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ORIGINAL ARTICLE

Pharmacokinetic, efficacy and safety evaluation of B-domain-deleted recombinant FVIII (SCT800) for prophylactic treatment in adolescent and adult patients with severe haemophilia A

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Abstract

Introduction: SCT800 is a recombinant human B-domain-deleted coagulation factor VIII (BDDrFVIII) developed in China.

Aim: To evaluate the repeat pharmacokinetics (PKs), efficacy, and safety of SCT800 in previously treated Chinese adolescent and adult patients with severe haemophilia A.

Methods: A phase III, multicentre, prospective, open-label, single-arm trial was conducted at 12 medical centres. Subjects received treatment for 24 weeks. PKs were assessed at the initial and repeated dosing 24 weeks later. The primary endpoint was annualized bleeding rate (ABR). Breakthrough bleeding episodes and inhibitor development were assessed.

Results: A total of 71 of 73 patients completed the study, and 18 were enrolled for the repeat PK investigation. Total exposure was 5643 exposure days. Overall, SCT800 showed comparable repeat PK profiles. The total ABR was 2.82 (95% confidence interval 2.01-3.96). During prophylaxis, 43.8% of patients had no bleeding episodes. The

majority (89.4%) of bleeding episodes were controlled with 1–2 injections of SCT800, the success rate (defined as 'excellent' or 'good' haemostatic response) for the treatment of bleeding episodes was 92.6%. The incidence of treatment-related adverse events was 53.4%. Drug-related AE incidence was 4.1%. The observed AEs were similar to those of other coagulation factor VIII, but lower in frequency. No subject developed an inhibitor, and no other safety concerns were identified.

Conclusions: SCT800 has robust PK characteristics, and is safe and efficacious for the prophylaxis and treatment of bleeding episodes in previously treated adolescent and adult patients with severe haemophilia A.

KEYWORDS
BDDrFVIII, China, haemophilia A, pharmacokinetics, prophylaxis

1 | INTRODUCTION

Haemophilia A is an X-linked hereditary recessive bleeding disorder characterized by the absence or deficiency of coagulation factor VIII (FVIII),[1] resulting in a prolonged clotting time that leads to frequent bleeding into joints and soft tissue, which may eventually result in disabling arthropathy.[2]

The current mainstay for managing haemophilia A is long-term replacement therapy with exogenous FVIII to maintain normal coagulation.[3] Prophylaxis has shown excellent clinical efficacy and overall benefits for paediatric and adult patients.[4] The World Federation of Haemophilia (WFH) suggests the initiation of prophylaxis at an early stage to achieve optimal haemostasis and to prevent chronic arthropathies.[5–7] However, in many parts of the world, opportunities for prophylaxis are limited. In the past decade, China has established the Hemophilia Treatment Center Collaborative Network of China, which has made significant advances in hemophilia.[8] A real-world study of 428 haemophilia patients based in a single centre in Tianjin showed that the proportion of children and adults receiving prophylaxis is significantly higher than a decade ago, from 2.0% (two patients) in 2012 to 66.7% (64 patients) in 2018, and from .4% in 2012 to 17.3% in 2018, respectively.[9] However, the prevalence of arthropathy and disability in haemophilia patients remains high in China.

