ADVATE HaEmophilia A Outcome Database (AHEAD): A Long-Term Registry Focusing on Joint Health Outcomes and Health-Related Quality of Life

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INTRODUCTION

- Noninterventional studies (NIS) have certain advantages over controlled interventional studies (eg, higher enrollment, no/low selection bias). However, most NIS focus only on the first 6–12 months of treatment, making health-related quality of life (HRQoL) and joint health difficult to assess because of inadequate study duration.[1]
- Hemophilic arthropathy is the most common cause of morbidity in patients with hemophilia. It has a significant impact on HRQoL and generally becomes pronounced at an early age (15–25 y).[2]
- Studies have confirmed the clinical benefits of prophylaxis compared with on-demand treatment for hemophilic arthropathy, including reduction in joint bleeds, less need for orthopedic surgery, fewer days lost from work, and better ability to undertake physical activities. Such benefits improve HRQoL for patients with hemophilic arthropathy.[3-5]
- The ADVATE HaEmophilia A Outcome Database (AHEAD) is an NIS designed to capture long-term data on joint health, HRQoL, hemophilia-related comorbidities, factor consumption, efficacy, and safety in patients receiving recombinant antihemophilic factor plasma/albumin-free method (rAHF-PFM; ADVATE, Baxter Healthcare Corporation, Westlake Village, CA, USA) within the scope of their routine clinical treatment (ie, prophylaxis, on-demand treatment, or immune tolerance therapy).
- Data from this Pan-European (Pan-EU) study is integrated with a sister study currently being conducted in Germany.[6]

PAN-EU AHEAD STUDY DESIGN AND OBJECTIVES

- This study is a postauthorization, prospective, noninterventional, multicenter study designed to describe the natural course of hemophilia A and associated orthopedic comorbidities, long-term HRQoL outcomes, safety, and efficacy in individuals receiving rAHF-PFM.
- The treating physician predetermines the treatment regimen, as well as the frequency of laboratory, radiologic, and clinical monitoring; additional testing or monitoring beyond the routine clinical management is not required.

Inclusion Criteria

- Patients must meet ALL of the following criteria:
  - ≤65 years old at the time of screening
  - Have moderately severe to severe hemophilia A (factor VIII [FVIII] ≤2%)
  - Prescribed rAHF-PFM by the treating physician
  - Provide written informed consent

Exclusion Criteria

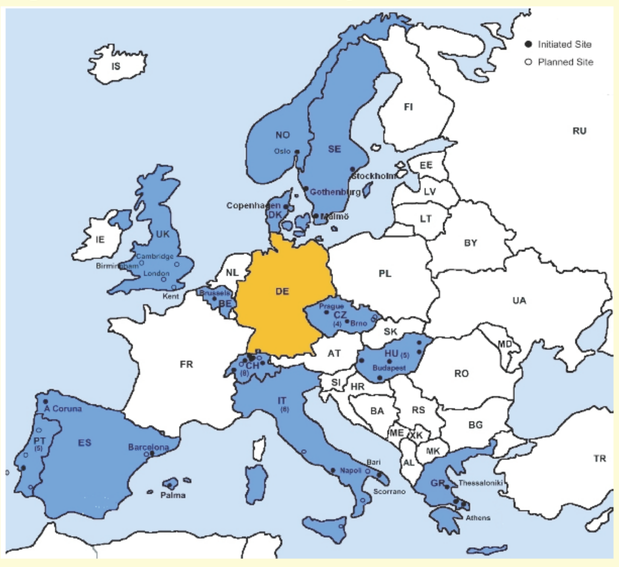
- Any known hypersensitivity to the active substance or any of the excipients or known allergic reaction to mouse or hamster proteins
- Has or will participate in another clinical study involving an investigational product or device within 30 days before study enrollment or during the study

Primary Objective

- To longitudinally report the joint health outcomes in individuals receiving rAHF-PFM in routine clinical practice. Outcomes will be assessed by physical examination using the pain, bleeding, and physical examination parameters of the Gilbert Scale.[7]
- Efficacy, HRQoL, and safety parameters will also be assessed.
  - Hemophilia-related arthropathy, defined based on imaging techniques (ie, radiography, magnetic resonance imaging)
  - Efficacy (annualized bleed rates, overall bleed management effectiveness)
  - Safety (immunogenicity, incidence of treatment-related adverse events [AEs])
  - Bleeding-related pain (measured by Visual Analog Scale)
  - HRQoL (eg, Haemophilia Activities List (HAL), pediatric HAL, short form-10 [SF-10], and SF-12)

PAN-EU RECRUITMENT AND OBSERVATION PERIOD

Figure 1. Pan-EU AHEAD Study Sites



AHEAD=ADVATE HaEmophilia A Outcome Database.

- **Recruitment:** 200 patients from EU countries (excluding Germany). Recruitment began June 2011 and will continue through 2013.
- **Observation period:** 4 years for each patient
- **Locations:** Recruitment from 46 sites in total planned; 29 sites from Belgium, Greece, Hungary, Spain, Sweden, Czech Republic, Italy, Denmark, and Switzerland have been initiated (Figure 1).
- **Status:** As of May 1, 2012, 66 individuals (all male; mean age, 24.1 y) have been enrolled, (with data available for 65) 48 (73.9%) with baseline FVIII ≤1% (severe hemophilia A), 5 (7.7%) with FVIII >1%–<2%, 5 (7.7%) with FVIII ≥2%, and 7 (10.8%) with unreported data.
- 43 patients are receiving prophylactic treatment and 18 are receiving on-demand treatment.
- 1 severe AE, not related to treatment, has been reported.
- Important baseline and demographic information are contained in Tables 1 and 2.

