
Dosage regimen	
300 mg once every 4 weeks	
Administration	
PB006 is supplied as a 15-mL concentrated (20 mg/mL) solution	
For administration, the 15-mL concentrate should be diluted in 100 mL of sodium chloride 9 mg/mL (0.9%) solution; the diluted PB006 solution for infusion should be administered by intravenous infusion over ~ 1 h	
Use in special populations	
Pregnancy	Use during pregnancy only if clearly needed; if a woman becomes pregnant while taking PB006, discontinuation of PB006 should be considered (potential risk of reproductive toxicity, based on animal data)
Lactation	Avoid breastfeeding during treatment with PB006

DMT disease-modifying therapy, *MRI* magnetic resonance imaging, *RRMS* relapsing-remitting multiple sclerosis

[a]Consult local prescribing information for details including pre- and post-medications, contraindications, warnings and precautions

[b]As a single DMT in adults with highly active disease

[c]Consult local prescribing information for exceptions and information about washout periods

time of dosing extrapolated to infinity was within the prespecified similarity margin of 0.8–1.25 for all pairwise comparisons between the three drugs. Analyses across a range of other pharmacokinetic parameters further supported the pharmacokinetic similarity between all three drugs [3].

The co-primary pharmacodynamic endpoints in the study were the baseline-adjusted CD19+ cell counts and the percentage α4-integrin receptor saturation [3]. Based on the demonstrated pharmacokinetic similarity between EU- and US-sourced reference natalizumab, data for the two reference drugs were pooled for the co-primary pharmacodynamic endpoint analyses [1].

Pharmacodynamic similarity between PB006 and reference natalizumab was demonstrated, with the 95% CIs of the geometric mean ratios for the co-primary pharmacodynamic endpoints within the prespecified similarity margin of 0.8–1.25 [3]. The pharmacodynamic similarity of PB006 to EU- and US-sourced reference natalizumab was further evaluated through secondary pharmacodynamic endpoints exploring changes in pharmacodynamic biomarkers which had been selected to reflect the natalizumab mechanism of action (Table 2), including soluble vascular cell adhesion molecule (sVCAM), soluble mucosal vascular addressin cell adhesion molecule (sMAdCAM), CD34+ cells and CD19+ cells [1]. Excepting the comparison of sVCAM levels between PB006 and EU-sourced reference natalizumab (95% CI 0.97–1.29), all secondary pharmacodynamic endpoints in the study were met, further supporting the pharmacodynamic similarity between PB006 and (EU- and US-sourced) reference natalizumab [3].

3 Clinical Efficacy

The similarity in clinical efficacy of PB006 to reference natalizumab was evaluated in the multicentre, randomized, double-blind, active-controlled, phase III ANTELOPE trial in adult patients (aged 18–60 years) with RRMS [4]. Eligible patients in ANTELOPE had experienced one or more documented relapse in the previous year, and at screening had at least one gadolinium-enhancing T1-weighted or nine or more T2-weighted brain lesions and a Kurtzke Expanded Disability Status Scale (EDSS) score of 0 to 5. Patients with prior immunosuppressant use and those who experienced a relapse within 30 days before screening and until the first dose of study drug were excluded. Additionally, the John Cunningham virus (JCV) index, based on anti-JCV antibody levels, was used for risk stratification [4]. With a JCV index of > 1.5 in patients with no prior immunosuppressant use being associated with an increased risk of developing progressive multifocal leukoencephalopathy (PML) [5], patients with a JCV index of > 1.5 at screening were excluded from the trial [4]. Randomization was stratified by gadolinium-enhancing lesions (absence or presence), the number of T2 lesions (≤ 15 or > 15) and JCV status (positive or negative) [4].

In total, 265 patients were randomized (1 : 1) to receive PB006 300 mg or reference natalizumab 300 mg by intravenous infusion every 4 weeks from week 0 to week 44 (12 infusions in total) (Fig. 1) [4]. At week 24, patients in the reference natalizumab group underwent rerandomization, with 30 patients switched to PB006 for the remainder of the study (to receive a total of six infusions of reference natalizumab and six infusions of PB006). One patient in the PB006 group withdrew consent before receiving any dose of study drug. Magnetic resonance imaging (MRI) was performed at weeks 0 (baseline), 8, 16, 20, 24 and 48 (end-of-study visit) and at a PML follow-up visit (week 68). The primary efficacy endpoint was the cumulative number of new active lesions on MRI of the brain (new

Table 2 Biosimilarity summary of PB006 [1, 2]

