Poster T-102

Local and General Tolerability of ADVATE Reconstituted in 2-mL Rather Than 5-mL Sterile Water for Injection: A Pediatric Post-Authorization Safety Surveillance Study

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INTRODUCTION

- ADVATE [antihemophilic factor (recombinant), plasma/albumin-free method]
  - > 13 y clinical trial and real world experience
  - > 1100 patients
  - ~23 billlion units (as of January 2016)
  - Favorable safety profile; low incidence of inhibitor development
  - Low annualized bleeding rate (ABR) in patients continuously on prophylaxis[1,2]
- ADVATE reconstituted in 2-mL sterile water for injection (SWFI) (ADVATE 2 mL) approved in 2011
  - 2-mL vs 5-mL sterile vial, provides patients option to infuse a smaller volume and thereby shorter infusion time
  - May be especially important for pediatric patients (< 2 years old) for whom anxiety and caregiver inexperience with infusions may be issues
- Safety considerations
  - Hypersensitivity reactions are an identified risk with FVIII concentrates
  - To date, no new safety signals related to hypersensitivity since the introduction of ADVATE 2 mL
  - Potential concern with shorter reaction time available to stop infusion if hypersensitivity reaction occurs
  - Caution is advised when infusing ADVATE 2 mL, especially in children[3]
- This was a prospective, non-interventional, **P**ost-**A**uthorization **S**afety **S**urveillance (PASS) study:
  - Collected safety and efficacy data on ADVATE 2 mL during routine clinical practice in children aged ≤ 12 years
  - Prospectively solicited reports of hypersensitivity/local site reaction/tolerability in children

OBJECTIVE

Primary Objective

- To assess the incidence of all local-site and general hypersensitivity and infusion-related reactions, irrespective of product-related causality for the adverse events (AEs).

Secondary Objective

- To assess incidence of AEs possibly or probably related (eg, immunogenicity, effectiveness) to ADVATE 2 mL
- To assess other outcomes between ADVATE reconstituted in 5 mL and 2 mL including:
  - FVIII treatment satisfaction and preference rating from caregiver
  - FVIII infusion volume and time to mix and infuse FVIII treatment

METHODS

Study Design

- Prospective, uncontrolled, open-label, non-interventional, observational, multicenter study
- 28 sites across 8 countries
- Observation period ~6 months from the date of enrollment

Study Population

- 65 subjects ≤ 12 years old with severe or moderately severe hemophilia A (FVIII ≤ 2%) and documented prior exposure to FVIII
  - 16 subjects ≤ 2 years
  - 27 subjects > 2 to ≤ 6 years
  - 22 subjects > 6 and ≤ 12 years

METHODS continued

Key Inclusion/Exclusion Criteria

- Subjects with severe or moderately severe hemophilia A (FVIII ≤ 2%)
  - Documented prior exposure to ADVATE (5 mL or 2 mL SWFI)
- Documented negative inhibitor test during ≤ 10 EDs prior to study entry
- Prescribed only ADVATE 2 mL during study observation
- No known hypersensitivity to active substance or any of the excipients

Optional Caregiver Survey

- Caregivers were asked to complete a short survey at the beginning and end of the 6-month observation period
  - Captures data on infusion experience and satisfaction with ADVATE reconstituted in 5 mL SWFI at the beginning of the study and with ADVATE reconstituted in 2 mL SWFI at the end of the study
  - Captures preferences between ADVATE reconstituted in 2 mL and 5 mL SWFI on a variety of factors including FVIII infusion volume, and time to mix and infuse FVIII treatment using ADVATE 2 mL

RESULTS

Patient Disposition and Demographics

- 65 patients enrolled, 1 patient withdrew due to a non-drug and non-study related issue
- 11/65 patients had ≤ 50 Exposure Days (EDs) prior to study entry
  - 8/65 patients had ≤ 20 EDs
  - 4/65 patients had ≤ 4 EDs
- Median number of exposure days (EDs) prior to study entry was 51.0 EDs (range: 1–624)
- 11/65 (17%) patients had a history of inhibitor development, 5 of which were high-titer, and 1 patient with a history of ITI within the last 2 years
- Median total study duration was 189 days (range: 128–295)

