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ORIGINAL RESEARCH

Safety and Efficacy of Moroctocog Alfa (AF-CC) in Chinese Patients with Hemophilia A: Results of Two Open-Label Studies

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Introduction: Moroctocog alfa albumin-free cell culture (AF-CC) increases plasma levels of factor VIII (FVIII) activity and, in China, is indicated for the control and prevention of bleeding episodes in patients with hemophilia A. This study aimed to evaluate the efficacy, safety, and recovery data of moroctocog alfa (AF-CC) in patients with hemophilia participating in two open-label studies, both conducted in China.

Methods: The authorization study (clinicaltrials.gov identifier NCT00868530) enrolled patients aged ≥6 years, previously treated with ≥1 exposure day of FVIII replacement therapy. The real-world study (clinicaltrials.gov identifier NCT02492984) enrolled patients of any age who were previously untreated or requiring surgical prophylaxis. In both studies, on-demand treatment was administered over 6 months. Key assessments included response to treatment, FVIII inhibitor development, and recovery.

Results: In the authorization study (N = 53; mean age, 23.2 years; severe hemophilia, 23%), response was excellent/good for 90% of infusions at 24 hours. Seven patients developed inhibitors. Mean (SD) FVIII recovery at the initial and final visits was 1.77 (0.50) and 1.67 (0.45) (IU/dL)/(IU/kg), respectively. In the real-world study (N = 85; mean age, 9.5 years; severe hemophilia, 58%), response was rated as excellent or good for most (87%) on-demand infusions and for all surgical prophylaxis patients (n = 14). Seven patients developed FVIII inhibitors. Mean (SD) FVIII recovery at the initial and final visits was 1.71 (0.50) and 1.68 (0.31) (IU/dL)/(IU/kg), respectively. No new safety signals were observed in either study.

Conclusion: On-demand treatment and surgical prophylaxis with moroctocog alfa (AF-CC) is safe and effective for both previously treated and previously untreated Chinese patients with hemophilia A.

Keywords: Asian, blood coagulation factor VIII, deficiency, factor VIII, ReFacto, Xyntha

Plain Language Summary

This report summarizes efficacy and safety results from two moroctocog alfa (AF-CC) studies in different populations of Chinese patients with hemophilia A, including patients who were previously treated or received factor VIII replacement therapy for surgical prophylaxis, and who were previously untreated with factor VIII replacement therapy. In these studies, moroctocog alfa (AF-CC) was administered on demand (or for surgical prophylaxis) to 185 patients at a dose consistent with product labeling in China. Investigators rated the hemostatic efficacy of on-demand moroctocog alfa (AF-CC) across both studies as excellent or good for ≥87% of infusions, with only one incident of non-response. For surgical prophylaxis, all responses were rated as excellent or good. Treatment with moroctocog alfa (AF-CC) was well tolerated, and inhibitors (assessed as a safety

outcome) developed in seven patients in each study for rates of 13.7% and 8.2%. Recovery of factor VIII activity was stable throughout both studies. Based on these results, on-demand treatment with moroctocog alfa (AF-CC) is a safe and effective therapeutic option for Chinese patients with hemophilia A. In both studies, the increase in factor VIII activity observed after standardized dosing was similar at the end of the study to what it was at study inception.

Introduction

Hemophilia A, an X-linked inherited bleeding disorder, is caused by a deficiency of coagulation factor VIII (FVIII). Treatment is based primarily on replacement of FVIII clotting factor concentrates, either prophylactically or on demand.[1] The treatment of hemophilia in China has progressed, with contributions from the World Federation of Hemophilia (WFH) and the development of the Hemophilia Treatment Center Collaborative Network of China (HTCCNC).[2] In addition, pharmaceutical companies and non-governmental organizations have helped to build and improve hemophilia treatment centers. According to a 2019 report, the network includes 115 regional hospitals and has registered approximately 18,000 patients with hemophilia, including 16,083 patients with hemophilia A.[3] However, it is estimated that the actual number of people with hemophilia A and B in China is 65,000 to 130,000,[3] suggesting that only a small percentage of patients are diagnosed and registered.[4–6] Despite improvements in care over the last decade, management of hemophilia in China remains a challenge because of factors such as insufficient health care infrastructure, inadequate awareness and knowledge of the disease, high costs, lack of medical insurance for a majority of patients, and limited availability or access to factor replacement products.[2,4–9] To mitigate treatment costs and limited access to resources, several studies led by the HTCCNC investigated the potential benefit of using low-dose prophylaxis to reduce the number of joint bleeding events and to improve quality of life.[3,9]