While emerging non-factor replacement and gene therapies have advanced the care of haemophilia patients, concentrated FVIII products remain key components of management in many countries. Currently, plasma-derived FVIII (pdFVIII) is the most commonly used FVIII in China. Only a few recombinant FVIII (rFVIII) products (i.e., Advate, Xyntha and Kovaltry) are available in China, and impose relatively high cost burdens to patients. The development of new and more affordable rFVIII products is urgent for the haemophilia community in China. SCT800 is the first Chinese-developed third-generation B-domain-deleted (BDD) rFVIII without human or animal plasma-derived protein at any stage of the preparation, and exhibits a favourable safety profile. The amino acid sequence of SCT800 is similar to the primary structure of Xyntha®. It is comprised of 1438 amino acids and has a molecular weight of approximately 170 kDa. An advanced manufacturing process with Chinese hamster ovary cells enables high-yield production without the addition of animal- or human-derived products. The product is produced by using a fed-batch cell culture technique, and is purified with a series of chromatographic processes, based on methods such as cation exchange, specific antibody affinity, anion exchange, size exclusion, and other steps to remove host-cell related and process-related impurities to obtain a pure recombinant protein product. Moreover, viral removal/inactivation steps (such as nanofiltration) were added to ensure higher safety. Results from preclinical studies,[10] a phase I pharmacokinetic (PK) study, and a phase III on-demand efficacy-safety study [unpublished data] have confirmed that SCT800 has PK profiles similar to those of Xyntha®, and exhibits high in vivo recovery (IVR), effective haemostatic response, good safety and high tolerability. The primary purpose of this study was to evaluate the repeat PKs, efficacy and safety of SCT800 in the prophylaxis and treatment of bleeding episodes in adolescents and adults with severe haemophilia A who have previously received FVIII therapy (NCT03815318).

2 | MATERIALS AND METHODS

2.1 | Patients

Patients were enrolled between 22 January 2019 and 16 January 2020. The eligibility criteria included: age 12–65 years and severe haemophilia A (baseline FVIII activity < 1%); previous treatment with FVIII concentrates for ≥150 exposure days (EDs); availability of treatment records of 3 months prior to screening; absence of FVIII inhibitor (<.6 Bethesda unit [BU/mL]); normal prothrombin time or International Normalized Ratio (INR) of ≤1.5; and platelet count $\geq 100 \times 10^9$/L. Exclusion criteria included: known hypersensitivity to rFVIII, mouse, or hamster proteins; personal or family histories of FVIII inhibitors; aspartate aminotransferase/alanine aminotransferase (ALT/AST) or blood urea nitrogen and creatinine ≥3x upper limit of normal; active hepatitis B or C; human immunodeficiency virus (HIV) infection; and coagulation disorder other than haemophilia A.

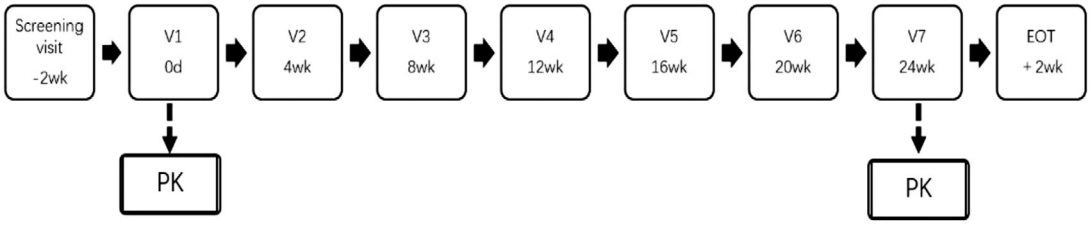

FIGURE 1 Trial design and patient flow. V1: The initial injection of all subjects was conducted in the research centre. Patients underwent initial dosing PK evaluation at V1 and repeated dosing PK evaluation at V7. V1–V7: In V2, V3 and V4, the interval between visits was 4 weeks ± 4 days, and 4 weeks ± 1 week in V5, V6 and V7. PK, pharmacokinetic

2.2 | Study design

All eligible subjects were administered 50 IU/kg of SCT800 intravenously at the first visit (V1), and then underwent a series of evaluation visits (Figure 1). During the study period, a minimum of 50 patients received 25–50 IU/kg of SCT800 for a minimum of 50 EDs of prophylaxis either every other day or three times per week. Dose adjustments were permitted if the subject experienced more than two spontaneous bleeding episodes within 1 month.

Haemostatic efficacy of SCT800 was assessed by the investigator on a four-point scale (excellent, good, fair and none).[11] Descriptions of bleeding episodes were recorded in subject diaries and verified by the investigator.

