Received: 10 October 2025 | Revised: 8 December 2025 | Accepted: 30 December 2025

https://doi.org/10.1016/j.jtha.2025.12.029

LETTER TO THE EDITOR

"A phase 1, open-label study to assess the pharmacokinetics, safety, and tolerability of a single intravenous injection of efanesoctocog alfa in adults with type 2N or type 3 von Willebrand disease": comment

Dear Editor:

We read with interest the study by Susen et al. [1], which evaluated the pharmacokinetics, safety, and tolerability of a *single* dose of efanesoctocog alfa (Altuviiio, Sanofi) in *adult* patients with type 2N and type 3 von Willebrand disease (VWD). The authors demonstrated high and sustained factor (F)VIII levels for up to 5 days, comparable to those observed in hemophilia A patients. Here, we report a *pediatric* patient with type 2N VWD receiving prophylactic treatment with efanesoctocog alfa and compare differences in FVIII levels obtained after plasma-derived clotting factor concentrate (CFC) and efanesoctocog alfa. Notably, we demonstrate similarly high and sustained FVIII levels at 1 week after efanesoctocog alfa administration.

An 8-year-old boy, diagnosed with hemophilia A at 4 years of age, was evaluated following relocation from South America. His past medical history was notable for recurrent bleeding episodes, including joint and muscle bleeds, one of which required a fasciotomy. Specific details of prior treatment were unavailable. Upon initial evaluation, laboratory testing revealed a prolonged activated partial thromboplastin time, along with a normal prothrombin time, complete blood count, and fibrinogen level. Local von Willebrand factor (VWF) testing revealed ristocetin cofactor activity of 168% (reference range, 43%-138%) and antigen of 122% (reference range, 60%-153%). VWF:glycoprotein 1bM (GPIbM), VWF collagen-binding assay, VWF-FVIII binding assay (VWF:FVIIIB), and multimeric analysis were sent. FVIII activity was 6% by one-stage assay (OSA; STA - C.K. PREST 5 Reagent, Diagnostica Stago) and 2.5% by chromogenic assay (CH; CRYO*check* FVIII Reagent, Precision BioLogic). FIX activity was normal. Shortly thereafter, the patient presented with right hip pain and was hospitalized for the management of right hip hemarthrosis. Based on a presumptive diagnosis of moderate hemophilia A, the patient was initiated on 50 IU/kg of recombinant FVIII (Advate, Baxalta/Takeda). The 30-minute peak OSA-FVIII level was 26.8%, and the 12-hour level was 5.1%. FVIII inhibitor was negative. A repeat ultrasound 24 hours later showed no change in the right hip hemarthrosis. Expedited processing of the previously sent tests revealed a VWF:GPIbM of 114 IU/dL (reference range, 50-174), a VWF collagen-binding assay of 119 IU/dL (reference range, 50-203), and a normal multimer distribution. Importantly, the patient's VWF:FVIIIB was <3% (reference ≥86%). The diagnosis was reclassified as type 2N VWD, and treatment was switched to 40 IU/kg of VWF containing CFC (Humate-P, CSL Behring GmbH). The patient was initially treated twice daily and gradually tapered to daily infusions after improvement in his right hip hemarthrosis. A decision was made to initiate continuous prophylaxis for the patient upon discharge.

Initially, prophylaxis was continued with Humate-P, and FVIII levels (assessed by OSA) were monitored at 30 minutes, 24 hours, and 96 hours posttreatment to guide infusion frequency (Figure). We also considered prophylaxis with emicizumab (Hemlibra, Genentech), given emerging data supporting its utility in VWD [2], but were unable to obtain insurance authorization. Based on the structure of efanesoctocog alfa and a single reported case of its perioperative use in an adult patient with type 2N VWD [3], we hypothesized that it would be effective in our patient, with the additional benefit of reducing the frequency of administration and treatment burden. As limited data were available regarding FVIII responses in type 2N VWD (our patient presented before the publication of the study by Susen et al. [1]), FVIII activity levels (assessed by OSA and CH) were obtained at 30 minutes and at 24, 96, and 168 hours postinfusion of 50 IU/kg of efanesoctocog alfa (Figure). VWF:GPIbM and VWF ristocetin cofactor activity assays were repeated at the same points, and the VWF:FVIIIB was repeated once; none were affected by efanesoctocog alfa infusions (data not shown). Follow-up testing revealed no mutations associated with hemophilia A (courtesy of 8Check, Octapharma Inc) but identified a homozygous pathogenic variant, *VWF* c.2446C>T (p.Arg816Trp), consistent with the diagnosis of type 2N VWD. This missense variant has been reported in both

