Concizumab: A Novel Anti-TFPI Therapeutic for Hemophilia

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**Authorship Contributions and Acknowledgments**

Amy Shapiro served as an investigator during the concizumab explorer4 trial, recruited patients into the study, and analyzed and interpreted the data. Dr. Shapiro would like to thank Katarina Cepo, Jesper Haaning, Thomas Porstmann, Louise Ostergaard and Stephanie Seremetis from Novo Nordisk for their review and input into the manuscript that informed this presentation (Shapiro et al., *Blood* 2019¹). Medical writing support for that study was provided by Physicians World Europe GmbH, Mannheim, Germany and was financially supported by Novo Nordisk A/S, Denmark.

**Conflict-of-interest disclosures**

Amy Shapiro has served as Principal Investigator for three Novo Nordisk-sponsored research studies.
Abstract

Concizumab is a novel subcutaneous prophylactic therapy for hemophilia. It is an hemostatic rebalancing agent that binds to the Kunitz-2 domain of tissue factor pathway inhibitor (TFPI), one of the molecules that contribute to downregulation of coagulation, thereby preventing TFPI from binding to and blocking the factor Xa (FXa) active site. When the TFPI inhibitory activity is decreased, sufficient FXa is produced by the factor VIIa/tissue factor complex to achieve hemostasis. Based on this mechanism of action, concizumab is expected to be equally effective in hemophilia A and B, regardless of inhibitor status. Moreover, the concizumab mechanism of action does not interfere with the regulation of coagulation downstream of TFPI. Results from two phase 2 trials in patients with hemophilia A/B with and without inhibitors demonstrated that concizumab had a favorable safety profile, with no deaths, no thromboembolic events and no adverse events leading to withdrawal. Clinical proof of concept in prevention of bleeding episodes was confirmed in both concizumab phase 2 trials across all hemophilia subtypes assessed, with a statistically significant and clinically relevant reduction in annualized bleeding rates observed in inhibitor patients compared with on-demand treatment. Based on the phase 2 results, the FDA granted concizumab Breakthrough Therapy designation for hemophilia B with inhibitor patients, a rare and vulnerable patient subgroup that currently has the highest unmet medical need. In the ongoing concizumab phase 3 trials, an optimized dosing regimen will be administered in patients with hemophilia A or B with and without inhibitors.
My name is Amy Shapiro and I am the CEO and co-medical director of the Indiana Hemophilia & Thrombosis Center in Indianapolis, Indiana, USA.

The title of my talk is: “Concizumab: A Novel Anti-TFPI Therapeutic for Hemophilia”.

A significant proportion of patients with hemophilia fail to achieve the desired outcomes with current prophylactic factor replacement therapy and/or they develop complications, such as inhibitory alloantibodies. Therefore, efforts to develop novel treatments that are both efficacious and safe are ongoing.

In addition, the treatment burden associated with current therapies that rely on intravenous administration represents a significant limitation for many patients with hemophilia. A drug that could be administered subcutaneously would therefore represent a substantial advance and is highly desirable among the hemophilia community. One such subcutaneous agent is concizumab, which is in clinical development for the treatment of patients with hemophilia A and B with and without an inhibitor.

Concizumab is a new class of non-factor, rebalancing agents that restores the hemostatic potential by binding tissue factor pathway inhibitor (TFPI). The rationale behind TFPI inhibition is that it extends the initiation phase of coagulation at sites of injury where tissue factor is exposed, thereby enhancing the remaining ability of the blood to form a clot, independent of the presence of factor VIII or factor IX.

TFPI exists in two isoforms; TFPIα is a soluble protein secreted by endothelial cells and activated platelets and TFPIβ is expressed primarily on the surface of the endothelium. TFPIα contains the Kunitz-1, -2 and -3 domains, while TFPIβ contains Kunitz-1 and -2 together with a C-terminal tail with a GPI anchor responsible for cell binding. Concizumab is a monoclonal antibody that binds the Kunitz domain 2 of both TFPIα and TFPIβ, thereby inhibiting TFPI’s neutralization of factor Xa and subsequently the tissue factor / factor VIIa complex. In addition, concizumab is expected to prevent TFPI’s inhibition of the early forms of the prothrombinase complex containing factor Xa and partially activated factor Va.

Based on its mechanism of action, concizumab is expected to be equally effective in hemophilia A and B, regardless of inhibitor status. This is of particular significance, given that
patients with inhibitors, and in particular those with hemophilia B and inhibitors, currently represent the subgroup with the highest unmet medical need among hemophilia patients.

Furthermore, the mechanism of action of concizumab is not expected to interfere with the function of major downstream coagulation inhibitors. Therefore, concizumab is able to increase the hemostatic capacity while not interfering with downstream control mechanisms, an important attribute in terms of ensuring the appropriate function of the coagulation system in the presence of the drug.

Concizumab is currently in phase 3 clinical development. The results from the main parts (that is, after at least 24 weeks of treatment) of two phase 2 trials were published in *Blood* towards the end of 2019\(^1\). Please see the November 28, 2019 issue of the journal for more details.

The phase 2 trials assessed the efficacy and safety of daily subcutaneous concizumab prophylaxis in a heterogeneous group of patients with hemophilia A or B with and without inhibitors. A total of 53 patients, consisting of 36 with hemophilia A, 9 hemophilia A with inhibitor patients and 8 hemophilia B with inhibitor patients were included in the trials. Patients received 0.15 mg/kg/day of concizumab, with potential dose escalation to 0.20 and 0.25 mg/kg/day, if 3 or more spontaneous bleeding episodes occurred within the preceding 12 weeks of concizumab treatment. A loading dose of 0.5 mg/kg was administered to patients in the inhibitor trial.