The trial design followed European Medicines Agency (EMA)[12] and Chinese regulatory agency guidelines. Written informed consent was obtained before any trial related activities. The protocol was approved by the ethics committees of the research centres. The trial was conducted in accordance with Good Clinical Practices[13] and the Declaration of Helsinki.[14]

2.3 | PK assessment

Eighteen subjects who entered the PK study at the first injection (V1) repeated the PK study at the 24th week (V7). The wash-out periods were 96 h for the initial PK, and 72 h for the repeat PK, which were selected according to the EMA guidelines for clinical investigations of FVIII.[15] According to the recommendation of the International Society of Thrombosis and Haemostasis (ISTH) and regulatory requirements,[11] patients received 50 IU/kg intravenous injections of SCT800. Blood samples were collected at 30 min prior to dosing and then at 15 min, 30 min, 1 h, 3 h, 6 h, 9 h, 12 h, 24 h, 28 h, 32 h and 48 h post dose.

FVIII:C testing was conducted in the central laboratory (Q2 Solutions, Beijing, China) for both a one-stage clotting assay[16] using an activated partial thromboplastin time assay kit, and a chromogenic substrate assay[17] with a chromogenic assay kit (Hemosil® SynthAsil, Instrumentation Laboratory, Bedford, MA, USA), respectively, by the ACL TOP 700 automatic analyzer.

2.4 | Efficacy

The primary efficacy endpoint of regular prophylaxis was annualized bleeding rate (ABR). The key secondary endpoint was annualized joint bleeding rate (AJBR). Other secondary endpoints included incremental IVR, doses of SCT800 for prophylaxis and bleeding treatment, haemostatic effects, number of infusions required to treat bleeding episodes, and adherence. IVR testing was performed at the first injection and at the 12th and 24th weeks. After a washout period of at least 48 h, 50 IU/kg (label potency) of SCT800 was administered for each IVR test. IVR was calculated based on the actual dose and peak value of FVIII:C detected within 1 h. In addition, haemophilia joint health score (HJHS) and quality of life (EQ-5D-3L) assessments were conducted at baseline (Visit 1) and at 24 weeks (Visit 7). For EQ-5D-3L, Score 1 was classified as 'no issue', and Scores 2 and 3 were classified as 'issue' for statistical analysis.

2.5 | Safety assessment

Safety assessment included monitoring of treatment-related adverse events (TEAE), vital signs, physical examination, laboratory safety parameters (haematology and biochemistry), electrocardiography (ECG), and inhibitor development. Inhibitor assays were performed before the first administration, and then at 4, 12 and 24 weeks, and at the end of treatment. Inhibitory antibodies were determined using the Nijmegen-modified Bethesda assay with a heat treatment step added to eliminate residual FVIII from the sample prior to testing in the central laboratory.[18] Inhibitor development was confirmed when two consecutive samples were tested positive (defined as ≥0.6BU/mL), in accordance with EMA guidelines.[12]

2.6 | Statistical analysis

No formal sample size calculation was performed because haemophilia A is a rare disease. Non-compartmental PK analysis[19] of plasma FVIII activity was performed using the model for bolus infusion in

