Safety and Effectiveness of Anti Inhibitor Coagulation Complex (AICC) in Routine Clinical Management: A Post-Authorization Safety Study (PASS)

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Introduction

The development of inhibitory antibodies to Factor VIII or Factor IX replacement therapy currently represents the most serious complication of hemophilia treatment.[1] The presence of inhibitors makes response to treatment more challenging, and patients with inhibitors have an increased risk of experiencing difficult-to-control bleeds that can cause life- and limb-threatening joint, muscle, and deep tissue bleeding.[2]

Activated prothrombin complex concentrate, AICC [FEIBA NF], has been a key therapeutic option for the prevention and management of bleeding in patients with inhibitors for over three decades.[3-9] FEIBA NF has been approved in more than 60 countries, with a prophylaxis indication in more than 40 countries. Launched in 2008, FEIBA NF is essentially the same as the previous formulation of FEIBA (VH) but with an additional viral removal step (35nm nano-filtration) added during the final stages of manufacturing.

FEIBA NF PASS is a prospective open-label, observational surveillance program that documents the adverse events (AEs) and hemostatic effectiveness associated with FEIBA NF use in routine clinical practice. Furthermore, the surveillance is identifying best practices in managing hemophilia patients with inhibitors on regular FEIBA prophylaxis.

FEIBA NF PASS was initiated in the United Kingdom (UK), France, and Spain in 2008, but has since expanded to a number of other countries. Complete data are available for subjects from UK, France, Germany, Spain, Belgium, Sweden, Poland, and Italy.

Methods

Study Objectives

- To identify practices in managing hemophilia patients with inhibitors on regular FEIBA NF prophylaxis
- To document general safety and tolerance
  - Incidence of AEs both unrelated and related to FEIBA NF
- Hemostatic effectiveness in treatment or prevention of hemorrhagic episodes in patients with hemophilia A or B, and inhibitory antibodies

Study Design

- A prospective, multicenter, open-label, non-interventional cohort study
- Patients who receive FEIBA NF for:
  - On demand treatment
  - Regular Prophylaxis
- The treatment regimen is determined by the treating physician in accordance with the prescribing information approved in the respective country
- Patients are monitored for 12 months ±2 months after enrollment
  - Post-observation follow-up at 24 ±2 months and 36 ±2 months after enrollment for patients in the UK

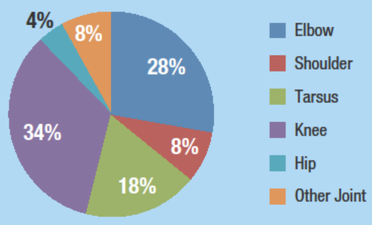
Inclusion/Exclusion Criteria

- Inclusion criteria (approved indications are country-specific)
  - Congenital hemophilia A or B with inhibitory allo-antibodies
  - Acquired hemophilia resulting from inhibitory auto-antibodies
- Exclusion criteria reflect the contraindications mentioned in the prescribing information. If the treating physician decides under special consideration of risk and benefit, to administer FEIBA NF, the patient can still be documented under the protocol.
- Data Presented in This Poster
- Complete data are available for 75 subjects who comprise the intent-to-treat group
- Data presented here designate patients by on demand or prophylaxis based on physician prescription at enrollment

Pre-Enrollment Demographics And Patient History

Figure 1: Target Joints in Congenital Hemophilia A & B Subjects with Inhibitors Reported Prior to Enrollment

Note: Each Patient Could Report More Than One Target Joint.



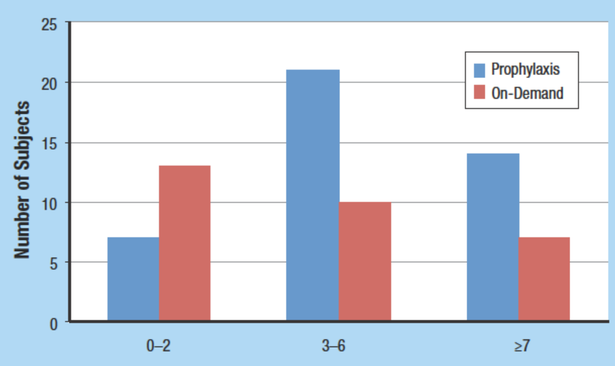
- A total of 130 target joints were reported in 48/65 (74%) congenital hemophilia A & B subjects prior to enrollment
- 75 target joints were reported in 30/43 (70%) subjects in the prophylaxis intent to treat group prior to enrollment
- 55 target joints were reported in 18/22 (82%) subjects in the on-demand intent to treat group prior to enrollment
- The intent-to-treat groups reported similar types of target joints prior to enrollment, with the largest number presenting in the knee

