

## VON WILLEBRAND DISEASE PROPHYLAXIS NETWORK (vWD PN)

### The VWD International Prophylaxis (VIP) Study Protocol Summary

**Principal Investigator:** Erik Berntorp, MD, PhD  
Department for Hematology and Coagulation Disorders  
Malmö University Hospital, SE-205 02 Malmö, Sweden

**Co-Principal Investigator:** Thomas Abshire, MD  
BloodCenter of Wisconsin  
Milwaukee, WI 53201-2178, USA

**Introduction.** The rationale for initiating prophylaxis in VWD is that it has been successfully used in severe hemophilia. Since joint hemorrhages with development of arthropathy can occur, particularly in Type 3 VWD, and frequent mucous membrane bleeds, GI bleeding, and menorrhagia can jeopardize quality of life or even be life threatening, it is logical to consider application of the experience learned in hemophilia to VWD. Data to support this come from a population-based study conducted in Sweden in a group of 52 subjects with VWF:RC<sub>0</sub><8% and FVIII:C<10% [Berntorp & Petrini 2005]. Other than the study by Berntorp and Petrini, no published data exist to document the efficacy and safety of prophylaxis in patients with VWD.

**Objectives.** The primary objectives of the VIP study are to identify people with VWD who may benefit from prophylaxis, study the effect of prophylaxis on bleeding frequency, and establish optimal treatment regimens for joint bleeding, GI bleeding, epistaxis, and menorrhagia.

Other objectives include retrospective examination of the effect of prophylaxis on bleeding frequency, and a retrospective natural history study of GI bleeding in VWD.

**Study Design.** The VIP study is international, multi-center and observational in design. Participants enrolled in the prospective phase will undergo an escalation of treatment from one to three dose levels of VWD product. They will begin on the level one dose and remain on this dose for the duration of follow-up (one year), or until they meet the criteria for escalation to level two or three. VWF/FVIII products labeled for VWD will be chosen for use at the discretion of the participating investigator and will not be provided as part of the study.

The retrospective portion of the study will be conducted by review of center records and bleeding logs or diaries maintained by study participants.

**Study Population.** The VWD population for consideration for entry includes those with Type 1 if  $\leq 20\%$  RCo and/or  $\leq 20\%$  FVIII; and DDAVP non-responsive; Type 2 if DDAVP non-responsive, or Type 2B; and Type 3; who meet bleeding indication criteria having defined patterns of gastrointestinal bleeding, joint bleeding, epistaxis, or menorrhagia.

Individuals in participating centers who are already on prophylaxis for VWD, for any indication, and individuals who were on a regimen of prophylaxis for at least six months that was discontinued because it was no longer required, or those with a history of GI bleeding due either to proven angiodysplasia or unexplained by other factors will be eligible for participation in the retrospective studies.

**Duration of Follow-up.** After enrollment in the prospective study, subjects will be followed for one year.

**Analytic Approach.** The primary objectives of the study are to identify subjects who will benefit from prophylaxis by establishing the pattern of bleeding in the year prior to evaluation for enrollment, study the effect of prophylaxis on bleeding frequency, and establish optimal treatment regimens. The analytic method will use the times until bleeding episodes in a multivariate survival analysis model. Bleeding frequency will be collected for the year prior to enrollment. The length of time bleed-free on prophylaxis will be compared to the experience in the year prior to enrollment. Comparison of dosing regimens will be made using Cox Proportional Hazards models with frailty parameters. This analysis will produce estimates of hazard ratios (DOSE-2 versus DOSE-1 and DOSE-3 versus DOSE-1) along with 95% confidence intervals and Wald test p-values.

The difference in frequency of bleeds while on on-demand therapy (retrospective data) will be compared with that of bleeding while on prophylaxis.

**Study Organization and Leadership.** The vWD PN is an investigator-initiated study funded through an unrestricted grant by CSL Behring, Marburg, Germany. Erik Berntorp, M.D., Ph.D. is the Principal Investigator and Thomas Abshire, M.D. is the Co-Principal Investigator of the network. A Steering Committee, co-chaired by Drs. Berntorp and Abshire, serves as the decision-making body of the study. Study coordination, data and statistical support is provided by Rho, Inc., Chapel Hill, NC, USA. Scientific and administrative Sub-committees of the Steering Committee will be formed as needed. The Steering Committee will serve as the Publications Committee for the network. Safety issues that arise in this study will be brought to the attention of the Data and Safety Monitoring Board, which will act as a safety oversight committee for the study and make recommendations to the Steering Committee.

## **XII. REFERENCE**

Berntorp & Petrini. Long-term prophylaxis in von Willebrand disease. *Blood Coagulation and Fibrinolysis* 2005;16 Suppl 1:S23-6.

**VON WILLEBRAND DISEASE PROPHYLAXIS NETWORK**  
**Steering Committee Members (Sub-Committee)**

Erik Berntorp (Chair) Malmö University Hospital Malmö, Sweden	Karin Kurnik (Joint Bleeding) Dr. von Haunersches-Children's Hospital Munich, Germany
Thomas Abshire (Co-Chair) BloodCenter of Wisconsin Milwaukee, Wisconsin, USA	Frank Leebeek (Joint Bleeding) Erasmus Medical Center, Rotterdam, The Netherlands
Mayte Álvarez (Gastrointestinal Bleeding) Unidad de Hemofilia Hospital Universitario La Paz Madrid, Spain	Michael Makris (Gastrointestinal Bleeding) Royal Hallamshire Hospital Sheffield, England
Jan Astermark (Epistaxis) Malmö University Hospital Malmö, Sweden	Pier Mannucci & Augusto Federici (Retrospective Studies) Angelo Bianchi Bonomi Hemophilia and Thrombosis Center Milan, Italy
Manuel Carcao (Epistaxis) Hemophilia Program, Hospital for Sick Children Toronto, Ontario, Canada	Prasad Mathew (Joint Bleeding) Ted R. Montoya Hemophilia Center Albuquerque, New Mexico, USA
Jorge DiPaola (Epistaxis) Mountain State Regional Hemophilia and Thrombosis Center Aurora, Colorado, USA	Rochelle Winikoff (Menorrhagia) Haemophilia Treatment Center Hôpital Ste-Justine Montreal, Québec, Canada
Joan Cox Gill (Menorrhagia) Comprehensive Center for Bleeding Disorders The Blood Research Institute Milwaukee, Wisconsin, USA	Sharyne Donfield (Data and Statistics) Rho, Inc. Chapel Hill, North Carolina, USA
Peter Kouides (Menorrhagia) Mary M. Gooley Hemophilia Center Rochester, New York, USA	