Moroctocog alfa is a B-domain–deleted recombinant FVIII product manufactured using an albumin-free cell culture (AF-CC) process.[10–12] Moroctocog alfa (AF-CC; Xyntha in China, the United States, Canada, and certain other regions, or ReFacto AF in Europe; Wyeth Pharmaceuticals, Inc. [Pfizer Inc], Philadelphia, PA, USA) has an enhanced viral safety profile relative to its predecessor product, moroctocog alfa (ReFacto), utilizing a nanofiltration to eliminate animal- and human-derived proteins.[10–12] Moroctocog alfa (AF-CC) is approved in China for the treatment of bleeding events and for surgical prophylaxis in patients with hemophilia A. The objective of this report is to present efficacy, safety, and recovery data from two open-label studies of moroctocog alfa (AF-CC) in Chinese patients with hemophilia A. The first was an authorization study conducted to meet regulatory requirements for approval of moroctocog alfa (AF-CC) in China (clinicaltrials.gov identifier NCT00868530), and the second was a real-world study conducted at treatment centers in China (clinicaltrials.gov identifier NCT02492984).[13]

Patients and Methods

Patients

Patients who were at least 6 years of age and had mild, moderate, or severe hemophilia A (FVIII activity >5%, 1%–5%, or <1%, respectively) with prior exposure to FVIII replacement therapy (≥1 exposure day [ED]) were eligible for enrolment in the authorization study. For HIV-positive patients, a documented CD4 count >200/μL was required within 6 months of study entry. Patients were excluded if they had a bleeding disorder in addition to hemophilia A and for the presence or history of FVIII inhibitors, current use of primary FVIII prophylaxis, planned elective surgery, or receiving immunomodulatory therapy or investigational therapy within 6 months of study entry.

In the real-world study, patients with hemophilia A of all ages, including previously untreated patients and those undergoing surgery, requiring surgical prophylaxis, were eligible for enrolment. Exclusion criteria were similar to those of the authorization study, with the exception of allowing patients with planned surgery to enroll in the study. Both studies were conducted in accordance with the Declaration of Helsinki and followed Good Clinical Practice guidelines, as well as local rules and regulations, and each study protocol was approved by an ethics committee. All patients or their parents/legal guardians provided written informed consent.

Study Design

The authorization study design was based on historical precedent to meet registration requirements in China. The study protocol was approved by an institutional review board at each study site (Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences; Peking Union Medical College Hospital; Ruijin

Hospital, Shanghai Jiao Tong University School of Medicine; Nanfang Hospital, Nanfang Medical University; The First Affiliated Hospital – Zhejiang University School of Medicine; and The First Affiliated Hospital of Soochow University). It was an open-label, multicenter study comprising a 28-day screening phase, initial and final visits, a 6-month on-demand treatment phase, and a follow-up telephone call approximately 30 days after the final visit. Recovery was assessed at the initial and final visits after administration of a single 50-IU /kg (± 5 IU/kg) dose. The real-world study was an open-label, single-arm, multicenter, prospective, post-authorization study. The study protocol was approved by an institutional review board at each study site (Blood Diseases Hospital, Chinese Academy of Medical Sciences; Ruijin Hospital, Shanghai Jiao Tong University School of Medicine; The First Affiliated Hospital of Soochow University; Jiangxi Provincial People's Hospital; Beijing Children's Hospital; Nanfang Hospital, Southern Medical University; The Affiliated Hospital of Xuzhou Medical University; The Second Affiliated Hospital of Chongqing Medical University; The Affiliated Hospital of Guizhou Medical University; Henan Provincial People's Hospital; The First Affiliated Hospital of Kunming Medical University; Children's Hospital of Chongqing Medical University; Chengdu Women's and Children's Central Hospital; Blood Center of Shandong Province; Tongji Hospital of Tongji Medical College of Huazhong University; and Children's Hospital of Shanghai).

