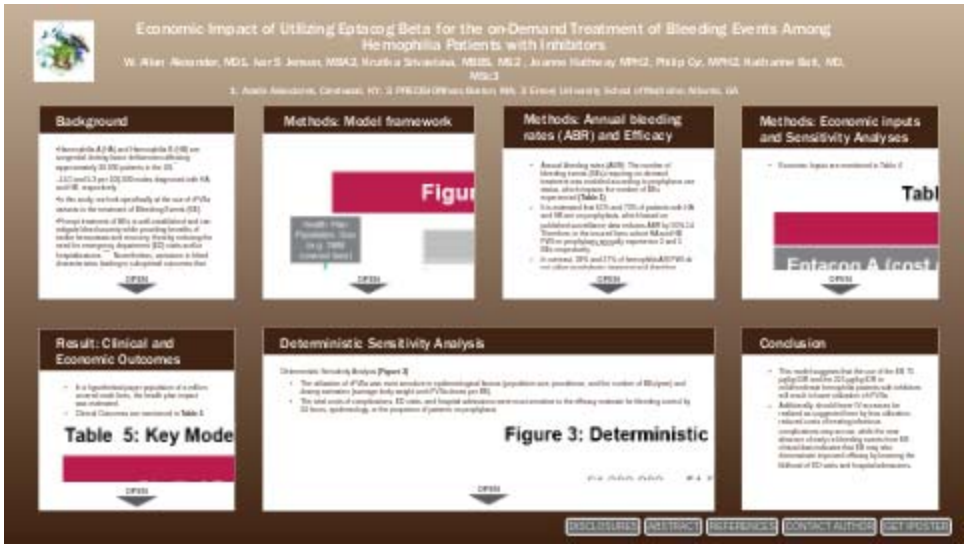
Economic Impact of Utilizing Eptacog Beta for the on-Demand Treatment of Bleeding Events Among Hemophilia Patients with Inhibitors



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BACKGROUND

•Haemophilia A (HA) and Haemophilia B (HB) are congenital clotting factor deficiencies affecting approximately 30,000 patients in the US.[1]

–14.5 and 5.3 per 100,000 males diagnosed with HA and HB, respectively.[1]

•In this study, we look specifically at the use of rFVIIa variants in the treatment of Bleedimg Events (BE).

•Prompt treatment of BEs is well-established and can mitigate bleed severity while providing benefits of earlier hemostasis and recovery, thereby reducing the need for emergency department (ED) visits and/or hospitalizations.[2-5] Nevertheless, variations in bleed characteristics leading to suboptimal outcomes that require dose adjustment; further, complications including early re-bleeding and thrombosis have been reported.[6,7]

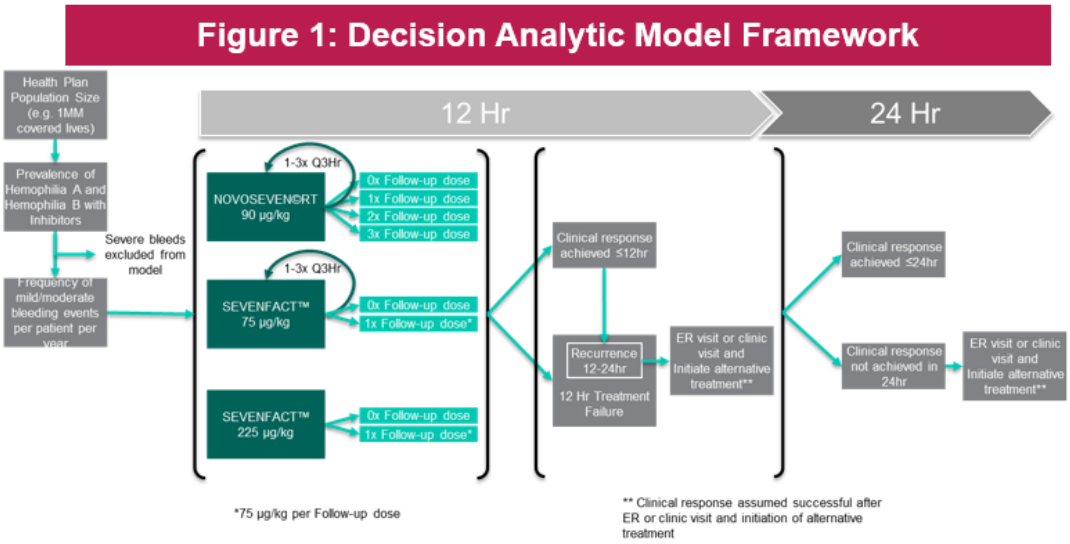
•A specific concern with rFVIIa treatment of a BE is the uncertainty of dose requirements. Physicians commonly instruct patients to administer follow-up doses with decreasing frequency of rFVIIa to ensure that bleeding has ceased, [8,9] thus safeguarding sustained hemostatic response and theoretically "clot stability."[10] Concerns about early re-bleeding in the first 24 hours after initial clinical response following rFVIIa (EA) administration have been described in prospective clinical trials with early re-bleed rates of 4-15%. Patients may reduce the risk of early re-bleeding by using supplemental dosing, with accompanying increased costs and thrombotic risk. Thus, unmet needs for more convenient and robust disease management still exist.

