Risk mitigation during concizumab prophylaxis in phase 3 clinical trials in patients with hemophilia A/B with and without inhibitors: management of breakthrough bleeds and dose optimization

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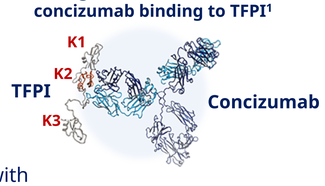
BACKGROUND and AIMS

- Concizumab is a monoclonal antibody against tissue factor pathway inhibitor (TFPI) with high-affinity for the second Kunitz (K2) domain of TFPI (**Figure 1**)[1]

Figure 1. Structure of concizumab binding to TFPI[1]

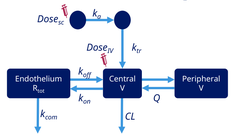


- Concizumab phase 3 trials investigating the subcutaneous prophylactic treatment of patients with hemophilia A/B with and without inhibitors are ongoing
- In phase 2 clinical trials, concizumab was well tolerated with no deaths, no adverse events leading to withdrawal, and no significant thromboembolic events[2-4]
- During the phase 3 clinical trials, 3 patients with different thrombotic risk factors who used concomitant factor-containing medication (high or frequent doses of breakthrough bleed treatment) on the day of (and in 2 cases also in the days preceding) the event onset developed non-fatal thromboembolic (TE) events, leading to a treatment pause for all patients
- The objective of this assessment was to ensure patient safety and mitigate the risk of adverse events (reduce the risk of the reoccurrence of TEs) during the reinitiation of phase 3 clinical trials

MATERIALS and METHODS

- An in-depth assessment of all available non-clinical and clinical data was performed, including
  - **Pharmacokinetic (PK) profile evaluation**
    - A population PK model (**Figure 2**) was updated based on data from combined concizumab phase 1 and 2 trials
  - **Thrombin generation studies on combining concizumab and additional hemostatic agents**
- To quantitate concizumab plasma distribution, an enzyme-linked immunosorbent assay (ELISA) was validated according to international bioanalytical method validation guidelines

Figure 2. PK model for concizumab dosing



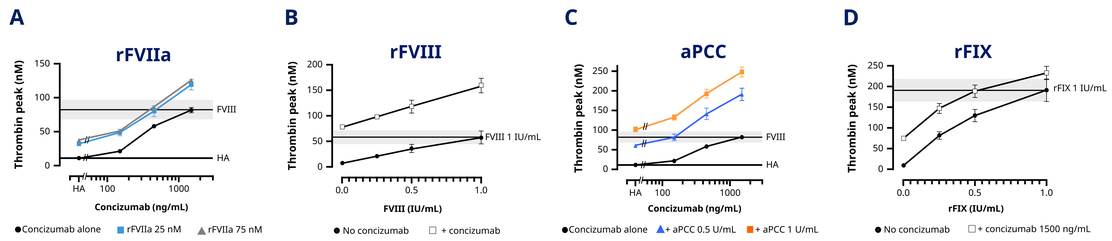
CL=clearance; IV=intravenous; Ka=absorption rate constant; kcom=elimination rate constant of the concizumab-TFPI complex; kon and koff=rate constants for binding of concizumab to endothelial TFPI; ktr=rate constant from the transit compartment; ng/mL=nanograms per milliliter; PK=pharmacokinetic; Q=inter-compartmental clearance; Rtot=amount of endothelial TFPI available for concizumab binding; SC=subcutaneous; V=volume.

RESULTS

- During the phase 2 trials, there were no significant TE events[2-4]
- In vitro thrombin generation studies (**Figure 3**) did not indicate significant drug-drug interactions when combining concizumab with physiologic doses of rFVIIa, rFVIII, aPCC, or rFIX[5]
  - The in vitro effects of concizumab in combination with rFVIIa, rFVIII, aPCC, or rFIX were mainly additive[5]
    - With a small (up to 20%) extra effect due to drug-drug interactions
  - These data supported the concomitant use of clinically relevant hemostatic agents for BTB during concizumab prophylaxis

Figure 3. In vitro effects of concizumab in combination with rFVIIa, rFVIII, aPCC, or FIX

The effect of rFVIIa (A), rFVIII (B), or aPCC (C) on thrombin generation (TG) in a hemophilia A plasma pool. The effect of rFIX (D) on TG in a hemophilia B plasma pool in the absence and presence of concizumab. The upper grey bars reflect the thrombin peak obtained with normal plasma level of FVIII or rFIX.



- Based on thorough assessment and consultations with advisors and an independent data monitoring committee, a risk mitigation plan was developed for reinitiation of concizumab treatment in phase 3 clinical trials, which included **(1)** updated BTB management guidance for mild/moderate bleeds and **(2)** a new concizumab dosing regimen

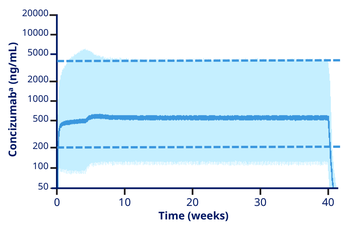
1. Updated BTB management guidance

- Using the lowest approved dose for each of the products used to treat the bleed (eg, 90 mcg/kg for rFVIIa) and lowest dose level per label for factor replacement products (eg, 20 IU/kg for FVIII and 30 IU/kg for FIX), with dosing intervals per label
- Closer monitoring of BTB treatment and confirmation of each dose given by investigators

2. New concizumab dosing regimen

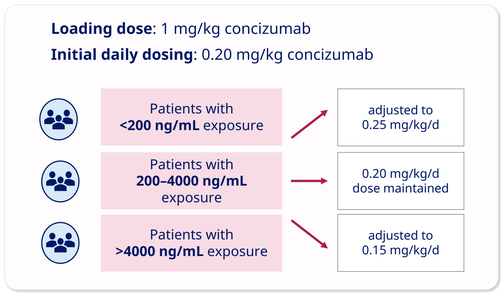
- **Figure 4** shows the simulated exposure profiles that supported the new concizumab dosing regimen, which included a loading dose of 1.0 mg/kg followed by an initial daily dose of 0.20 mg/kg and dose adjustment based on exposure levels (**Figure 5**)
- Based on concizumab exposure at week 4 (measured using ELISA), patients with exposure <200 ng/mL are to be adjusted to 0.25 mg/kg/d, and patients with exposure >4000 ng/mL are to be adjusted to 0.15 mg/kg/d within the initial 5- to 8-week dose adjustment period (**Figure 5**)
- The PK model predicted:
  - 28%-30% of patients would have levels <200 ng/mL
  - 60%-62% of patients would have levels between 200-4000 ng/mL
  - 10% of patients would have levels >4000 ng/mL

Figure 4. Simulated exposure profiles for new concizumab dosing regimen



[a]Line is geometric mean simulations and shaded area is 90% prediction interval. The stippled blue line represents the 200 ng/mL exposure level indicated for beginning of efficacy.

Figure 5. Dosing regimen and adjustment



A potential dose adjustment will take place at visit 4a.1 or 9a.3 and will be based on the concizumab exposure level measured at the previous visit 4a or 9a.2

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CONCLUSIONS

A risk mitigation strategy, including BTB management guidance and a new dosing regimen with dose adjustment based on concizumab exposure level, allowed for a restart of concizumab treatment of patients in both pivotal phase 3 clinical trials.