Patients were monitored according to local standard of care. In both studies, moroctocog alfa (AF-CC) was prepared, reconstituted, and administered according to the product's package insert in China[14] (Supplemental Table 1). In the authorization study, patients were treated at a study center. In the real-world study, patients or caregivers/parents were trained on how to administer moroctocog alfa (AF-CC) off-site and maintained an infusion log, including information on the infusion date and time, amount of moroctocog alfa (AF-CC) infused, reason for infusion, and 4-point assessment. On-demand treatment ended after approximately 6 months or when patients achieved approximately 50 (±5) EDs. Recovery was assessed for all surgical prophylaxis patients as well as others at the investigators' discretion after administration of a single 50-IU/kg (± 5 IU/kg) dose. For surgical prophylaxis patients, treatment duration was based on the nature of the surgery and the patient's condition. The final visit for surgical prophylaxis corresponded to the last surgical prophylactic dose of moroctocog alfa (AF-CC).

Assessments

Hemostatic efficacy was assessed in both studies using a 4-point Investigator Hemostatic Efficacy Assessment scale (1, excellent; 2, good; 3, moderate; 4, no response); this was the primary efficacy outcome for the authorization study and was included in the real-world study as an efficacy measure. It was performed at 8 and 24 (±1) hours postinfusion in the authorization study. In the real-world study, the response to on-demand treatment was assessed by the patient/caregiver via a patient diary (there were no predefined times of efficacy assessment), and assessments were reviewed by the investigator. The response to surgical prophylaxis was assessed by the investigator and/or surgeon. Bleeding episodes were classified as spontaneous or traumatic. Secondary efficacy outcomes included the mean number of infusions needed to control a bleeding episode, the mean dose of moroctocog alfa (AF-CC) per hemorrhagic event, and the incidence of less-than-expected therapeutic effect (LETE). In the real-world study, additional efficacy measures were annualized bleeding rates (ABRs; calculated as the number of bleeding events in the on-demand period divided by the number of days in the on-demand period/365.25) for patients receiving on-demand treatment for at least 14 days; for surgical prophylaxis patients, blood loss and transfusion requirements were evaluated as abnormal, normal, and absence, and the number of units and types of blood products transfused were recorded.

Safety

The primary safety outcome was the development of FVIII inhibitor activity. In the authorization study, two samples were collected at screening, initial recovery, and final recovery, and during the acute phase, if clinically indicated; one sample was preliminarily tested at a local laboratory, if available, and one sample was sent to the central laboratory for confirmatory testing. In the real-world study, samples were collected at screening, on day 1, and at the end of treatment/early termination; all tests for inhibitors were performed at local laboratories. Positive results were defined as ≥0.6 Bethesda units/mL. The incidence rate for inhibitors was summarized by prior FVIII ED status: all patients, patients with 1 to 100 EDs, and patients with >100 EDs (the cutoff of 100 EDs was

selected because of the rarity of heavily treated Chinese patients at the time of the study). The incidence of adverse events (AEs), including serious AEs (SAEs), allergic-type reactions, and thrombogenicity, was recorded.

Statistical Analyses

In both studies, efficacy outcomes were analyzed in patients who received treatment and who had one or more evaluable efficacy assessments. Safety analyses were conducted for all patients who received one or more doses of the study drug. Overall descriptive analyses of the patient cohort and the efficacy and safety data were conducted; quantitative variables were summarized using mean, median, minimum/maximum, and standard deviation (SD). For patients with a positive FVIII inhibitor test result, efficacy data from the first date of inhibitor development (laboratory value) forward were censored. The incidence of inhibitors per patient was estimated separately for each subset based on EDs, along with the corresponding 95% confidence intervals (CIs), using normal approximation. FVIII activity recovery was calculated for patients without inhibitors as the ratio of the change in FVIII activity measured before infusion and at 30 (±5) minutes following completion of the infusion, and the dose administered and calculated ([FVIII activity after treatment − FVIII activity before treatment]/[dose/weight]). Recovery was summarized by visit.

Based on the nature of the real-world study, no statistical hypotheses were tested, and results are presented using descriptive statistics. Data were evaluated for subgroups, including age (ie, <6 years, 6–12 years), previously untreated patients, severe hemophilia patients, and surgical prophylaxis patients. The ABRs were calculated based on total bleeding events, bleeding type, and bleeding location.

Results

Patients

Fifty-three patients completed the initial visit in the authorization study and 85 patients received treatment in the real-world study (on-demand treatment, n = 73; surgical prophylaxis, n = 14; 2 patients rolled over from surgical prophylaxis to on-demand treatment and were counted for each group; Figure 1). Baseline demographic and clinical characteristics for the two study populations are summarized in Table 1.

