ORIGINAL ARTICLE

A prospective, multicenter, clinical Study to evaluate the Safety, Pharmacokinetics, and Efficacy of Bleed Outcomes, with HemoRel-A® in severe Hemophilia A Patients

Mayur Mewada[1], Subhaprakash Sanyal[2], Savita Rangarajan[3,4], Prasad Apsangikar[5*], Ajay Kumar Yadav[6], Manoj Naik[7], Santosh Nair[8]

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Abstract

Purpose: To evaluate efficacy for an on-demand treatment of acute bleeding events, pharmacokinetics, safety, and tolerability of HemoRel-A® in severe hemophilia A.

Methods: A total of 44 male subjects with severe hemophilia A with an annualized bleed rate of 12 while on-demand treatment with factor VIII (FVIII) were enrolled in the study and received HemoRel-A® for bleed treatment. The efficacy of HemoRel-A® was evaluated based on a four-point scale (excellent, good, moderate, or none). Six-point pharmacokinetic (PK) assessment was performed following a single dose of 50 IU/kg in 12 subjects after a 7-day wash-out period. Safety evaluations were performed at each visit and inhibitor testing was performed in all patients at screening and end of study.

Results: Forty-four male subjects received at least a single dose of the study medication and were included in the intent-to-treat (ITT) analysis and safety outcome. In 23 (7.52%) out of the 306 bleeding events, HemoRel-A® efficacy was rated as excellent, in 272 (88.89 %) bleeds it was rated as good, and in 11 (3.68%) bleeding events it was rated as moderate. No failure of efficacy was noted in any of the bleeding events. Thus overall out of 306 bleeding events, 295 (96.41%) showed excellent or good efficacy. Pharmacokinetic assessment based on plasma FVIII activity measured by the chromogenic assay in 12 patients showed comparative results similar to FVIII preparations. A total of 12 adverse events (AEs) were reported in this study. There was no inhibitor development in this previously treated patients (PTP) cohort.

Conclusion: HemoRel-A® was established to be efficacious and safe in the treatment of acute bleeding events in subjects with severe hemophilia A.

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Introduction

Hemophilia A is a congenital, X-linked bleeding disorder with a prevalence of 1 in 5,000 male live births. If not treated adequately, frequent bleeding into joints leads to crippling arthropathy and impaired quality of life. Treatment with exogenous FVIII, using either plasma-derived or recombinant FVIII concentrates, restores normal hemostasis, and improves health and lifestyle of hemophilia patients.[1] Prophylaxis is widely recommended for the treatment of severe hemophilia A.[1] Secondary prophylaxis encompasses prophylactic treatment of children, adolescents, and adults with established progressive arthropathy.[1] Although earlier start of prophylaxis results in better joint status, secondary prophylaxis can reduce the number of bleeds and reduce the risk of serious bleeds, delay joint damage, improve functional capacity and quality of life, and reduce pain.[1] The most important and often life-threatening side-effect of hemophilia treatment currently is high risk of developing neutralizing antibodies. The risk appears to be even more serious when using recombinant FVIII products, as revealed by recent clinical studies highlighting an immunogenicity risk that was twice as high with some recombinant FVIII products than with some plasma-derived products.[2] The recently published Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) study concluded that the risk of inhibitors was higher with recombinant products as compared to von Willebrand factor (VWF) containing FVIII.[3] As a large number of patients were recruited from the Indian subcontinent, the results are even more relevant to the Indian context.[3] Experience with country like Slovakia in the treatment of previously untreated patients with severe hemophilia A showed 14% inhibitor formation after plasma-derived FVIII and 67% after recombinant FVIII products.[4]

Bioengineered FVIII variants, including current extended half-life (EHL) products are still regulated to a large extent by interaction with VWF. Therefore, half-life of VWF is the limiting factor to half-life extension of FVIII with techniques available today. All approaches described above achieve only moderate increase of half-life.[5] The World Federation of Hemophilia does not express a preference for recombinant over plasma-derived concentrates.[6] Development of neutralizing antibodies against replacement agents administered to prevent or treat various clinical conditions is a longstanding and growing problem faced by patients and medical providers.[7]

The present study was undertaken as a postmarketing evaluation of an indigenous plasma-derived FVIII for establishing safety, efficacy, bleeding events, and pharmacokinetics with HemoRel-A® in patients with severe hemophilia A on episodic treatment regimen.

