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LOW INHIBITOR RATE AND ASSESSMENT OF BINDING ANTIBODIES IN PREVIOUSLY UNTREATED PATIENTS WITH SEVERE HEMOPHILIA A TREATED WITH RURIOCTOCOG ALFA PEGOL: FINAL RESULTS FROM A PROSPECTIVE PHASE 3 STUDY

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INTRODUCTION

A phase 3, prospective, open-label study (NCT02615691) was conducted to investigate the immunogenicity, safety, and efficacy of rurioctocog alfa pegol (Adynovate; Baxalta US Inc., a Takeda company, Lexington, MA, USA) in PUPs aged <6 years with severe hemophilia A[1]

Approximately 30% of PUPs with severe hemophilia A are estimated to develop neutralizing antibodies that impair FVIII activity (FVIII inhibitors), a serious complication associated with FVIII replacement therapies[2-4]

Non-neutralizing FVIII-binding antibodies have also been found in some patients who do not have FVIII inhibitors.[4,5] Non-neutralizing binding antibodies may alter a protein's pharmacokinetic or pharmacodynamic profile; however, the biological significance of FVIII-binding antibodies remains unclear[4]

METHODS

A phase 3, prospective, multicenter, uncontrolled, open-label study conducted from November 2015 to October 2024

Enrolled participants

Key inclusion criteria:
- Aged <6 years with severe hemophilia A (FVIII <1%)
- Previously untreated with ≤2 EDs to rurioctocog alfa pegol, octocog alfa, or plasma transfusion

Key exclusion criterion:
- A history or presence of FVIII inhibitory antibodies* at screening

Received ≥1 dose of rurioctocog alfa pegol

On demand:
10–50 IU/kg (up to 80 IU/kg), depending on bleeding severity

Prophylaxis:
25–50 IU/kg (up to 80 IU/kg, at investigator discretion) ≥1×/week

Participants received rurioctocog alfa pegol for ≥100 EDs or until FVIII inhibitor development*

Completed the study

Primary endpoint:
Incidence of FVIII inhibitor development*

Secondary endpoint assessed:
Presence of binding IgG and IgM antibodies to FVIII, PEG-FVIII, and PEG

Ethics approval was obtained, and all participants/legally authorized representatives provided written informed consent.
*≥0.6 BU/mL, assessed using the Bethesda assay or the Nijmegen modification of the Bethesda assay.

BINDING ANTIBODY ASSESSMENT

IgM and IgG antibodies binding to FVIII, PEG, or PEG-FVIII were analyzed at regular intervals using a two-step, ELISA-based approach in accordance with regulatory guidelines[6,7] and established principles[4,8,*]

Screening assay
- Initial ELISA for detection of binding antibodies
- Cut-off optimized to minimize false-negative results, allowing ~5% false-positive rate
- Defines the lower limit of detection for any binding antibodies

Confirmatory assay
- Competition-based ELISA confirming specificity of antibodies detected by the screening assay
- Excludes false-positive results
- Confirmation of specificity required an antibody titer ≥1:80

Antibody classification

Pre-existing antibodies: Positive result at screening or baseline, prior to first rurioctocog alfa pegol exposure
Persistent antibodies: Positive results at ≥3 consecutive study visits
Transient antibodies: Positive results not meeting criteria for pre-existing or persistent antibodies

*For additional methodological details, see Horling FM, et al. *Blood Adv* 2024;8:2726-39.

OBJECTIVE

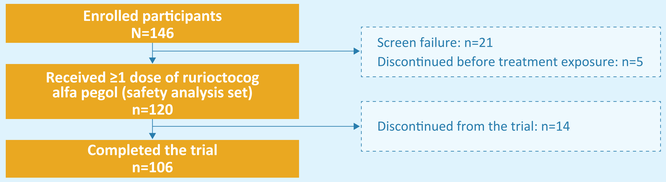
- **To evaluate the potential of rurioctocog alfa pegol to induce FVIII inhibitors as well as IgM and IgG antibodies against FVIII, PEG, and PEG-FVIII from this phase 3 study**

CONCLUSIONS

- **Although 50 of 92 participants without inhibitors with ≥100 EDs to rurioctocog alfa pegol developed binding antibodies, the FVIII inhibitor rate remained low**
- **Notably, PEG-FVIII IgG antibodies were observed in 47 participants without inhibitors, despite fewer participants developing FVIII or PEG IgG antibodies**

PARTICIPANT DISPOSITION

146 participants were enrolled from 55 sites in 19 countries, of whom 120 received ≥1 dose of rurioctocog alfa pegol



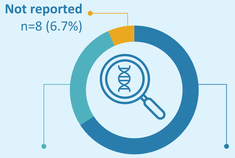
PARTICIPANT CHARACTERISTICS

All 120 participants who received ≥1 dose of rurioctocog alfa pegol were male; median (range) age, 0.8 (0.1–5.0) years[9]

67 PARTICIPANTS
had a family history of hemophilia A

6 PARTICIPANTS
had a family history of FVIII inhibitors

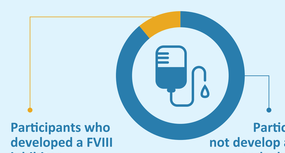
79 PARTICIPANTS
had high-risk FVIII gene variants



