Prospective ADVATE Immune Tolerance Induction Registry (PAIR): Results of an Interim Analysis

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INTRODUCTION

- Approximately 20%–35% of patients with severe hemophilia A and 3%–13% of those with mild to moderate disease develop inhibitory antibodies that impact the efficacy of factor VIII (FVIII) replacement therapy.[1-3]
- The risk for development of inhibitors is dependent on various patient characteristics; type of FVIII gene mutation, family history, and ethnicity are all risk factors for inhibitor formation.[4-9]
- Without intervention, it is believed that high inhibitor titers persist indefinitely in most cases, rendering patients unresponsive to FVIII therapy and impacting complications and outcomes.[10,11]
- Several approaches have been developed to induce FVIII immune tolerance, involving frequent FVIII infusions until inhibitor titers are ablated and FVIII pharmacokinetics normalize.
- FVIII regimens from 25 IU/kg every other day up to 200 IU/kg daily have demonstrated overall success rates of approximately 70%, including treatment regimens with recombinant antihemophilic factor plasma/albumin-free method (rAHF-PFM, ADVATE).[3-10]
- To expand the knowledge base of the use of rAHF-PFM for immune tolerance induction (ITI) in clinical practice, a global prospective ADVATE ITI registry (PAIR) was created and began recruitment in July 2007.
- Here we present interim results from a preliminary analysis with data available as of March 22, 2012.

OBJECTIVE

- To assess the safety/tolerability and success of rAHF-PFM during ITI therapy in clinical practice

METHODS

Study Design
- Prospective, uncontrolled, open-label, noninterventional study
- rAHF-PFM ITI dosing regimen and monitoring schedule is at the discretion of the treating physician.
- Data are collected from patient diaries and clinic visits from ITI start to finish.
- Postobservation follow-up will be performed 12 months following ITI therapy completion to determine whether FVIII immune tolerance has been maintained. Outcome assessments are described in Table 1.

Primary and Secondary Endpoints
- The primary objective was to assess the safety of rAHF-PFM during ITI therapy in clinical practice.
- Secondary objectives included the following:
  - Success rate of rAHF-PFM ITI (Table 1)
  - Incidence of central venous access device (CVAD)–related infections during rAHF-PFM ITI
  - Correlation of ITI success with patient characteristics, treatment variables, and intercurrent infections

Inclusion/Exclusion Criteria
- Diagnosis of hemophilia A
- Development of an inhibitor to FVIII following the use of any FVIII concentrate
- Prescribed rAHF-PFM ITI by physician, independent of decision to participate in PAIR
- No previous failure of ITI therapy with rAHF-PFM and no hypersensitivity to the active substance or any of its excipients

Safety/Tolerability
- All adverse events (AEs) occurring during rAHF-PFM ITI therapy were assessed for causality, seriousness, and severity.
- If inhibitor development occurred before rAHF-PFM ITI initiation and had not been reported, the event was to be reported as a serious AE (SAE).

RESULTS

- As of March 22, 2012, 44 patients were enrolled; 8 (18.2%) were still undergoing ITI, 31 (70.5%) had completed ITI, and 23 (52.3%) had completed 12-month follow-up.
- Median age at ITI initiation was 2.0 years (range, 0.08–56.3 y), and ITI duration ranged from 1–33 months. All patients were male and 29 (65.9%) were white (Table 2).

Table 1. PAIR Clinical Outcome Assessments: Success Criteria

General	• Achievement of negative FVIII inhibitor titer (<0.6 BU or local laboratory cutoff) in any observational study patient
Precise	• When available, PK information as described below will be used to assess the clinical outcome of ITI therapy in patients with severe hemophilia A and inhibitors to FVIII
Complete	• ≤33 mo of ITI initiation, inhibitor titer <0.6 BU, FVIII recovery data ≥66% of expected recovery (following 50-IU/kg dose, recovery measured at 30±5 min after FVIII infusion), and FVIII half-life ≥6 h • Both PK parameters should be measured following minimal 48-h treatment-free washout period • If cutoff limit for inhibitor detection is not 0.6 BU, the standards at the local laboratory will prevail
Partial	• Upon termination of ITI therapy (≥9 mo and <33 mo of ITI treatment), inhibitor titer remains <5 BU or negative titer (<0.6 BU) with FVIII recovery <66% of expected recovery, or FVIII recovery >66% of expected recovery but FVIII half-life <6 h associated with clinical response to FVIII therapy
Failure	• Does not meet complete or partial success criterion OR • Following the first 3 mo of treatment and before completing 33 mo of ITI, failure to achieve an ongoing ≥20% reduction in inhibitor titer, during each interim nonrefapping 6-mo period of ITI in the absence of documented infection • This implies that 9 mo is the minimum treatment period and 33 mo the maximum possible duration of unsuccessful ITI • This criterion for ITI failure will cease to apply once the patient achieves a titer of ≤5 BU
Unassessable per protocol	• Does not meet criteria for complete success, partial success, or failure