Methods

Study Design and Patients

The study was done as a prospective, multicenter, clinical study to evaluate the efficacy, safety, and PK of HemoRel-A® in severe hemophilia A patients. The study was conducted in compliance with the ethical principles that originated in the Declaration of Helsinki and ICH-GCP protocol, DCGI, and

[1]Assistant Professor, Department of Medicine, KJ Somaiya Medical College, Hospital and Research Centre; [2]Consultant Hematologist and Hemato-Oncologist, Fortis Hospitals Limited, Mumbai, Maharashtra, India; [3]Faculty of Medicine, University of Southampton, United Kingdom; [4]KJ Somaiya Super Speciality Hospital, Clinical Trial Unit, Mumbai; [5]Head, Department of Medical Affairs and Pharmacovigilance; [6]Head, Department of Clinical Research; [7]Head Pharmacovigilance; [8]Divisional Medical Head, Reliance Life Sciences Pvt. Ltd., Navi Mumbai, Maharashtra, India; *Corresponding Author

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Schedule Y and/or New Drugs and Clinical Trials Rules, 2019. The study was initiated at the sites only after obtaining approval from the EC in writing for the study protocol and other study documents. Similarly, all amendments, except those involving administrative changes, were submitted to the respective EC for approval prior to implementing the changes.

Immunocompetent (CD4 lymphocytes >200/μL) male subjects aged between 18 and 65 years (both inclusive) with severe hemophilia A (documented FVIII levels <1%) with history of >12 bleeding events in past 12 months, who were receiving on-demand treatment were included. Number of exposure days (ED) before inclusion was >50 ED. Subjects with history of inhibitors to FVIII, having inherited or acquired bleeding disorder or any major illness were excluded.

Study Treatment

Patients were treated for acute bleeds as per predefined criteria based on site of bleeding, body weight, and the clinical status of the patient. Doses and dose intervals were adapted as per site of hemorrhage. Patients did not receive any FVIII product for at least 7 days prior to the bleeding episode. Factor VIII activity in plasma was expressed either as a percentage (relative to normal human plasma) or in IU (relative to an international standard for FVIII in plasma). The study duration for each subject varied depending on the occurrence of bleeding events.

Outcome Measures

Primary objective of the study was to evaluate efficacy of HemoRel-A® for an on-demand treatment of acute bleeding events and secondary objective(s) was to evaluate PK, safety, and tolerability of HemoRel-A®. Response of acute bleeding events to treatment based on a four-point scale (excellent, good, moderate, or none) was kept as the primary end-point (Table 1). The details of bleeding events were captured based on type and location of bleeds. Doses and dose intervals were adapted as per site of hemorrhage. The details of bleeding events and consumption of FVIII were documented.

Subjects were monitored for bleeding events (muscle or joint bleeds) during the study in order to have evaluable data of at least 300 bleeds. Subjects were treated for acute bleeds (bleeds <24 hours old) as per predefined criteria based on site of bleeding, body weight, and the clinical status of the patient.

Two bleeding events at the same anatomical site were considered as separate events if they occurred at least 2 weeks apart. Bleeding at different anatomical sites was considered as separate bleeding events. Therapeutic response to traumatic and spontaneous bleeding events was evaluated in this study.

The secondary end-points included evaluation of safety with physical examination, vital signs, AEs, abnormal laboratory parameters, and immunogenicity (baseline and end of study). Pharmacokinetic assessments by chromogenic assay were done for the FVIII concentrate.

