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ORIGINAL RESEARCH

A Phase 1/2, Open-Label, Single-Dose, Multicenter Study to Evaluate the Pharmacokinetics and Safety of Human Plasma-Derived Protein C Concentrate in Japanese Patients with Severe Congenital Protein C Deficiency (SCPCD)

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Purpose: Severe congenital protein C deficiency (SCPCD) is a rare, life-threatening disorder. Plasma-derived protein C concentrate is recommended for the acute and long-term management of SCPCD; however, data in Japanese patients are lacking. In this study, the pharmacokinetics (PK) and safety of protein C concentrate were investigated in a Japanese population.

Patients and Methods: This study was an open-label, phase 1/2, nonrandomized, noncontrolled, multicenter clinical trial in Japanese patients with SCPCD (ClinicalTrials.gov: NCT04984889). Patients received a single intravenous dose (80 IU/kg) of human plasma-derived protein C concentrate. The primary endpoints were plasma protein C activity levels and PK parameters. Secondary endpoints for safety included adverse events (AEs).

Results: All five enrolled patients (mean age, 15.2 years; mean weight, 34.0 kg) received the predefined dose of protein C concentrate and were included in PK and safety analyses. The geometric mean (coefficient of variation [CV]%) maximum concentration (C_{max}) was 1.679 IU/mL (31.7%) and the geometric mean (CV%) area under the curve (AUC_{inf}) was 21.88 IU·h/mL (47.1%). The median (range) half-life for protein C in plasma was 10.7 (7.35–12.4) hours. C_{max} and AUC_{inf} tended to be higher in older patients (≥20 years old) than in younger patients (<20 years old), whereas half-life was similar regardless of age. One patient had a mild treatment-related AE of pyrexia. No serious AEs or deaths were reported.

Conclusion: PK parameters for protein C concentrate in Japanese patients with SCPCD were determined to be comparable to studies in western populations. A single intravenous 80 IU/kg dose was well tolerated, with no serious treatment-related AEs.

Keywords: pharmacokinetics, phase 1/2 clinical trials, protein C concentrate, protein C deficiency, SCPCD, thrombotic disorders

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Introduction

Severe congenital protein C deficiency (SCPCD) is a rare autosomal recessive disorder arising from homozygous or compound heterozygous variants in the protein C gene (*PROC*).[1] These result in low or undetectable levels of protein C activity, leading to a critical defect in the control of thrombosis and hemostasis.[1] Patients with SCPCD typically present with life-threatening purpura fulminans and disseminated intravascular coagulation in the first 72 hours after birth, although clinical manifestations can also occur in late infancy.[2,3] Other presenting features include intracranial hemorrhage and/or thrombosis, along with ophthalmic, renal, and gastrointestinal lesions.[2,4–6] These initial manifestations result in neurological complications, blindness, or limb loss if appropriate treatment is not started promptly.[7,8]

Considered an "ultra-rare" disease, SCPCD has an estimated incidence of one in 250,000 to one in 4 million births.[1,7,9] SCPCD is associated with high mortality, and a large proportion of deaths may occur in utero or before diagnosis and treatment, as indicated by a discordance between the number of surviving patients and the estimated gene frequency.[1,10] In a retrospective nationwide survey conducted from 2014 to 2018 in Japan, 190 patients were estimated to have neonatal thromboembolism (within 28 days of birth) during this 5-year period, and the incidence was calculated to be 0.39 cases per 10,000 live births.[11] In that study, nine patients with homozygous, compound heterozygous, or heterozygous *PROC* variants were identified.