Relapse	• Determined during postobservation 12-mo follow-up after inhibitor disappearance
	• Following inhibitor disappearance, positive inhibitor titer should be confirmed within a 2-wk period OR
	• Following inhibitor disappearance, negative inhibitor titer
	  − Recovery <66% (when measured at 1 h ± 30 min after FVIII infusion) should be confirmed ≤2-wk period OR
	  − FVIII half-life of <6 h (when measured after a 48-h treatment-free washout period) should be confirmed ≤2-wk period

BU=Bethesda unit; FVIII=factor VIII; ITI=immune tolerance induction; PAIR=Prospective ADVATE Immune Tolerance Induction Registry; PK=pharmacokinetic.

Table 2. Baseline Demographics and Disease Characteristics in Patients Receiving rAHF-PFM ITI

Parameter	Patients With FVIII ≤1% (n=38)	All Patients (N=44)
Median age at ITI start, mo (range)	19.0 (1.0–320)	23.5 (1–676)
Race, n (%)		
White	24 (63.2)	29 (65.9)
Asian	1 (2.6)	1 (2.3)
Black	4 (10.5)	4 (9.1)
Hispanic	3 (7.9)	3 (6.8)
Other/missing	6 (15.8)	7 (15.9)
Family history of inhibitor, n (%)		
Yes	10 (26.3)	11 (25.0)
No	25 (65.8)	30 (68.2)
Unknown	3 (7.9)	3 (6.8)
Median titer, BU (range)		
At diagnosis	4.9 (0.7–173.0)	4.9 (0.5–173.0)
Peak before ITI*	15.5 (0.7–225.2)	15.5 (0.7–225.2)
Immediately before ITI	4 (0–91.7)	3.95 (0–91.7)

BU=Bethesda unit; FVIII=factor VIII; ITI=immune tolerance induction.
*If peak titer before ITI therapy was not reported, the maximum of all titer measurements made before ITI was used.

- 38 of 44 patients had severe hemophilia A (FVIII ≤1%).
- High titers of inhibitors (≥5 BU) were seen in 30 (68.2%) patients; 27 (71.1%) patients had both FVIII values ≤1% and inhibitor titers ≥5 BU.
- The most common dose in all patients and in those with severe hemophilia was 90–130 IU/kg/d (Table 3).

Table 3. Initial ITI Dose Regimens

	Patients With FVIII <1% (Severe Hemophilia A) (n=38)		All Patients (N=44)	
Dose, IU/kg/d	High Titer, n (%) (n=13)	Low Titer, n (%) (n=25)	High Titer, n (%) (n=15)	Low Titer, n (%) (n=29)
≥200	3 (23.1)	1 (4.0)	3 (20.0)	1 (3.4)
131–199	1 (7.7)	1 (4.0)	2 (13.3)	1 (3.4)
90–130	7 (53.8)	15 (60.0)	8 (53.3)	18 (62.1)
<90	2 (15.4)	8 (32.0)	2 (13.3)	9 (31.0)

BU=Bethesda unit; FVIII=factor VIII; ITI=immune tolerance induction.
High titer inhibitor: ≥5 BU; low titer inhibitor: <5 BU.

- In patients who completed ITI treatment, 18 (58.1%) experienced general success; 16/27 (59.3%) and 2/4 (50%) experienced partial success in the severe and nonsevere hemophilia groups, respectively; and 2/27 (7.4%) and 1/4 (25%) relapsed in the severe and nonsevere hemophilia groups, respectively (Table 4 [completer analysis set] and Figure 1).
- Median times to first and second negative titers for all patients were 4.17 months and 5.78 months, respectively.
- In the per-protocol analysis set, 18 (69.2%) patients achieved general success; 16 of those patients had severe hemophilia and 2 had nonsevere hemophilia.