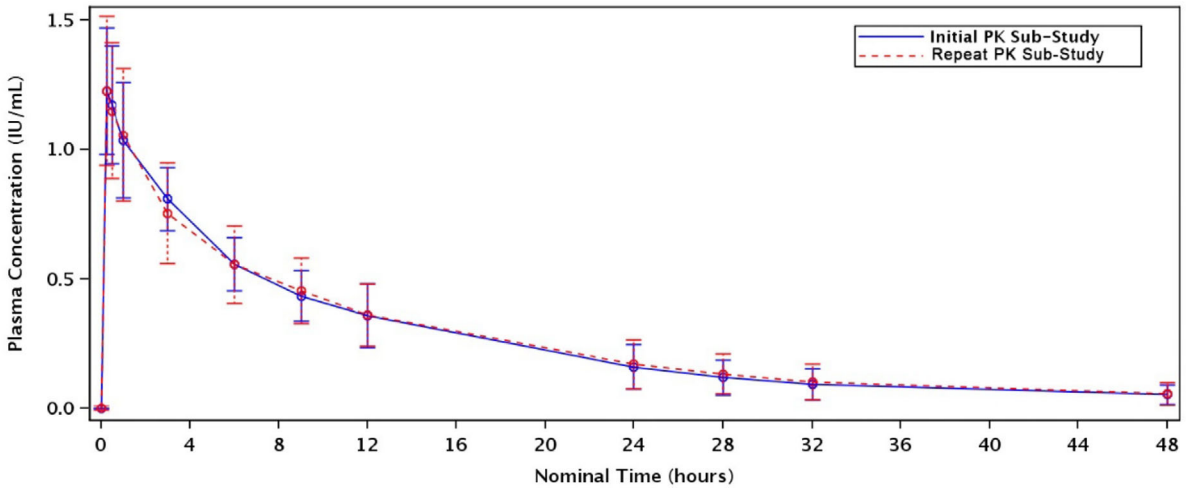

FIGURE 2 Mean ± SD plasma FVIII activity (IU/mL) vs. time profiles of SCT800 at nominal times (chromogenic assay, N = 18). Values were obtained at baseline (day 0) and week 24 based on the central laboratory potency and FVIII activity assessment

WinNonlin® software (Phoenix Build 7.0, Pharsight Corporation). Efficacy analyses were conducted in subjects who had at least one administration and post-baseline measurement (full analysis set). Safety analyses were assessed in all subjects exposed to SCT800. Summative statistical analysis was used for continuous variables, and frequency analysis was performed for categorical variables.

ABRs (365.25 days) during prophylaxis were calculated as mean (SD), median (range) and a fitted mean according to a negative binomial regression model (95% confidence intervals [CIs]) corrected for overdispersion. The safety endpoint of inhibitor development was evaluated using the Bayesian analysis model,[20,21] and the β distribution was used to simulate the incidence of inhibitor development. Other efficacy and safety endpoints, and repeat PK parameters were analyzed by descriptive statistics.

3 | RESULTS

3.1 | Patient distribution and baseline characteristics

Eighty-eight patients were screened in 12 medical centres in China. A total of 73 patients (23 adolescents and 50 adults) met study eligibility criteria and received at least one SCT800 administration. Seventy-one (97.3%) patients completed the study. All treated subjects received regular prophylaxis for ≥50 EDs. PK was assessed in a subgroup of 18 patients following the initial dosing and repeated dosing 24 weeks later.

According to medical records from three months prior to study initiation, 18 patients (24.7%) had received only routine prophylaxis, and 55 patients (75.3%) had received only on-demand therapy before study entry. Among patients who had received prophylaxis, 29 patients (39.7%) were treated with rFVIII, 33 (45.2%) were treated with pdFVIII, and seven (9.6%) were treated with unknown products (a patient may

TABLE 1 Patient demographics and baseline characteristics

	N = 73
Age (years)	
Mean (SD)	21.3 (8.0)
Median (Min, Max)	19.0 (12, 48)
Age group, N (%)	
12–17 years old	23 (31.5)
≥18 years old	50 (68.5)
Race, N (%)	
Asian	73 (100.0)
Weight (kg)	
Mean (SD)	62.1 (14.7)
Median (Min, Max)	60.0 (35.0, 100.0)
[a]**HJHS score, N (%)**	
Mean (SD)	25.0 (18.5)
Median (Min, Max)	23.0 (0, 81)
Treatment 3 months prior to enrolment	
Prophylaxis	18 (24.7)
On-demand treatment	55 (75.3)
Number of bleeds 3 months prior to enrolment	
Prophylaxis	
Mean (SD)	3.1 (2.7)
Median (Min, Max)	2.0 (1,10)
On-demand treatment	
Mean (SD)	7.7 (7.0)
Median (Min, Max)	5.0 (1, 26)
HIV-positive, N (%)	0
HCV-positive, N (%)	3 (4.1%)

Abbreviations: N, number of patients. HJHS, Hemophilia Joint Health Score.
[a]Assessment of HJHS: total: 0 (best) to 124 (worst).