Manuscript handled by: Giancarlo Castaman

Final decision: Giancarlo Castaman, 30 December 2025

© 2026 International Society on Thrombosis and Haemostasis. Published by Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

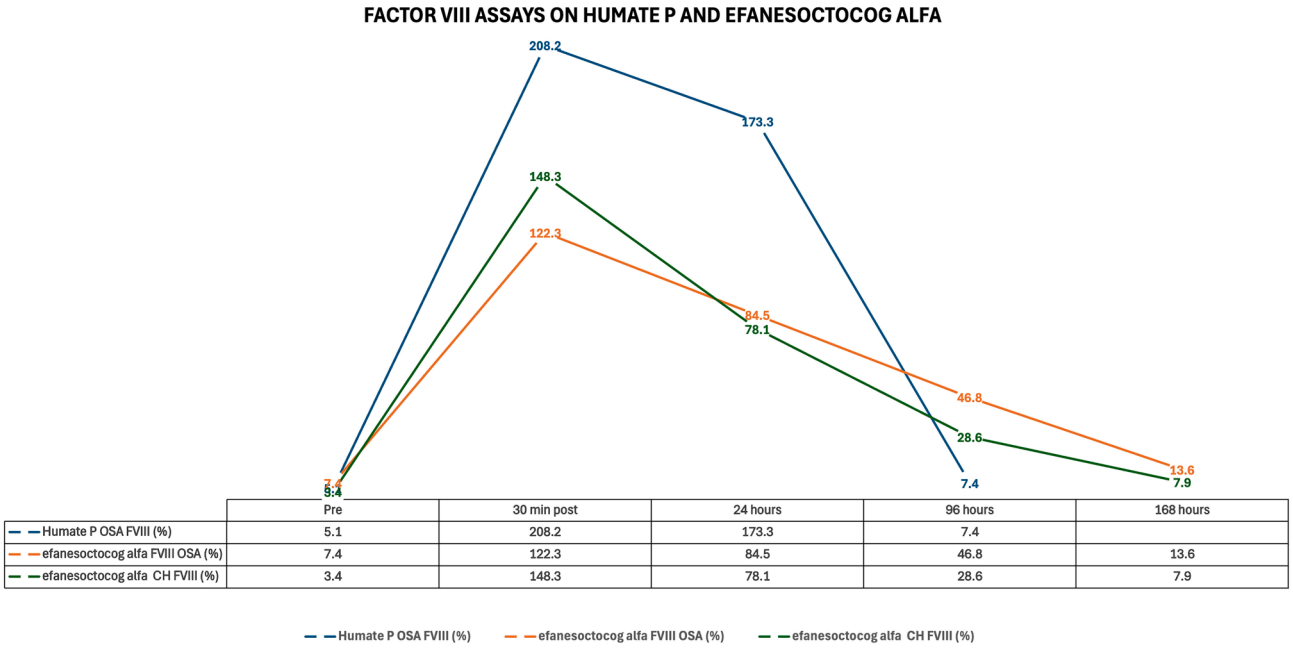

FIGURE Factor (F)VIII assays on Humate-P and efanesoctocog alfa. CH, chromogenic assay; OSA, one-stage assay; Post, posttreatment; Pre, pretreatment.

homozygous and compound heterozygous states in patients with type 2N VWD. The homozygous mutation is typically associated with a clinically severe type 2N VWD, owing to a severe defect in the FVIII binding capacity of VWF [4]. Currently, the patient has been maintained on weekly efanesoctocog alfa 50 IU/kg without any recurrence of bleeding or inhibitor development for 8 months, following caregiver training in home administration of factor.