Early and effective treatment of patients with SCPCD is required to avoid long-term complications.[7] Current treatments for SCPCD in Japan include fresh frozen plasma, activated protein C, and oral anticoagulants.[5,12,13] However, as of 2020, plasma-derived, virus-inactivated protein C concentrate is recommended by the International Society on Thrombosis and Haemostasis (ISTH) as the preferred option for the acute and long-term treatment of patients with SCPCD.[3] Protein C concentrate is approved in both the USA and Europe for the prophylaxis and treatment of venous thrombosis and purpura fulminans in patients with SCPCD.[14,15] In a phase 2/3 study involving 15 patients with SCPCD in the USA, 95% of protein C concentrate treatments administered for purpura fulminans or acute thrombotic events were considered "effective", with the remaining 5% considered "effective with complications unrelated to the protein C concentrate".[10] No protein C inhibitory antibodies were detected. Additionally, there were no treatment-related or serious adverse events (AEs) reported.[10] Protein C concentrate is used clinically in the USA and Europe for acute treatment, short-term prophylaxis, and long-term prophylaxis in patients with SCPCD.[16]

At the time this study was conducted, protein C concentrate was not available in Japan. Furthermore, despite the clinical use of protein C concentrate in other countries, there were no data available on the pharmacokinetics (PK) and safety of protein C concentrate in a Japanese population. Therefore, this study aimed to evaluate the PK and safety of protein C concentrate in Japanese patients with SCPCD.

Materials and Methods

Study Design

This was an open-label, phase 1/2, single-dose, nonrandomized, noncontrolled, multicenter study conducted from September 2021 to March 2022 at four centers in Japan (ClinicalTrials.gov: NCT04984889). The study was conducted in accordance with Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, as well as other applicable national and local ethical and legal requirements. All study documents were approved by the Institutional Review Board at each participating center (Chiba University Hospital, Nara Medical University Hospital, Saitama Prefectural Children's Medical Center and Chiba Children's Hospital) before study initiation. Written informed consent was obtained from patients or their legal representative before study initiation.

All patients received a single intravenous infusion of an 80 IU/kg dose of plasma-derived protein C concentrate (human) (TAK-662) over 15 minutes. The patients were admitted to the study site from study day −1 (the day before protein C concentrate administration) through to day 3, then returned on day 7 for a follow-up safety assessment.

Patients

Owing to the low prevalence of SCPCD, the planned sample size was more than three patients, based on feasibility. Patients were eligible for participation if they had a diagnosis of SCPCD (homozygous or compound heterozygous), were

asymptomatic, and were of Japanese ethnicity. Key exclusion criteria included a body weight of less than 8 kg, any thrombosis in the 2 weeks before receiving the study drug, and the use of any investigational product other than protein C concentrate in the 60 days before administration of the study drug. The use of oral anticoagulants was allowed without restrictions.

Pharmacokinetic Analyses

The primary endpoints of the study were plasma protein C activity levels and PK parameters calculated based on plasma protein C activity levels, including but not limited to maximum concentration (C_{max}), area under the plasma concentration versus time curve from time zero to infinite time (AUC_{inf}) or to the last quantifiable concentration (AUC_{last}), half-life ($t_{1/2}$), incremental recovery (IR), and in vivo recovery (IVR). Blood sampling was performed immediately before infusion and at 0.5, 1, 2, 4, 8, 12, 24, and 36 hours after the end of infusion. Protein C activity levels were determined using the HemosIL® Protein C chromogenic assay kit (Instrumental Laboratory, Japan). In this chromogenic assay, protein C in plasma is activated in vitro by a protein fraction derived from the venom of the copperhead snake *Agkistrodon contortrix*, then the activated protein C is quantified with a synthetic chromogenic substrate. The paranitroaniline released is monitored kinetically at 405 nm and is directly proportional to the protein C activity level in the sample.

Safety Assessment

The safety assessment included AEs, clinical laboratory parameters, and vital signs. The primary variable for the safety assessment was the number of patients with treatment-related AEs. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0.

Statistical Methods

PK parameters were determined using a noncompartmental method with Phoenix WinNonlin version 8.1 (Certara, L.P., Princeton, New Jersey, USA). Descriptive statistics were used to summarize the data. Arithmetic and geometric means and coefficients of variation (CV%) were computed for PK parameters where applicable.