TABLE 2 PK profiles of SCT800 at baseline and 24 weeks post-dosing

	One stage assay (N = 18)		Chromogenic assay (N = 18)	
Parameter[a]	baseline	week 24	baseline	week 24
AUC_{last}	8.89 ± 2.36	9.97 ± 3.08	12.36 ± 3.58	12.71 ± 4.40
$AUC_{0\text{-}inf}$	9.40 ± 2.74	10.72 ± 3.76	13.35 ± 4.37	13.83 ± 5.47
C_{max} (IU/mL)	1.08 ± .28	1.08 ± .24	1.25 ± .23	1.23 ± .28
$t_{1/2}$ (h)	10.26 ± 3.27	10.95 ± 4.34	11.52 ± 3.61	11.43 ± 3.96
CL (mL/h/kg)	6.34 ± 2.13	5.81 ± 2.22	5.09 ± 1.62	5.15 ± 1.90
MRT (h)	13.45 ± 4.58	14.84 ± 5.80	14.73 ± 4.97	15.63 ± 5.54
V_{ss} (mL/kg)	79.40 ± 16.81	77.84 ± 18.27	68.91 ± 9.54	73.28 ± 17.46
IVR (IU/dL)/(IU/kg)	1.97 ± .51	1.96 ± .45	2.01 ± .36	1.98 ± .46

Abbreviations: AUC_{last}, area under the activity- time curve from zero to last qualifiable FVIII activity; $AUC_{0\text{-}inf,}$ area under the activity- time curve from time zero extrapolated to infinity; C_{max}, peak plasma drug concentration; $t_{1/2,}$ terminal clearance half-life; C_L, plasma clearance rate; MRT, mean residence time; $V_{ss,}$ volume of distribution at steady-state; IVR, ratio of the peak blood concentration to the actual dose. N, number of patients.
[a]All data are indicated by mean ± SD.

be treated with several different FVIII products). The median FVIII prophylactic dose was 14.21 ± 8.94 IU/kg. Most patients received single-dose prophylaxis. Overall, the on-demand treatment recipients showed higher median bleeding rates than prophylaxis recipients (5.0 vs. 2.0 per 3 months). Baseline characteristics are presented in Table 1.

3.2 | PK assessments

Eighteen patients were assigned to the PK study (age 15–46 years). FVIII plasma activity after the initial (V1) and repeated (V7) dosing are shown in Figure 2 (chromogenic substrate assay). The doses administered for the PK study in the initial and repeated dosing were 49.5 ± 1.10 IU/kg and 50.0 ± 1.15 IU/kg, respectively. PK parameters are summarized in Table 2. Measurement of PK parameters in one patient in the follow up study was limited to $t_{1/2}$ due to lipemia. Only one adolescent had PK data at baseline and at 24 weeks. Stable and consistent PK profiles were demonstrated between the initial and repeated dosing by both the one-stage and chromogenic assays.

In patients who underwent prophylaxis, IVR (IU/dL)/(IU/kg) were stable, with mean IVRs of 2.20 ± 1.32, 2.29 ± 0.65 and 2.08 ± 0.47 at 0, 12, and 24 weeks, respectively. Mean FVIII 48 h trough levels after the first dose of SCT800 measured by the one-stage assay were 0.04 IU/mL (range: 0.01–0.20 IU/mL). FVIII levels 48 h after the initial dosing were ≥1% in 78% of patients.

3.3 | Efficacy

3.3.1 | Prevention of bleeding episodes

Patients received prophylaxis in a regimen of 20–50 IU/kg administered either every other day or three times a week according to the investigator's discretion, taking into account the patient's pre-enrolment treatment regimen and bleeding types. A total of 55 patients (75.3%) received the three times per week regimen, while 20 (27.4%) received every other day regimen.

The overall efficacy assessments of SCT800 prophylaxis are shown in Table 3. The mean ABR based on estimates from a negative binomial regression model was 2.82 (95% CI 2.01, 3.96), and the estimated mean AJBR was 2.07 (95% CI 1.40–3.06). The estimated mean ABRs for adolescents and adults were 2.82 (95% CI 1.55–5.16) and 2.82 (95% CI 1.87–4.25), respectively. The estimated mean ABRs of spontaneous and traumatic bleeding episodes were 1.29 (95% CI 0.87–1.92) and 1.33 (95% CI 0.82–2.16), respectively. In patients who received prophylaxis three times a week, the observed ABR was 2.49 (95% CI 1.67–3.73). These were not increased relative to patients who received SCT800 every other day, in whom the observed ABR was 3.69 (95% CI 2.00–6.81).