FVIII INHIBITORS

11 participants developed inhibitory antibodies to FVIII; inhibitor rate (95% CI), 0.11 (0.06–0.19)[9]

100 PARTICIPANTS
either had ≥100 EDs to rurioctocog alfa pegol or developed a FVIII inhibitor*



11 PARTICIPANTS
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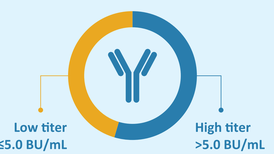
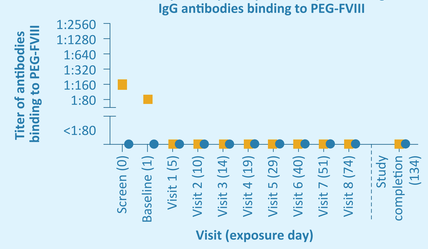


*Of the 120 participants in the safety analysis set, 20 discontinued the study or completed the study with <100 EDs and are not included in this analysis. None of these participants developed a confirmed FVIII inhibitor.

BINDING ANTIBODIES

50 participants without inhibitors with ≥100 EDs* tested positive for IgM and/or IgG antibodies, of whom 18 were positive for >1 antibody species; persistent and transient PEG-FVIII IgG antibodies were the most frequently detected antibody species

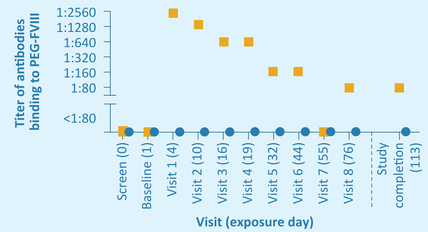
Example of a participant with pre-existing IgG antibodies binding to PEG-FVIII



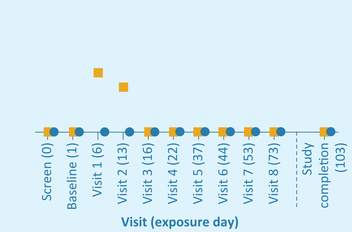
Total number of participants with pre-existing antibodies

Antibody species	Pre-existing
FVIII-binding IgG	3
FVIII-binding IgM	0
PEG-FVIII–binding IgG	7
PEG-FVIII–binding IgM	4
PEG-binding IgG	0
PEG-binding IgM	9

Example of a participant with persistent IgG antibodies binding to PEG-FVIII



Example of a participant with transient IgG antibodies binding to PEG-FVIII



■ IgG binding to PEG-FVIII ● IgM binding to PEG-FVIII

Total number of participants with persistent and transient antibodies

Antibody species	Persistent	Transient
FVIII-binding IgG	0	4
FVIII-binding IgM	0	0
PEG-FVIII–binding IgG	19	21
PEG-FVIII–binding IgM	0	1
PEG-binding IgG	3	7
PEG-binding IgM	0	0

*Of the 120 participants who received ≥1 dose of rurioctocog alfa pegol, 92 without inhibitors with ≥100 EDs to rurioctocog alfa pegol were analyzed for binding antibodies.

LIMITATIONS

- Antibody detection required a confirmatory titer threshold of ≥1:80; therefore, low-titer antibodies <1:80 may be present in samples reported as antibody negative

ABBREVIATIONS

BU, Bethesda units; ED, exposure day; ELISA, enzyme-linked immunosorbent assay; FVIII, factor VIII; Ig, immunoglobulin; PEG, polyethylene glycol; PUP, previously untreated patient.

REFERENCES

1. Sidonio RF Jr, et al. *Expert Rev Hematol* 2023;16:793-801. 2. Gouw SC, et al. *N Engl J Med* 2013;368:231-9. 3. Kenet G, et al. *J Thromb Haemost* 2023;21:3109-16. 4. Whelan SF, et al. *Blood* 2013;121:1039-48. 5. Reipert BM, et al. *Blood Adv* 2020;4:5785-96. 6. US Department of Health and Human Services, Food and Drug Administration. 2019. https://www.fda.gov/media/119788/download. Accessed May 11, 2026. 7. European Medicines Agency. 2017. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-immunogenicity-assessment-therapeutic-proteins-revision-1_en.pdf. Accessed May 11, 2026. 8. Horling FM, et al. *Blood Adv* 2024;8:2726-39. 9. Sidonio RF Jr, et al. *Res Pract Thromb Haemost* 2025;9(Suppl 2):102931.

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DISCLOSURES

ST, CCL, and JG: Employees of Takeda Development Center Americas, Inc.; shareholders of Takeda. BMR: Consultancy fees from Takeda. MG: Employee of IMC Krems University of Applied Sciences (a contract research laboratory for Takeda). HG: Principal investigator for several clinical studies at Oslo University Hospital; writing support for Bayer and Sobi. JA: Honoraria/consultancy fees from Sobi; speaker bureaus for CSL Behring, Novo Nordisk, Roche, and Sobi. RFS: Grants/research support from HEMA Biologics, LFB, Octapharma, and Takeda; honoraria/consultancy fees from Alnylam, Bayer, Genentech/Roche, HEMA Biologics, Hemab, LFB, Novo Nordisk, Octapharma, Pfizer, Star Therapeutics, and Takeda; leadership positions with ATHN, ISTH ACPC, and HFA medical advisor.

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