•A new bypassing agent, eptacog beta is now available that could potentially benefit patient treatment outcomes: coagulation factor VIIa (recombinant) – jncw; (INN name – eptacog beta; SEVENFACT®, HEMA Biologics, LLC, Louisville, KY and LFB Framingham, MA).

–Eptacog beta rFVIIa has been developed for on-demand treatment of BEs occurring in adolescent and adult HA and HB patients with inhibitors. In the PERSEPT 1 trial, described previously, two initial doses of EB used mostly in the home setting demonstrated dose dependent efficacy in HA and HB patients with inhibitors.[11]

•A decision analytic health economic model was developed to compare the utilization and outcomes of two differing rFVIIa products, eptacog alfa (EA) and eptacog beta (EB).

METHODS: MODEL FRAMEWORK



- A decision-analytic economic model from a US payer perspective over a one-year time horizon was developed that utilizes recent, peer-reviewd and/or published data from prospective clinical trials with similar endpoints.
- Recombinant rFVIIa product utilization was modeled for on-demand rFVIIa treatment of mild and moderate BEs in HA and HB patients with inhibitors.
- The model follows patients from the point of initial administration of rFVIIa through presumed hemostasis or refractory bleeding at 12 hours and 24 hours, as well as failure due to early re-bleeding before 24 hours (Figure 1)
- The model compares the standard dosing regimen and 24-hour effectiveness of
    1. the prospective, conservative dosing of EA (90 µg/kg q 3 hours until clinical response) in the control arm of the adept™2 trial (q 2 hours is the approved EA dose interval), to
    2. the two dosing regimens studied in the PERCEPT 1 trial of EB (75 µg/kg q 3 hrs. and 225µg/kg initially followed by 75 µg/kg q 3 hrs. beginning 9 hours later if no clinical response).[10-13]

METHODS: ANNUAL BLEEDING RATES (ABR) AND EFFICACY

- Annual bleeding rates (ABR): The number of bleeding events (BEs) requiring on-demand treatment was modeled according to prophylaxis use status, which impacts the number of BEs experienced **(Table 1)**
- It is estimated that 61% and 73% of patients with HA and HB are on prophylaxis, which based on published surveillance data reduces ABR by 50%.14 Therefore, in the insured lives cohort HA and HB PWI on prophylaxis annually experience 2 and 5 BEs respectively.[6,14-16,21]
- In contrast, 39% and 27% of hemophilia A/B PWI do not utilize prophylactic treatment and therefore encounter 23.3 and 24 BEs per year, respectively.[15,16]

Table 1: Bleeding episodes requiring hemostatic agent (per 100,000 population)

	Hemophilia A	Hemophilia B
Proportion of patients on prophylaxis	61%	73%
Annual bleeding rate for patients on prophylaxis	2	5
Proportion of patients not on prophylaxis	39%	27%
Annual bleeding rate for patients not on prophylaxis	23.3	24

- Efficacy parameters are mentioned in **Table 2.** Bleeding control ≤12 hours, Failure rate at 12 hours, Bleeding recurrence 12-24 hours, Bleeding control ≤24 hours are from the literature[11-13,23]

Table 2: Efficacy (Study Derived Bleeding Event Analysis)[10, 11, 12, 18, 22]

	Eptacog alfa	Eptacog beta* 75 µg/kg	Eptacog beta* 225 µg/kg
Bleeding control ≤12 hours	86.4 (n=227)	82%	91%
Failure rate at 12 hours	13.6%	18%	9%
Bleeding recurrence 12-24 hours	6.7%	0.0%	0.5%
Bleeding control ≤24 hours	86.2% (n=225)	96.7%	99.5%
Failure rate at 24 hours	13.8%	3.2%	0.5%

- The model calculates the utilization of each rFVIIa product based on published dosing recommendations for the initial and subsequent dosing, mentioned in **Table 3**