The dose frequency of prophylaxis was adjusted according to the incidence of bleeding episodes. Five patients adjusted their dosage of SCT800 and two of the five patients also adjusted their prophylaxis frequency according to IVR and bleeding frequency. The mean consumption per patient of SCT800 for prophylaxis was 5607.4 IU/kg per year, with a mean dose level of 34.8 IU/kg (range: 25.1–46.8 IU/kg). Compliance with prophylaxis was high; patient adherence to both prophylactic dosing and frequency was within the range of 80%–120%.

3.3.2 | Treatment of bleeding episodes

A total of 94 bleeding episodes occurred and were treated in 39 (53.4%) patients. Thirty-two subjects (43.8%) did not experience a bleeding episode during the trial. There were 2 cases of untreated bleeding. The majority of bleeding episodes occurred in joints (78.7%), most frequently in the knee (28.7%), ankle (23.4%), and elbow joints (19.1%) (Table S1). Forty-four (46.8%) bleeding episodes were spontaneous, 44 (46.8%) were traumatic, and 6 (6.4%) were classified as 'other'. In total, 97.9% of bleeding episodes were mild or moderate, and there were no life-threatening bleeding episodes.

TABLE 3 Annualized bleeding rates of patients

	Bleeds/patient/year		
	Adolescent (12-17 years) 23 patients	Adult (≥18 years) 50 patients	All (≥ 12 years) 73 patients
Total			
(N)	**12**	**27**	**39**
Median (IQR)	2.10 (4.30)	2.00 (4.10)	2.00 (4.10)
Estimated mean (95% CI)	2.82 (1.55, 5.16)	2.82 (1.87, 4.25)	2.82 (2.01, 3.96)
Spontaneous bleeds			
N	**8**	**14**	**22**
Median (IQR)	.00 (2.20)	.00 (2.10)	.00 (2.10)
Estimated mean (95% CI)	1.20 (.56, 2.58)	1.33 (.84, 2.12)	1.29 (.87, 1.92)
Traumatic bleeds			
N	**7**	**19**	**26**
Median (IQR)	.00 (2.10)	.00 (2.00)	.00 (2.10)
Estimated mean (95% CI)	1.09 (.59, 2.01)	1.44 (.75, 2.76)	1.33 (.82, 2.16)
Joint bleeds			
N	**11**	**21**	**32**
Median (IQR)	.00 (2.20)	.00 (2.10)	.00 (2.10)
Estimated mean (95% CI)	2.03 (1.05, 3.92)	2.08 (1.28, 3.41)	2.07 (1.40, 3.06)

Abbreviations: CI, confidence interval; IQR, interquartile range; N, number of subjects who experienced bleeding episodes and numbers are not additive as individual subjects may have had more than one type of bleeding episode. Mean annualized bleeding rates were estimated using a Poisson model corrected for overdispersion.

Treatment was considered successful (excellent or good response) in 92.6% (95% CI 85.3, 97.0) of the 94 bleeding episodes. Bleeding episodes were resolved after a single SCT800 infusion in 76.6%, while 12.8% required two infusions. (Table 4). The mean dose for the treatment of bleeding episodes was 41.9 IU/kg (range: 14.1–314.6 IU/kg).

3.3.3 | Joint and quality of life assessment

HJHS and EQ-5D-3L calculated at the baseline and the end of the study was compared. After 24 weeks of regular prophylaxis, total HJHS scores decreased by 1.2 ± 5.3. The health status index increased by .059 ± .134, and the best health status (0–100) increased by 7.9 ± 12.8 (Table 5). Regarding the mobility score, subjects who chose 'I can walk around without any difficulty' in V7/end of treatment (EOT) showed significant improvement compared with the baseline (39 cases in baseline vs. 51 cases in V7/EOT, $P = .041$). In the pain/discomfort score, subjects who chose 'I don't have any pain or discomfort' at V7/EOT showed a significant improvement compared with the baseline (37 cases at baseline vs. 57 cases with V7/EOT, $P < .001$). The scores for self-care, usual activity, and anxiety/depression at V7/EOT were similar to baseline.

