Reduction in Dosing Frequency and ABRs in Previously Treated Pediatric (<12 years) Patients With Severe Hemophilia A During Prophylactic Treatment With Pegylated Recombinant Factor VIII Compared to Pre-Study Prophylactic Regimen With Other FVIII Concentrates

Eric Mullins,[1] Maria Teresa Alvarez-Roman,[2] Chur Woo You,[3] Bruce Ewenstein,[4] Werner Engl,[5] Borislava G. Pavlova,[5] Jennifer Doralt,[5] Brigitt Abbuehl[5]

[1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States; [2]Hospital Universitario La Paz, Madrid, Spain; [3]Konyang University, Daejeon, South Korea; [4*]Shire, Cambridge, MA, United States; [5*]Shire, Vienna, Austria

INTRODUCTION

- Prophylactic administration of factor VIII (FVIII) is generally considered the standard of care in patients with severe hemophilia A (FVIII level < 1%), as it has been demonstrated to reduce or prevent bleeding and the risk of developing chronic arthropathy and a reduced quality of life.
- The frequency of prophylactic infusions remains a challenge to patient compliance. The average half-life of FVIII products is in the range of 10 to 14 hours,[1,2] necessitating 3 infusions per week or 1 infusion every other day to maintain trough FVIII levels ≥ 1% of normal to effectively prevent or reduce spontaneous bleeding episodes.[3]
- Full-length, pegylated, recombinant FVIII (BAX 855, ADYNOVATE) was designed to provide an extended half-life and allow for a reduced frequency of prophylactic infusions. ADYNOVATE is manufactured by covalently binding a branched PEG reagent (molecular weight: 20 kDa) to the licensed rFVIII (ADVATE) with PEG chains predominantly localized to the B-domain of the FVIII molecule.[4]
- In the phase 1 and pivotal phase 2/3 studies, the mean half-life and the mean residence time of ADYNOVATE compared with that of ADVATE were 1.4–to 1.5-fold higher.[5]
- In the pivotal phase 2/3 study in adolescents and adults:
  - ADYNOVATE administered twice weekly resulted in an annualized bleeding rate (ABR) reduced by 90.0% compared to that observed during on-demand treatment ($P < 0.0001$)
  - The median ABR was 1.9; 39.6% of compliant subjects had no bleeding episodes and 57.4 % of subjects did not experience any spontaneous or joint bleeding during prophylaxis.[6]

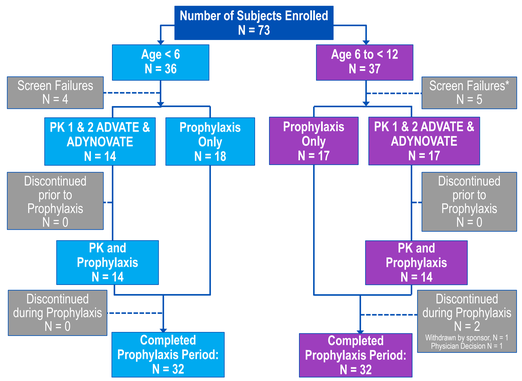
OBJECTIVE

- In this global, open-label phase 3 trial in pediatric PTPs < 12 years, the ABR during study was compared with ABR during pre-study prophylaxis using other FVIII concentrates (including ADVATE).

METHODS

- Previously treated pediatric patients < 12 years with severe hemophilia A and no history of FVIII inhibitors or at screening received twice weekly prophylactic treatment with ADYNOVATE (50 ± 10 IU/kg) for ≥ 6 months or 50 exposure days (EDs).

Figure 1: Subject Disposition Flowchart



* Two subjects counted as Screen Failures were later enrolled (Unique Subject ID 261202-110013 and 261202-511003).

RESULTS

Table 1: ABRs Before and During Prophylactic Study Treatment With ADYNOVATE Administered Twice Weekly - Stratified by Prophylactic Treatment Frequency Before Study

Frequency	Statistic	ABR		
Prophylactic Treatment With Any FVIII Concentrate Before Study		Before Study	During Study	Difference
2x/week	n	15	15	15
	Mean (SD)	5.60 (3.91)	2.59 (2.05)	-3.01 (4.67)
	IQR (Q1, Q3)	8.00 (2.00, 10.00)	2.30 (1.70, 4.00)	8.70 (-7.00, 1.70)
3x/week	n	33	33	33
	Mean (SD)	3.91 (5.03)	2.28 (3.41)	-1.63 (5.35)
	IQR (Q1, Q3)	4.00 (1.00, 5.00)	3.80 (0.00, 3.80)	5.90 (-4.00, 1.90)

- ABRs were reduced by means of 3.01 and 1.63 in patients receiving 2x/week and 3x/week pre-study prophylactic treatment regimens, respectively (Table 1, Figure 2).
- Few patients had received treatment more than 3x/week pre-study: n = 4 on 3.5x/week and n = 3 on 4x/week.