Hemostatic Efficacy

Among 51 patients evaluable for efficacy in the authorization study (2 patients did not have at least 1 evaluable efficacy assessment), the mean (SD) Investigator Hemostatic Efficacy Assessment score was 1.9 (0.7) at 8 hours, with 639 evaluable infusions, and 1.7 (0.6) at 24 hours, with 626 evaluable infusions. Response was rated as excellent or good for 87.0% and 90.0% of infusions at 8 hours and 24 hours, respectively (Table 2). The mean (SD) frequency and dose of moroctocog alfa (AF-CC) infusions per bleeding episode were 1.2 (0.7) infusions and 1226 IU (1208), respectively, with 1.1 (0.7) EDs per bleeding episode. No LETE was reported.

For on-demand treatment of new bleeding events in the real-world study, 86.9% of responses were rated as excellent or good (Table 2). The mean (SD) number of moroctocog alfa (AF-CC) infusions per each new bleeding event was 1.6 (0.9), with 63.0%, 21.9%, 8.6%, 6.0%, and 0.5% of bleeding events resolving with 1, 2, 3, 4, and >4 infusions, respectively. The mean (SD) dose of moroctocog alfa (AF-CC) per infusion was 26.1 (9.0) IU/kg. One of 1610 bleeding episodes met the criteria for LETE, for an observed overall incidence of 0.06% (95% CI, 0–0.35). The mean (SD) ABR for all patients receiving on-demand treatment was 44.8 (24.2); mean (range) of ABRs was 25.1 (0–77.7) for spontaneous bleeding, 19.5 (0–65.3) for traumatic bleeding, 28.0 (0–98.6) for joint bleeding, 13.8 (0–-66.8) for soft tissue/muscle bleeding, and 2.9 (0–14.1) for other bleeding. Results were similar for subgroup analyses based on age, disease severity, and prior factor exposure (data not shown).

For surgical prophylaxis in the real-world study, all responses were rated as excellent or good. On the day of surgery, ratings of excellent or good were reported for 71.4% and 28.6% of patients, respectively, and during the postoperative period, for 75.5% and 24.5%, respectively. All blood loss during surgery was considered normal by the investigators, and transfusions were required for two of the 14 patients receiving surgical prophylaxis. Mean (SD) infusion dose for surgical prophylaxis was 29.0 (9.8) IU/kg.

Safety

In the authorization study, FVIII inhibitors were detected in 7 of 51 (13.7%) patients during the study (Table 3). Of the seven patients (previously treated [>100 EDs], n = 1; minimally treated [≤100 EDs], n = 5; unspecified, n = 1),