Table 1. Pan-EU AHEAD Baseline and Demographic Information

Characteristic	Patients, n (%)
Mean age, y (range)	24.1 (1–64)
Baseline FVIII severity	n=65
≤1%	48 (73.9)
>1%–<2%	5 (7.7)
≥2%	7 (10.8)
Missing	5 (7.7)
rAHF-PFM treatment at baseline	n=66
Prophylaxis	43 (65.2)
On demand	18 (27.2)
Missing	5 (7.6)
Current rAHF-PFM dose, frequency	250–3000 IU/kg Q2D to TIW*
Joint arthropathy at baseline	
Yes	27 (40.9)
No	30 (45.5)
Missing	9

AHEAD=ADVATE HaEmophilia A Outcome Database; FVIII=factor VIII; Q2D=every 2 days; rAHF-PFM=recombinant antihemophilic factor plasma/albumin-free method; TIW=3 times weekly.
*Although 66 patients were enrolled, baseline and demographic information for 65 was available.
*For both on-demand and prophylaxis regimens.

Table 2. Pan-EU AHEAD EDs

	Patients, n (%) n=65
ED to all FVIII concentrate before rAHF-PFM	
0	16 (24.6)
1–4	1 (1.5)
5–20	1 (1.5)
21–50	0
51–100	0
101–150	1 (1.5)
>150	27 (41.5)
Unknown/missing	19 (29.2)
rAHF-PFM ED range at baseline	
0	1 (1.5)
1–4	0
4–20	3 (4.6)
21–50	0
51–100	4 (6.2)
101–150	4 (6.2)
>150	39 (60.0)
Unknown/missing	14 (21.5)

AHEAD=ADVATE HaEmophilia A Outcome Database; ED=exposure day; FVIII=factor VIII; rAHF-PFM=recombinant antihemophilic factor plasma/albumin-free method.

GERMAN AHEAD RECRUITMENT AND OBSERVATION PERIOD

Figure 2. German AHEAD Study Sites

AHEAD=ADVATE HaEmophilia A Outcome Database.

Led by Professor Johannes Oldenburg (Bonn); Professor Rainer Zimmermann (Heidelberg); and Drs Karin Kurnik (Munich), Angela Huth-Kuhne (Heidelberg), and Robert Klamroth (Berlin)

- **Recruitment target:** 500 patients in ≥30 hemophilia treatment centers (HTCs) in Germany; opened June 2010 and continues through 2013
- **Observation period:** 4 years for each patient
- **Locations:** 30 German HTCs have initiated observations (Figure 2).
- **Status:** 251 individuals have been enrolled as of May 1, 2012.
- The most recent baseline and demographic information for the German AHEAD study are listed in Tables 3 and 4.
- As of May 1, 2012, 2 SAEs at least possibly related to rAHF-PRM treatment: 1 was de novo high-titer inhibitor in an MTP at 5EDs and another was de novo high-titer inhibitor in an MTP at 37EDs.

Table 3. German AHEAD Baseline and Demographic Information*

Characteristic	Patients, n (%) n=251
Mean age, y	29.5
Patients, n	239
Missing. n	12
Baseline FVIII severity	
Moderate (1–≤5%)	43 (18.1)
Severe (<1%)	195 (81.9)
Missing, n	13
rAHF-PFM treatment at baseline	
Prophylaxis	180 (78.3)
On demand	49 (21.3)
ITI	1 (0.4)
Missing, n	21
≥1 Joint arthropathy	
Missing/no joint documented, n	30
Yes	102 (46.2)
No	119 (53.8)

AHEAD=ADVATE HaEmophilia A Outcome Database; FVIII=factor VIII; rAHF-PFM=recombinant antihemophilic factor plasma/albumin-free method.
*German AHEAD inclusion criteria allowed FVIII ≤5%.

Table 4. German AHEAD EDs

	Patients, n (%) n=251
ED to all FVIII concentrate before rAHF-PFM	
Missing	241
1–3	3 (30.0)
4–20	1 (10.0)
21–50	0
51–100	0
101–150	0
>150	6 (60.0)
rAHF-PFM ED range at baseline	
Missing	55
1–3	2 (1.0)
4–20	3 (1.5)
21–50	9 (4.6)
51–100	5 (2.6)
101–150	5 (2.6)
>150	172 (87.8)

AHEAD=ADVATE HaEmophilia A Outcome Database; ED=exposure day; FVIII=factor VIII; rAHF-PFM=recombinant antihemophilic factor plasma/albumin-free method.

SUMMARY

- The AHEAD study is designed to collect important information on long-term joint health outcomes, hemostatic efficacy, HRQoL, and safety in patients treated with rAHF-PFM under the conditions of routine clinical practice.
- This vast database, which will involve a large cohort of patients at various stages of disease and with various comorbidities, will serve as a significant resource for analysis of treatment, patient-related variables and associated long-term outcomes, and effects on patients' HRQoL.
- Since recruitment began, 66 patients have been recruited for the ongoing Pan-EU AHEAD study and 251 for the German AHEAD sister study. A total of 59 HTCs are now open for both studies combined.
- For additional information on study design and participation, please contact Baxter Bioscience Medical Information at medinfo@baxter.com.

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MEETING INFORMATION

World Federation of Hemophilia 2012 World Congress
Paris, France – July 8–12, 2012

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