An Integrated Analysis of Long Term Safety of an Extended Half-Life, Pegylated, Full-length Recombinant Factor VIII (BAX 855) in the Treatment of Hemophilia A in 234 Pediatric, Adolescent and Adult Patients

Werner Engl[1], Lisa Patrone[2], Jacqueline Dyck-Jones[2], Anne Prener[3], and Brigitt E. Abbuehl[1]

[1*]Shire, Vienna, Austria; [2*]Shire, Westlake Village, CA, [3*]Shire, Cambridge, MA

INTRODUCTION

- Patients with severe hemophilia A have < 1% of normal factor VIII (FVIII) levels and experience frequent bleeding, which can be prevented by regular prophylaxis with FVIII replacement.[1]
- BAX 855 is built on the full-length recombinant FVIII (rFVIII) of rAHF-PFM (ADVATE) and manufactured via the same plasma/albumin-free platform. Controlled pegylation with polyethylene glycol was chosen to extend the half-life while maintaining the integrity of the ADVATE protein.
- The pivotal PROLONG-ATE clinical trial demonstrated that BAX 855 is safe and efficacious for prophylactic use and in the treatment of bleeding episodes in patients with hemophilia A and confirmed an extended half-life for BAX 855 compared to ADVATE.[2, 3]

METHODS

Table 1: Data From 5 Studies

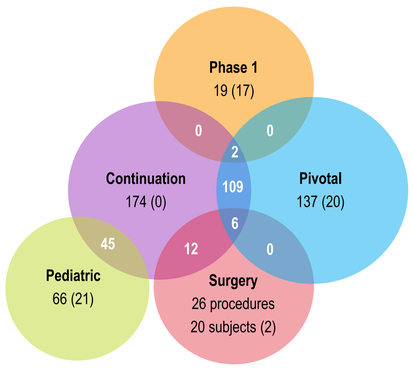
- To further assess the safety of BAX 855, data from 5 studies were pooled.

Study ID	Description	Study Status	Subjects Treated	Doses Administered
261101 NCT01599819	Phase 1: PK, safety	Complete	19	PK: 30 ±3 IU/kg and 60 ± 6 IU/kg
261201 NCT01736475	Pivotal: Phase 2/3, PK, efficacy, safety, immunogenicity	Complete	137	PK and prophylaxis: 45 ± 5 IU/kg On-demand treatment: 10 to 60 ± 5 IU/kg
261202 NCT02210091	Pediatric PTP: Phase 3, PK, efficacy, safety, immunogenicity	Complete	66	Prophylaxis: 50 ± 10 IU/kg PK: 60 ± 5 IU/kg
261204 NCT01913405	Phase 3, Perioperative management, safety and efficacy	Ongoing	20 patients 26 procedures	Tailored dose to achieve FVIII target levels for Major procedures: 80 to 100% of normal Minor procedures: 30 to 60% of normal
261302 NCT01945593	Phase 3b, Long-term efficacy, safety, immunogenicity	Ongoing	174	Fixed Prophylaxis depending on age, twice weekly OR PK-tailored Prophylaxis to maintain trough FVIII level ≥3%

Figure 1. Subject Disposition

Total number of treated subjects: 234

N (n): number of subjects (number of unique subjects)



METHODS (continued)

Table 2. Demographics

- 233 treated patients were male and 1 was female

	< 6 years N = 32	6 to < 12 years N = 34	12 to < 18 years N = 26	≥ 18 years N = 142	All Ages N = 234
Age: Median (min-max)	4.0 (1–5)	8.0 (6–11)	15.0 (12–17)	30.0 (18–60)	23.0 (1–60)

Figure 2. Race

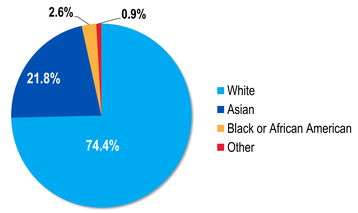


Figure 3. Exposure to BAX 855

(Total = 81,762,479 IU)

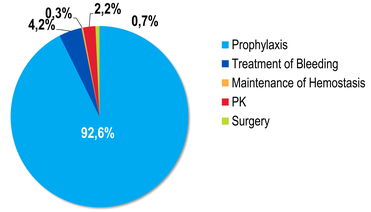


Figure 4. Exposure Days

(Total = 25,578 Days)

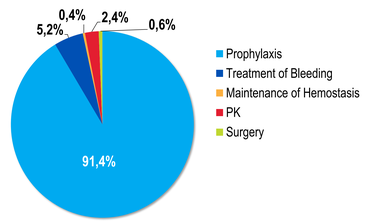


Table 3. Exposure Days per Treated Patient by Age

	< 6 years N = 32	6 to < 12 years N = 34	12 to < 18 years N = 26	≥ 18 years N = 142	All ages N = 234
Mean	62.4	61.7	151.6	123.5	109.3
± SD	± 10.2	± 16.1	± 61.7	± 73.7	± 68.6
Median (Q1;Q3)	58.5 (54;68)	62.5 (54;70)	154.5 (126;196)	145 (59;179)	103.5 (55;168)

RESULTS

Table 4. Immunogenicity
Development of Inhibitors (Neutralizing Antibodies) to FVIII

Number of Exposure Days	Did Not Develop Inhibitor	Developed Inhibitor	Proportion Developing Inhibitor	95% CI for Proportion Developing Inhibitor
< 20	8	0	NA	NA
20 to < 50	16	0	NA	NA
≥ 50	186	0	0	0 to 0.020
≥ 100	114	0	0	0 to 0.032
≥ 150	72	0	0	0 to 0.050

Study 261101 (Ph1 PK) was excluded.

