Morocctocog Alfa (AF-CC) for Prophylaxis and Treatment of Bleeding Episodes in Previously Treated Patients with Hemophilia A in India

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Received: 1 June 2022 / Accepted: 19 September 2022 / Published online: 27 November 2022
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Abstract

Purpose Hemophilia A is an X-linked congenital disorder, characterized by factor VIII (FVIII) deficiency. Globally, India has the highest population of patients with hemophilia, and there is a clear unmet need for appropriate and effective treatment for this patient population. This multicenter, open-label, post-approval study evaluated the safety and efficacy of morocctocog alfa in patients with moderate or severe congenital hemophilia A in India.

Methods Intravenous morocctocog alfa was administered 30±5 IU/kg 3 times weekly for bleeding prophylaxis, according to the local product document. Participants were treated for up to 8 weeks, with an up to 4-week screening period and a subsequent post-treatment, 28-day safety observation period. Participants continued in the study until at least 24 exposure days or a period of up to 8 weeks on morocctocog alfa.

Results A total of 50 participants were enrolled, and 48 (85.7%) completed the study. No participants developed FVIII inhibitors during the study. The mean (SD) annualized bleeding rate during morocctocog alfa prophylaxis was 0.79 (2.0) with a median (range) of 0.00 (0.0, 6.8). The mean (SD) annualized total factor consumption (TFC) per participant was 287,432 (93,866) IU; the mean (SD) annualized TFC by weight per participant was 4176 (858) IU/kg. Morocctocog alfa was well tolerated with no reported treatment-emergent adverse event-related dose reductions, discontinuations, or serious adverse events.

Conclusion Morocctocog alfa was safe, effective, and well tolerated in Indian participants with congenital moderate to severe hemophilia A. No participant developed FVIII inhibitors during the study.

Keywords Factor VIII deficiency · Antihemorrhagic · Clinical study · India

Introduction

Hemophilia A is an X-linked congenital disorder, characterized by factor VIII (FVIII) deficiency [1, 2]. Hemophilia A manifests as spontaneous bleeding into the muscles and joints, which, if inadequately managed, becomes painful and destructive to joint architecture [1, 2].

Global survey data from the World Federation of Hemophilia (WFH) indicate that India has the largest population of individuals with hemophilia A worldwide, with 19,690 cases (incidence: 1.4 per 100,000 people) reported in 2020, followed by the United States, with 13,915 cases (4.2 per 100,000 people) [3]. By comparison, the incidence of hemophilia A varies across the Asian region, with 0.8 cases per 100,000 in Indonesia (n= 2214) and 1.1 cases per 100,000 in the Philippines (n= 1155) compared with 2.2 per 100,000...
in Thailand (n=1557) and 3.0 per 100,000 in Malaysia (n=950) [3].

In India, a large proportion of individuals with hemophilia either remain undiagnosed or present for treatment at a late stage, with many cases unregistered. Consequently, the actual prevalence of hemophilia A is probably underestimated, and when individuals are diagnosed, they typically have more severe disease [4]. Based on these data, India carries a disproportionate amount of the global hemophilia A health care burden, signifying an unmet need for appropriate and effective treatment for this patient population. The current standard of care encompasses prophylactic or on-demand treatment with recombinant or plasma-derived clotting factor concentrate, or prophylaxis with a monoclonal antibody, such as emicizumab [1].

For those with moderate or severe hemophilia A, intravenous replacement with exogenous FVIII is typically used to prevent or treat hemorrhage [1]. Treatment for hemophilia accounts for the majority of the overall cost of management, with clotting factor concentrates accounting for more than 86% of direct costs in individuals without inhibitors [5]. High treatment costs are recognized as a barrier for access to treatment. However, the beneficial quality-of-life outcomes associated with prophylaxis are likely to outweigh the cost of treatment [5–7].

Despite the prevalence of hemophilia A, the use of FVIII (both standard and extended half-life products) is much lower in India than in many other parts of Asia and the rest of the world [3]. Recent 2020 WFH estimates for mean per capita FVIII use in 2019 were 0.289 IU/total population in India compared with estimates ranging from 0.622 IU/total population for Thailand to 2.219 in Singapore, 7.105 in the United States, and 9.026 in the United Kingdom [3]. Moroc-tocog alfa (AF-CC) is a third-generation recombinant FVIII produced using advanced manufacturing and purification, and is free of exogenous human- and animal-derived protein [8–11]. It is approved in India for the control and prevention of hemorrhagic episodes and for routine and surgical prophylaxis in participants with hemophilia A (congenital FVIII deficiency or classic hemophilia) [12, 13]. This post-approval study evaluated the safety and efficacy of moroc-tocog alfa in participants with moderate or severe congenital hemophilia A in India.

Materials and Methods

Study Design

This single-country, multicenter, open-label, single-arm interventional study was conducted in India between January 25, 2020, and September 24, 2020. Participants were screened for a period of 4 weeks and then treated for up to 8 weeks post-treatment, followed by a 28-day safety observation period. Participants continued in the study until at least 24 exposure days (EDs) or a period of up to 8 weeks on moroc-tocog alfa (whichever occurred first). Intravenous moroc-tocog alfa was administered 30±5 IU/kg 3 times weekly for bleeding prophylaxis, according to the local product document (LPD). For on-demand treatment, the amount and frequency of administration of moroc-tocog alfa were individually tailored according to clinical assessment.

