Direct PK comparison of

JIVI® vs. ADYNOVATE®:

A randomized, crossover study in adult patients with severe hemophilia A

INDICATION

- JIVI ® is a recombinant DNA-derived, Factor VIII concentrate indicated for use in previously treated adults and pediatric patients 7 years of age and older with hemophilia A (congenital Factor VIII deficiency) for:
  - On-demand treatment and control of bleeding episodes.
  - Perioperative management of bleeding.
  - Routine prophylaxis to reduce the frequency of bleeding episodes.
- Limitations of use
  JIVI is not indicated for use in:
  - Children <7 years of age due to a greater risk for hypersensitivity reactions and/or loss of efficacy.
  - Previously untreated patients (PUPs).
  - Treatment of von Willebrand disease.

SELECTED IMPORTANT SAFETY INFORMATION

- JIVI is contraindicated in patients who have a history of hypersensitivity reactions to the active substance, polyethylene glycol (PEG), mouse or hamster proteins, or other constituents of the product.

Please see full Indications and Important Safety Information throughout. For additional important risk and use information, please see the full Prescribing Information for Jivi.

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Dosing with Jivi® for routine prophylaxis

Jivi® dosing frequency can be adjusted based on bleeding episodes

		For patients ≥12 years
Start simply	**TWICE WEEKLY**	Recommended starting regimen for Jivi is twice weekly (30-40 IU/kg) for all prophylaxis patients.[1]*
Adjust	**EVERY 5 DAYS**	Based on bleeding episodes, less frequent dosing of Jivi every 5 days (45-60 IU/kg) can be used.[1]*
Fine-tune regimen	**UP OR DOWN**	From there, you have the flexibility to adjust your patient's dosing frequency up or down as needed, based on bleeding episodes.[1]

*100% of patients in the every-5-days and twice-weekly dosing arms remained on the same dosing regimen for the duration of the main study.[1]

Learn about dosing information for patients 7 to <12 years of age at www.jivihcp.com or refer to the full Prescribing Information.

SELECTED IMPORTANT SAFETY INFORMATION

- Hypersensitivity reactions, including severe allergic reactions, have occurred with JIVI. Monitor patients for hypersensitivity symptoms. Early signs of hypersensitivity reactions, which can progress to anaphylaxis, may include chest or throat tightness, dizziness, mild hypotension and nausea. If hypersensitivity reactions occur, immediately discontinue administration and initiate appropriate treatment.

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PK parameters of Jivi® in patients ≥12 years of age from the PROTECT VIII trial (arithmetic mean±SD)[1]

- Measured following a single dose (25 IU/kg and 60 IU/kg)[1]

	Chromogenic assay		One-stage assay	
PK parameters (unit)	25 IU/kg n=7	60 IU/kg* n=29	25 IU/kg n=7	60 IU/kg* n=29
AUC (IU*h/dL)	1640±550	4060±1420	1640±660	4150±1060
C_{max} (IU/dL)	64.2±9.2	167±30	69.4±11.3	213±71
$t_{½}$ (h)	18.6±4.6	17.9±4.0	21.4±13.1	17.4±3.8
MRT_{IV} (h)	26.7±6.6	25.8±5.9	29.0±14.0	24.5±5.4
V_{ss} (mL/kg)	42.8±5.0	39.4±6.3	44.7±5.4	36.0±6.5
CL (mL/h)	142±33	121±53	146±44	114±41
CL (mL/h/kg)	1.68±0.39	1.63±0.52	1.74±0.54	1.52±0.38
Recovery [(IU/dL)/(IU/kg)]	2.13±0.47	2.53±0.43†	2.21±0.55	3.25±0.84†

PK, pharmacokinetic; SD, standard deviation; AUC, area under the curve; C_{max}, maximum drug concentration in plasma after single dose; $t_{½}$, terminal half-life; MRT_{IV}, mean residence time after an IV administration; V_{ss}, apparent volume distribution at steady-state; CL, clearance.

*Combined data from phase 1 and phase 2/3 studies.

†Recovery value could not be calculated for one subject.

SELECTED IMPORTANT SAFETY INFORMATION

- JIVI may contain trace amounts of mouse and hamster proteins. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.
- Hypersensitivity reactions may also be related to antibodies against polyethylene glycol (PEG).

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Crossover study examining PK characteristics of **Jivi®** and **Adynovate®** (N=18)[2]*

The small size of the patient cohort could be a potential limitation of this study.[2]

Study description

The PK profiles of Jivi® and Adynovate® were compared in a randomized, open-label, single-dose, crossover study with a washout period between doses.