Results

Patient Characteristics

Five patients were screened and enrolled in the study. All five patients received the defined dose of protein C concentrate (80 IU/kg) and were included in the PK and safety analyses. Patient demographic and baseline characteristics are shown in Table 1. Two patients were between 20 and 30 years of age, two patients were between 10 and 19 years of age, and one patient was less than 10 years of age. The mean (standard deviation [SD]) age was 15.2 (8.9) years. Mean (SD) body

Table 1 Patient Demographic and Baseline Characteristics

Characteristic	n=5
Age, years	
Mean (SD)	15.2 (8.9)
Age category, n (%)	
<10 years	1 (20)
10–19 years	2 (40)
20–30 years	2 (40)
Sex, n (%)	
Male	4 (80)
Female	1 (20)
Weight at screening, kg	
Mean (SD)	34.0 (20.0)
Median (range)	20.5 (20.2–64.4)

(*Continued*)

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Table 1 (Continued).

Characteristic	n=5
Duration of diagnosed protein C deficiency, years	
Mean (SD)	15.39 (9.32)
Median (range)	15.5 (3.3–27.4)
Protein C activity level at diagnosis, %	
Mean (SD)	8.54 (3.85)
Median (range)	10.0 (1.7–11.0)
History of thrombotic complications/skin necrosis, n (%)	
Yes	5 (100)
Purpura fulminans	5 (100)
Coumarin-induced skin necrosis/warfarin-induced skin necrosis	0
Thrombotic complication	2 (40)
No	0
Previous treatment with blood products, n (%)	
Yes	2 (40)
No	3 (60)
Prophylactic treatment received, n (%)	
Yes	1 (20)
4-factor prothrombin complex concentrate	1 (20)
No	4 (80)
Concomitant medications, n (%)	
Vitamin K antagonist	4 (80)
Direct FXa inhibitor	1 (20)

Abbreviations: FXa, activated factor X; SD, standard deviation.

weight was 34.0 (20.0) kg. Four of the patients were male and the median (range) protein C activity level at diagnosis was 10.0% (1.7–11.0%). One patient was receiving prophylactic treatment with a 4-factor prothrombin complex concentrate containing 22.5 U/mL of protein C. For this patient, the study drug was administered at least 36 hours after prophylactic treatment. Four patients were receiving a vitamin K antagonist (warfarin) and one patient was receiving a direct activated factor X inhibitor (edoxaban). No patients received fresh frozen plasma in the week before or after protein C administration. All five patients had a history of purpura fulminans and two had also experienced thromboembolic events.

Plasma Protein C Activity Levels and PK Parameters

Immediately before protein C concentrate infusion, four patients had protein C activity levels of less than 0.1 IU/mL, and one patient had a protein C activity level of 0.21 IU/mL. Baseline-corrected protein C activity levels in plasma are shown in Figure 1 and PK parameters are shown in Table 2. The median (range) $t_{1/2}$ of protein C was 10.7 (7.35–12.4) hours and the geometric mean (CV%) C_{max} was 1.679 IU/mL (31.7%). The geometric mean (CV%) AUC_{inf} was 21.88 IU·h/mL (47.1%). The median (range) IR and IVR were 0.0171 (0.0143–0.0298) (IU/mL)/(IU/kg) and 87.4% (62.2–147%), respectively.

Both C_{max} and AUC_{inf} appeared to be higher in older patients (≥20 years old) than in younger patients (<20 years old) (Figure 1), whereas $t_{1/2}$ was similar between patients regardless of age. A comparison of the PK parameters for protein C in patients older and younger than 20 years is shown in Table 3.