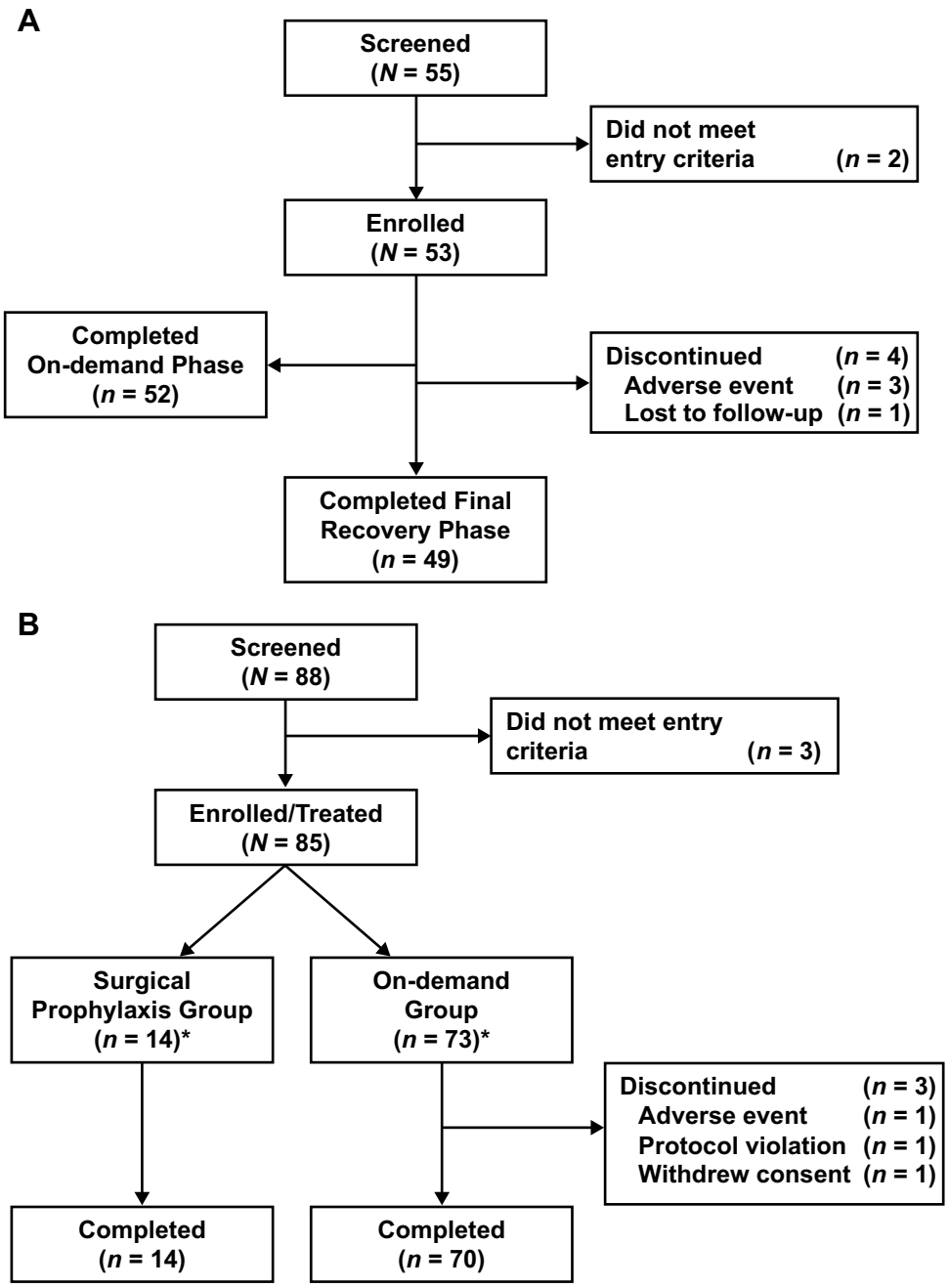

Figure 1 Patient disposition in the authorization study (**A**) and in the real-world study (**B**). *Two patients rolled over from the surgical prophylaxis group to the on-demand group and were counted in each group, but were included only once in the overall population.

four had known intron 22 inversion, of whom two patients with peak titers of 15 BU/mL and 20 BU/mL recovered. In the real-world study, seven patients (8.2%) developed FVIII inhibitors, six in the on-demand treatment group and one in the surgical prophylaxis group (Table 3). Only one patient developed a high-titer FVIII inhibitor, and five of the patients had 50 or more EDs prior to study entry. FVIII inhibitor events were considered resolved by the investigator for five patients.

Adverse events were reported by 19 (35.9%) patients in the authorization study (Table 4) and 74 (87.1%) patients in the real-world study (Table 5). In both studies, most AEs were mild or moderate in severity. Other than FVIII inhibitor activity, AEs considered by investigators to be related to treatment were gingival bleeding (one event) and hypersensitivity (two events in one patient) in the authorization study, and abnormal hepatic function (one event) in the real-world study. In the authorization study, SAEs (other than FVIII inhibitor activity)

Table 1 Demographic and Baseline Clinical Characteristics (Safety Analysis Set)

Parameters	Authorization Study (N = 53)	Real-World Study (N = 85)
Age, years, mean (SD)	23.2 (10.0)	9.5 (9.0)
Male, n (%)	53 (100)	84 (98.8)
Chinese nationality, n (%)	53 (100)	85 (100)
Height, cm, mean (SD)	166.8 (12.1)	128.2 (26.8)
Weight, kg, mean (SD)	58.3 (14.9)	30.5 (17.6)
Hemophilia severity, n (%)		
Mild	1 (1.9)	4 (4.7)
Moderate	40 (74.5)	32 (37.6)
Severe	12 (22.6)	49 (57.6)
Age at first FVIII replacement, years, mean (SD)	9.0 (9.9)	N/A
Prior FVIII exposure days, n (%)		
0	N/A	13 (15.3)
0–100	36 (67.9)	N/A
>100	17 (32.1)	N/A
>0–20	N/A	10 (11.8)
>20–50	N/A	14 (16.5)
>50–150	N/A	19 (22.4)
>150	N/A	29 (34.1)
Positive family history of hemophilia A, n (%)	20 (37.7)	33 (38.8)
Positive virology, n (%)		
Hepatitis C antibody	17 (32.1)	N/A
Human immunodeficiency virus	0	N/A

Abbreviations: FVIII, factor VIII; N/A, not assessed; SD, standard deviation.

occurred in two patients (both with severe hemophilia), one gastrointestinal hemorrhage (unrelated) and one gingival bleeding (possibly related); these patients received 12 and two infusions of moroctocog alfa (AF-CC) to achieve hemostasis, respectively. In the real-world study, one patient had an SAE of gingival injury (unrelated) and was discontinued from the study.