Pharmacokinetic assessment was performed based on plasma FVIII activity measured by the chromogenic assay[8] in 12 out of 44 patients participating in the study after a 7-day wash period. Blood samples were taken at preinfusion (within 15 minutes prior to infusion), and at 10 minutes, 30 minutes, 1, 3, 6, 9, 24, 28, 32 and 48 hours postinfusion. The PK parameters included incremental recovery, *in vivo* half-life, area under the curve (AUC), and clearance. Incremental recovery was determined as the peak level recorded in the first hour after infusion and reported as [IU/mL]/[IU/kg]. Safety evaluations were performed at each visit to the study center with evaluation of physical examination, vital signs, AEs, and abnormal laboratory parameters. Inhibitor testing was performed in all patients at screening and end of study.

Table 1: Assessment of response of acute joint/muscle bleeding episodes to treatment category[9]

Category	*Response*
Excellent	Complete pain relief within 8 hours and/or complete resolution of signs of bleeding after the initial injection and not requiring any further replacement therapy for relief of persistent symptoms and signs in the same joint within 72 hours.
Good	Significant pain relief and/or improvement in signs of bleeding within approximately 8 hours after a single injection, but requiring more than one dose of replacement therapy within 72 hours for complete resolution.
Moderate	Modest pain relief and/or improvement in signs of bleeding within approximately 8 hours after the initial injection and requiring more than one injection within 72 hours but without complete resolution.
None	No or minimal improvement, or condition worsens, within approximately 8 hours after the initial injection.

Statistical Analyses

Objective of the study was to evaluate at least 300 bleeds. Statistical analysis of HemoRel A® was performed on the PK parameters by using Pharsight Phoenix WinNonLin® version 8.0 or higher. Response of acute bleeding events to treatment was based on a four-point scale (excellent, good, moderate, or none) for evaluation. Doses and dose intervals were adapted as per site of hemorrhage.[9] The details of bleeding events and consumption of FVIII were documented. The incidence of AEs occurring during the study will be summarized by preferred term and body system for each treatment group.

Results

Subject Disposition

A total of 44 subjects were enrolled in this study. All 44 subjects received at least single dose of the study medication, hence 44 subjects were included in the ITT and safety modified ITT (mITT) population. Out of 44 subjects, one subject participated only in PK assessment and did not contribute to the efficacy assessment. The remaining 43 subjects were included in the per-protocol population for the analysis. All 12 subjects were considered for the PK assessment. Four subjects (9.00%) had early termination due to noncompliance and four subjects were lost to follow-up. All the 44 subjects included in ITT were male subjects. The mean age of these subjects was 28.27 (± 8.23) years, mean weight

Table 2: Subject disposition

Variable	*HemoRel-A® (N = 44)*
Safety population	44
ITT population	44
Per-protocol population	43
Study completed	40 (90.91%)
Early termination	4 (9.09%)
Reason for discontinuation	
The subject was noncompliant with protocol specifications	0 (0.00%)
The subject was erroneously included in the study	0 (0.00%)
AEs	0 (0.00%)
The investigator feels it is in the subject's best interest to be withdrawn	0 (0.00%)
The study is terminated by the sponsor	0 (0.00%)
Lost to follow-up	4 (9.09%)
The subject withdrew consent	0 (0.00%)
Subject death	0 (0.00%)
Other	0 (0.00%)

was 65.01 (± 15.95) kg, while mean body mass index was 23.71 (± 5.79). The details of the patient disposition are shown in Table 2.

Efficacy and PK Analysis

The efficacy of HemoRel-A® was evaluated based on the response of acute bleeding events to treatment on a four-point scale (excellent, good, moderate, or none). There were 306 acute bleeding events, including 299 episodes of muscle and joint bleeds, six episodes of mucosal bleeds, and one episode of traumatic bleeding. The response to HemoRel-A® in these bleeding events is presented in Table 3.