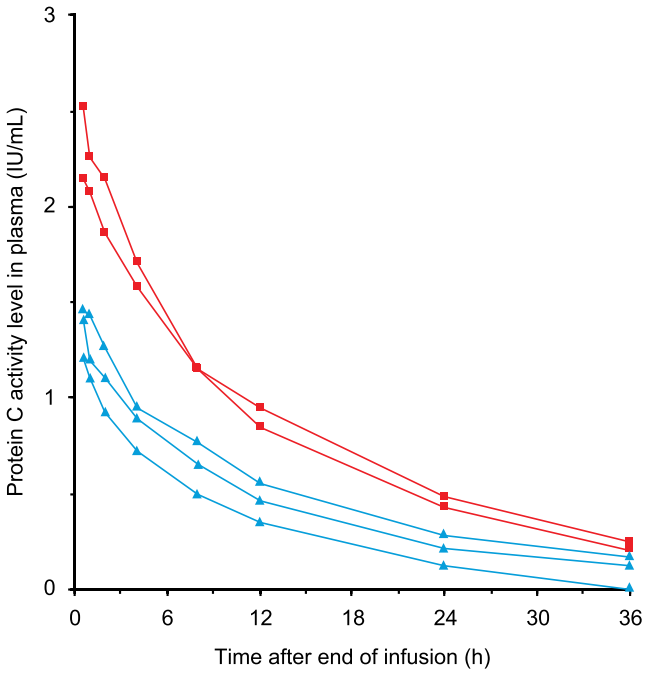

Figure 1 Plasma protein C activity levels in Japanese patients over time (n=5). Patients were administered a single intravenous 80 IU/kg dose of protein C concentrate. Blood sampling was performed immediately before infusion and at 0.5, 1, 2, 4, 8, 12, 24, and 36 hours after the end of infusion. Protein C activity levels were determined using the HemosIL® Protein C chromogenic assay kit and data are presented as corrected values after subtracting the baseline (pre-dose) protein C activity level. Individual plasma concentrations of protein C are shown on a linear scale, by patient. Red squares denote patients ≥20 years of age and blue triangles denote patients <20 years of age.
Abbreviation: h, hours.

Safety Assessment

AEs were reported in two patients. One patient had pyrexia, which was deemed treatment-related, and one patient had purpura, which was not considered treatment-related. All AEs were mild in severity and resolved. No serious AEs or deaths were reported. No clinically meaningful changes were observed in clinical laboratory parameters (hematology and chemistry measures) or vital signs.

Table 2 Pharmacokinetic Parameters of Protein C in Plasma (n=5)

Parameter[a]	Mean	SD	Geometric Mean	Geometric CV, %	Median	Min	Max
t_{max}, hours	NA	NA	NA	NA	0.53	0.43	0.60
C_{max}, IU/mL	1.746	0.557	1.679	31.7	1.45	1.21	2.52
AUC_{inf}, IU · h/mL	23.60	9.702	21.88	47.1	21.9	11.7	34.2
AUC_{last}, IU · h/mL	20.75	8.582	19.24	47.0	18.7	10.4	29.7
$t_{1/2}$, hours	10.55	1.959	10.38	20.8	10.7	7.35	12.4
MRT, hours	15.21	2.826	14.98	20.8	15.5	10.6	17.8
CL, mL/kg/h	4.199	1.955	3.868	47.1	3.88	2.47	7.24
V_{ss}, mL/kg	60.35	18.24	57.93	33.7	69.2	38.9	76.8
IR, (IU/mL)/(IU/kg)	0.02063	0.006588	NA	NA	0.0171	0.0143	0.0298
IVR, %	95.71	31.22	NA	NA	87.4	62.2	147

Notes: [a]PK parameters are calculated based on plasma protein C activity levels, as determined using the HemosIL® Protein C chromogenic assay kit.
Abbreviations: AUC_{inf}, area under the plasma concentration versus time curve from time zero to infinite time; AUC_{last}, area under the plasma concentration versus time curve from time zero to last quantifiable time; CL, total body clearance; C_{max}, maximum concentration; CV, coefficient of variation; IR, incremental recovery; IVR, in vivo recovery; Min, minimum; Max, maximum; MRT, mean residence time; NA, not applicable; SD, standard deviation; $t_{1/2}$, half-life; t_{max}, time to maximum concentration; V_{ss}, volume of distribution at steady state.