Table 1: Baseline Demographics

	≤ 2 Yrs (N = 16) n (%)	> 2 to ≤ 6 Yrs (N = 27) n (%)	> 6 to ≤ 12 Yrs (N = 22) n (%)	Total (N = 65) n (%)
Age				
Mean	1.1	4.6	8.4	5.0
Median	1.0	5.0	8.0	5.0
SD	0.68	1.15	1.50	3.05
Min	0	3	7	0
Max	2	6	11	11
History of FVIII inhibitor				
History of inhibitor development	0 (0.0)	4 (14.8)	7 (31.8)	11 (16.9)
Number of positive inhibitors tests in history				
0	16 (100.0)	23 (85.2)	15 (68.2)	54 (83.1)
1	0 (0.0)	3 (11.1)	7 (31.8)	10 (15.4)
3	0 (0.0)	1 (3.7)	0 (0.0)	1 (1.5)
Hemophilia severity class				
moderately severe	3 (18.8)	4 (15.4)	4 (18.2)	11 (17.2)
Severe*	13 (81.3)	22 (84.6)	18 (81.8)	53 (82.8)

* one subject's data is missing; site confirmed as severe Hemophilia A patient

RESULTS continued

Safety and Tolerability

- No subjects experienced hypersensitivity reactions
- No inhibitors were detected during study observation

Table 2 : Adverse Events Reported During Study Observation

	Number of patients (%) Event count N= 65
Adverse Events (AEs)	26 (40.0) 61
Study drug-related AEs (Adverse Drug Reactions [ADRs])	0 (00.0) 0
Serious AEs	9 (13.8) 13
Study drug-related serious AEs (serious ADRs)	0 (00.0) 0
Deaths	0 (00.0) 0

Table 2a : Serious Adverse Events Reported During Study Observation

System Organ Class Preferred Term	Number of patients (%) Event count N= 65
Infections and Infestations	4 (6.2)
Device related sepsis	1 (1.5)
Gastroenteritis	1 (1.5)
Gastroenteritis rotavirus	1 (1.5)
Tonsillitis	1 (1.5)
Dental and Gingival Conditions*	2 (3.1)
Dental caries	2 (3.1)
General Disorders and Administration Site Conditions	2 (3.1)
Extravasation	1 (1.5)
Oedema peripheral	1 (1.5)
Musculoskeletal and Connective Tissue Disorders	2 (3.1)
Arthralgia	1 (1.5)
Joint swelling	1 (1.5)

A patient with more than one finding in a specific category was only counted once. Percentage based on total no. of patients.
* High Level Group Term (HLGT)

- No study-drug-related Adverse Events (AE) occurred during study observation
- Nine subjects experienced 13 serious AEs; most were infections and infestations that were judged by the investigator(s) as non-related to study treatment

Effectiveness

- Continuous and regular prophylaxis treatment in 56/65 patients (86.2%):

100% of those who provided ratings (n = 55) achieved an overall effectiveness rating as excellent (81.8%) or good (18.2%) – See Table 3

- Bleeding episodes :
  - Zero bleeds in 30/65 subjects (46.2%)
  - Total of 94 bleeding episodes that required ADVATE treatment, considered as minor for 80.9% and major for 2.1%
  - 81.9% of the bleeding events treated with ADVATE did not result in patient missing school and/or normal activities
  - A total of 161ADVATE infusions performed for a total of 94 bleeds
- 6 invasive procedures in 5 subjects : 3 surgical interventions and 3 dental extractions

The post-operative global effectiveness was rated as excellent in 100% (n = 6)