Recovery

In the authorization study, the mean (SD) recovery of FVIII activity at initial and final visits was 1.77 (0.50) IU/dL per IU/kg (n = 44) and 1.67 (0.45) IU/dL per IU/kg (n = 43), respectively; no significant difference was noted in recovery between visits. In the real-world study, the mean (SD) recovery of FVIII activity was 1.71 (0.50) IU/dL per IU/kg (n =28) at day 1 and 1.68 (0.31) IU/dL per IU/kg (n = 7) at end of treatment.

Discussion

The advent of involvement of the WFH and the establishment of the Hemophilia Treatment Centers Collaborative Network of China in the early 1990s led to a vast improvement in the treatment paradigm for patients with hemophilia during the last few decades.[7] However, challenges remain in achieving standards of care for hemophilia that are close to those in countries with advanced health care infrastructure, given the large rural population, limited access to care, and competing priorities for health care resources in this country of more than 1.3 billion people.[4,7,8] Thus, data collection in these studies proved challenging because of the lack of centralized management of patient records. For instance, documentation of exposure days in the registration study was difficult to obtain, and exposure data may not have been accurately captured for all patients. The real-world study was conducted according to approved labeling for moroctocog alfa (AF-CC) in China as well as the current standards of care, which do not support the use of moroctocog alfa (AF-CC) for prophylaxis. Nevertheless, the results of these studies support the efficacy and safety of moroctocog alfa (AF-CC) for on-demand treatment in Chinese patients with mild, moderate, or severe hemophilia A. Recovery of FVIII was stable for the duration of both studies. Response to on-demand treatment with moroctocog alfa (AF-CC) was rated as excellent or good for at least 85% of infusions. In a small number of patients undergoing surgery, moroctocog alfa (AF-CC) was effective as surgical prophylaxis (100% rated as excellent or good), with no new safety signals observed. No instance of LETE was reported in the authorization study, and one case occurred in the real-world study. Moroctocog alfa (AF-CC) was generally well tolerated, and AEs were consistent with those reported in previous global studies.[10,15–17] Compared with the efficacy and safety results from those studies, which were conducted in countries other than China, no substantial differences were observed.

The risk of inhibitor development is influenced by a number of patient- and treatment-related factors, including age, ethnicity, extent of prior exposure to FVIII replacement therapy, intensity of treatment, and underlying FVIII gene mutation type.[18–21] Inhibitor development is a serious complication in approximately 30% of previously untreated patients with hemophilia A during the initial 50 EDs, and the prevalence is greater among patients with severe hemophilia than in those with mild

Table 2 Summary of Efficacy Outcomes

Parameters	Authorization Study				Real-World Study			
	8 Hours Postinfusion		24 Hours Postinfusion		On-Demand		Surgical Prophylaxis	
	N	%	N	%	N	%	N	%
Investigator Hemostatic Efficacy Assessment scores[a]								
Excellent	179	28.0	216	33.8	741[b]	46.0	10[c]	71.4
Good	377	59.0	359	56.2	633	39.3	4	28.6
Moderate	77	12.1	48	7.5	229	14.2	0	0.0
None	6	0.9	3	0.5	5	0.3	0	0.0
Not determined	0	0.0	13	2.0	2	0.1	–	–
"Excellent" or "good" Hemostasis Efficacy Rating Scale scores	556	87.0	575	90.0	1374	85.3	14	100.0
No. of infusions needed to treat each new bleeding event[a]	N/A	–	1.2	±0.72	1.6	±0.94	N/A	–
Patients needing one treatment to resolve bleeding event	0	0.0	0	0.0	1015	63.0	0	0.0
LETE incidence	0	0.0	0	0.0	1/1610	0.06	0	0.0
ABR[a]	N/A	–	N/A	–	44.76	24.19	N/A	–

Notes: [a]Mean (standard deviation). [b]First infusion. [c]Day of surgery.
Abbreviations: ABR, annualized bleeding rate; LETE, less-than-expected therapeutic effect; N/A, not available.