Overall in the phase 2 trials, increasing concizumab concentration was associated with lower free TFPI and normalized thrombin generation potential, consistent with the drug’s mechanism of action.

In addition, and as anticipated, elevated D-dimer and prothrombin fragment 1+2 levels were observed across all concizumab dose levels, reflecting the hemostatic effect of TFPI inhibition by concizumab.

In the phase 2 trials, once-daily subcutaneous concizumab demonstrated a favorable safety profile. There were no deaths, no thromboembolic events and no adverse events leading to withdrawal. Most adverse events were mild and unlikely related to concizumab.

The development of anti-drug antibodies represents a complication for novel antibody-based therapies for hemophilia. During the concizumab phase 2 trials, a total of six patients tested
positive in anti-drug antibody tests, with very-low to medium titers. It is worth noting that none of these were associated with a change in clinical status or observed concizumab efficacy.

Clinical proof of concept in terms of bleed prevention was demonstrated by both concizumab phase 2 trials across all hemophilia subtypes assessed. Results from the inhibitor trial confirmed a statistically significant and clinically relevant reduction in annualized bleeding rates compared with on-demand treatment (the estimated ABR with concizumab was 4.5 vs 20.4 in the rFVIIa on-demand arm).

Importantly, based on the results obtained with concizumab in hemophilia B with inhibitor patients, a Breakthrough Therapy designation was granted by the FDA for this patient subgroup, recognizing the potential substantial benefit that concizumab could provide in this vulnerable patient population for whom currently inadequate prophylactic treatment is available and for whom options are generally limited to bypassing agents.

The favorable safety and efficacy profile that concizumab exhibited during the phase 2 trials was further reflected in the fact that all patients who completed the main part of the trials chose to continue on to the extension phase.

A key point of interest surrounding novel treatments in patients with hemophilia is that concomitant use of other pro-coagulant agents, as required to treat breakthrough bleeding or during surgery, may increase the risk of thrombotic complications. In the concizumab phase 2 trials, recombinant activated factor VII and factor VIII were used to treat breakthrough bleeds in patients with and without inhibitors, respectively, without observed safety concerns.

In March 2020, the concizumab phase 3 trials, explorer7 and explorer8, which were initiated in late 2019, were paused by Novo Nordisk following reports of two arterial and three venous non-fatal thrombotic serious adverse events in three patients (one in explorer7 and two in explorer8). All three patients had thrombotic risk factors present at baseline, and had used concomitant hemostatic medication on the day of, and in two cases in the days up to, event onset. The trials were subsequently placed on clinical hold by the FDA.

Novo Nordisk, alongside a large taskforce of experts, carefully analyzed all available trial data, including from the three patients who experienced the thrombotic events, and developed a risk mitigation strategy for resuming the trials. The risk mitigation includes guidelines for the concomitant use of hemostatic agents in the management of bleeding episodes while on concizumab prophylaxis and updates to the concizumab dosing regimen, designed to
minimize the risk that additional patients treated with concizumab will develop thrombotic events. At the time of this recording, the FDA has agreed to the new safety measures and guidelines and the clinical hold has been lifted, allowing re-initiation of the phase 3 trials.

Recruitment for the two phase 3 concizumab trials has now resumed. Based on the results from the phase 2 trials, favorable efficacy in the phase 3 pivotal trials may be expected, and it is hoped that the risk mitigation measures that have been put in place will safeguard against further thrombotic adverse events. We anticipate the results with great interest.

In conclusion, the results from the extensive concizumab phase 2 program have shown that concizumab represents a well-tolerated subcutaneously administered prophylactic therapy that is suitable for all patients with hemophilia A and B either with or without an inhibitor; importantly, the rare and vulnerable hemophilia B with inhibitors population are in need of improved therapies for prophylaxis. The data obtained from the concizumab phase 2 trials and patient need have allowed the phase 3 studies to proceed with risk mitigation in place.

Thank you for listening and for your attention.
References

1. Shapiro AD, Angchaisuksiri P, Astermark J, et al. Subcutaneous concizumab prophylaxis in hemophilia A and hemophilia A/B with inhibitors: phase 2 trial results. Blood. 2019;134(22):1973-1982.

2. Berntorp E, Dolan G, Hay C, et al. European retrospective study of real-life haemophilia treatment. Haemophilia. 2017;23(1):105-114.

3. Hacker MR, Geraghty S, Manco-Johnson M. Barriers to compliance with prophylaxis therapy in haemophilia. Haemophilia. 2001;7(4):392-396.

4. Ljung R. Aspects of prophylactic treatment of hemophilia. Thromb J. 2016;14(Suppl 1):30.

5. Petrini P. Identifying and overcoming barriers to prophylaxis in the management of haemophilia. Haemophilia. 2007;13 Suppl 2:16-22.

6. Santagostino E, Mancuso ME. Venous access in haemophilic children: choice and management. Haemophilia. 2010;16 Suppl 1:20-24.

7. Broze GJ, Jr., Girard TJ. Tissue factor pathway inhibitor: structure-function. Front Biosci (Landmark Ed). 2012;17:262-280.

8. Mast AE. Tissue Factor Pathway Inhibitor: Multiple Anticoagulant Activities for a Single Protein. Arterioscler Thromb Vasc Biol. 2016;36(1):9-14.