Explorer8: Study of concizumab in people living with haemophilia without inhibitors

Explorer8 is a phase 3 clinical trial to assess the efficacy and safety of concizumab in people with haemophilia A or B without inhibitors.[1] The use of concizumab in people with haemophilia without inhibitors is investigational and not approved by regulatory authorities anywhere in the world.

What is the explorer clinical development programme?

The explorer programme aims to evaluate the efficacy and safety of concizumab (an anti-tissue factor pathway inhibitor (TFPI) monoclonal antibody) in all people with haemophilia, including people with inhibitors.[1,2,3,4,5,6,7,8,9] Inhibitors are an immune system response that causes standard replacement therapy to stop working.[10]

What did the explorer8 study investigate?

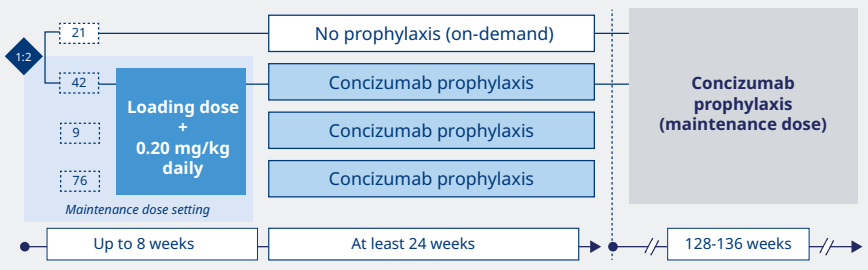
Explorer8 aimed to establish the efficacy and safety of concizumab as a prophylactic treatment for people with haemophilia A or B without inhibitors.[1]

What is the explorer8 study design?

The explorer8 study included 148 participants from 86 locations across the world. Participants were placed in groups based on whether they usually take medicine aimed to treat bleeds (bypassing agent on-demand) or to prevent bleeds (prophylaxis), see Figure 1.[1]

Participants had regular clinic visits throughout the study where blood samples were taken. They were also asked to record information into an electronic diary during the study and wear an activity tracker.[1]

Figure 1[1]



Inclusion criteria:[1]

- Males aged 12 years and over
- Congenital severe haemophilia A (FVIII below 1%) or moderate/ severe haemophilia B (FIX equal to or below 2%)
- No presence of inhibitors

What did the explorer8 study measure?

- The primary analysis compared the number of treated spontaneous and traumatic bleeding episodes, measured as annualised bleeding rate (ABR) between no prophylaxis vs concizumab prophylaxis.[1]
- The confirmatory secondary analysis compared the number of treated spontaneous and traumatic bleeding episodes, measured as ABR between prophylaxis with previous standard of care therapy vs concizumab prophylaxis.[1]
- Safety, patient-reported outcomes, pharmacokinetics (presence of the drug in the body over a period of time), and pharmacodynamics (effects of the drug in the body, such as production of thrombin) were also assessed.[1]

What are the preliminary results?

In the context of the study population, concizumab prophylaxis reduced the number of bleeds in people with haemophilia A and B compared to those on no prophylaxis:[11]

86% **reduction in treated spontaneous and traumatic bleeds for people with haemophilia A (primary endpoint)[11]**

Estimated mean ABR was 2.7 (95% CI, 1.6–4.6) for concizumab versus 19.3 (95% CI, 11.3–33.0) for no prophylaxis (ABR ratio, 0.14 [0.07–0.29]; P<0.001) (N=27)

79% **reduction in treated spontaneous and traumatic bleeds for people with people with haemophilia B (primary endpoint)[11]**

Estimated mean ABR was 3.1 (95% CI, 1.9–5.0) for concizumab versus 14.8 (95% CI, 8.1–26.9) for no prophylaxis (ABR ratio, 0.21 [0.10–0.45]; P<0.001) (N=36)

Non-inferiority of concizumab to previous prophylaxis was not confirmed (secondary endpoint)[11]

ABR ratio was 1.4 [0.7–2.6] in haemophilia A and 1.8 [0.8–3.8] in haemophilia B without inhibitors. Median ABR was numerically comparable between concizumab versus previous prophylaxis (2.3 vs 2.2 for haemophilia A; 1.4 vs 2.1 for haemophilia B)

A reduction in treatment burden scores were also reported in people on concizumab prophylaxis versus no prophylaxis.[12] The safety and tolerability profile of concizumab was within the expected range with no thromboembolic events reported after treatment restart. The most common adverse events reported during the study include: COVID-19 (13%), Fibrin D-dimer increased (8%), upper respiratory tract infection (7%), nasopharyngitis (6%) and prothrombin fragment 1.2 increased (6%).[11]

What was the conclusion?

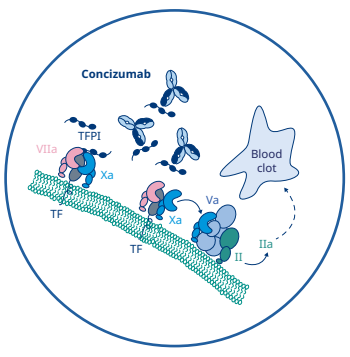
The results of explorer8 demonstrate the potential of concizumab to reduce bleeding in people with haemophilia A or B without inhibitors whilst improving aspects of health-related quality of life and treatment burden.[11]

Are there further studies for concizumab planned?

Concizumab is also being evaluated in children living with haemophilia A or B, with or without inhibitors, in the investigational explorer10 paediatric study expected to complete in 2024.[12]

What is concizumab and how does it work?

Concizumab is designed to act independently from clotting factors VIII (FVIII) and IX (FIX) by enhancing the initiation phase of the blood clotting process through increased Factor Xa (FXa) activity. This allows further thrombin generation – a protein that is important in the prevention of bleeds.[13,14]



Novo Nordisk Data on File.

Glossary:

Annualised bleeding rate: the number of reported bleeding events within one year. Prophylaxis treatment: a regular treatment to prevent bleeds

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