INTRODUCING THE BIOSIMILAR PARADIGM TO NEUROLOGY – THE TOTALITY OF EVIDENCE FOR THE FIRST BIOSIMILAR NATALIZUMAB

BioDrugs

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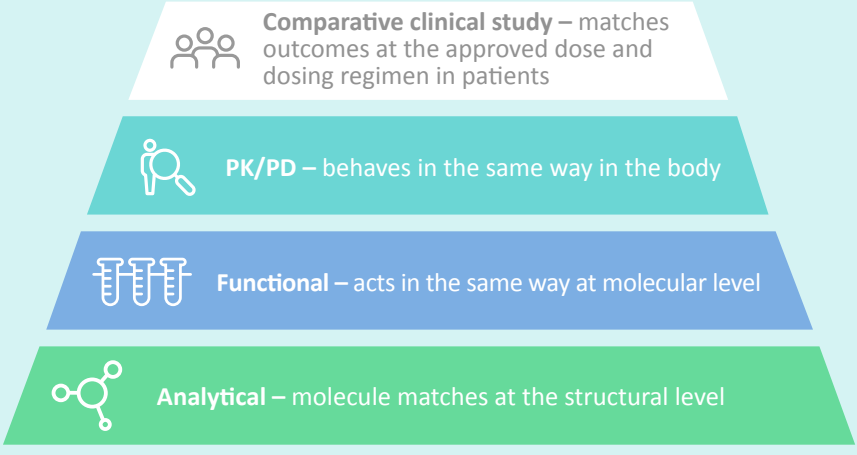
Totality of Evidence (ToE)

What is ToE and why is it required?

The ToE is a comprehensive data package typically built from analytical and functional data, which are the cornerstone of a biosimilar development process, together with clinical study data, through a tightly regulated approach. These data confirm that a biosimilar and its reference medicine have matching efficacy, safety, and immunogenicity with no significant differences between their clinical outcomes. The ToE is used by regulatory authorities, for example the US Food and Drug Administration and European Medicines Agency, to assess the approval of proposed biosimilar medicines

The ToE for regulatory approval of a proposed biosimilar medicine



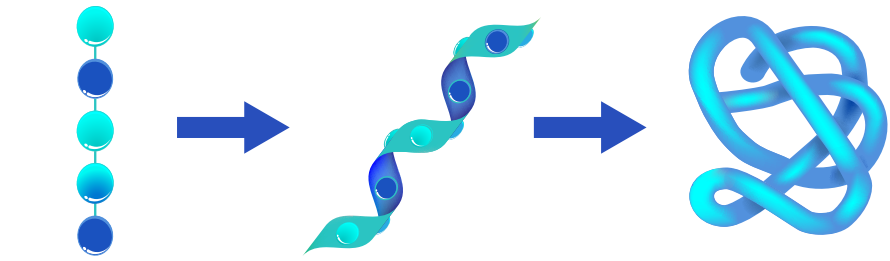
What is biosimilar natalizumab?

Biosimilar natalizumab (PB006 [biosim-NTZ]; developed by Polpharma Biologics S.A and marketed globally as Tyruko®, Sandoz) is a biosimilar to reference natalizumab (Tysabri® [ref-NTZ], Biogen, Cambridge, MA*) for the treatment of relapsing forms of multiple sclerosis. It is the first biosimilar medicine developed for use in multiple sclerosis

Analytical and functional characterization of biosim-NTZ

Biosim-NTZ has the same structure as ref-NTZ

Highly sensitive, state-of-the-art analytical techniques showed that the structure of biosim-NTZ matched that of ref-NTZ, from the most basic to the highly complex 'building blocks' of their structures



Primary amino acid sequence

Secondary protein structure

3D arrangement of atoms in a protein

- Biosim-NTZ was shown to have an identical amino acid sequence and indistinguishable 3D structure to ref-NTZ
- Biosim-NTZ exhibited Fab-arm exchange (see glossary) at similar rates to ref-NTZ, showing that the antibody reacts in the same way once in the body

*Tysabri® is a registered trademark of Biogen MA, Inc.

