10 November 2022
EMA/913542/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ceprotin

International non-proprietary name: human protein C

Procedure No. EMEA/H/C/000334/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Abbreviation	Definition
AE	Adverse event
APC	Activated protein C
BW / bw	Body Weight
CHMP	Committee for Medicinal Products for Human Use
CISN	Coumarin-induced skin necrosis
CSR	Clinical study report
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
EC	Endothelial Cells
EMA	European Medicines Agency
EPCR	Endothelial Protein C Receptor
EU	European Union
FDA	Food and Drug Administration
FFP	Fresh Frozen Plasma
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IND	Investigational New Drug
INR	International Normalized Ratio
IU	International unit
IV	Intravenous
LMWH	Low Molecular Weight Heparin
LTP	long-term prophylaxis
MAA	Marketing Authorisation Application
NMRI	Naval Medical Research Institute
NOAEL	No Observed Adverse Effect Level
OD	On demand
PAI-1	Plasminogen activator-inhibitor 1
PC	Protein C
PCC	Prothrombin Complex Concentrate
PF	Purpura fulminans
PK	Pharmacokinetic(s)

Abbreviation	Definition
PROC	Protein C Gene
PSUR	Periodic Safety Update Report
RDC	Retrospective Data Collection (studies IMAG-039, IMAG-041 and compassionate use)
RWE	Real Word Evidence
SAWP	Scientific Advice Working Party
SC	Subcutaneous
SCPCD	Severe congenital protein C deficiency
SAPCD	Severe acquired protein C deficiency
SOC	System organ class
TAFI	Thrombin Activatable Fibrinolysis Inhibitor
TM	Thrombomodulin

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Takeda Manufacturing Austria AG submitted to the European Medicines Agency on 30 March 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include long-term prophylaxis (deletion of wording 'short-term' and currently listed conditions) of purpura fulminans and coumarin induced skin necrosis in patients with severe congenital protein C deficiency, based on a re-analysis of long-term prophylaxis data from the pivotal Study 400101; a phase 2/3 clinical study undertaken to evaluate PK, safety and efficacy of CEPROTIN in patients with severe congenital PC deficiency for the treatment of acute thrombotic episodes, for short-term thromboembolic prophylaxis and for long-term prophylactic treatment. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated and the Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial changes in sections 4.4 and 4.8 of the SmPC and Package Leaflet.
Version 2.0 of the RMP has also been submitted. In addition, MAH took the opportunity to correct the address of the manufacturer of the biological active substance in Annex II following variation EMEA/H/C/000334/IAIN/0126/G.

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Armando Genazzani

Timetable	Actual dates
Submission date	30 March 2022
Start of procedure:	23 April 2022
CHMP Rapporteur Assessment Report	15 June 2022
PRAC members comments	29 June 2022
CHMP Co-Rapporteur Critique	22 June 2022
CHMP members comments	11 July 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 July 2022
Request for supplementary information (RSI)	21 July 2022
CHMP Rapporteur Assessment Report	17 October 2022
CHMP members comments	28 October 2022
Updated CHMP Rapporteur Assessment Report	3 November 2022
Opinion	10 November 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Congenital protein C deficiency is an inherited thrombotic disease. Approximately 95% of affected individuals have heterozygous protein C deficiency, which is associated with thrombosis in adults. The rest has severe congenital protein C deficiency (SCPCD), which is caused by a homozygous genetic defect and is inherited in an autosomal recessive pattern. Double (compound) heterozygous defects, where the patient has a separate defect on each of the alleles of the protein C gene (*PROC*), inherited from each parent independently, can also result in SCPCD with symptoms indistinguishable from homozygous protein C deficiency. The *PROC* genotype is identified by a genetic analysis (Alhenc Gelas et al. 2020; Dreyfus et al. 1995). SCPCD (homozygous or compound heterozygous forms) is extremely rare (1 in 500 000 to 1 in 750 000 births), but partial deficiencies (heterozygous forms) are much more frequent (1 in 200 to 1 in 500) (Dinarvand and Moser 2019; Mathias et al. 2004).

In addition, SCPCD is characterised by either a reduced level of circulating protein (type I), or less frequently (10-15% of cases), by (approximately) normal antigen level but decreased activity (type II) (Alhenc Gelas et al. 2020).

State the claimed therapeutic indication

The MAH is submitting this application to extend the current indication which included different conditions (e.g. surgery) for short-term prophylaxis to the full label of prophylaxis in patients with severe congenital protein C deficiency, namely: "CEPROTIN is indicated for prophylaxis and treatment of purpura fulminans and coumarin-induced skin necrosis in patients with severe congenital protein C deficiency."