Figure 2: Mean (SD) ABRs Before Study and During Prophylactic Study Treatment With ADYNOVATE - Stratified by Prophylactic Treatment Frequency Before Study

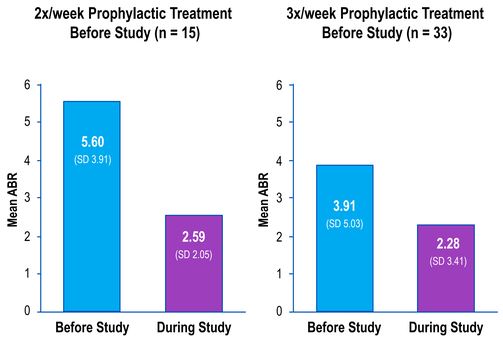
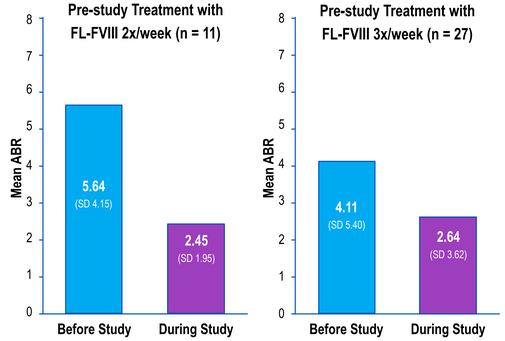


Table 2: ABRs Before Study and During Prophylactic Study Treatment With ADYNOVATE (2x/week) - Stratified by Product Type Before Study

Product	Frequency Before Study	Frequency During Study	Statistic	ABR		
				Before Study	During Study	Difference
Full-length FVIII	2x/week	2x/week	n	11	11	11
			Mean (SD)	5.64 (4.15)	2.00	-4.00
			IQR (Q1, Q3)	8.00 (2.00, 10.00)	2.30 (1.70, 4.00)	8.70 (-7.00, 1.70)
Plasma-derived FVIII	2x/week	2x/week	n	3	3	3
			Mean (SD)	7.00 (2.65)	2.00	-4.00
			IQR (Q1, Q3)	5.00 (5.00, 10.00)	3.90 (0, 3.90)	8.90 (-10.00, -1.10)
Full-length FVIII	3x/week	2x/week	n	27	27	27
			Mean (SD)	4.11 (5.40)	1.90	-1.00
			IQR (Q1, Q3)	4.00 (1.00, 5.00)	3.90 (0, 3.90)	6.20 (-4.20, 2.00)
Plasma-derived FVIII	3x/week	2x/week	n	2	2	2
			Mean (SD)	4.5 (4.95)	0	-4.50
			IQR (Q1, Q3)	7.00 (1.00, 8.00)	0 (0, 0)	7.000 (-8.00, -1.00)
B-domain deleted FVIII	3x/week	2x/week	n	4	4	4
			Mean (SD)	2.25 (2.06)	0	-2.00
			IQR (Q1, Q3)	3.50 (0.50,4.00)	1.90 (0, 1.90)	5.40 (-4.00, 1.40)

- Most subjects with pre-study prophylactic schedule of 2 or 3 infusions per week had received full-length FVIII (FL-FVIII) products (n = 38), whereas a total of 10 subjects had received plasma-derived (pd-FVIII; n = 5) or B-domain deleted FVIII (BDD-FVIII; n = 5) products.
- Mean and median ABRs were lower during prophylactic treatment with ADYNOVATE compared to all pre-study treatment methods(Table 2, Figure 3).

Figure 3: Mean ABRs (SD) Before Study and During Prophylactic Study Treatment With ADYNOVATE - Stratified by Frequency Before Study



- Among the 48 subjects with a pre-study prophylactic schedule of 2 or 3 infusions per week, 50.0% had not been treated previously with ADVATE.
- Patients experienced a reduction of bleeding episodes during the study irrespective of their historical treatment status (Table 3, Figure 4).

SUMMARY

- The majority of subjects were able to reduce dosing frequency by at least one prophylactic infusion per week compared to pre-study treatment while using ADYNOVATE.
- The mean total ABR decreased for those previously treated 2x/week from 5.60 to 2.60, and for those previously treated 3x/week from 3.91 to 2.28 during prophylactic treatment with ADYNOVATE.

CONCLUSION

- Twice weekly prophylactic infusions with ADYNOVATE resulted in fewer bleeding episodes compared with pre-study prophylactic treatment while reducing the frequency of infusions in the majority of pediatric patients, indicating improved efficacy of ADYNOVATE prophylaxis.

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DISCLOSURES

EM, MTA-R, and CWY were investigators in this study, which was sponsored by Baxalta, now part of Shire. WE, BP, JD and BA are full-time employees of Baxalta, now part of Shire, which sponsored the study.

The study was registered at www.clinicaltrials.gov <http://www.clinicaltrials.gov/> as NCT02210091 and at www.clinicaltrialsregister.eu under EudraCT Number 2014 000742 30.

*Author an employee of Baxalta ([4]Baxalta US Inc; [5]Baxalta Innovations GmbH), now part of Shire.