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Biosim-NTZ matched ref-NTZ in stability tests

It is important that medicines are tested under different conditions to check their stability, such as high temperature and oxygen levels, exposure to light, and acidic conditions

Biosim-NTZ was compared against ref-NTZ under a variety of conditions. No significant differences in performance for any storage or stability conditions were observed between biosim-NTZ and ref-NTZ

Biosim-NTZ and ref-NTZ had a matching effect on natalizumab's intended target

Biosim-NTZ and ref-NTZ bound to their target in the same way. In the body, activating these receptors would stop the specific immune cells moving from the blood vessels into the brain or gut. This indicates that biosim-NTZ works in the same way and has the same mode of action as ref-NTZ

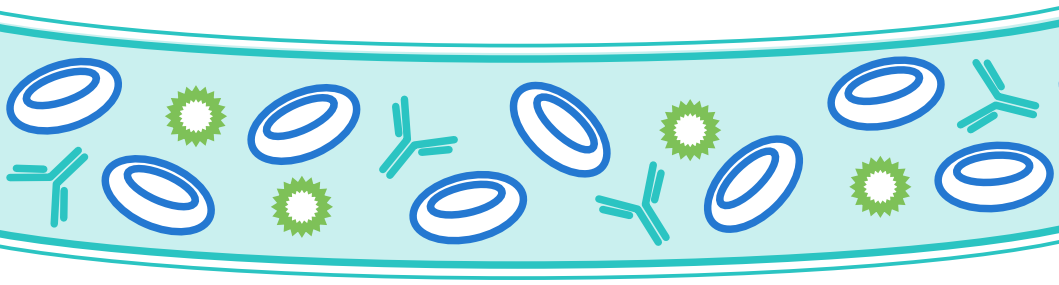
What does the analytical and functional characterization study tell us?

The state-of-art analytical and functional assessments confirmed matching profiles between biosim-NTZ and ref-NTZ in terms of how they are built, how they behave under different conditions, and how they affect their target cells. As the molecules match and act in the same way, they can be expected to have the same clinical effect in the body

PK/PD clinical study in healthy subjects

- 453 healthy participants split into two groups
- 18–65 years
- 18.5–30.0 kg/m^2
- Single intravenous infusion of 3 mg/kg biosim-NTZ or ref-NTZ
- 85 days' duration

Biosim-NTZ behaved the same way in the body as ref-NTZ



After receiving biosim-NTZ, the amount of medicine in the blood was measured. These measurements confirmed that biosim-NTZ was present in the blood at similar concentrations to ref-NTZ

Biosim-NTZ attached to its target receptors in the same way as ref-NTZ, stopping immune cells from entering the brain. This could be seen by an increase of blocked immune cells in the blood

Following the increase of these immune cells in the blood, biosim-NTZ had the same effect on them as ref-NTZ over time, showing that biosim-NTZ and ref-NTZ acted the same way in the body

Biosim-NTZ did not show any differences in safety or immunogenicity compared to ref-NTZ

Similar incidences of side effects were observed with biosim-NTZ and ref-NTZ. Both biosim-NTZ and ref-NTZ caused a similar reaction in the body's immune response, affecting the same cellular and molecular targets over the same period of time

What do the results of the PK/PD study tell us?

The PK/PD analysis indicated that biosim-NTZ behaves in the body in the same way, and has the same effect on the same target cells as ref-NTZ

Comparative clinical study in patients with relapsing-remitting multiple sclerosis (RRMS)

A comparative clinical study was conducted in the intended RRMS patient population to complete the ToE data package for biosim-NTZ. The study also analyzed the effect of biosim-NTZ after switching from ref-NTZ

264 patients with RRMS split into two groups

18–60 years

≥1 relapse in the past year and specified brain lesion presence*

300 mg intravenous infusions of biosim-NTZ or ref-NTZ every 4 weeks for a total of 12 infusions

Treated for 48 weeks

48 centers across Europe

*'**Specified brain lesion presence**' was defined as having either ≥1 T1-weighted lesions or ≥9 T2-weighted brain lesions. T1 and T2 are technical terms used for different types of brain scans.