- Previously treated male patients aged 18-65 years with severe hemophilia A (FVIII <1 IU/dL) previously treated with any FVIII product for ≥150 exposure days.
- Primary endpoint: $AUC_{(0\text{-}t_{last})}$† based on one-stage clotting assay.

Dosing

In the preplanned analysis, the 50 IU/kg doses administered in this study were calculated based on the 1000 IU nominal potencies on the vial labels for the 2 products.

Pre-study wash-out period ≥3 days for SHL products ≥5 days for EHL FVIII products.

PK assessment

PK samples were collected predose, and at 11 time points: 0.25, 0.5, 1, 3, 6, 8, 24, 48, 72, 96, and 120 hours after infusion.

PK, pharmacokinetic; $AUC_{(0\text{-}t_{last})}$, area under the curve (from time 0 to last data point).

*Adapted from Solms et al.

†Area under the curve is the total amount of a drug that reaches the bloodstream, measured by plasma concentration, over time.[3]

SELECTED IMPORTANT SAFETY INFORMATION

- Neutralizing antibody (inhibitor) formation has occurred following administration of JIVI. Carefully monitor patients for development of Factor VIII inhibitors, using appropriate clinical observations and laboratory tests. If expected plasma Factor VIII activity levels are not attained or if bleeding is not controlled as expected with administered dose, suspect the presence of an inhibitor (neutralizing antibody).

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Potency-adjusted PK analyses of **Jivi®** and **Adynovate®**[2]*

The preplanned analysis was followed by a post hoc analysis

- In the preplanned analysis, the 50 IU/kg doses administered in this study were calculated based on the 1000 IU nominal potencies provided on the vial labels of the 2 products
- In this study, the actual potencies were 1030 IU/vial for Jivi® and 1141 IU/vial for Adynovate®. This resulted in actual administered doses which were approximately:
  - 3% higher than the planned 50 IU/kg dose for Jivi®
  - 14.1% higher than the planned 50 IU/kg dose for Adynovate®
- A subsequent post hoc analysis of PK parameters was conducted using the actual potencies of the 2 products being compared

*Adapted from Solms et al.

SELECTED IMPORTANT SAFETY INFORMATION

- An immune response associated with IgM anti-PEG antibodies, manifested as symptoms of acute hypersensitivity and/or loss of drug effect, has occurred with JIVI administration. In the clinical trials, the IgM anti-PEG antibodies disappeared within 4-6 weeks. No immunoglobulin class switching from IgM to IgG has been observed.
- A low post-infusion Factor VIII level, in absence of detectable Factor VIII inhibitors, may be due to loss of treatment effect related to high titers of anti-PEG IgM antibodies. In these cases, discontinue JIVI and switch patients to a different anti-hemophilic product.

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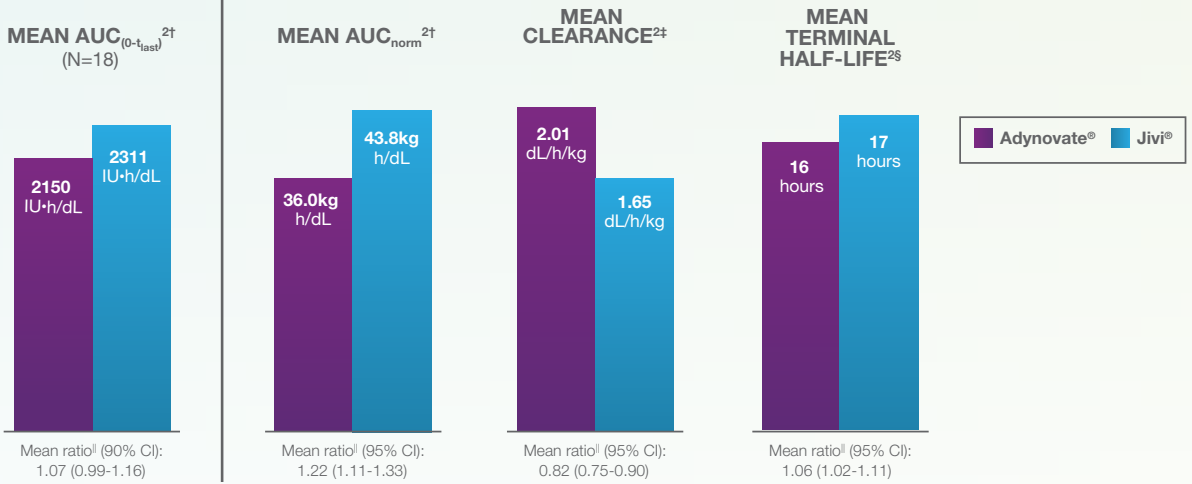
Comparative PK results for **Jivi®** vs **Adynovate®**[2]

Based on nominal potencies of the 2 products per vial labels

Potency-adjusted PK Results (N=18)
In the post-hoc analyses, PK results were based on the actual potencies in the vials of the 2 products



PK, pharmacokinetic; $AUC_{(0\text{-}t_{last})}$, area under the curve (from 0 to last data point); AUC_{norm}, dose-normalized area under the curve; CI, confidence interval.