Mechanism of action	A recombinant humanised anti-α4-integrin antibody that binds to the α4-subunit of α4β1 and α4β7 integrins expressed on the surface of all leukocytes except neutrophils, thereby inhibiting the α4-mediated adhesion of leukocytes to their counter-receptors, vascular cell adhesion molecule-1 and mucosal vascular addressin cell adhesion molecule-1; disruption of these molecular interactions prevents transmigration of mononuclear leukocytes across the endothelium into parenchymal tissue [1]
Physicochemical characterisation	Identical primary structure and similar physicochemical and biophysical properties to EU-sourced reference natalizumab [2]
Pharmacodynamic similarity	Similar to reference natalizumab with respect to CD19+ cell counts, percentage α4-integrin receptor saturation and several other relevant pharmacodynamic biomarkers [3]
Pharmacokinetic similarity	Three-way pharmacokinetic similarity was demonstrated between PB006 and EU- and US-sourced reference natalizumab (90% CIs of the geometric mean for serum test/reference ratios were within the prespecified margin for similarity of 0.8–1.25 for all comparisons) [3]
Immunogenicity	Similar total incidence of antidrug antibody and natalizumab-neutralising antibody positivity between patients receiving PB006 and reference natalizumab in the phase III ANTELOPE trial [4]
Efficacy and tolerability	Similar efficacy and tolerability to reference natalizumab in patients with relapsing-remitting multiple sclerosis in the phase III ANTELOPE trial [4]

gadolinium-enhancing T1-weighted lesions and new/enlarging T2-weighted lesions) over 24 weeks in the per-protocol population [4].

In the full analysis set (FAS) population ($n = 264$), patients had a mean age of 36.7 years [4]. Baseline disease characteristics were well balanced between the PB006 ($n = 131$) and reference natalizumab ($n = 133$) groups, with a mean time since diagnosis of 5.3 and 5.3 years, a mean time since last relapse of 5.1 and 5.9 months and a mean EDSS score of 3.4 and 3.2 in the respective groups. Approximately 40% of patients in each group were positive for anti-JCV antibodies at baseline (27% across groups with a JCV index of ≤ 0.9 and 13% with a JCV index of 0.9–1.5). In total, 93.6% of patients in the FAS population completed the 24-week primary treatment period (93.1% in the PB006 group, 94.0% in the reference natalizumab group) with 90.5% of patients completing the 48-week total study treatment period [4].

The similarity in clinical efficacy of PB006 to reference natalizumab was demonstrated in the ANTELOPE trial [4]. In the primary endpoint analysis, the model-based mean difference in cumulative number of new active lesions between treatment groups at week 24 was 0.17 (least-squares means: PB006, 0.34; reference natalizumab, 0.45), with the 95% CI (− 0.61 to 0.94) for the point estimate within the prespecified margin of ± 2.1. A sensitivity analysis conducted in the FAS population supported the primary endpoint findings. After database lock, it was identified that in 62 (23.4%) of the 265 patients who underwent randomization one or more stratification factor had been incorrectly recorded at baseline. Given that the study was blinded and randomization was performed based on the strata as entered, data integrity was not considered to be affected. An additional analysis conducted based on the corrected stratification factors and performed to assess any potential impact of the erroneous stratification supported the robustness of the primary endpoint findings, with the 95% CI (− 0.10 to 0.23) for the point estimate (0.06) again within the prespecified margin of ± 2.1 [4].

The similarity in efficacy between PB006 and reference natalizumab was further supported by a range of secondary radiological outcomes, with no significant between-group differences observed, and by the findings from secondary clinical endpoints, including the annualised relapse rate (ARR) and the mean change from baseline in EDSS score at 24 and 48 weeks [4]. In the FAS population, in the PB006 and reference natalizumab groups, respectively, the ARRs at 24 weeks were 0.21 and 0.15, and at 48 weeks were 0.17 and 0.13. Analyses in the safety switch population, which included all patients who received one or more dose of study drug after the rerandomization timepoint, also showed a similar ARR between all treatment groups (PB006, $n = 122$; reference natalizumab, $n = 95$; reference natalizumab/PB006 switch, $n = 30$), both at rerandomization at 24 weeks (0.11–0.19 across groups) and at 48 weeks (0.11–0.17). Minimal changes from baseline in EDSS score were observed in both the PB006 and reference natalizumab groups in the FAS population, both at 24 weeks (− 0.03 and 0.00) and at 48 weeks (− 0.14 and − 0.05). Similarly, in the safety switch population, changes in EDSS score from week 24 to week 48 were minimal and similar between all treatment groups (− 0.02 to − 0.10 across groups) [4].