*Access estimates based on data from based on adept™2 and PERSEPT 1 clinical trial results. ** EA 12-hour efficacy as reported in the adept™2 trial was corrected to be comparable to the requirements of the PERSEPT 1 trial of EB. Thus, additional treatments after 12 hours and prior to 24 hours counted as 12-hour efficacy failures and had a corresponding effect on reported 12-hour EA bleeding control.18 Only 225 of 227 bleeding events had results at both 12- and 24-hours in that trial. ǂ EB 12- and 24-hour bleeding control shown is derived from published reports of the PERSEPT 1 clinical trial[12,22]

Table 3: Dosing Regimens (determining the utilization)

Study Dosing regimens	Eptacog alfa	Eptacog beta 75 µg/kg	Eptacog beta 225 µg/kg
Initial dose regimen (IDR)	90 µg/kg	75 µg/kg	225 µg/kg
Subsequent doses	90 µg/kg	75 µg/kg	75 µg/kg
Frequency	Repeated every 3 hours until hemostasis is achieved		If hemostasis is not achieved within 9hr, additional 75 µg/kg doses may be administered every 3 hours until hemostasis is achieved
Total average doses/bleeding event administered to reach hemostasis first 24 hr	3.2	2.5	1.4
Average number of follow-up doses	1	0	0

- Complications: Haemophilia patients' inhibitors often require an intravenous central catheter (PICC) line, which is associated with the risk of infection. The annualized rate of infection was informed by the literature.
  - Infection risk in the literature describes *conceptual proportionality*: **implant time α number of uses α risk of infection.**[19]
  - The rate of infection in patients with inhibitors was shown to be one infection in 8.5 patient months = annualized rate of 1.4 infections per patient-year.

METHODS: ECONOMIC INPUTS AND SENSITIVITY ANALYSES

- Economic Inputs are mentioned in Table 4

Table 4: Costing inputs [8,20,22]

	Cost
Eptacog A (cost per mg)	$2.33
Eptacog B (cost per mg)	$2.28
ED visit	$891
Hospital admission	$52,886
Hospital Costs for Infections (Bacteremia ICD-10 R78.81)	$12,139

- Several sensitivity analyses were conducted to evaluate the most influential parameters.
  - In a deterministic sensitivity analysis (DSA), all model parameters were varied by +/- 20%, holding the other inputs fixed.
  - To test the model's robustness, a probabilistic sensitivity analysis (PSA) was conducted using Monte Carlo simulation (1,000 runs) where all parameters could vary across a pre-specified range, as determined by draws from assigned distributions. Gamma, beta, and normal distributions were utilized to determine the ranges for costs and resource use, rates and percentages, and body weight, dosing and population estimates respectively.

RESULT: CLINICAL AND ECONOMIC OUTCOMES

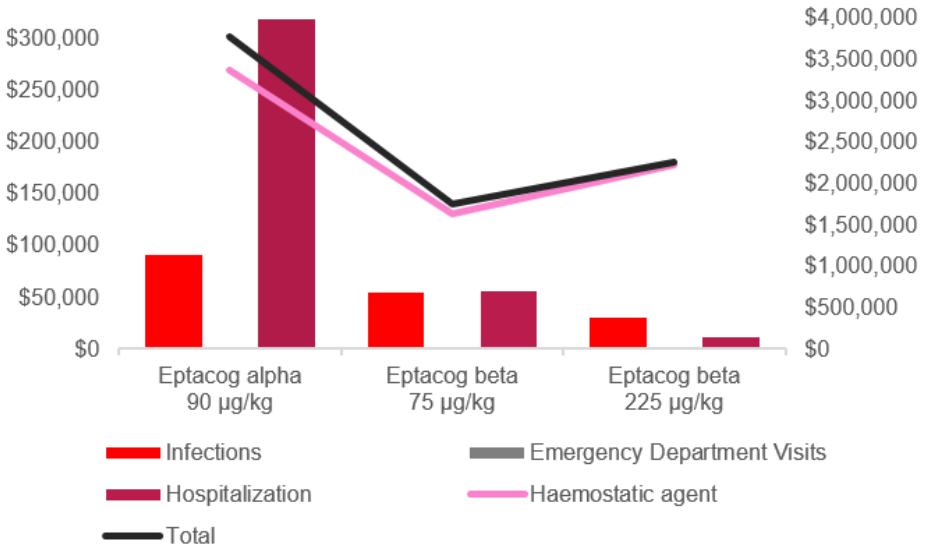
- In a hypothetical payer population of a million covered male lives, the health plan impact was estimated.
- Clinical Outcomes are mentioned in **Table 5**