Table 3 : Effectiveness of ADVATE 2 mL for Prophylaxis Treatment

	FVIII < 1% (N = 48)	FVIII ≤ 2% (N = 7)	Missing (N = 1)	Total (N = 56)
Overall effectiveness for prophylaxis treatment – categorized, n (%)				
Excellent	37 (78.7)	7 (100.0)	1 (100.0)	45 (81.8)
Good	10 (21.3)	0 (0.0)	0 (0.0)	10 (18.2)
Fair	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
None	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	1	0	0	1

Optional Caregiver Survey

- Caregiver satisfaction remained consistent from screening through end of trial (EOT)
- ≥ 90% of respondents provided ratings of "very satisfied" or "satisfied" for:
  - Amount of liquid needed for infusion
  - Time needed to infuse treatment
  - Time needed to mix and infuse treatment
  - Ease of infusing treatment
  - Overall convenience of treatment
  - With treatment in general
- Caregiver satisfaction ratings demonstrated improvements from screening to EOT with respect to anxiety of child and caregiver administrating ADVATE 2 mL versus ADVATE 5 mL (Table 4)

Table 4 : Caregiver Satisfaction Survey Regarding Anxiety Over Infusion of Factor at Screening and End of Trial

	≤ 2 Yrs (N = 16)	> 2 to ≤ 6 Yrs (N = 27)	> 6 to ≤ 12 Yrs (N = 22)	Total (N = 65)
QS11: With Amount of Anxiety Child Has, n (%)				
Screening				
1 = Very Satisfied	0 (0.0)	6 (30.0)	7 (43.8)	13 (28.9)
2 = Satisfied	3 (33.3)	6 (30.0)	6 (37.5)	15 (33.3)
3 = Neither Satisfied Nor Dissatisfied	4 (44.4)	4 (20.0)	2 (12.5)	10 (22.2)
4 = Dissatisfied	2 (22.2)	3 (15.0)	1 (6.3)	6 (13.3)
5 = Very Dissatisfied	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.2)
EOT				
1 = Very Satisfied	2 (40.0)	9 (39.1)	10 (58.8)	21 (46.7)
2 = Satisfied	1 (20.0)	6 (26.1)	1 (5.9)	8 (17.8)
3 = Neither Satisfied Nor Dissatisfied	2 (40.0)	6 (26.1)	5 (29.4)	13 (28.9)
4 = Dissatisfied	0 (0.0)	1 (4.3)	1 (5.9)	2 (4.4)
5 = Very Dissatisfied	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.2)
QS12: With Amount of Anxiety I Have, n (%)				
Screening				
1 = Very Satisfied	1 (11.1)	7 (35.0)	7 (43.8)	15 (33.3)
2 = Satisfied	3 (33.3)	8 (40.0)	6 (37.5)	17 (37.8)
3 = Neither Satisfied Nor Dissatisfied	3 (33.3)	5 (25.0)	3 (18.8)	11 (24.4)
4 = Dissatisfied	2 (22.2)	0 (0.0)	0 (0.0)	2 (4.4)
EOT				
1 = Very Satisfied	2 (40.0)	9 (39.1)	8 (47.1)	19 (42.2)
2 = Satisfied	1 (20.0)	7 (30.4)	3 (17.6)	11 (24.4)
3 = Neither Satisfied Nor Dissatisfied	2 (40.0)	6 (26.1)	5 (29.4)	13 (28.9)
4 = Dissatisfied	0 (0.0)	0 (0.0)	1 (5.9)	1 (2.2)
5 = Very Dissatisfied	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.2)

CONCLUSION

- This study documents the safety, effectiveness, and tolerability of ADVATE 2 mL in patients ≤ 12 years with severe/moderately severe hemophilia A
  - No subjects experienced hypersensitivity reactions
  - No study-drug-related AEs; no inhibitors reported
- Survey ratings demonstrated improvements in anxiety of child and caregiver from screening to EOT
- These data suggest that use of ADVATE 2 mL:
  - Is safe and effective in pediatric patients (≤ 12 years old)
  - May be particularly advantageous in situations where patient or caregiver anxiety or inexperience are associated with administering higher volume infusions

Disclosures: *Author an employee of Baxalta ([4,5]Baxalta US, Inc), now part of Shire.

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