Participants

Males aged 12 through 65 years with congenital moderate or severe hemophilia A (FVIII activity [FVIII:C] ≤ 5%) and a documented history of at least 50 EDs to FVIII-containing products were included. Participants were excluded if they had a prior history of FVIII inhibitors or positive inhibitor testing (≥ 0.6 Bethesda unit [BU]/mL) during screening, had any bleeding disorder other than hemophilia A, were immunocompromised with HIV, had planned surgery within 6 months of the study initiation, or participated in other studies involving other investigational drugs within 30 days of study initiation.

End Points

The safety end points were FVIII inhibitor development (≥ 0.6 BU/mL), as confirmed by central laboratory testing (primary end point), and treatment-emergent adverse events (TEAEs), including the incidence of serious adverse events (SAEs), classified according to the Medical Dictionary of Regulatory Activities (MedDRA) v23.1; TEAEs were monitored from the first dose of study drug until treatment end date plus 28 days. Efficacy end points included the annualized bleeding rate (ABR) calculated based on bleeding events that required on-demand infusion with moroc-tocog alfa while receiving moroc-tocog alfa as prophylaxis, annualized total factor consumption (TFC) in IU/kg and by weight (IU/kg), and number of moroc-tocog alfa infusions required to treat each new bleeding episode.

Statistical Analysis

Participants who received at least 1 dose of moroc-tocog alfa were included in the safety analyses. Adverse events (AEs) were summarized using descriptive statistics. Those who received at least 1 dose of moroc-tocog alfa and had evaluable data for the corresponding end point were included in the efficacy end point analyses; data were summarized using descriptive statistics. The primary endpoint for this study was the proportion of subjects for which FVIII inhibitors...
were detected at visit 4. Because of the size and nature of this study, a 2-sided 90% confidence interval (CI) was chosen for the corresponding proportion, which was computed using the exact method. For annualized TFC by weight, dose by weight was summed per subject then annualized, i.e. (total units by weight / treatment interval duration) \times 365.25, and then used for descriptive statistics calculation. Post hoc analyses computed the proportion of participants who had no treated bleeding events during the prophylaxis period; 95% CIs were calculated, applying the exact method.

Some participants missed moroctocog alfa doses during the study owing to COVID-19 restrictions; bleeding events that may have occurred while participants were not receiving moroctocog alfa prophylaxis were not included in the ABR calculations.

Results

Study Population

Of 56 screened participants, 50 were enrolled; of these, 48 (86%) participants completed the study. Two participants (4%) were discontinued during the open-label treatment period: 1 participant withdrew consent during treatment, and 1 completed treatment but did not return for an end-of-treatment evaluation because of COVID-19. All 50 enrolled participants were males of Indian Asian origin, with a mean (standard deviation [SD]) age of 29.6 (9.8) years (Table 1). The mean (SD) number of previous FVIII EDs was 171.5 (240.4) days. A total of 24 (48%) participants had a family history of hemophilia. The majority (49/50, 98%) of participants had no family history of inhibitors to FVIII products. Factor mutation was not classified in any participants, and no participants had a history of inhibitors or allergy to FVIII products.

The total mean (SD) treatment interval duration was 68.2 (26.3) days (median [range]: 59.5 [45.0, 183.0]). The total mean (SD) EDs per participant during the study was 23.9 (0.6) days (median [range]: 24.0 [20.0, 24.0]), and the mean (SD) EDs per participant for prophylaxis was 23.8 (0.6) days (median [range]: 24.0 [20.0, 24.0]). FVIII other than morocrocog alfa was received by 22 (44%) participants for the treatment of bleeding episodes that occurred during follow-up. Because of COVID-19 restrictions, 1 participant received nonstudy treatment during the treatment period for a bleeding event, per investigator discretion.

Safety

Three (6%) participants experienced 6 TEAEs (Table 2). All cases were mild in severity, and none were considered by the investigators to be related to moroctocog alfa. One participant reported an AE of arthralgia during the follow-up period, which was not treatment-emergent. No TEAE-related dose reductions, discontinuations, and SAEs were reported.

Clinical Outcomes

No participants developed FVIII inhibitors (≥0.6 BU/mL) during the course of the study, as confirmed by central laboratory testing. The upper and lower bounds of the 2-sided 90% CI for the proportion of participants for which FVIII inhibitors were detected at visit 4 were 0.00% and 0.06%, respectively, confirming that the likelihood of a participant developing FVIII inhibitors is <0.1%. A total of 7 (14%) participants reported a single bleeding event (5 [10%] spontaneous and 2 [4%] traumatic) each requiring a single
All but 1 of the 77 bleeding episodes that occurred during the follow-up period (after the end-of-treatment visit) were spontaneous, and most were treated with other FVIII treatment given on the same day, or 1 day after the bleeding on-demand moroctocog alfa infusion (Table 3). The mean (SD) ABR during moroctocog alfa prophylaxis was 0.79 (2.0) with a median (range) of 0.00 (0.0, 6.8).