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Table 3 Comparison of Protein C Pharmacokinetic Parameters by Age

Parameter[a]	Mean±SD		Median (Range)	
	<20 Years of Age (n=3)	≥20 Years of Age (n=2)[b]	<20 Years of Age (n=3)	≥20 Years of Age (n=2)
C_{max}, IU/mL	1.357±0.129	2.14, 2.52	1.41 (1.21–1.45)	2.33 (2.14–2.52)
AUC_{inf}, IU · h/mL	17.04±5.109	32.7, 34.2	17.6 (11.7–21.9)	33.4 (32.7–34.2)
AUC_{last}, IU · h/mL	14.87±4.208	29.4, 29.7	15.6 (10.4–18.7)	29.6 (29.4–29.7)
$t_{1/2}$, hours	10.15±2.553	10.4, 11.9	10.7 (7.35–12.4)	11.1 (10.4–11.9)
MRT, hours	14.64±3.684	15.0, 17.2	15.5 (10.6–17.8)	16.1 (15.0–17.2)
CL, mL/kg/h	5.311±1.734	2.47, 2.59	4.82 (3.88–7.24)	2.53 (2.47–2.59)
V_{ss}, mL/kg	73.49±3.915	38.9, 42.4	74.5 (69.2–76.8)	40.6 (38.9–42.4)
IR, (IU/mL)/(IU/kg)	0.01602±0.001508	0.0253, 0.0298	0.0167 (0.0143–0.0171)	0.0275 (0.0253–0.0298)
IVR, %	78.37±14.02	96.7, 147	85.5 (62.2–87.4)	122 (96.7–147)

Notes: [a]PK parameters are calculated based on plasma protein C activity levels, as determined using the HemosIL® Protein C chromogenic assay kit. [b]As there are only two patients in this category, individual values are shown in this column, rather than mean±SD.
Abbreviations: AUC_{inf}, area under the plasma concentration versus time curve from time zero to infinite time; AUC_{last}, area under the plasma concentration versus time curve from time zero to last quantifiable time; CL, total body clearance; C_{max}, maximum concentration; IR, incremental recovery; IVR, in vivo recovery; MRT, mean residence time; SD, standard deviation; $t_{1/2}$, half-life; V_{ss}, volume of distribution at steady state.

Discussion

This study evaluated the PK and safety of a single dose of protein C concentrate in five asymptomatic Japanese patients with SCPCD. The median (range) $t_{1/2}$ of protein C in this study was 10.7 (7.35–12.4) hours, consistent with the US phase 2/3 clinical trial in patients with SCPCD, in which the median (range) half-life was reported to be 12.1 (7.8–15.1) hours.[10] In the present study, AUC and C_{max} tended to be lower in patients younger than 20 years old, suggesting higher protein C clearance and larger volume of distribution (V_{ss}) in children than in adults. In the US study, the half-life of protein C was 7.8−12.4 hours in pediatric patients 3−6 years of age and 14.1−15.1 hours in patients 15 and 16 years of age, while the clearance was 0.051−0.054 dL/kg/h at 3−6 years and 0.042−0.043 dL/kg/h at 15 and 16 years, indicating faster clearance and shorter half-life in young children.[10] Although the reason for this age-related difference in PK has not been fully understood, it was suggested that the optimal dose may therefore be different between young children and adults, and that doses should be individualized by frequent monitoring of protein C activity levels in each patient. Based on these findings, the US package insert for protein C concentrate recommends that potential differences in PK should be taken into account when determining a dosing regimen for children.[15]

The PK of protein C concentrate in young children with SCPCD has been evaluated in several case studies. Vukovich et al reported a half-life of 8.3 hours after administration of 100 U/kg protein C concentrate in a 10-month-old patient with SCPCD.[17] Marlar et al determined the half-life of protein C to be 6−8 hours in two infants with SCPCD.[18] Auberger used various assays to measure the half-life of protein C in a 7-year-old patient with SCPCD and determined the half-life to be approximately 10 hours.[19] Overall, the PK parameters reported in these publications are similar to the PK parameters obtained in the US phase 2/3 study of protein C concentrate.[10] In the present study, C_{max}, which is determined by the drug dose and the V_{ss}, tended to be lower in patients younger than 20 years of age. IR is inversely related to V_{ss}; therefore, a larger V_{ss} in children corresponds to a smaller IR. In the previous publications, discussions focused solely on half-life and did not mention V_{ss}. However, the present full PK analysis suggests that age differences in V_{ss} and IR may also exist.

