Direct PK comparison of

JIVI® vs. ADYNOVATE®:

A randomized, crossover study in patients with severe hemophilia A

INDICATIONS

- Jivi antihemophilic factor (recombinant), PEGylated-aucl, is a recombinant DNA-derived, Factor VIII concentrate indicated for use in previously treated adults and adolescents (12 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 less than 12 years of age due to a greater risk for hypersensitivity reactions.
  - Jivi is not indicated for use in previously untreated patients (PUPs).
  - Jivi is not indicated for the 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.

Jivi®
antihemophilic factor (recombinant) PEGylated-aucl

Explore dosing and...

Dosing with Jivi® for routine prophylaxis

Indicated for previously treated patients ≥12 years of age[1]

Start simply	TWICE **WEEKLY**	**For all prophylaxis patients:** Recommended starting regimen is Jivi® **twice weekly** (30–40 IU/kg)[1]
Step up	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		**Based on bleeding episodes:** The dosing frequency may be further **adjusted up or down**[1]

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.

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

Jivi®
antihemophilic factor (recombinant) PEGylated-aucl

...PK parameters of **Jivi®** in patients ≥12 years of age[1]

PK parameters of Jivi® in 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†

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

†Recovery value could not be calculated for one subject.

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.

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).

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

Jivi®
antihemophilic factor (recombinant) PEGylated-aucl

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 can occur following administration of Jivi. Carefully monitor patients for the 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).

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

Jivi®
antihemophilic factor (recombinant) PEGylated-aucl

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

- A clinical immune response associated with IgM anti-PEG antibodies, manifested as symptoms of acute hypersensitivity and/or loss of drug effect, has been observed primarily in patients < 6 years of age. The symptoms of the clinical immune response were transient. Anti-PEG IgM titers decreased over time to undetectable levels. No immunoglobulin class switching was observed.

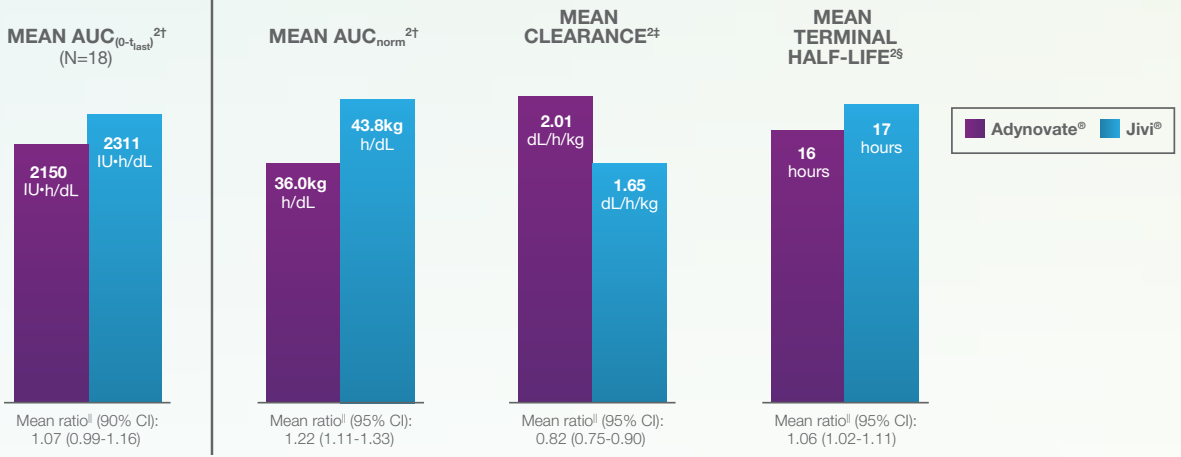
Please see full Indications and Important Safety Information throughout. For additional important risk and use information, please see the full Prescribing Information for Jivi.

Jivi®
antihemophilic factor
(recombinant) PEGylated-aucl

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

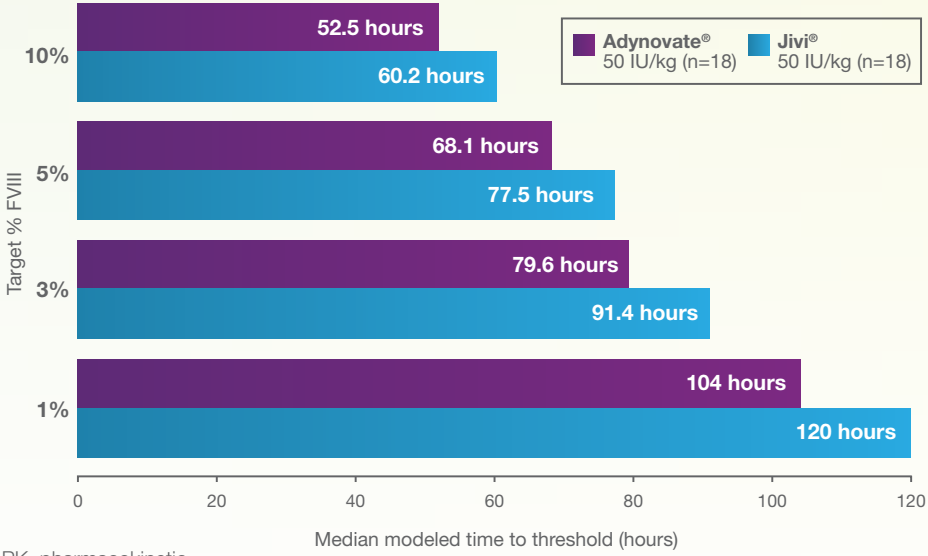
- In case of clinical suspicion of loss of drug effect, conduct testing for Factor VIII inhibitors and Factor VIII recovery. A low post-infusion Factor VIII level in the absence of detectable Factor VIII inhibitors indicates that loss of drug effect is likely due to anti-PEG antibodies. Discontinue Jivi and switch patients to a previously effective Factor VIII 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.

Jivi®
antihemophilic factor (recombinant) PEGylated-aucl

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 frequently (≥5%) reported adverse reactions in clinical trials in previously treated patients (PTPs) ≥12 years of age were headache, cough, nausea, and fever.

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

Jivi®
antihemophilic factor (recombinant) PEGylated-aucl

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

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; 2018. **2.** Solms A, Shah A, Berntrop 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.* Published online September 24, 2020. doi:10.1007/s00277-020-04280-3. **3.** Anderson PL. The ABCs of pharmacokinetics. http://www.thebody.com/content/art875.html. Accessed April 2018. **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.

Jivi®
antihemophilic factor
(recombinant) PEGylated-aucl