Phase I/II, open-label, multicenter, safety, efficacy and PK study of a recombinant coagulation factor IX albumin fusion protein (rIX-FP) in subjects with hemophilia B

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ABSTRACT

Recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) is a novel recombinant albumin fusion protein designed to extend the half-life of recombinant factor IX (rFIX), which is used in the management of hemophilia B. Clinical evaluation of rIX-FP in humans is underway, including a recently completed phase I/II, open-label, multicenter, study that assessed the safety, pharmacokinetics, and efficacy of rIX-FP in patients with severe hemophilia B. A total of 17 patients received rIX-FP (25 IU/kg) as either on-demand therapy (n = 4) for 20 weeks or weekly prophylaxis (n = 13) for up to 44 weeks. Preliminary results confirm that rIX-FP has an excellent safety profile and a pharmacokinetic profile highlighted by a marked extended half-life, suggesting that weekly prophylaxis with rIX-FP at a dose of 25 IU/kg may be appropriate in patients with severe hemophilia B, and that extended dosing intervals (10–14 days) may be feasible in some patients. A phase II/III study evaluating the safety and efficacy of rIX-FP in patients with hemophilia B is underway.

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Hemophilia B is a severe bleeding disorder that arises from deficiency or dysfunction of coagulation factor IX (FIX), a protein with a molecular weight of approximately 57 kDa that plays a critical role in coagulation. FIX is activated by either activated factor XI or the combination of activated factor VII and tissue factor [1]. Activated FIX then forms an integral part of the tenase enzyme complex that activates factor X. Loss of FIX results in spontaneous and uncontrolled bleeding episodes that, in some cases, can be life-threatening.

The management of hemophilia B includes replacement treatment with FIX administered either at the start of a bleed (on-demand therapy), at regular intervals to prevent development of bleedings (primary prophylaxis), or before activities with increased risk of bleeding (secondary prophylaxis). The advantages of prophylaxis in terms of joint preservation, reduction in life-threatening bleedings, including intracranial bleeds, marked improvement in quality of life, including the ability to conduct an almost normal lifestyle, is well established [2–4]. Currently available FIX products used to treat hemophilia B, including plasma-derived (pdFIX) and recombinant (rFIX) concentrates, have a relatively short half-life, requiring frequent intravenous infusions two or three times per week to achieve adequate prophylaxis [5–7].

Advances in recombinant DNA technology have enabled scientists to design novel proteins with improved function over the naturally occurring proteins. One example of this technology is the development of fusion proteins, which are created by fusion of two genes to produce a novel gene that is expressed as a single polypeptide that retains the properties of both the original gene products. This technology has been used to extend the half-life of rFIX by fusing it to albumin, a naturally occurring and well-characterized protein with a long half-life. In animal models, the novel recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) has been shown to have a half-life that is 2- to 4-fold longer than that of rFIX, and with comparable hemostatic efficacy [1,8,9]. The improved pharmacokinetic (PK) properties of rIX-FP suggest that adequate bleeding prophylaxis may be achieved with less frequent dosing, thereby improving the convenience of therapy and quality of life for patients with hemophilia B. As part of the clinical development program for rIX-FP, a phase I/II, open-label, multicenter, study (PROLONG-9FP; NCT01361126) was conducted to evaluate the safety, PK profile, and efficacy of rIX-FP in patients with severe hemophilia B [10]. The trial design and preliminary results of this study are reported here.

Study design

The primary objective of this phase I/II study was to determine the safety of rIX-FP when given as on-demand therapy or prophylaxis for patients with hemophilia B. Secondary objectives included PK assessment of rIX-FP 25 IU/kg over a 10–14-day treatment period, and the clinical response to weekly prophylaxis with rIX-FP. The study was conducted at two centers: one in Bulgaria and the other in Israel.

Abbreviations: AE, adverse event; AUC, area under the curve; EOS, end of study; FIX, factor IX; IR, incremental recovery; pdFIX, plasma-derived FIX; PK, pharmacokinetic; rFIX, recombinant factor IX; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; ULN, upper limit of normal.

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Results

Patient characteristics

A total of 17 patients were enrolled in the study. Of these patients, four received on-demand therapy at a center in Bulgaria (all had received on-demand treatment prior to study entry) and 13 received prophylaxis at a center in Israel (10 had received prophylaxis and three had received on-demand treatment prior to study entry). Patient characteristics are listed in Table 1.