3.4 | Safety

Safety was assessed in all 73 patients exposed to SCT800. The mean study duration was 24.3 weeks (range: 4.0–26.5 weeks) with 5668 SCT800 administrations, corresponding to a mean of 77.4 EDs (range: 11–98 EDs). A total of 39 (53.4%) patients reported ≥1 TEAE, all of which were mild or moderate in severity. The most common AEs (≥5%) were respiratory infections in 17 (23.3%) patients, hyperuricemia in 6 (8.2%), cough in 5 (6.8%), and nasopharyngitis in 4 (5.5%). One patient (1.4%) interrupted SCT800 prophylaxis once due to an upper respiratory tract infection. One (1.4%) episode of moderate upper gastrointestinal bleeding was considered a severe adverse event (SAE), but was unlikely related to the study drug. The patient was hospitalized for 2 days. No clinically relevant changes occurred in vital signs, physical examinations, laboratory parameters or ECG.

Four minor AEs were judged by the investigator as study drug-related in three patients (4.1%). They were diarrhoea in 2 (2.7%) patients, and somnolence and increased blood pressure in 1 (1.4%) patient each. No patients withdrew from the study due to AEs or SAEs. No inhibitor development, thromboembolism, or hypersensitivity reactions were observed during the study.

4 | DISCUSSION

This prospective study evaluated the repeat PKs, efficacy and safety of SCT800 in the prophylaxis and treatment of bleeding episodes in patients with severe haemophilia A. The PK parameters of SCT800 remained consistent between the initial and the repeated dosing at the 24th week, with stable PK profiles. The results of the repeat PK

TABLE 4 Bleeding episodes and haemostatic efficacy of SCT800

	All patients (N = 73)
Number of bleeds	94
Cause of bleeds, N (%)	
Spontaneous	44 (46.8)
Traumatic	44 (46.8)
Other	6 (6.4)
Site of bleeds, N (%)	
Joint	74 (78.7)
Muscular/soft tissue	11 (11.7)
Other[a]	16 (17.2)
Classification of bleeds, N (%)	
Mild/moderate	92 (97.9)
Severe	2 (2.1)
Haemostatic response, N (%)[b]	
Excellent	50 (53.2)
Good	37 (39.4)
Moderate	7 (7.4)
None	0
Success rate, N (%)[c]	87 (92.6)
Infusions to treat the bleeds (from start to stop of bleed), N (%)	
1 Infusion	72 (76.6)
2 Infusions	12 (12.8)
3 Infusions	9 (9.6)
4 Infusions	1 (1.1)
Infusions to treat a bleeding episode (mean ± SD)	1.4 ± 1.2

Abbreviation: N, number of bleeding episodes.

[a]The category 'other' included gastrointestinal, oral, subcutaneous and nasal mucosa.

[b]Classification of the haemostatic response of SCT800, when used for treatment of bleeding episodes, is according to ISTH criteria.[7]

[c]Success is defined as 'excellent' or 'good' homeostatic response.

study were slightly better than those of the phase I study, presumably due to the better quality control of the repeat PK study (no concentration outliers). IVR was above 2.0 (IU/dL)/(IU/kg), and did not change significantly over time, consistent with the results of other rFVIII products[22,23] and providing strong evidence of the haemostatic efficacy of SCT800.

The low ABR and estimated mean AJBR observed in this study confirm the prophylactic efficacy of SCT800. The median ABR was 0, lower than the reported median ABRs for all bleeding episodes of .9–5.2 for BDDrFVIII,[22,24,25] 1.0–1.6 for full-length recombinant FVIII (FLrFVIII),[23,26,27] and .96–1.93 for long-acting rFVIII.[28–30] Discrepant ABR results between these reports may be related to differences in trial design, such as dose, frequency, patient age and joint status, and monitoring frequencies.

The ABRs of traumatic bleeding episodes were similar to or higher than those of spontaneous bleeding episodes, and the ABRs of adults were similar to or higher than the ABR of adolescents. Bleeding occurred most frequently in joints. The authors speculate that these findings are related to Chinese economic conditions, in that overwork in adults can readily lead to traumatic bleeding episodes.