Table 3 Characteristics of Patients with Treatment-Emergent Factor VIII Inhibitor

Patient No.	Age (Years)	Disease Severity at Diagnosis	Prior FVIII EDs/ Moroctocog Alfa EDs Before Inhibitor Development	Genetic Mutation	Initial Titer/ Peak Titer (BU)[a]	Outcome	Clinical[b] Significance
Authorization study[c]							
010	18	Severe	192/12	Intron 22 inversion	7.6/20	Recovered	Significant
030	29	Unknown	100/23	Unknown	0.6/0.6 (transient)	Unknown	Not significant
001	2	Severe (<1%)	30/19	Unknown	2/2	Unknown	Unclear
086	29	Severe (<1%)	20/10	Intron 22 inversion	15/15 (transient)	Recovered	Minimal
081	32	Severe	15/8	Intron 22 inversion	12/22	Not recovered	Significant
069	20	Unknown	12/11	Intron 22 inversion	320/320	Unknown	Significant
106	41	Unknown	Unknown/14	Unknown	0.9/0.9	Not recovered	Not significant
Real-world study—On-demand treatment group							
191002	6	Moderate (1–5%)	60/36	NA	16/64	Not recovered	Not significant
041003	5	Moderate (1–5%)	>150/38	NA	2/2 (transient)	Recovered	Not significant
051004	17	Severe (<1%)	>200/28	NA	0.7/0.7 (transient)	Recovered	Not significant
051008	15	Severe (<1%)	>320/32	NA	0.7/0.7 (transient)	Recovered	Not significant
191004	4	Moderate (1–5%)	35/18	NA	1/2	Not recovered	Not significant
191006	4	Moderate (1–5%)	129/29	NA	1/1 (transient)	Recovered	Not significant
Real-world study—Surgical prophylaxis group							
061007	47	Mild (>5–40%)	14/16	NA	1.2/1.2 (transient)	Recovered	Not significant

Notes: [a]High titer was defined as ≥5 BU. [b]Clinical significance was determined by the sponsor and investigator on a case by case basis. [c]The two patients who were inhibitor positive at screening (ie, not a treatment-emergent adverse event) were excluded from this analysis).
Abbreviations: BU, Bethesda unit; ED, exposure days; FVIII, factor VIII; NA, not assessed.

Table 4 Adverse Events, Regardless of Relationship to Study Drug, Reported in the Authorization Study (N = 53; Safety Analysis Set)

Events	No. of Events	Patients	
		n	%
All adverse events	32	19	35.9
Anti-FVIII antibody positive	9	9[a]	17.0
Injury	8	6	11.3
Decreased blood potassium	2	2	3.8
Hypersensitivity	2	1	1.9
Joint sprain	2	1	1.9
Diarrhea	1	1	1.9
Gingival bleeding	1	1	1.9
Upper gastrointestinal hemorrhage	1	1	1.9
Pyrexia	1	1	1.9
Hepatic steatosis	1	1	1.9
Fall	1	1	1.9
Joint dislocation	1	1	1.9
Joint injury	1	1	1.9
Arthritis	1	1	1.9

Note: [a]Two of nine patients who were anti-FVIII positive at screening were excluded from the efficacy and inhibitor rate analyses, but were included in the safety population.
Abbreviation: FVIII, factor VIII.

Table 5 Adverse Events, Regardless of Relationship to Study Drug, Reported by >10% of Patients Overall in the Real-World Study (N = 85; Safety Analysis Set)

Adverse Events, n (%)	On-Demand (n = 73)		Surgical Prophylaxis (n = 14)		Overall (n = 85)[a]	
	N	%	N	%	N	%
Patients with AEs	65	89.0	10	71.4	74	87.1
Joint swelling	34	46.6	3	21.4	37	43.5
Arthralgia	24	32.9	2	14.3	26	30.6
Nasopharyngitis	18	24.7	0	0	18	21.2
Pain in extremity	18	24.7	0	0	18	21.2
Pyrexia	15	20.5	2	14.3	17	20.0
Peripheral swelling	15	20.5	0	0	15	17.6
Muscle swelling	11	15.1	0	0	11	12.9
Cough	10	13.7	0	0	10	11.8
Fall	9	12.3	0	0	9	10.6
Ecchymosis	9	12.3	0	0	9	10.6