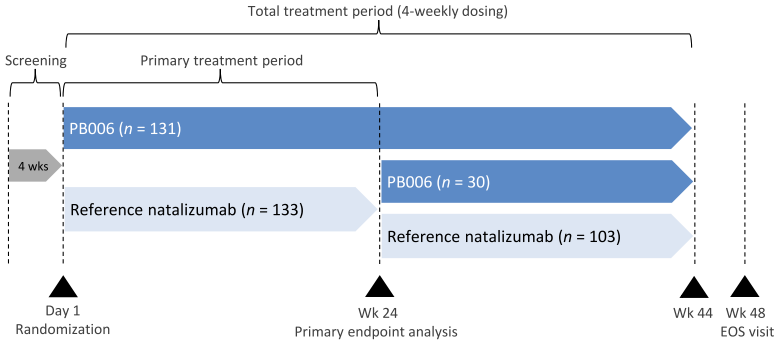

Fig. 1 Design of the phase III ANTELOPE trial in patients with relapsing-remitting multiple sclerosis [4]. *EOS* end-of-study, *wk(s)* week(s)

4 Tolerability and Safety

PB006 displayed similar tolerability and safety to reference natalizumab in the phase III ANTELOPE trial in adult patients with RRMS (Sect. 3) [4]. In the PB006, reference natalizumab and reference natalizumab/PB006 switch groups, respectively, treatment-emergent adverse events (TEAEs) were experienced by 64.9%, 68.9% and 73.3% of patients; event rates per 100 patient-years in the respective groups were 192.3, 194.7 and 219.6. Among all treatment groups, the most common TEAEs by system organ class were infections and infestations (reported in 29.8%, 33.0% and 50.0% of patients in the PB006, reference natalizumab and reference natalizumab/PB006 switch groups, respectively) and nervous system disorders (25.2%, 23.3% and 26.7%), with the most common (incidence of $\geq$ 10% in any group) individual TEAEs being headache (19.1%, 18.4% and 13.3%), nasopharyngitis (8.4%, 7.8% and 16.7%), COVID-19 (8.4%, 5.8% and 13.3%) and depression (2.3%, 1.0% and 10.0%). Across all treatment groups, most TEAEs were grade 1 in severity. Grade 3 TEAEs occurred in four patients in the PB006 group up to week 48 (one case each of increased alanine aminotransferase, increased blood triglycerides, nasal septum deviation and urticaria), in one patient in the reference natalizumab group (pain in extremity) and in no patients in the reference natalizumab/PB006 switch group. No grade 4 or grade 5 TEAEs were reported in any group [4]. The similarity between PB006 and reference natalizumab in terms of tolerability and safety was also supported by the single-dose trial in healthy subjects (Sect. 2), with no notable differences in the numbers and types of TEAEs observed between groups in the trial [3].

A JCV index of $\leq$ 1.5 was one of the inclusion criteria for the ANTELOPE trial (Sect. 3). At week 48 of the trial, seroconversion to a JCV index of > 1.5 was reported in a similar percentage of patients in the PB006 (6.0%) and reference natalizumab (5.9%) groups [4]. No cases of PML were reported either in the ANTELOPE trial (Sect. 3) [4] or the single-dose study (Sect. 2) [3].

5 Immunogenicity

PB006 appeared to have similar immunogenicity to reference natalizumab, based on findings from the ANTELOPE trial (Sect. 3) [4]. In the PB006 and reference natalizumab groups, respectively, the total incidence of antidrug antibody (ADA) positivity at week 24 was 79% and 74%, with 69% and 66% of patients positive for natalizumab-neutralising antibodies (NAbs). No increase in immunogenicity was observed in patients switching from reference natalizumab to PB006, with no patients who were negative for ADAs or NAbs at week 24 subsequently seroconverting to positivity for ADAs or NAbs after switching from reference natalizumab to PB006 [4].

6 Conclusion

PB006 is a natalizumab biosimilar with similar efficacy, tolerability, safety and physicochemical and biological characteristics to the reference product (Table 2). Based on the structural, physicochemical and functional analyses, as well as clinical data available in patients with RRMS (Table 2), PB006 has been approved in the EU for the same indications for which reference natalizumab is approved (Table 1).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40261-024-01360-4.

Declarations

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Authorship and Conflict of interest During the peer review process, the manufacturer of PB006 was offered an opportunity to review this article. Changes resulting from comments received were made on the basis of scientific and editorial merit. Matt Shirley is a salaried employee of Adis International Ltd/Springer Nature, and declares no relevant conflicts of interest. All authors contributed to this article and are responsible for its content.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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