Dosing in our study was at the investigators' discretion. The actual dose level was 34.8 IU/kg per prophylactic infusion, in the middle range of the recommended dose (20–50 IU/kg). This was consistent with the prophylactic dosing regimen reported in other studies.[23,28]

The efficacy of SCT800 in the treatment of bleeding episodes in this study compares favourably with those of other rFVIII products,[22,23,25–30] although these comparisons were again limited by differences in methodologies, patient populations and other factors. This study followed the WFH 2012 guidelines for the treatment of bleeding episodes,[31] and dosage was determined according to bleeding types assessed by the investigators. The mean actual dose for the treatment of bleeding episodes of 41.9 IU/kg was comparable to that of most reports.[22,30] We did not identify a meaningful change in the HJHS score, which might be due to the receipt of irregular prophylaxis or on-demand treatment prior to the study, the short study duration, and small sample size. EQ-5D-3L scores, especially pain and mobility scores, improved significantly as well as the best health status, suggesting that long-term SCT800 prophylaxis can improve the quality of life for haemophilia A patients. This may be related to a higher prophylactic dose and frequency compared to baseline and a high adherence to treatment.

Inhibitor development was monitored in the central laboratory before the initial administration, as well as ED10-15 (12w), ED35-45 (16w), and ED50-75 (24w). All subjects were exposed to SCT800 for ≥75 EDs. No inhibitor development was observed in previously treated patients. Further clinical studies are needed in previously untreated patients and in patients with histories of inhibitor development.

SCT800 was well-tolerated and showed an incidence of AEs of 53.4%, which was comparable to those of rFVIII products.[22,23,25–30] No subjects discontinued the study due to AEs. The reported AE profile was similar to that described for other rFVIII products.[22,23,25–30] AEs judged to be related to the study drug were infrequent and mild. The SAE of moderate upper gastrointestinal bleeding was unrelated to the study drug. There were no deaths, SAEs, or hypersensitivity reactions related to the use of SCT800, which further confirmed the favourable safety and tolerability of SCT800.

5 | CONCLUSION

This study demonstrated that the PK profile of SCT800 was consistent and robust. SCT800 can reduce ABR and maintain haemostasis, thus improving the quality of life of haemophilia A patients. No patients developed FVIII inhibitors during the study. The incidence of drug-related AEs was low, and the safety profile showed that SCT800 was very well tolerated. Therefore, SCT800 provides an excellent choice for prophylaxis and treatment of haemophilia A patients.

TABLE 5 Health status index at baseline and 24-week follow-up

Index	Baseline(N = 73)	24-week(N = 73)	Changes(N = 73)
Health status index			
Mean ± SD	.820 ± .149	.880 ± .147	.059 ± .134
Median (Min, Max)	.788 (.505, 1.000)	.887 (.466, 1.000)	.000 (-.283, .495)
Ideal health status index			
Mean ± SD	76.9 ± 17.14	84.8 ± 13.66	7.9 ± 12.80
Median (Min, Max)	80.0 (10, 100)	90.0 (40, 100)	5.0 (-10, 50)

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CONFLICT OF INTERESTS

Renchi Yang has received speaker/consultancy fees from Bayer, Novo Nordisk, Pfizer, Roche, Sinocelltech, and Takeda. Liangzhi Xie and Weiying Gu are employed by Sinocelltech Ltd. and have an ownership in the company. The remaining authors stated that they had no interests which might be perceived as posing a conflict or bias.

AUTHOR CONTRIBUTIONS

Renchi Yang and Feng Xue conceived the study design. Feng Xue, Xielan Zhao, Jing Sun, Xiaojing Zeng, Fenge Yang, Ming Xu, Ziqiang Yu, Weiying Gu, Ying Feng, Wenqian Li, Changcheng Zheng, Hui Bi and Renchi Yang contributed to the acquisition and interpretation of data. All authors critically reviewed and revised the manuscript. The final version of this manuscript was approved by all authors. Feng Xue and Xielan Zhao contributed equally to this work and should be regarded as cofirst authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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