Table 4. Summary of Patient Outcomes for ITI Therapy

	Severe Hemophilia	Nonsevere Hemophilia	Total
Per-protocol analysis set	**n=23**	**n=3**	**n=26**
General success,* n (%)	15(65.2)	3 (100.00)	18 (69.2)
Precise criteria, n (%)			
Complete success†	NA	NA	NA
Partial success‡	16 (69.6)	2 (66.7)	18 (69.2)
Relapse§	2 (8.7)	1 (33.3)	3 (11.5)
Failure	5 (21.7)	0	5 (19.2)
Completer analysis set	**n=27**	**n=4**	**n=31**
General success,* n (%)	15 (55.6)	3 (75.0)	18 (58.1)
Precise criteria, n (%)			
Complete success†	NA	NA	NA
Partial success‡	16 (59.3)	2 (50.0)	18 (58.1)
Relapse§	2 (7.4)	1 (25.0)	3 (9.7)
Failure	5 (18.5)	0	5 (16.1)
Unassessable	3 (11.1)	1 (25.0)	4 (12.9)
Success by investigator	1 (3.7)	0	1 (3.2)
Median time to first negative titer,‖ mo (range)	4.5 (0.33–16.56)	2.8 (0.07–12.32)	4.17 (0.07–16.56)
Median time to second negative titer,¶ mo (range)	5.06 (1.68–17.71)	6.19 (0.26–19.32)	5.78 (0.26–19.32)

BU=Bethesda unit; ITI=immune tolerance induction; PK=pharmacokinetic.
*There was a discrepancy between last titer measurements between 2 study forms for 1 patient; however, because there was a later titer measurement of 0 BU during ITI therapy and the investigator reported ITI success, "general success" was assigned for this patient.
†Sufficient PK data were not available to determine complete success.
‡1 patient achieved partial success with a titer <5 BU, but the investigator reported that ITI success was not anticipated within 33 mo.
§6 patients were reported to have achieved ITI success by the investigator, but the confirmatory titers were not available.
‖Only patients who had a first negative titer were included (severe hemophilia, n=17, nonsevere hemophilia, n=4).
¶Only patients who had a second negative titer were included (severe hemophilia, n=17, nonsevere hemophilia, n=4).

Figure 1. Per-Protocol Kaplan-Meier Estimated Cumulative Success Rates Over 18 Months

Analysis Sets — Full, Completers, Per-Protocol
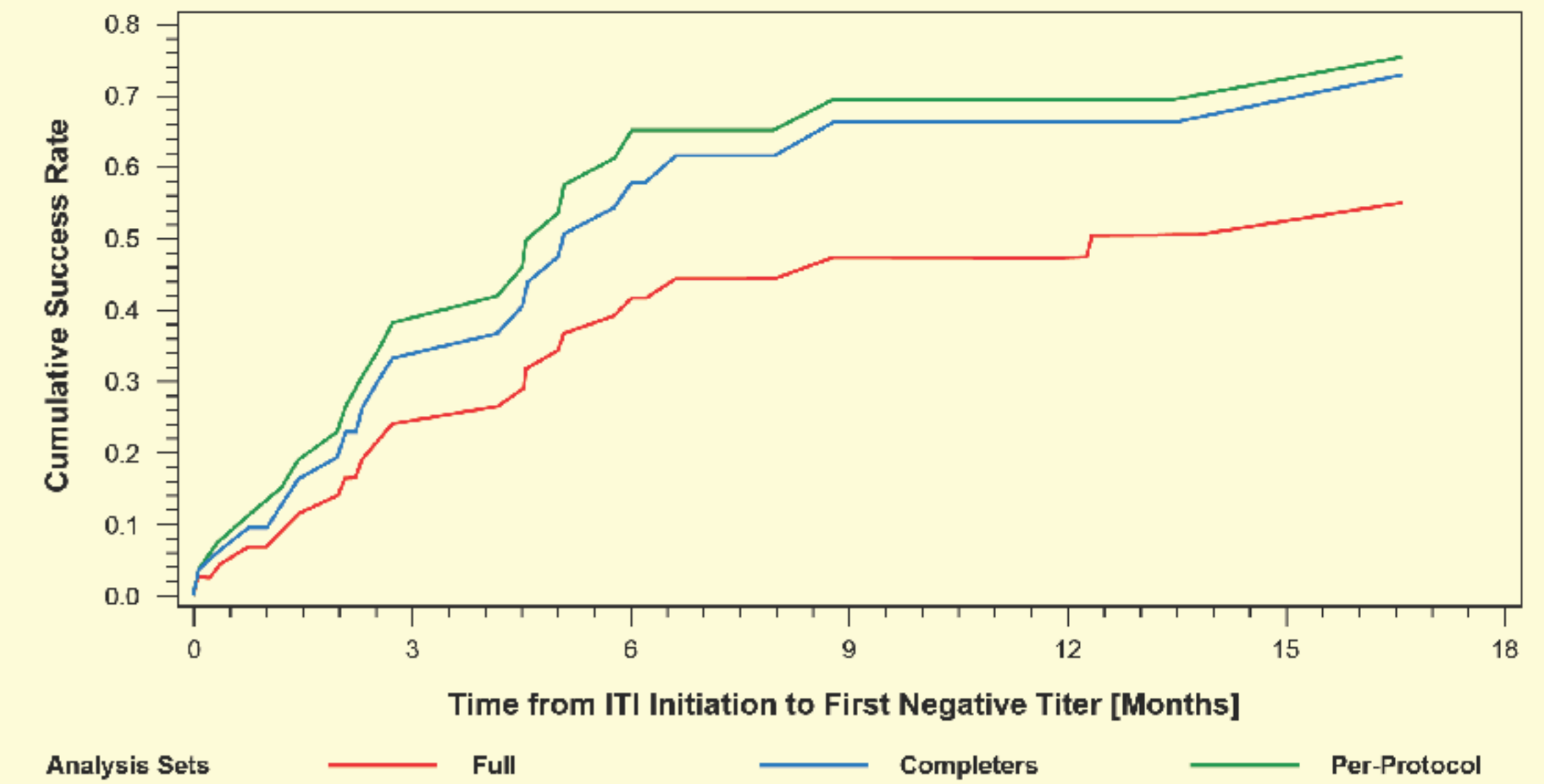
Table 5. Kaplan-Meier Estimated of Success for Achievement to First Negative Titer Over 18 Months