Table 5: Key Model results

Studied Dosing Regimens	EA	EB IDR 75 µg/kg	EB IDR 225 µg/kg
Clinical outcomes			
Number of failures at 12 hours	7.5	9.8	4.9
Number of re-bleeding events 12-24 hrs	3.6	1.3	0.5
Number of failures at 24 hrs (including re-bleeds)	7.5	1.3	0.3
ED visits due to failures and re-bleeding	1.5	0.3	0.1
Hospital admissions	6.0	1.0	0.2
Average number of IV Accesses per BE	4.2	2.5	1.4
Total number of IV accesses	228.9	136.1	76.2
Infection Frequency per Patient-Year	1.40	0.83	0.47
Total number of potential infections	7.4	4.4	2.5
Total units of hemostatic agent per 1M insured lives cohort in year (µg)	**1,441,975**	**714,785**	**972,108**
Total 1 mg units consumed	1,470	762	980

- Economic Outcomes are illustrated in **Figure 2**
  - If all PWI switch from EA to EB 75µg/kg or to EB 225µg/kg for on-demand use, a health plan would reduce the total costs from $3.7million to $1.7million (54%) or to $2.3million (40%), respectively.
  - The majority of the savings are driven by reduced drug costs of $1.7million (85%) or $1.1million (76%), from the lower acquisition costs of EB and reduced consumption by 48% or 33%, with EB 75µg/kg or 225µg/kg, respectively. The remaining savings were from reduced ED visits, hospitalizations and IV-access complications

Figure 2: Annual health plan of rFVIIa on haemostatic agent, complication, ED and hospital costs

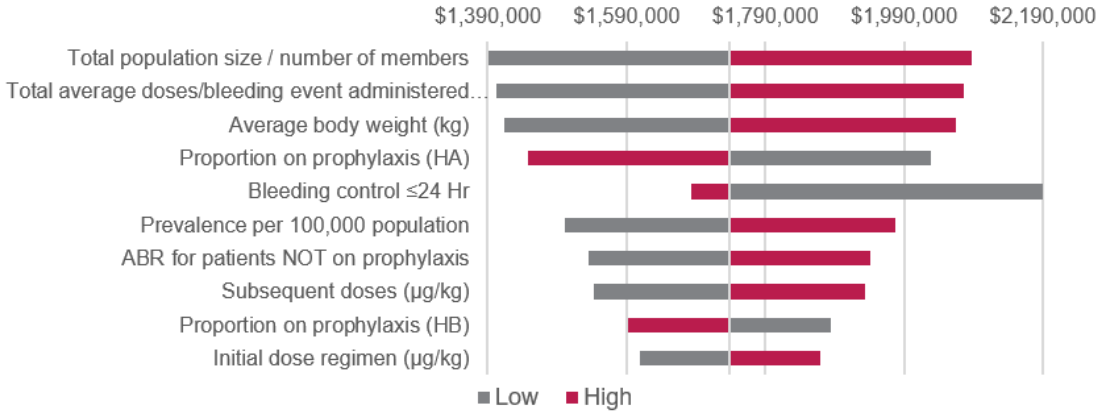


DETERMINISTIC SENSITIVITY ANALYSIS

Deterministic Sensitivity Analysis **(Figure 3)**

- The utilization of rFVIIa was most sensitive to epidemiological factors (population size, prevalence, and the number of BEs/year) and dosing estimates (average body weight and rFVIIa doses per BE).
- The total costs of complications, ED visits, and hospital admissions were most sensitive to the efficacy estimate for bleeding control by 24 hours, epidemiology, or the proportion of patients on prophylaxis