Although VWD is the most common bleeding disorder, and long-term VWF prophylaxis is conditionally recommended in patients with severe or frequent bleeding [5], there remains a paucity of robust prophylaxis studies delineating appropriate dosing schedules and treatment frequency. Recent studies have reported mean weekly doses of 125.7 IU/kg [6] to 20 to 40 IU/kg per dose [7], with CFC frequency ranging from 1.9 [6] to 2 to 3 times per week [7]. Although one study showed that healthcare resource utilization improved in terms of the number of inpatient visits and surgeries after initiation of prophylaxis, there was an increase in outpatient visits [6], indicating an ongoing high treatment burden.

Type 2N VWD is a rare subtype caused by a qualitative defect in the D'-D3 region of VWF, resulting in a reduced ability to bind FVIII, leading to rapid clearance and low circulating FVIII levels [4]. Due to decreased circulating FVIII levels and normal or near-normal VWF levels, type 2N VWD often mimics hemophilia A, as exemplified by our patient. As demonstrated by the response to Advate in our patient, treatment with recombinant FVIII is often ineffective for long-term management in type 2N VWD due to its short half-life and early clearance. Desmopressin is an option for treatment in patients with type 2N VWD, but response depends on genotype (patients with the R854Q mutation respond best) [8], and it is not an option for long-term prophylaxis. Emicizumab, a potentially feasible therapeutic option, is currently under investigation in ongoing clinical trials for severe VWD (ClinicalTrials.gov identifiers: NCT05500807 and NCT06998524). To date, its use in VWD has been largely limited to patients with alloantibodies [2], and it is not suitable for the treatment of active bleeding events. Plasma-derived and recombinant CFCs are commonly used in the management of type 2N VWD but may cause a delayed FVIII response and variable elevations in FVIII and VWF levels due to differences in the composition of these concentrates [8]. This variability can lead to excessively high FVIII levels, as seen in our patient (Figure), and a theoretical increased risk of thrombosis. Also, as illustrated in the Figure, our patient would have required twice-weekly Humate-P infusions, as the OSA-FVIII level was 7.4% at 96 hours. In contrast, efanesoctocog alfa yields a rapid and sustained elevation in FVIII activity without affecting endogenous VWF levels [8]. In our patient, we were able to sustain an OSA-FVIII activity of 13.6% at 7 days, making weekly prophylaxis a feasible option. Nonetheless, evidence supporting its use in VWD is currently limited and warrants further investigation. Typically, the CH-FVIII assay overestimates efanesoctocog alfa levels, and we observed a similar discrepancy between the OSA- and CH-FVIII assays immediately after infusion of efanesoctocog alfa (likely reflective of efanesoctocog alfa levels). Interestingly, we observed a reverse discrepancy (ie, a higher OSA-FVIII than CH-FVIII) at 96 and 168 hours. Whether this reflects the effect of an increase in the patient's intrinsic FVIII level (due to binding to the D'-D3 region of efanesoctocog alfa) is speculative but supported by a study in a mouse model [9]. This observation needs to be confirmed, as we did not perform the efanesoctocog alfa-specific capture CH assay, as described by Susen et al. [1].

Our case contributes to the literature and underscores the importance of consideration of type 2N VWD as a differential diagnosis, even in males "diagnosed" with hemophilia A. Appropriate testing for type 2N or type 3 VWD, including VWF:FVIIIB and genetic testing, should be considered for all patients, or, at a minimum, for those who do not show an appropriate response to FVIII CFCs. To our knowledge, this is the first report of efanesoctocog alfa prophylaxis in a child with type 2N VWD, adding to the emerging evidence on its use in VWD beyond hemophilia A [10]. Previous studies have primarily focused on adults and evaluated only a single dose. We demonstrate the potential advantage of once-weekly dosing with efanesoctocog alfa, which reduces treatment burden and offers the option of a single treatment product for both prophylaxis and on-demand management.

AUTHOR CONTRIBUTIONS

M.H. collected all the data, wrote the first draft of the manuscript, and approved the final manuscript; C. Sabo and C. Stadler helped with study concept, data collection, and approved the final manuscript; M.R. conceptualized the manuscript, analyzed the data, revised the first draft critically for important intellectual content, and wrote and edited the final version.

DECLARATION OF COMPETING INTERESTS

M.H., C. Sabo, and C. Stadler have no conflicts of interest. M.R. has served as a member of the Scientific Advisory Board for Novo Nordisk, Sanofi, Sobi, and Takeda.