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Biosim-NTZ showed the same effectiveness as ref-NTZ in managing RRMS

Biosim-NTZ and ref-NTZ effectively prevented the formation of new brain lesions in the brain in the same way, achieving the main objective of this study. Additionally, disease activity was suppressed similarly by both biosim-NTZ and ref-NTZ. This was shown by repeated brain scans

Both medicines had the same positive effect in minimizing relapses and maintaining disability scores for patients during the same time period, which shows that both medicines were equally effective in managing the risk of disease relapse

Safety results

Similar incidences of side effects were observed with biosim-NTZ and ref-NTZ

- The main reasons people stopped taking ref-NTZ or biosim-NTZ were itching and hives, which are known side effects of natalizumab
- No side effects were classified as serious, and there were no fatal cases or severe reactions
- No cases of progressive multifocal leukoencephalopathy, a rare and potentially serious viral infection of the brain, were identified during the treatment period or the follow-up visit

In patients with RRMS, biosim-NTZ did not show any differences in immunogenicity compared to ref-NTZ

Both biosim-NTZ and ref-NTZ caused a similar effect in the body's immune response and this effect remained unchanged even when patients switched from ref-NTZ to biosim-NTZ. No difference was observed between the two treatments

Switching from ref-NTZ to biosim-NTZ did not affect treatment outcomes

A subgroup of patients were switched from ref-NTZ to biosim-NTZ halfway through the study. Switching from ref-NTZ to biosim-NTZ did not affect how the treatment impacted patient disease and safety outcomes

What do the results of this comparative clinical study mean?

Patients with RRMS who received biosim-NTZ had the same outcomes as those who received ref-NTZ. These outcomes included how well the treatment managed the disease, its safety, and how the body responded to the treatment over time. When patients switched from ref-NTZ to biosim-NTZ during the study, there were no significant changes in treatment effectiveness or safety

The ToE confirmed biosimilarity of biosim-NTZ to ref-NTZ

Biosim-NTZ was shown to match ref-NTZ in terms of how it is built, how it works, and how safe and effective it is, fulfilling the evidence required to prove the suitability of biosim-NTZ in the intended treatment population

Where can readers find more information on these studies?

PK/PD study of PB006 publication | Antelope study of PB006 in RRMS publication

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Glossary

Biologic medicine: A biologic medicine is a pharmaceutical drug whose active substance is made by or extracted from living cells, tissues or microorganisms such as bacteria or yeast

Biosimilar medicine: A biosimilar is a biologic medicine that is a successor to an existing biologic, also known as the reference medicine, for which the patent and exclusive marketing rights have expired. To be approved for use, a biosimilar has to match the reference medicine in terms of efficacy, safety, and immunogenicity. A biosimilar medicine can be used in the same way as its reference medicine, and the same treatment outcomes can be expected by patients and physicians

Reference biologic: 'Reference biologic', 'reference medicine', or 'existing biologic' are all names given to an approved medicine for which a biosimilar is being developed

Totality of Evidence (ToE): The 'Totality of Evidence' is a data package, gathered through a comprehensive method, which is used by European and US regulators to approve biosimilar medicines. It combines data from various studies to show that the biosimilar matches the reference medicine to work just as safely and effectively

Pharmacokinetic and pharmacodynamic (PK/PD) study: PK and PD measurements are used to understand how a medicine works in the body. For biosimilar studies, PK and PD measurements are directly compared in head-to-head comparisons with the reference medicine to demonstrate that the biosimilar and reference medicine have the same effects on PK and PD outcomes

Comparative clinical study: For a biosimilar medicine, comparative clinical studies are used to show that the biosimilar has the same effect as the existing biologic in how it treats the disease and how safe it is for patients

Switching: Switching describes a change from one treatment to another that will have the same effect, such as when a patient moves from an existing biologic medicine to a biosimilar medicine

Fab-arm exchange: Fab-arm exchange is when two similar antibodies swap parts. This can happen to antibody medicines inside the body and might change how they work against their target; so when relevant, it is carefully measured during biosimilar development

Immunogenicity: Immunogenicity of a medicine refers to its ability to trigger a reaction in the body's immune system that results in production of antibodies against the medicine. These antibodies may stop a treatment from working properly, which makes it very important to measure immunogenicity for relevant medicines

Natalizumab: Natalizumab is an antibody medicine that attaches to a specific target on immune cells to prevent them from leaving the bloodstream and entering the brain and gut. By doing this, it helps prevent inflammation and damage in these areas

Reference natalizumab: Reference natalizumab (Tysabri®; Biogen*) is the reference medicine for biosimilar natalizumab PB006 and is approved by European and US health authorities for the treatment of relapsing forms of multiple sclerosis

Biosimilar natalizumab (PB006): Biosimilar natalizumab (Tyruko®; Sandoz), has been developed and approved by European and US health authorities as a biosimilar to reference natalizumab

*Tysabri® is a registered trademark of Biogen MA, Inc.

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