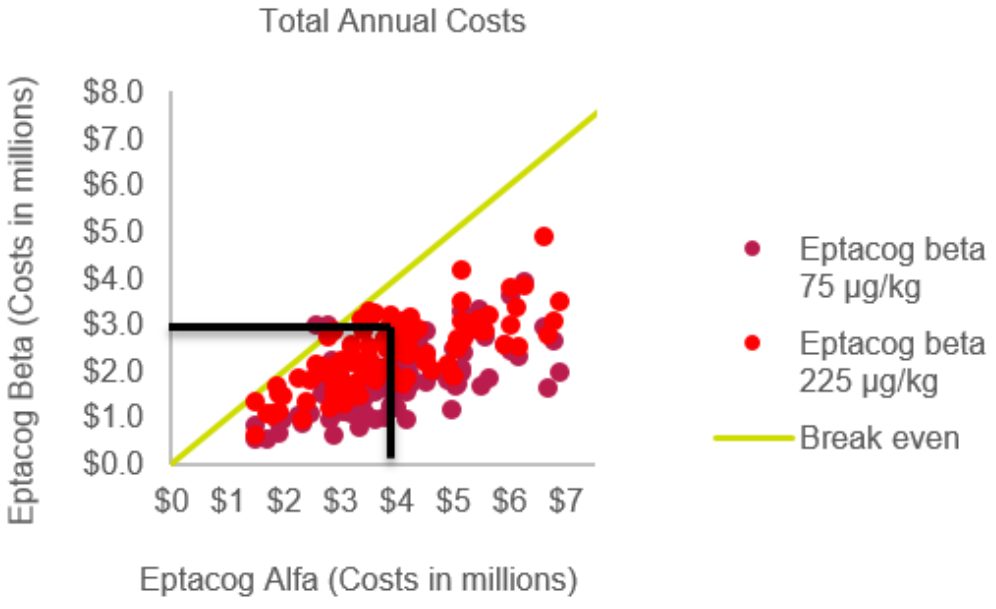
Figure 3: Deterministic Sensitivity Analysis



Probabilistic Sensitivity Analysis

- For utilization-based total costs of complications, ED visits, and hospital admissions, EB 75 µg/kg and 225 µg/kg had lower costs than EA in 94% and in 100% of the model simulations, respectively. **(Figure 4)**
- **In 98% and 96% of model simulations, EB 75 µg/kg and 225 µg/kg, respectively, would consume less rFVIIa than EA**

Figure 4: Probabilistic sensitivity analysis of costs



CONCLUSION

- This model suggests that the use of the EB 75 µg/kg IDR and the 225 µg/kg IDR in mild/moderate hemophilia patients with inhibitors will result in lower utilization of rFVIIa.
- Additionally, should fewer IV accesses be realized as suggested here by less utilization, reduced costs of treating infectious complications may accrue, while the near absence of early re-bleeding events from EB clinical dats indicates that EB may also demonstrate improved efficacy by lowering the liklihood of ED visits and hospital admissions.

DISCLOSURES

The manuscript was funded by Hema Biologics™, LLC. The authors approved all content and result in this manuscript without being subject to sponsor censorship. Jensen IS, Cyr P, Hathway J, and Srivastava KJ are employees of and PRECISIONheor, which provides consulting services to the pharmaceutical industry, including HEMA Biologics, LLC. Batt, K. is an advisor to PRECISIONheor. Alexander, A is a former employee of Hema Biologics™, LLC and provides consulting services to the pharmaceutical industry.

ABSTRACT

OBJECTIVES

A mainstay of treatment in haemophilia patients with inhibitors (PWI) is recombinant Factor VIIa (rFVIIa)bypassing agent. The FDA recently approved a new rFVIIa (eptacog beta (EB)) variant that may reduce bypassing agent use for on-demand treatment of bleeding events (BEs). The aim of this study was to quantify the clinical and economic value associated with the use of EB vs Coagulation rFVIIa eptacog alfa (EA), for on-demand treatment of bleeding episodes (BE) occurring in PWI.

METHODS

A decision-analytic model was developed to compare the utilization, clinical outcomes, and costs of EA andEB among hemophilia PWI utilizing on-demand treatment of BEs over the course of one year. Treatment regimens of rFVIIa were based on prescribing information. Clinical efficacy was informed by clinical trial data. Epidemiology and costs for emergency department (ED) visits, hospital admissions, and intravenous-access (IV-access) complications were informed by literature. Drug costs were 2020 wholesale acquisition costs.

RESULTS

In a cohort of 1 million insured males, 5 PWI annually receive on-demand treatment for 54 mild/moderates. If all PWI switch from EA to EB 75μg/kg or to EB 225μg/kg for on-demand use, a health plan would reduce the total costs from $3.7million to $1.7million (54%) or to $2.3million (40%), respectively. The majority of the savings are driven by reduced drug costs of $1.7million (85%) or $1.1million (76%), from the lower acquisition costs of EB and reduced consumption by 48% or 33%, with EB 75μg/kg or 225μg/kg, respectively. The remaining savings were from reduced ED visits, hospitalizations, and IV-access complications.

CONCLUSIONS:

The model suggests the use of EB may reduce the cost of rFVIIa from lower acquisition costs and fewer vials consumed. Additionally, fewer cases of re-bleeding or unresolved bleeding and fewer IV accesses with EB therapy results in lower costs of ED visits, hospitalizations, and IV-access complications.

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