Striving for a Bleed Free World – an Interim Analysis from the AHEAD Global & German Studies

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INTRODUCTION

- Repeated bleeding into joints is one of the most serious complications of hemophilia A. More than two to three bleeds into the same joint may cause irreversible and progressive structural damage that compromise health-related quality of life (HRQoL).[1,2]
- The goal of zero bleeding episodes – or as close to zero as possible – is key to preserving joint health and improving HRQoL in patients with hemophilia.[2]
- The AHEAD (ADVATE Hemophilia A Outcome Database) study is designed to assess long-term outcome data in patients with hemophilia A receiving treatment in routine clinical practice.

OBJECTIVE

This study aims to evaluate effectiveness of a prophylactic treatment regimen of ADVATE in severe and moderate (FVIII < 5%) hemophilia A patients in a real world setting.

METHODS

Study Design:

- Post-authorization, prospective, non-interventional, multicenter study
- Global recruitment target of > 1000 severe to moderate hemophilia A patients receiving ADVATE on-demand (OD), as standard or pharmacokinetic (PK)-guided prophylaxis, or immune tolerance induction (ITI) therapy
- Observation period: 4 – up to 8 years per subject
- Main inclusion criteria: Moderate to severe hemophilia A (factor VIII activity [FVIII:C] ≤ 5%); ADVATE is the routinely prescribed treatment
- Study endpoints include long-term joint health outcomes, annualized (joint) bleeding rates (ABR/AJBR), factor consumption, and safety

- We evaluate overall annual (joint) bleeding rate in patients prospectively followed up in the frame of the AHEAD study.
- We present here the preliminary results from an interim analysis. ABR/AJBR data in the German arm were calculated based on patient diaries; data in International arm were calculated based on data reported by physicians

ENROLLMENT STATUS

Enrollment Update

- Study start:
  - June 2010 German Arm
  - June 2011 International Arm

- Status as of 30 June 2016:
  - 956 patients (401 in Germany, 555 in the International study arm) enrolled
  - 133 study sites initiated in: Australia, Austria, Belgium, Brazil, Canada, Colombia, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Norway, Poland, Portugal, Russia, Slovenia, Spain, Sweden, Switzerland and United Kingdom

REFERENCES

1. Srivastava A et al. *Haemophilia.* 2013;19:e1-47.
2. Gringeri A, Ewenstein B, and Reininger AJR. *Haemophilia.* 2014;1-5.

DISCLOSURES

*Author is an employee of Baxalta ([8]Baxalta Healthcare SA; [9]Baxalta Deutschland GmbH, [10]Baxalta Innovations GmbH) now part of Shire.

The study was sponsored by Baxalta, now part of Shire.

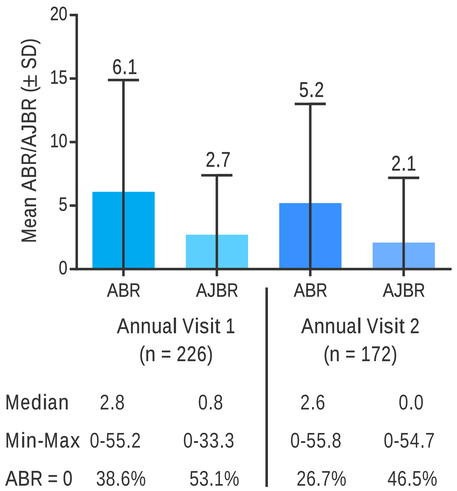
RESULTS

GERMAN STUDY ARM

Interim Analysis German Study Arm

- As of April/May 2015, 371 patients have been enrolled in the German study arm, of whom 324 completed the year 1 and 239 completed the year 2 visits.
- Median age at screening was 27.0 years (min-max: 1.0–80.0) and 80.9% of patients had severe HA (FVIII < 1%).
- 285 (76.8%) were on prophylaxis, 76 (20.5%) were OD and 4 (1.1)% on ITI treatment.