Analysis Set	Evaluation Time Point, mo	Patients, n	Events, n	Censored, n	Estimated Success Rate, %	95% CI
Per protocol	6	26	17	0	65.4	47.5–82.5
	9	26	18	1	69.7	51.8–85.9
	18	26	19	3	75.8	57.0–90.7
Completers	6	31	17	2	58.0	41.1–75.9
	9	31	19	5	66.6	49.0–83.3
	18	31	20	7	73.3	54.2–89.2
Full	6	44	17	4	42.0	28.5–58.6
	9	44	19	7	47.5	33.4–64.1
	12	44	20	9	50.8	36.2–67.3
	18	44	21	13	55.3	39.7–72.2

Safety/Tolerability
- No SAEs were considered treatment related, and all AEs related to treatment were considered nonserious (Table 6).

Table 6. AEs Reported and Discontinuations During rAHF-PFM ITI

AEs	All Patients (N=44)
Total AEs, n	250
Total SAEs, n (%)	45 (18.0)
Related SAEs, n (%)	0
Total nonserious AEs, n (%)	205 (82.0)
Unrelated nonserious AEs, n (%)	192 (76.8)
Related nonserious AEs,* n (%)	13 (5.2)
Discontinuations	
Patient withdrew, n	2
Physician decisions, n	1
Lost to follow-up, n	2

AE=adverse event; FVIII=factor VIII; ITI=immune tolerance induction; rAHF-PFM=recombinant antihemophilic factor plasma/albumin-free method.
*Related nonserious AEs included FVIII inhibition (n=4); nausea (n=2); arthralgia (n=2); and catheter site pain, medical device complication, pyrexia, upper respiratory tract infection, and urticaria (n=1 each).

CVAD Complications
- The most common AEs unrelated to study product were associated with CVAD use (Table 7).
- CVAD-associated complications occurring in >1 patient were line infections, insertion, malfunction, and removal.

Table 7. Summary of CVAD-Associated Complications

CVAD Complication Type	Events, n (%)	Patients, n (%)
Hospitalization	3 (5.2)	1 (2.3)
Line infection: major (systemic/septic)	8 (14.0)	5 (11.0)
Line infection: minor (local site)	18 (31.0)	5 (11.0)
Line insertion	7 (12.0)	6 (14.0)
Line insertion site bleed	9 (16.0)	3 (6.8)
Line insertion site swelling	1 (1.7)	1 (2.3)
Line malfunction (≤2-wk interruption)	7 (12.0)	5 (11.0)
Line removal	4 (6.9)	4 (9.1)
Pain following portacath bleed	1 (1.7)	1 (2.3)

CVAD=central venous access device.

CONCLUSIONS

- As of March 22, 2012, preliminary data were available for 44 patients who had been enrolled in PAIR for the use of rAHF-PFM.
- The most commonly prescribed regimen in patients with high inhibitor titers was 90–130 IU/kg/d.
- rAHF-PFM was found to be efficacious in a variety of ITI dosing regimens, as currently used in clinical practice.
- No product-related SAEs and only 13 related nonserious AEs were reported.
- Complications associated with CVAD use were commonly reported.
- The projected cumulative success rate in PAIR at 18 months (per protocol, 75.8%; completers, 73.3%) seems consistent with the results published for the International ITI Study (69.7%).[12]
- These preliminary data suggest that ITI treatment with rAHF-PFM is both safe and effective.

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