Another important factor reported to affect the PK parameters of protein C is the patient's clinical condition, specifically, the occurrence of acute thrombosis or purpura fulminans. Dreyfus et al investigated the use of protein C replacement therapy in infants with SCPCD who had thrombosis associated with purpura fulminans or disseminated intravascular coagulation.[4] The half-life of protein C was observed to be as short as 2−3 hours during the acute phase, when the coagulation system was activated, but lengthened to approximately 10 hours after the coagulation system had stabilized.[4] Two review articles concluded that there is large interindividual variability of the half-life of protein C, ranging from 4.4 −15.9 hours (median: 10−12 hours), and that the half-life is substantially shortened during the acute phase of thrombosis.[2,20] Based on these findings, the US package insert for protein C concentrate notes that both the half-life and the increase in

plasma protein C activity levels may be considerably reduced in patients with acute thrombosis.[15] The EU summary of product characteristics also contains a similar precaution.[14]

In both the US phase 2/3 study[10] and our study, PK measurements were performed while patients with SCPCD were asymptomatic, and therefore, the results are not expected to be affected by the onset of any thrombosis symptoms. However, D-dimer was not measured in any of the studies, and the assessment was based only on clinical symptoms. Therefore, the presence of thrombophilia cannot be completely ruled out, and neither can the possibility of thrombophilia as a confounding factor.

Intravenous administration of protein C concentrate was well tolerated in the Japanese patients with SCPCD in this PK study. Only two patients experienced AEs (pyrexia and purpura), which were mild in severity. The event of pyrexia was considered treatment-related by the investigator. This AE occurred once (lasting from study day 2–3) and subsequently resolved. No serious AEs or deaths were reported. These safety results are consistent with reports from the USA and Europe.[10,14,15,21]

Protein C concentrate is recommended by the ISTH as the preferred option for acute treatment, short-term prophylaxis, and long-term prophylaxis for SCPCD, and is already in clinical use in the USA and Europe.[3,16] As of March 2024, protein C concentrate has also been approved in Japan based on the results of this clinical study. This study is the first to report clinical data on the use of protein C concentrate in Japanese patients with SCPCD. Overall, the PK and safety data generated in our study provide clinically relevant information for the use of protein C concentrate in Japanese patients. There were considerable interindividual variations in PK parameters in our study, which supports that in clinical practice, each individual patient's protein C activity level should be monitored and the dose regimen for protein C concentrate adjusted in response, to ensure that the optimal dose is received in both acute and prophylactic settings.

The phenomenon of interindividual PK variability is also observed in patients with hemophilia A, another disorder of the coagulation system. In that disorder, characterized by a genetic deficiency in coagulation factor VIII (FVIII), PK studies of FVIII replacement therapy have identified differences in clearance and half-life between younger and older patients.[22,23] The standard of hemophilia A treatment has evolved from on-demand treatment of FVIII deficiency during bleeding episodes to prophylaxis aimed at mitigating the bleeding phenotype.[24] Individualized prophylaxis regimens, considering not only body weight but also various patient-specific factors such as age, pattern of bleeding, activity level, and individual PK, are increasingly recognized as essential.[25] Therefore, in considering treatment regimens tailored to patients' PK, the individualized treatment approaches used in hemophilia A management may also be applicable to the treatment of SCPCD. For example, given the previously discussed shortening of protein C half-life during thrombotic events, and the time required to measure protein C activity levels, it is essential to carefully observe the patient's improvement in clinical symptoms such as purpura fulminans, and in laboratory markers of disseminated intravascular coagulation, to determine the need for additional infusion of protein C concentrate.[3] In particular, D-dimer levels after protein C administration are considered a useful indicator of adequate protein C replacement and potential purpura fulminans recurrence.[3]

Limitations of this study include the small number of patients and that it was non-comparative.