Table 1: Patient Demographic Characteristics

	Prophylaxis*	On-Demand*	Total
Gender			
Male	43	27	70
Female	0	5	5
Total	43	32	75
Type of Hemophilia			
Cong. Hem. A	42	21	63
Cong. Hem. B	1	1	2
Acquired Hem.	0	10	10
Total	43	32	75
Age (years)			
Mean Age	22	51.8	34.8
Range	(1 - 71)	(0 - 93)	(0 - 93)

* Regimen is intent to treat: upon entry into study

Figure 2: Number of Bleeds in Previous 12 Months by Regimen Prescribed at Baseline

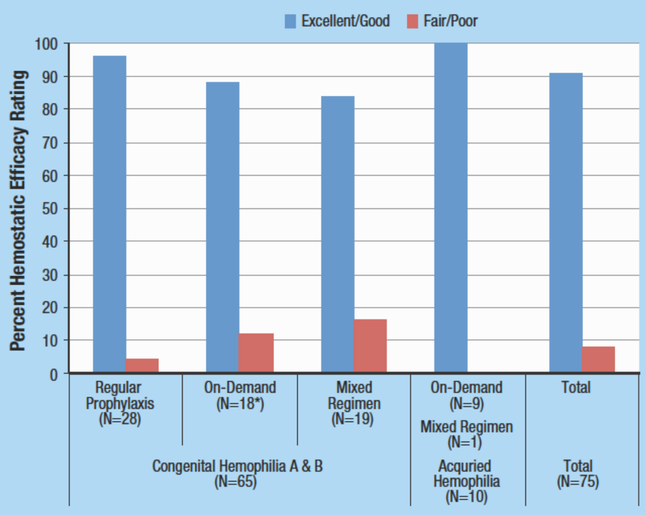


- Data were missing for 1 subject in the prophylaxis intent to treat group
- Data were missing for 2 subjects in the on-demand intent to treat group

Results

Effectiveness

Figure 3: Overall Hemostatic Effectiveness Rating by Physician (from final assessment)



Excellent/good overall rating:

Congenital hemophilia A & B with inhibitors

- 96% (27/28) of subjects treated with prophylaxis therapy
- 88% (15/17*) of subjects treated with on-demand therapy
- 84% (16/19) subjects treated with a mixed regimen

Acquired hemophilia

- 100% (10/10) of subjects treated with on demand or a mixed regimen

Total Completed Subjects

- 91% (68/75) of all subjects

* 18 patients in on-demand intent-to-treat arm, however, 1 patient had a rating of not applicable. Effectiveness based on patients with a rating (n=17).

Table 2: Median Dose and Mean Infusion Rate for FEIBA

FEIBA Regimen	Prophylaxis	On-demand	Total
Mean Infusion Rate* (U/kg/min)	3.4	4	3.8
(range)	(0.9 – 7.3)	(1.4 – 23.5)	(0.9 – 23.5)
Number of subjects	19	21	38
Median Dose per Infusion (U/kg)	67.5	75	67.3
(range)	(30.3 – 135.8)	(33.3 – 243.8)	(30.3 – 243.8)
Number of subjects	47	40	72

* Mean calculated based on data documented by patients

- Patients prescribed FEIBA prophylaxis dosed a median of once every 2.2 days

Safety

Overall Safety Summary (% of subjects)

- 169 AEs occurred in 46/75 subjects in the total population (61.3%)
- In Prophylaxis intent-to-treat arm, 50 AEs occurred in 21/43 subjects (48.8%)
- In On-demand intent-to treat arm, 77 AEs occurred in 29/32 subjects (90.6%)

Congenital Hemophilia A & B

- 104 AEs occurred in 37/65 subjects (56.9%)