Clinical response and PK parameters

Efficacy is currently under evaluation, but preliminary results are promising. All 13 prophylaxis subjects were maintained on weekly prophylaxis with rIX-FP throughout the study, and all bleeding episodes that occurred in the on-demand group were successfully treated with rIX-FP to achieve hemostasis.

PK data are also currently under analysis, but preliminary results suggest marked improvements in half-life, IR, AUC, and clearance. The baseline-corrected FIX activity after rIX-FP infusion 25 IU/kg can be seen in Fig. 2, which overlays the data derived from the current study with that of the phase I study [11,12]. This shows that the data from the current study are consistent with those achieved in the seven patients in the 25 IU/kg cohort included in the phase I study. Notably, mean FIX activity was 4.4% on Day 7 in the current study.

In Fig. 3, the mean baseline-corrected FIX activity achieved with 25 IU/kg rIX-FP infusion in the current study is compared with FIX activity after a 50 IU/kg dose of either rFIX or pdFIX, as determined in the prior phase I study [11,12]. The data indicate that the 5% threshold for FIX activity was crossed much sooner with rFIX or pdFIX (after 48 hours) than with rIX-FP, despite the higher doses given.

Four of the 17 patients in the current study did not have a PK analysis: two patients had a PK analysis during the prior phase I study; one patient bled during the PK analysis and required additional factor treatment; and in one patient, there was a technical problem with the laboratory samples. Individual PK parameters for the current study are not yet available, but are expected to be consistent with those achieved in the phase I study [11,12].

Safety

The current safety analysis is based on more than 600 exposure days to rIX-FP. We found that rIX-FP has an excellent safety profile. Approximately 40 AEs were reported, but none were considered related to rIX-FP treatment. No serious AEs were reported. There

Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients, n (%)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>Race – Caucasian, n (%)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>26</td>
</tr>
<tr>
<td>Range</td>
<td>13–46</td>
</tr>
<tr>
<td>Number of patients aged 13–18 years, n (%)</td>
<td>5 (29)</td>
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<tr>
<td>Body weight, kg</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>64</td>
</tr>
<tr>
<td>Range</td>
<td>36–95</td>
</tr>
<tr>
<td>Total factor IX exposure days</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>815</td>
</tr>
<tr>
<td>Range</td>
<td>415–1450</td>
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<tr>
<td>Viral infections, n (%)</td>
<td></td>
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<tr>
<td>Hepatitis C</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1 (6)</td>
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</tbody>
</table>
was no evidence of hypersensitivity reactions, and none of the 17 patients developed inhibitors to FIX. There were no withdrawals from the study.

Conclusions and future directions

In this phase I/II study, rIX-FP has demonstrated an excellent safety profile during 6–10 months of use. Preliminary PK results are consistent with those from the previous phase I study of rIX-FP. Clinical response data suggest that weekly prophylactic treatment with rIX-FP may be appropriate in patients with severe hemophilia B and that some patients may enjoy extended effective prophylactic treatment at intervals of 10–14 days.

Eligible patients who have completed this study will be enrolled in an ongoing phase II/III trial of rIX-FP (NCT01496274). The end-of-study visit for the phase I/II study will be combined with screening for enrollment in the phase II/III study. The design of the phase II/III study is shown in Fig. 4. This study will assess the safety, efficacy, and PK of rIX-FP when given as on-demand therapy or prophylaxis in patients with hemophilia B who have previously received coagulation factor replacement therapy. On-demand patients will receive treatment as needed for the first 6 months and then switch to weekly prophylaxis for 6 months. Prophylaxis patients will receive weekly rIX-FP for 6 months, and may subsequently switch to a longer dosing interval (i.e. every 10–14 days) for an additional 6 months. In both groups, patients will have the option to participate in a surgical substudy, which will assess the safety and efficacy of rIX-FP when given before, during, and after surgical intervention. The primary endpoints of the study are the change in the frequency of spontaneous bleeding events between on-demand and prophylactic treatments and the number of patients who develop inhibitors to FIX over a 12-month period. Secondary endpoints include the following:

- the proportion of bleeding episodes requiring one or two infusions of rIX-FP to achieve hemostasis
- the investigators’ overall assessment of hemostatic efficacy
- treatment-related AEs
- the number of patients who develop antibodies against rIX-FP
- PK parameters (half-life, IR, AUC, and clearance).
Results of this ongoing study will help further define the safety and PK profile of rIX-FP as well as the potential benefits of rIX-FP in the management of hemophilia B.

**Conflict of interest**

The author received research support from CSL Behring to conduct the study, for lecture fees and honoraria for consultancy.

**Role of the funding source**

The funding source provided support for the symposium.

**References**