Conclusion

This study characterized the PK parameters for protein C concentrate in Japanese patients with SCPCD, which were consistent with previous findings in non-Japanese populations. A single intravenous dose of protein C concentrate was well tolerated in a Japanese patient population, with no serious treatment-related AEs. The results of this study provide clinically relevant data for the use of protein C concentrate as a treatment for SCPCD in Japan.

Abbreviations

AE, adverse event; AUC_{inf}, area under the plasma concentration versus time curve from time zero to infinite time; AUC_{last}, area under the plasma concentration versus time curve from time zero to the last quantifiable concentration; CL, total body clearance; CV, coefficient of variation; FVIII, coagulation factor VIII; FXa, activated factor X; h, hours; $t_{1/2}$, half-life; IVR, in vivo recovery; IR, incremental recovery; ISTH, International Society on Thrombosis and Haemostasis; Max, maximum; C_{max}, maximum concentration; MedDRA, Medical Dictionary for Regulatory Activities; Min, minimum; MRT, mean

residence time; NA, not applicable; PK, pharmacokinetics; *PROC*, protein C gene; SD, standard deviation; SCPCD, severe congenital protein C deficiency; t_{max}, time to maximum concentration; V_{ss}, volume of distribution.

Data Sharing Statement

Takeda does not plan to share data supporting the results reported in this article as there is a reasonable likelihood that individual patients could be reidentified due to the limited number of study participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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References

1. Goldenberg NA, Manco-Johnson MJ. Protein C deficiency. *Haemophilia*. 2008;14(6):1214–1221. doi:10.1111/j.1365-2516.2008.01838.x
2. Kroiss S, Albisetti M. Use of human protein C concentrates in the treatment of patients with severe congenital protein C deficiency. *Biologics*. 2010;4:51–60. doi:10.2147/btt.s3014
3. Minford A, Brandao LR, Othman M, et al. Diagnosis and management of severe congenital protein C deficiency (SCPCD): communication from the SSC of the ISTH. *J Thromb Haemost*. 2022;20(7):1735–1743. doi:10.1111/jth.15732
4. Dreyfus M, Masterson M, David M, et al. Replacement therapy with a monoclonal antibody purified protein C concentrate in newborns with severe congenital protein C deficiency. *Semin Thromb Hemost*. 1995;21(4):371–381. doi:10.1055/s-2007-1000658
5. Ohga S, Kang D, Kinjo T, et al. Paediatric presentation and outcome of congenital protein C deficiency in Japan. *Haemophilia*. 2013;19(3):378–384. doi:10.1111/hae.12097
6. Tang X, Zhang Z, Yang H, et al. Clinical and genetic features of Chinese pediatric patients with severe congenital protein C deficiency who first presented with purpura fulminans: a case series study and literature review. *Thromb Res*. 2022;210:70–77. doi:10.1016/j.thromres.2021.12.026
7. Chalmers E, Cooper P, Forman K, et al. Purpura fulminans: recognition, diagnosis and management. *Arch Dis Child*. 2011;96(11):1066–1071. doi:10.1136/adc.2010.199919
8. Price VE, Ledingham DL, Krumpel A, et al. Diagnosis and management of neonatal purpura fulminans. *Semin Fetal Neonatal Med*. 2011;16(6):318–322. doi:10.1016/j.siny.2011.07.009