Acquired Hemophilia

- 65 AEs occurred in 9/10 subjects (90.0%)

Table 3: Number of Serious and Nonserious Adverse Events

	Non-serious AE	Related Non-serious AE[a]	SAE	Related SAE[b]	Deaths[c]
Congenital Hemophilia A & B					
Prophylaxis	34	2	15	0	0
On-demand	20	1	19	1[b1]	1
Unknown treatment phase	15	0	1	0	0
Total	69	3	35	1	1
Acquired Hemophilia					0
Prophylaxis	1	0	0	0	0
On-demand	25	3	13	2[b2]	2
Unknown treatment phase	15	0	11	0	0
Total	41	3	24	2	2

a. **Related Non-serious AEs:** nausea; allergic pruritus; prolonged prothrombin time; lymphopenia; constipation; pneumonia; haemarthrosis

b. **Related Serious AEs:** (b1) haemarthrosis, (b2) catheter related infection and thrombophlebitis superficial
   - 86 yo female with AHA developed Superficial thrombophlebitis and DVT following co-administration of rFVIIa and FEIBA NF during the course of the study.

c. All deaths were considered unrelated to study drug.

Summary

- FEIBA NF PASS enrollment has closed and complete data are available for patients from UK, France, Germany, Spain, Belgium, Sweden, Poland, and Italy.
- The mean age at enrollment for the prophylaxis intent-to-treat group was substantially younger than that for the on demand intent-to-treat group (22.0 vs. 51.8 years of age, respectively, **Table 1**).
- Prior to enrollment, a greater percentage of congenital hemophilia A & B subjects in the prophylaxis intent-to-treat group reported having zero target joints (30% in the prophylaxis intent-to-treat group as compared to 18% in the on demand intent-to-treat group).
- Patients prescribed prophylaxis therapy had a greater number of bleeding episodes in the 12 months prior to study enrollment (**Figure 2**).
- Mean infusion rate was higher in the study (3.8 U/kg/min) than what is recommended in the FEIBA prescribing information (2.0 U/kg/min)(**Table 2**).[10]
- Patients prescribed FEIBA prophylaxis infused a median of once every 2.2 days, which is consistent with the prophylaxis regimen studied in the FEIBA PROOF Study.[11]
- Overall hemostatic effectiveness ratings by the treating physicians (from the final assessment) were either excellent or good in 91% (68/75) of patients who completed the study (**Figure 3**).
- Nine adverse events (6 non-serious and 3 serious) were identified as possibly related to FEIBA NF therapy (**Table 3**).
- The proportion of subjects with AEs (90.0% vs. 56.9%), SAEs (80.0% vs. 30.8%) and suspected related AEs (40.0% vs. 6.2%) was higher in subjects with acquired hemophilia than in those with congenital hemophilia (Mean age – 78.5 vs. 28.0, respectively).

Conclusions

- **Complete data are presented from the FEIBA NF PASS study documenting the real world use of FEIBA NF for both prophylaxis and on demand treatment in congenital hemophilia patients with inhibitors and acquired hemophilia A.**
- **In both of these conditions, FEIBA NF demonstrated a favorable benefit/risk profile. Expectedly, a higher percentage of patients with acquired hemophilia A experienced adverse events compared to congenital hemophilia patients with inhibitors.**
- **FEIBA NF also showed a high level of effectiveness in a real-world setting in congenital hemophilia patients with inhibitors and patients with acquired hemophilia A.**
- **In addition to two recently completed clinical trials[3,11] evaluating FEIBA NF use in prophylaxis, the data collected herein will contribute in guiding practice in the management of patients with hemophilia and inhibitors on regular FEIBA prophylaxis.**
- **FEIBA NF PASS provides an opportunity to collect data on hemophilic patients with inhibitors during routine care, and serves as an invaluable tool for documenting the safety and effectiveness of FEIBA NF in prophylaxis, and bleed management.**

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Presented at the WFH 2014 World Congress in Melbourne, Australia • May 11-15, 2014

If you have any additional questions, please feel free to contact Baxter Bioscience Medical Information at medinfo@baxter.com.

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DOI: 10.3252/pso.eu.WFH2014.2014