A post hoc analysis showed that during prophylaxis, 42/50 (84%) participants had no bleeding episodes that required treatment. Seven participants each had 1 bleeding episode that was treated with moroctocog alfa. One participant had a bleeding event and received nonstudy treatment during the treatment interval duration owing to COVID-19 restrictions. Participants are counted only once per treatment per event.
event. During the treatment period, 7 participants had a bleeding event (1 each), but none of them discontinued prophylaxis. The mean (SD) annualized TFC per participant was 287,432 (93,866) IU; the mean (SD) annualized TFC by weight per participant was 4176 (858) IU/kg (Table 3).

Discussion

This phase 4 study confirms the safety and efficacy of moroctocog alfa in Indian participants with moderate to severe hemophilia A receiving prophylaxis with moroctocog alfa for 8 weeks, which corresponded to a minimum of 24 EDs. Moroctocog alfa was generally well tolerated, with only 4 (8%) participants reporting an AE, of which 3 (6%) were treatment-emergent AEs. All AEs were mild, and none were considered related to treatment. No participant developed FVIII inhibitors (≥0.6 BU/mL), as confirmed by central laboratory testing.

Among participants receiving moroctocog alfa for a duration of 8 weeks, the mean ABR was <1 (0.79). All 7 bleeding episodes observed during the study and included in the analysis were effectively managed with a single on-demand infusion of moroctocog alfa. Of note, 24 participants were receiving on-demand treatment prior to enrollment and initiation of short-term prophylaxis in this study; despite this, no participant developed inhibitors, and few experienced bleeding events while receiving prophylaxis with moroctocog alfa.

There is a clear unmet need for effective prophylactic regimens in India, which has the largest number of participants with hemophilia A globally but with relatively low per capita use of FVIII treatment [3]. In the current study, moroctocog alfa was effective for the control and prevention of hemorrhagic episodes, with a mean ABR of less than 1.0 observed, and a single on-demand infusion successfully treated participants who experienced a bleeding event.

Further analyses to determine whether a reduction in the number of bleeding events, along with the consequent reduction in the need for on-demand infusions, could potentially diminish overall health care burden and enhance patients’ quality of life would be beneficial. In addition, further study is required to determine whether transition from an on-demand regimen to a prophylaxis regimen could allay concerns regarding bleeding risk, and potentially lead to an increase in FVIII activity levels and a decrease in bleeding events. The relatively short 8-week duration of the current study did not allow for long-term collection of meaningful data on the efficacy of bleeding event prevention and quality-of-life outcomes. Nevertheless these findings provide valuable insight on the efficacy of moroctocog alfa in an Indian population with hemophilia A.

In conclusion, moroctocog alfa was safe and effective in Indian participants with congenital moderate to severe hemophilia A. No participant developed FVIII inhibitors during the study, and the safety data were consistent with the known safety profile of moroctocog alfa. Moroctocog alfa was effective for controlling and preventing hemorrhagic episodes when used according to the LPD.

Acknowledgements

Medical writing support was provided by Anna Batterhill, MSc, and Michael Morren, RPh, MBA, of Peloton Advantage, an OPEN Health company, and Marion James, PhD, of Engage Scientific Solutions, and was funded by Pfizer Inc.

Author’s contribution

Principal investigator: Nirmalkumar Choraria. Study investigators: Savita Rangarajan, M. Joseph John, and Shashikant Apte. Enrollment of patients: Nirmalkumar Choraria, Savita Rangarajan, M. Joseph John, and Shashikant Apte. Collection and assembly of data: Nirmalkumar Choraria, Savita Rangarajan, M. Joseph John, and Shashikant Apte. Data analysis: Pritam Gupta. Data interpretation, manuscript review and revisions, and final approval of manuscript: all authors.

Funding

This study was sponsored by Pfizer Inc.

Data Sharing Statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Declarations

Competing Interests

Nirmalkumar Choraria and Shashikant Apte have no conflicts to disclose. Savita Rangarajan has served on advisory boards for Pfizer and Sanofi Sigilon; on speakers’ bureaus for Pfizer and Takeda; and as a consultant for Reliance Life Sciences. M. Joseph John has received honoraria as a speaker/consultant and/or advisory board member, and has received research grants for attendance at educational meetings from Dr Reddy’s Lab, Grifols, Janssen, Mylan, Novo Nordisk, Pfizer, Roche, and Takeda. Pritam Gupta, Shyam Parvatini, Rohit Chand, Seema Pai, G. S. H. Ramakanth, Jeremy Rupon, Chhabra Amit, Hitesh Bhaskarroy Muley, and Damien Simonceau are employees of Pfizer Inc. and may own stock/options in the company.

Ethical Approval

The final protocol, amendment and informed consent documentation were reviewed and approved by the IRB/EC at each of the investigational centers participating in the study. Investigators were required to inform their IRBs/ECs of the study’s progress and occurrence of any serious and/or unexpected adverse events.

Informed Consent

Written informed consent was provided by all participants or their parents/guardians.

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