Overall, out of 306 bleeding events, in 23 (7.52%) bleed events HemoRel-A® showed excellent efficacy, in 272 (88.89 %) bleeding events it showed good efficacy, in 11 (3.59%) bleeding events it showed moderate efficacy, and in none of the bleeding events it failed to show any efficacy. Thus overall out of 306 bleeding events, in 295 (96.41%) HemoRel-A® showed excellent or good efficacy. There were 299 cases of muscle or joint bleed events, out of which in 23 (7.69 %) bleed events it showed excellent efficacy, in 265 (88.63%) bleed events it showed good efficacy, in 11(3.68%) events it showed moderate efficacy while in none of the bleeding events it failed to show any efficacy. There were six cases of mucosal bleed events and one case of traumatic bleeding event, where it showed good efficacy. All 12 subjects completed the PK assessment. After administration of 50 IU/kg HemoRel-A®, the mean C_{max} was 59.103 IU/dL, AUC_{0-t} was 606.136 IU hr/dL, the median T_{max} was 0.5 hours, the half-life was 15.603 hours which matches that of EHL products. The incremental recovery of C_{max} was 0.012 [IU/mL]/[IU/kg]. The mean linear graph for the FVIII concentration levels is presented in Figure 1.

Safety and Immunogenicity Analysis

In this study, all 44 subjects received at least one dose of the study medication as per study protocol. Hence all 44 subjects were considered for the safety analysis. A total of 323 infusions of HemoRel-A® were administered to 44 subjects. The mean total dose received by each subject per infusion was 2036.38 IU, corresponding to dose of 31.94 IU/kg for each infusion. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 21.0. Adverse event with a relationship to study medication as definite, probable, or possible were termed as "related." Adverse events, and which were not related, or unlikely related to the study medication were termed as "unrelated." Adverse events for which the causality was not known or could not be assessed were termed as "unknown." In this study, a total of 12 AEs were reported. There were four (9.09%) subjects who had atleast one AE. There were two (4.55 %) subjects with at least one AE related to study medication. No serious AEs were reported in this study. No deaths were reported in this study. No subject was discontinued due to AE. Table 4 shows the summary of AEs observed in the study population.

The most common AEs were pyrexia [3 (6.82%) 4], chills [2 (4.55%) 3], and pain in extremity [1 (2.27%) 2]. According to system organ class, the most commonly reported treatment-emergent (TE) AEs were related to general disorders and administration site conditions [4 (9.09%)], musculoskeletal and connective tissue disorders [1 (2.27%)], and nervous system disorders [1 (2.27%)].

There were nine TEAEs reported belonging to general disorders and administration site, affecting four (9.09%) subjects, including pyrexia, chills, asthenia, and pain. There were two TEAEs reported belonging to musculoskeletal and connective tissue disorders, affecting one (2.27%) subject, both subjects suffered from pain in extremity. There was one TEAE reported belonging to nervous system disorders affecting one (2.27%) subject (headache). Out of 12 TEAEs only four were possibly related to the study drug, remaining eight TEAEs were unrelated to the study drug. All the TEAEs (12) were mild in severity. All TEAEs were resolved without any sequel.

Immunogenicity assessment was performed using Nijmegen–Bethesda modification method. Blood samples were collected for measurement of inhibitor at screening and end of study. The samples with ≥0.4 Nijimegen–Bethesda units antigen level after processing, were considered to be positive for inhibitor. A total of 33 samples were analyzed at the end of study for the development of inhibitor. Only one of these samples was found to be positive for the inhibitor at the end of study. The subject with positive inhibitor result was further assessed for any impact on safety or efficacy of the drug. The subject consistently responded

Table 3: Summary of efficacy response to bleed events

Variable	*Number of episodes*	*Excellent*	*Good*	*Moderate*	*None*
Overall	306	23 (7.52%)	272 (88.89%)	11 (3.59%)	0 (0.00%)
Muscle/joint bleed	299	23 (7.69%)	265 (88.63%)	11 (3.68%)	0 (0.00%)
Mucosal bleed	6	0 (0.00%)	6 (100.00%)	0 (0.00%)	0 (0.00%)
Traumatic	1	0 (0.00%)	1 (100.00%)	0 (0.00%)	0 (0.00%)