Note: [a]Two patients rolled over from the surgical prophylaxis group to the on-demand group and were counted in each group, but were included only once in the overall population.

or moderate disease.[20–23] In both of the current studies, inclusion criteria were broad with respect to several risk factors, including disease severity, age, and prestudy EDs. The overall observed incidence rates of inhibitor development were 13.7% and 8.2% in the authorization and real-world studies, respectively. In the authorization study, the majority (4/7) of events occurred in patients who had not yet reached 50 EDs and were therefore at a higher risk of inhibitor development, of whom 3 also had the high-risk intron 22 inversion mutation.[20,24] Of the three patients with >50 or unknown EDs, two had low-titer inhibitors without clinical significance, while one patient with an intron 22 inversion mutation had a high-titer inhibitor with clinical significance. In the real-world study, five of the seven inhibitors detected were transient, low-titer and without clinical significance. All inhibitor testing in the real-world study was done locally and not confirmed at a central laboratory. Taken together, this calls into question the clinical significance of these transient low-titer inhibitors. Interestingly, the two patients with persistent inhibitors both had moderate severity hemophilia and developed inhibitors after 50 EDs of any FVIII product. The underlying mutation for these two patients is not known. At the last report, neither inhibitor had resolved; however, there were no reported clinical manifestations of the FVIII inhibition. Treatment-emergent AEs in this Chinese population were consistent with the complications of hemophilia (eg, bleeding and joint disorders) and with the established safety profile of moroctocog alfa (AF-CC) in non-Chinese hemophilia patients.[10,14] Nearly all AEs in these studies were mild or moderate in severity. The results of the current two studies add to those of three prospective, open-label studies that evaluated the efficacy and safety of other recombinant FVIII products in Chinese patients with mild, moderate, or severe hemophilia A.[25–27]

The recovery assessments in this study are similar to results previously reported in Chinese children aged 6 to less than 12 years (1.7 [IU/dL]/[IU/kg]; n=3) but lower than results reported for those aged 12 years and older (2.5 [IU/dL]/[IU/kg]; n=10).[28]

These studies were not without limitations, including the open-label design and small sample sizes. Such limitations are inherent given the nature of this rare disease[29,30] and are consistent with those of previous studies assessing the use of recombinant FVIII products in Chinese patients.[25–27] As previously noted, the lack of centralized management of patient records may have confounded accurate documentation of some data (eg, exposure data and inhibitor testing). The challenges associated with data acquisition in rare diseases are based on their small, geographically diverse populations as well as evidence gaps related to the natural history and course of the

disease.[29,30] These studies were robust in their assessment of patients with few restrictions and broad risk factors for inhibitor development, thus potentially providing a comprehensive representation of Chinese hemophilia patients in the usual care setting. Furthermore, the authorization study was designed with a 6-month observation period with a minimum of three inhibitor tests, which represents one of the more extensive and thorough FVIII inhibitor assessments to date in the Chinese population.

Conclusions

These studies demonstrated that on-demand treatment with moroctocog alfa (AF-CC) is a safe and effective option for Chinese patients with hemophilia A. Increasing disease awareness, as well as expanding the accessibility and use of recombinant FVIII therapies, remains an important goal in improving the management of patients with hemophilia A in China.

Abbreviations

ABR, annualized bleeding rate; AE, adverse event; AF-CC, albumin-free cell culture; BU, Bethesda unit; CI, confidence interval; ED, exposure day; FVIII, factor VIII; IV, intravenous; LETE, less-than-expected therapeutic effect; SAE, serious adverse event; SD, standard deviation; WFH, World Federation of Hemophilia.

Data Sharing Statement

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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Author Contributions

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; participated in drafting the article or revising it critically for important intellectual content, with the support of a medical writer provided by Pfizer Inc; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

R. Yang, Y. Zhao, X. Wang, J. Sun, R. Wu, C. Jin, J. Jin, and D. Wu have no interests that might be perceived as posing a conflict or bias. J. Rupon, J. M. Korth-Bradley, and B. Luo, are employees of Pfizer Inc and may own stock/options in the company. F. Huard, P. Rendo, F. Sun, L. Xu, and Y. C. Liu were employees of Pfizer Inc at the time of this study. The authors report no other conflicts of interest in this work.

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