9. Sardella M, Belcher G. Pharmacovigilance of medicines for rare and ultrarare diseases. *Ther Adv Drug Saf*. 2018;9(11):631–638. doi:10.1177/2042098618792502
10. Manco-Johnson MJ, Bomgaars L, Palascak J, et al. Efficacy and safety of protein C concentrate to treat purpura fulminans and thromboembolic events in severe congenital protein C deficiency. *Thromb Haemost*. 2016;116(1):58–68. doi:10.1160/TH15-10-0786
11. Egami N, Ochiai M, Ichiyama M, et al. Clinical impact of heritable thrombophilia on neonatal-onset thromboembolism: a nationwide study in Japan. *J Pediatr*. 2021;238:259–267.e252. doi:10.1016/j.jpeds.2021.07.001
12. Watanabe K, Arakawa Y, Yanagi M, et al. Management of severe congenital protein C deficiency with a direct oral anticoagulant, edoxaban: a case report. *Pediatr Blood Cancer*. 2019;66(6):e27686. doi:10.1002/pbc.27686
13. Hayami T, Yamaguchi A, Kato T, et al. Purpura fulminans in congenital protein C deficiency successfully treated with fresh frozen plasma and thrombomodulin. *J Dermatol*. 2018;45(6):e165–e166. doi:10.1111/1346-8138.14194
14. European Medicines Agency. CEPROTIN. Product information; 2007. Available from: https://www.ema.europa.eu/en/documents/product-information/ceprotin-epar-product-information_en.pdf. Accessed October 10, 2024.
15. U.S. Food & Drug Administration. CEPROTIN. Package insert; 2007. Available from: https://www.fda.gov/media/75033/download?attachment. Accessed October 10, 2024.
16. Wang M, Hertfelder H-J, Swallow E, et al. Real-world treatment of patients with severe congenital protein C deficiency with protein C concentrate: a physician survey. *Thrombosis Update*. 2024;14:100159. doi:10.1016/j.tru.2024.100159
17. Vukovich T, Auberger K, Weil J, et al. Replacement therapy for a homozygous protein C deficiency-state using a concentrate of human protein C and S. *Br J Haematol*. 1988;70(4):435–440. doi:10.1111/j.1365-2141.1988.tb02513.x
18. Marlar RA, Sills RH, Groncy PK, et al. Protein C survival during replacement therapy in homozygous protein C deficiency. *Am J Hematol*. 1992;41(1):24–31. doi:10.1002/ajh.2830410106
19. Auberger K. Evaluation of a new protein-C concentrate and comparison of protein-C assays in a child with congenital protein-C deficiency. *Ann Hematol*. 1992;64(3):146–151. doi:10.1007/BF01697402
20. Knoebl PN. Severe congenital protein C deficiency: the use of protein C concentrates (human) as replacement therapy for life-threatening blood-clotting complications. *Biologics*. 2008;2(2):285–296. doi:10.2147/btt.s1954
21. Moritz B, Rogy S, Tonetta S, et al. Efficacy and safety of a high purity protein C concentrate in the management of patients with severe congenital protein C deficiency. In: 31st Hemophilia Symposium Hamburg 2000: Epidemiology Inhibitors in Hemophilia Therapy and Monitoring of Bleeds in Acute and Intensive Care Medicine Pediatric Hemostaseology Case Reports; 2002.
22. Collins PW, Blanchette VS, Fischer K, et al. Break-through bleeding in relation to predicted factor VIII levels in patients receiving prophylactic treatment for severe hemophilia A. *J Thromb Haemost*. 2009;7(3):413–420. doi:10.1111/j.1538-7836.2008.03270.x
23. Steele MR, Nagel K, Chan AK. Pharmacokinetics of recombinant and plasma-derived factor VIII products in paediatric patients with severe haemophilia A. *Haemophilia*. 2014;20(1):e100–101. doi:10.1111/hae.12310
24. Valentino LA, Pipe SW, Collins PW, et al. Association of peak factor VIII levels and area under the curve with bleeding in patients with haemophilia A on every third day pharmacokinetic-guided prophylaxis. *Haemophilia*. 2016;22(4):514–520. doi:10.1111/hae.12905
25. Collins PW. Personalized prophylaxis. *Haemophilia*. 2012;18(s4):131–135. doi:10.1111/j.1365-2516.2012.02838.x