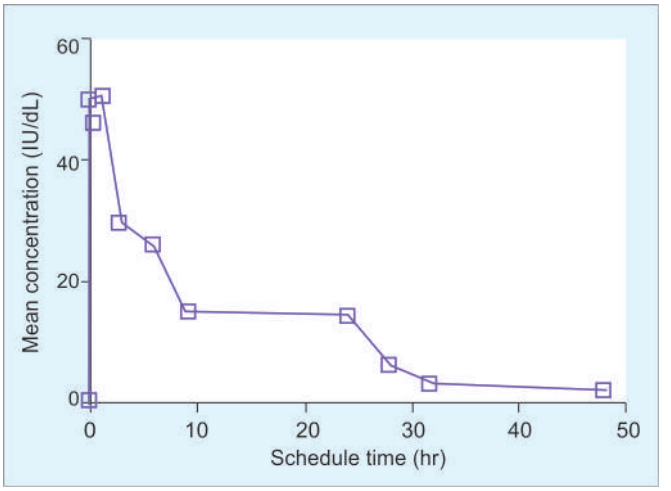

Fig. 1: Mean linear graph for FVIII concentration against time

Table 4: Overall summary of AEs (ITT population)

Variable	*HemoRel-A® (N = 44) n (%) E*
Subjects with AEs	
At least one AE	4 (9.09%) 12
At least one TEAE	4 (9.09%) 12
At least one TEAE related to study drug	2 (4.55%) 4
At least one TE severe AE	0 (0.00%) 0
At least one TE serious AE	0 (0.00%) 0
Death	0 (0.00%) 0
Subjects discontinued due to TEAE	0 (0.00%) 0

well to the treatment throughout the study and did not report any AE. There were no observations related to any loss of efficacy over period of time. There were no reports of any major immunologically mediated reactions to the drug administration. Thus, HemoRel-A® administration did not raise any concerns related to its immunogenicity during this study.

Discussion

Patients with severe hemophilia A (FVIII coagulant activity < 0.01 IU/mL) suffer from repeated and spontaneous bleeding episodes mainly within muscles and joints, resulting in disabling musculoskeletal damage and chronic arthropathy. Prophylaxis with FVIII concentrate is a widely accepted treatment for severe hemophilia A patients in order to prevent spontaneous bleeding and subsequent joint damage.[10] However prophylaxis is not widely used in India due to cost constraints. Most patients are on episodic therapy for bleeds. This study evaluated the outcome of bleed treatment using HemoRel-A® based on the response of acute bleeding events to treatment on a four-point scale (excellent, good, moderate, or none). Overall out of 306 bleeding events, 295 (96.41%) showed excellent or good efficacy. The efficacy response remained consistent over multiple bleeding events experienced by the subjects. Similar efficacy responses were noted in the literature, Mahlangu et al.[11] and Konkle et al.[12] In the PK assessment, the $t_{1/2}$ (half-life) was 15.603 hours with a maximum range of 31.298, which can be said to be comparable to modern EHL products which were shown to have range of half-life between 14.3 and 19 hours in one of the comparative literature.[13] It is plausible that given the similarity in PK data with EHL products the efficacy of this product for prophylaxis use maybe similar to EHL products but this needs to be tested in a separate clinical trial setting. All the AEs were mild and resolved completely without any sequelae. No Factor VIII inhibitors were noted in these previously treated patients.[14]

Based upon above $t_{1/2}$, efficacy and safety results, it can be concluded that HemoRel-A®, the purified FVIII preparation marketed by Reliance Life Sciences Pvt. Ltd. is an efficacious and safe alternative for the bleed treatment for Hemophilia-A and is comparable to modern FVIII preparations. In comparison with literature, the half-life in PK analysis and majority of subjects showing excellent or good efficacy in bleeding events were seen as well matching with the data of EHL products.

Orcid

Savita Rangarajan https://orcid.org/0000-0001-7367-133X
Prasad Apsangikar https://orcid.org/0000-0001-7111-5380

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