*Half-life and CI are not weight-dependent parameters, so they are not normalized.

†Area under the curve is the total amount of a drug that reaches the bloodstream, measured by plasma concentration over time.[3]

‡Clearance is the rate by which a drug is eliminated from the body.[4]

§Half-life is the time it takes for the amount of a drug in the blood to decrease by one half.[5]

‖Geometric least squares.[2]

SELECTED IMPORTANT SAFETY INFORMATION

- A reduced recovery of Factor VIII after start of JIVI treatment may be due to transient low titers of anti-PEG IgM antibodies. In these cases, increase the dose of JIVI until recovery of Factor VIII returns to expected levels.

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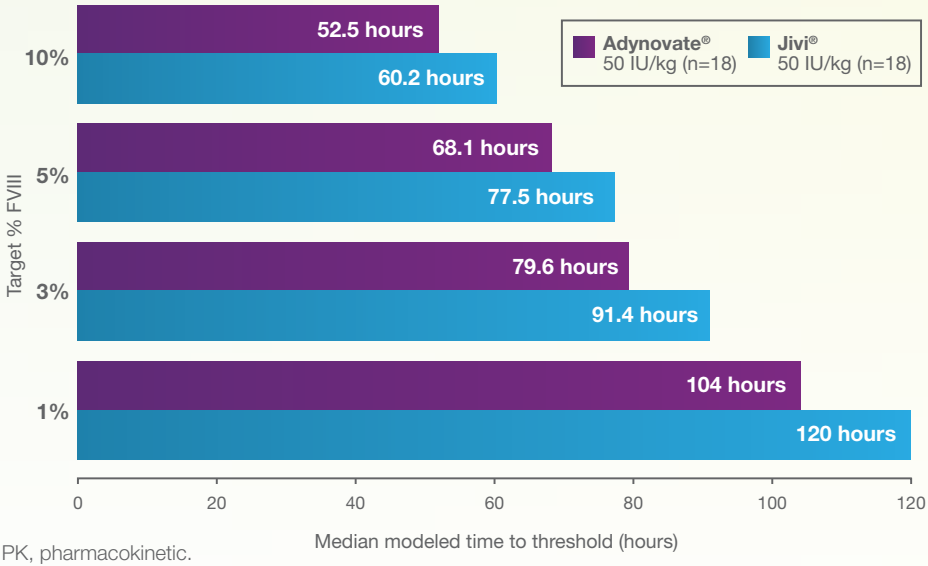
Median time to target FVIII threshold levels with **Jivi**® vs **Adynovate**®[2]

Estimated from a population PK model (N=18) based on potency-adjusted results[2]*



PK, pharmacokinetic.

*Adapted from Solms et al. A population PK model was developed based on data obtained by a one-stage assay to simulate time to reach FVIII thresholds of 1%, 3%, 5%, and 10% FVIII.[2]

SELECTED IMPORTANT SAFETY INFORMATION

- The most common (incidence ≥5%) adverse reactions in clinical trials in previously treated patients (PTPs) ≥7 years of age were headache, fever, cough, and abdominal pain.

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You are encouraged to report side effects or quality complaints of prescription drugs to the FDA. Visit **www.fda.gov/medwatch** or call 1-800-FDA-1088.

References: 1. Jivi® Prescribing Information. Whippany, NJ: Bayer LLC; May 2025. **2.** Solms A, Shah A, Berntorp E, et al. Direct comparison of two extended half-life PEGylated recombinant FVIII products: a randomized, crossover pharmacokinetic study in patients with severe hemophilia A. *Ann Hematol*. 2020;99(11):2689-2698. doi:10.1007/s00277-020-04280-3. **3.** Anderson PL. The ABCs of pharmacokinetics. HealthCentral Corporation. Accessed May 6, 2025. http://www.thebody.com/content/art875.html. **4.** Dhillon S, Gill K. Basic pharmacokinetics. In: Dhillon S, Kostrzewski A, eds. *Clinical Pharmacokinetics*. London, UK: Pharmaceutical Press; 2006. **5.** Ratain MJ, Plunkett WK Jr. Principles of pharmacokinetics. In: Kufe DW, Pollock RE, Weichselbaum RR, et al, eds. *Holland-Frei Cancer Medicine*. 6th ed. Hamilton, Ontario: BC Decker; 2003.

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