Figure 1: ABR and AJBR in the German Study Arm



INTERNATIONAL STUDY ARM

Interim Analysis International Study Arm

- The second interim analysis of September 2015 includes 376 patients from the International Study arm, of whom 243 completed the year 1 and 154 completed the year 2 visits.
- Median age at screening was 15 years (min-max: 0–72) and 68.4% of patients had severe HA (FVIII < 1%).
- 293 (78.1%) were on prophylaxis, 77 (20.5%) were OD and 5 (1.3)% on ITI treatment.

Figure 2: ABR and AJBR in the International Study Arm

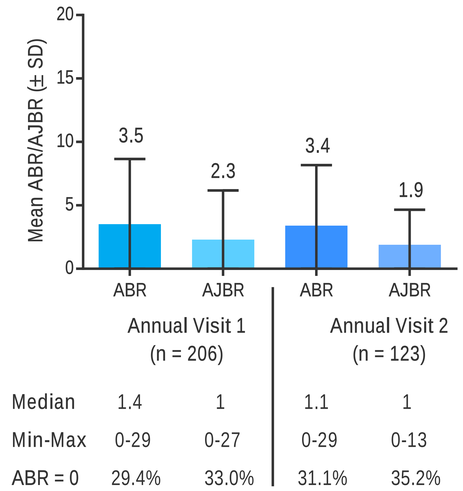


Table 1: Bleeding Rates in the First 2 Years of Observation German Study Arm

International Arm	Bleeding Rate Year 1		
Bleeding Rate Year 2	≤ 2 bleeds (n = 48)	> 2 to ≤ 5 bleeds (n = 17)	> 5 bleeds (n = 22)
≤ 2 bleeds	33	8	5
> 2 to **≤ 5** bleeds	7	6	7
> 5 bleeds	8	2	9
missing	0	1	1

Table1. Annual bleeding rates categorized for year 1 and 2 from the International AHEAD study arm.

Table 2: Bleeding Rates in the First 2 Years of Observation International Study Arm

German Arm	Bleeding Rate Year 1	
Bleeding Rate Year 2	≤ 2 bleeds (n = 135)	> 2 bleeds (n = 36)
≤ 2 bleeds	86	7
> 2 bleeds	48	29
missing	2	0

Table 2. Annual bleeding rates categorized for year 1 and 2 from the German AHEAD study arm.

Interim Prophylaxis Effectiveness Results

- As of April/May 2015, 371 patients have been enrolled in the German study arm and as of September 2015, 376 in the International study arm. Severe HA was reported for the majority of patients; and the majority of subjects received prophylactic therapy at baseline. In total 567 patients have completed annual visit 1 and 393 patients completed annual visit 2.
- Median annualized bleed rates at annual visit 1 and 2 were 2.8 and 2.6 for severe/moderate patients on prophylaxis in the German arm and 1.4 and 1.1 for severe/moderate patients on prophylaxis in the International study arm.
- Zero bleeds were reported for 38.6% and 26.7% of patients at annual visit 1 and 2 in Germany (severe HA) and 29.4% and 31.1% in the International study arm (severe and moderate patients).
- Similarly, zero joint bleed rates were reported for 53.1% and 33% at annual visit 1 and 46.5% and 35.2% at annual visit 2 for the German and International study arm respectively.
- In the International study arm, of 87 severe HA patients on prophylaxis who were followed up for bleeding rate for both years, 48 (55.2%) showed ≤ 2 bleeds in the first year. Of these patients 33 (68.8%) continued to show the same bleeding rate in the second year. Moreover, 13 additional patients were able to decrease their bleeding rate to no more than 2 bleeds a year.
- Similarly, 226 patients could be evaluated for bleed rate in the first year and 172 in the second year in the German study arm. Of these, 43.4% (first year) and 44.8% (second year) had less than 2 bleeds.

DISCUSSION & CONCLUSION

- While this analysis shows good effectiveness results in terms of percentage of patients achieving the target of zero bleeds, future research should expand the efforts to investigate why more than 50% of patients continued to suffer from bleeding episodes despite prophylactic treatment.
- Enhanced individualization of prophylaxis regimens based on patients' characteristics and individual PK response bears great potential to optimize outcome and perhaps allow for a more efficient use of an expensive resource.

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