Michelle Hyde[1]
Cynthia Sabo[1]
Charity Stadler[1]
Madhvi Rajpurkar[2]

[1]*Division of Hematology Oncology, Department of Pediatrics, Central Michigan University, Children's Hospital of Michigan, Detroit, Michigan, USA*
[2]*Department of Pediatrics, Division of Hematology Oncology, Central Michigan University, Wayne State University, Children's Hospital of Michigan, Detroit, Michigan, USA*

Correspondence
Madhvi Rajpurkar, Central Michigan University, 3901 Beaubien St., Detroit, MI, 48201, USA.
Email: Rajpu1ma@cmich.edu

ORCID

Madhvi Rajpurkar https://orcid.org/0000-0002-5884-6776

REFERENCES

[1] Susen S, Trossaërt M, Zilberstein M, Mamikonian L, Santagostino E, Yarramaneni A, Wong N, Willemze A, Seth Chhabra E. A phase 1, open-label study to assess the pharmacokinetics, safety, and tolerability of a single intravenous injection of efanesoctocog alfa in adults with type 2N or type 3 von Willebrand disease. *J Thromb Haemost*. 2026;24:79–87.

[2] Giuffrida AC, Siboni SM, Baronciani L, Poli G, Gandini G, Peyvandi F. Emicizumab in type 3 von Willebrand disease: report of a case with an alloantibody and literature review. *Semin Thromb Hemost*. 2025;51:73–80.

[3] Ryu JH, Bauer KA, Schulman S. Periprocedural management of type 2N von Willebrand disease with efanesoctocog alfa. *J Thromb Haemost*. 2023;21:3508–10.

[4] Seidizadeh O, Peyvandi F, Mannucci PM. Von Willebrand disease type 2N: an update. *J Thromb Haemost*. 2021;19:909–16.

[5] Connell NT, Flood VH, Brignardello-Petersen R, Abdul-Kadir R, Arapshian A, Couper S, Grow JM, Kouides P, Laffan M, Lavin M, Leebeek FWG, O'Brien SH, Ozelo MC, Tosetto A, Weyand AC, James PD, Kalot MA, Husainat N, Mustafa RA. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. *Blood Adv*. 2021;5:301–25.

[6] Roberts JC, Janbain M, Marden JR, Sundaresan S, Swallow E, Nieto N, Jones B, Caicedo J. Real-world treatment patterns and outcomes in people with von Willebrand disease treated prophylactically with recombinant von Willebrand factor in the United States. *Expert Rev Hematol*. 2025;18:547–60.

[7] Sidonio RF Jr, Dubey L, Vilchevska KV, Inati A, Djambas Khayat C. Efficacy and safety of plasma-derived von Willebrand factor/factor VIII concentrate (wilate) prophylaxis in children and adolescents with von Willebrand disease - WIL-31 study post hoc analysis. *Res Pract Thromb Haemost*. 2025;9:102719. https://doi.org/10.1016/j.rpth.2025.102719

[8] Daniel MY, Ternisien C, Castet S, Falaise C, D'Oiron R, Volot F, Itzhar N, Pan-Petesch B, Jeanpierre E, Paris C, Zawadzki C, Desvages M, Dupont A, Veyradier A, Repessé Y, Babuty A, Trossaërt M, Boisseau P, Denis CV, Lenting PJ, et al. Type 2N von Willebrand disease: genotype drives different bleeding phenotypes and treatment needs. *J Thromb Haemost*. 2024;22:2702–12.

[9] Yee A, Gildersleeve RD, Gu S, Kretz CA, McGee BM, Carr KM, Pipe SW, Ginsburg D. A von Willebrand factor fragment containing the D'D3 domains is sufficient to stabilize coagulation factor VIII in mice. *Blood*. 2014;124:445–52.

[10] Malec L, Peyvandi F, Chan AKC, Königs C, Zulfikar B, Yuan H, Simpson M, Álvarez Román MT, Carcao M, Staber JM, Dunn AL, Chou SC, d'Oiron R, Albisetti M, Demissie M, Santagostino E, Yarramaneni A, Wong N, Abad-Franch L, Gunawardena S, et al. Efanesoctocog alfa prophylaxis for children with severe hemophilia A. *N Engl J Med*. 2024;391:235–46.