Epidemiology

Patients with severe hereditary disease often present shortly after birth with PF, congenital blindness, and disseminated intravascular coagulation (DIC) [Marlar A et al, J Pediatr 1989; 114:528-534, Hattenbach LO et al Ophthalmic manifestations of congenital protein C deficiency. J AAPOS 1999; 3(3):188–190]. The predicted prevalence of severe PC deficiency is 1 in 25,000- 40,000 individuals [Chalmers E et al Purpura fulminans: recognition, diagnosis and management. Arch Dis Child. 2011, Nov;96(11):1066-71]. However, only 20 patients with severe PC deficiencies within North America and the UK have been reported in the literature [Goldenberg NA et al, Haemophilia 2008; 14(6):1214-1221.2,9, Chalmers E et al Purpura fulminans: recognition, diagnosis and management. Arch Dis Child. 2011, Nov;96(11):1066-71.]. This disparity between the observed and reported prevalence of severe congenital disease may be a result of underreporting and a high rate of perinatal mortality prior to diagnosis [Tait RC et al. Prevalence of protein C deficiency in the healthy population. Thromb Haemost 1995; 73(1):87-93.Preston FE et al. Increased fetal loss in women with heritable thrombophilia. Lancet 1996; 348(9032):913-916., Greer IA. Inherited thrombophilia and venous thromboembolism. Best Pract Res Clin Obstet, Gynaecol 2003; 17(3):413-25].

According to registry data from the International Society on Thrombosis and Haemostasis, an estimated 2.25/million people have SCPCD worldwide. Within the UK, 11 cases of SCPCD have been reported. Based on a carrier prevalence estimate of 0.3%, 135 cases of SCPCD would be expected indicating that SCPCD may be underdiagnosed [Othman M,et al, Thrombosis and hemostasis health in pregnancy: Registries from the International Society on Thrombosis and Haemostasis. Res Pract Thromb Haemost. 2019 Aug 1;3(4):607-614.14].

There are three forms of PF, including acute infectious, neonatal, and idiopathic PF, and each form has different prevalence. Acute infectious PF is the most common form of the disease. The prevalence of this form was estimated to be 10-20% of patients who develop meningococcal septicemia, where the estimated incidence of meningococcal disease was 1 case per 100,000 people per year [Patel J. Recognition and Management of Acute Purpura Fulminans: A Case Report of a Complication of Neisseria meningitidis Bacteremia. Cureus. 2021 Mar 4;13(3):e1370458,59].

The estimated prevalence of hereditary neonatal PF related to severe PC deficiency was about 1 in 1,000,000 live births worldwide [Perera TB, Murphy-Lavoie HM. Purpura Fulminans. 2021 Jul 21. In: StatPearls [Internet], Treasure Island (FL): StatPearls Publishing; 2022 Jan–. Kim MC].

Coumarin induced skin necrosis (CISN) is a rare complication of oral anticoagulation with an estimated prevalence of 0.01% to 0.1% in patients receiving coumarin derivatives [Pabinger I et al. Coumarin induced acral skin necrosis associated with hereditary protein C deficiency. Blut 1986;52(6):365-370, Becker CG. Oral anticoagulant therapy and skin necrosis: Speculations on pathogenesis. Adv Exp Med Biol 1987; 214:217-22277,78, Warkentin TE. Heparin-induced thrombocytopenia: a ten-year retrospective. Ann Rev Med 1999; 50(1):129-147]

Biologic features, aetiology and pathogenesis

The level of protein C activity is 65-135% in healthy adults and 30-40% at birth. Protein C concentration remains slightly low through childhood and achieves the adult range after puberty. For heterozygous protein C deficiency, the level of protein C activity is 30-50% in adults, and 30% or lower in newborns. Furthermore, for homozygous or double heterozygous protein C deficiency, the level of protein C activity is extremely low (less than 1%) (Goldenberg and Manco-Johnson 2008; Tcheng et al. 2008).

Patients with homozygous or double heterozygous protein C deficiency, typically present with clinical manifestations within the first few hours or days of life. Severe fetal protein C deficiency may also result

in miscarriage or intrauterine thromboses. Since the microcirculation is the major site of function of the protein C pathway, the consequences of severe protein C deficiency typically first become manifest in the capillaries of the skin, then progress to the vessels of the eyes (leading to vitreous hemorrhage and retinal detachment), brain and kidneys. Blindness, which is permanent, is believed to occur *in utero* during the third trimester period or soon after birth (Barnes et al. 2002; Sirachainan et al. 2003). The clinical signs of PF are the result of capillary thrombosis with secondary bleeding and consist of ecchymotic skin lesions that, if untreated, rapidly develop into hemorrhagic bullae (Abu-Amero et al. 2003). The gangrenous necrosis symptoms appear mainly on the extremities, but also on the buttocks, abdomen, scrotum, and scalp, and may necessitate amputation. In addition, multi-organ failure may also occur by thromboembolic disease with severe disseminated intravascular coagulation (DIC). If the condition is left untreated, the progression of the thrombotic lesions results in blindness, severe brain damage, multi-organ failure and death (Civantos et al. 1987; Marciniak et al. 1985; Pegelow et al. 1988; Pulido et al. 1987; Seligsohn et al. 1984; Tarras et al. 1988). After the newborn period, venous thromboembolism such as deep vein thrombosis (DVT), pulmonary embolism and cerebral sinus thrombosis, superior mesenteric vein thrombosis and arterial thrombosis such as cerebral infarction, has been reported in childhood and adults.