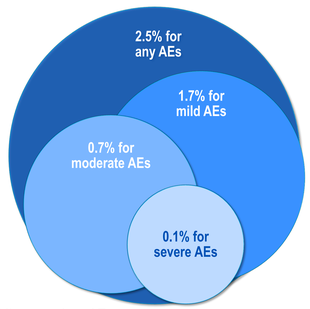
Development of Persistent Binding Antibodies to FVIII, PEG-FVIII, PEG, CHO

- None of the 234 treated patients developed a persistent binding antibody response during the studies
  - 26 patients had pre-existing binding antibodies, ie before BAX 855 exposure: 3 for FVIII, 3 for PEG. 23 for PEG-FVIII
  - 12 patients developed transient IgG binding antibodies (ie, negative at screening and then detectable at 1 or 2 consecutive visits that were not detectable at subsequent visits or at study completion): 6 for FVIII, 10 for PEG-FVIII
  - No conclusion can be drawn yet in 3 subjects who developed binding antibodies shortly before or at the data cut-off date.
  - No impact on hemostatic efficacy or safety
  - None of the patients had any binding antibodies to CHO protein

Adverse Events

- Of 234 treated patients, 165 (70.5%) experienced 652 AEs

Figure 5. Rate of AEs per Infusion



- 2.4% (618/25724) non-serious AEs
- 0.1% (34/25724) serious AEs

Table 5. Related AEs (or Adverse Drug Reactions) Following Treatment

System Organ Class	Preferred Term	Number of Events	Number (%) of Subjects N = 234	Number Per 100 Infusions N[a] = 25724	Number year N[b] = 266.11
Nervous System Disorders	Headache	8	5 (2.1%)	8 (0.03)	8 (0.030)
Gastrointestinal Disorders	Nausea	2	2 (0.9%)	2 (0.01)	2 (0.008)
Gastrointestinal Disorders	Diarrhoea	1	1 (0.4%)	1 (0.00)	1 (0.004)
Vascular Disorders	Flushing	1	1 (0.4%)	1 (0.00)	1 (0.004)

[a] Total number of BAX 855 infusions.

[b] Total patients' observation period in years.

- 34 SAEs in 24 (10.3%) of 234 patients
- NONE were considered related to treatment
- No deaths occurred during the conduct of the study*
  - *1 death of neuroendocrine tumor occurred 21 days post discontinuation of product and withdrawal from the study, considered not related to BAX 855

Study	SAEs (n = 34)
261201 Pivotal (5)	Osteoarthritis, herpes zoster infection neurological, humerus fracture, muscle haemorrhage, neuroendocrine carcinoma
261202 Pediatric (4)	acute gastritis, abdominal pain, febrile neutropenia, pancytopenia
241204 Periop. (4)	esophageal ulcer, 3 cases of diabetic gastroparesis
261301 Long term (21)	Pancreatitis (2 cases), pneumonia, incision site abscess, splenic haematoma, splenic rupture, traumatic fracture, pneumonia, cholecystitis, appendicitis, femoral neck fracture, spontaneous abortion in partner, malaria, anaemia, traumatic fracture, urinary tract infection, device related sepsis, device related infection, haematoma, scapula fracture, head injury

Laboratory and Vital Sign Assessments

- No trends were observed with changes:
  - In laboratory parameters from baseline to last study visit
  - In vital signs evaluated pre- and post-infusion given at the study site

Summary

- 234 treated patients including 1 female, median age 23.0 years, mostly White and Asian
- Long-term exposure with median of 103.5 exposure days per patient
- No patients developed inhibitory antibodies to FVIII (≥0.6 BU/mL), including 186 patients with ≥ 50 EDs, 114 with ≥ 100 EDs, and 72 with ≥ 150 EDs.
- No persistent binding antibodies to FVIII, PEG-FVIII, PEG, or CHO
- 652 AEs in 70.5% of treated patients
- The rate of any AE per infusion was 2.5%
- Adverse drug reactions included headache, nausea, diarrhea, and flushing
- 34 SAEs in 10.3% of patients
- No deaths or related SAEs occurred during the conduct of the study
- No trends with changes in laboratory parameters or vital signs

CONCLUSION

- From this integrated analysis, BAX 855 was safe and well tolerated in 234 pediatric, adolescent and adult PTPs with severe hemophilia A. The common adverse events considered related to BAX 855 treatment were consistent with the safety profile of ADVATE.

REFERENCES

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Disclosures: *Authors are employees of Baxalta ([1]Baxalta Innovations GmbH, [2,3]Baxalta US, Inc,), now part of Shire.

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