Management

CEPROTIN is currently the only treatment option available to substitute protein C in severe congenital PC deficiency (Dreyfus et al. 1995). Prior to licensure of CEPROTIN, other therapeutic options for the treatment of congenital PC deficiency included the use of fresh frozen plasma (FFP), low-molecular weight heparin (LMWH), and liver transplantation (Loop et al. 2004; Pescatore 2001).

In the late eighties, only FFP and long-term treatment either with vitamin K antagonists or with FFP and/or prothrombin complex concentrates (PCCs) were available for the treatment of severe PC deficiency. However, these treatments have several disadvantages (Kroiss and Albisetti 2010). Since protein C is a trace protein with a concentration of 4 µg/mL, the volume of FFP required to raise protein C to normal levels can lead to fluid overload, especially in children, with the risk of pulmonary edema, hypertension, hyperproteinemia, or proteinuria (Auberger et al. 1990; Auletta and Headington 1988; Casella et al. 1988; Civantos et al. 1987; Garcia-Plaza et al. 1985; Hartman et al. 1989 and 1990; Hintz et al. 1987; Majer et al. 1989; Marlar et al. 1989 and 1992; Pegelow et al. 1988; Pulido et al. 1987; Sills et al. 1984; Tarras et al. 1988; Vukovich et al. 1988). One case has been reported where a teenage patient developed severe allergic reactions to FFP. Furthermore, FFP carries the risk of transmitting blood-borne viruses (Manco-Johnson and Nuss 1992; Marlar et al. 1992). Nonetheless, FFP would be considered the standard of care if PC replacement therapy were not available (Sirachainan et al. 2003). Due to the presence of the coagulation factors II, VII, IX, and X, replacement therapy with PCCs may further increase the risk of thrombotic complications in these patients, who are already prone to thrombosis.

The prophylaxis of thromboembolic complications due to severe PC deficiency has been attempted using different approaches than for general PC replacement. Oral anticoagulation with coumarin derivatives, such as warfarin, may be used to decrease coagulation activity. However, during the initial phase of oral anticoagulation the activity of protein C is more rapidly suppressed than that of the procoagulant factors (II, VII, IX and X), which may result in a recurrence of symptoms as well as bleeding complications (especially in neonates and young children, where consistent International Normalized Ratio [INR] levels are difficult to achieve). Such complications have been observed in patients with severe congenital PC deficiency who were treated with oral anticoagulants (Abu-Amero et al. 2003; Auberger et al. 1990; Branson et al. 1983; Gatti et al. 2003; Hartman et al. 1989; Hartman et al. 1990; Manco-Johnson and Nuss 1992; Pegelow et al. 1988; Pulido et al. 1987; Tarras et al. 1988; Yuen et al. 1986). Moreover,

there is concern about the long-term effect of coumarin derivatives on bone matrix protein in growing children (Barnes et al. 2002; Dreyfus et al. 1995; Menon et al. 1987).

Heparin, though not successful when given alone, may be a useful adjunct to PC replacement therapy (Loop et al. 2004; Majer et al. 1989; Marciniak et al. 1985; Marlar et al. 1992; Rappaport et al. 1987; Sills et al. 1984). However, there is a risk of heparin-induced thrombocytopenia (HIT) and risk of osteoporosis with long-term use, especially in children (Gatti et al. 2003; Massicotte 2000).

Successful prophylactic use of LMWH was reported in a child who presented with a deep vein thrombosis (DVT) and a measurable PC activity of 7% (Monagle et al. 1998). A further successful treatment with LMWH was reported in a patient with myeloid/natural killer cell precursor acute leukemia who was also homozygous for PC deficiency (Shimamoto et al. 2003). Although the disadvantages of long-term use of LMWH in children have not yet been thoroughly evaluated, the incidence of HIT and osteoporosis seems to be less with LMWH than with coumarin or heparin (Dix et al. 2000; Massicotte 2000; Streif et al. 1999).

Liver transplantation has been performed in a small number of pediatric patients with congenital PC deficiency as an alternative to PC replacement therapy (Kroiss and Albisetti 2010). Although liver transplantation was curative for severe congenital PC deficiency in a few cases, it necessitates lifelong immunosuppression and is associated with a potential risk of autoantibody formation against protein C produced by the transplanted organ, due to polymorphism (Casella et al. 1988).

Severe congenital PC deficiency being a lifelong condition, long-term prophylaxis with CEPROTIN could prevent thromboembolic complications and overcome the drawbacks of alternative treatment options.

2.1.2. About the product

CEPROTIN is a human, plasma-derived, monoclonal-purified concentrate of protein C.

CEPROTIN 500 IU is prepared as a powder containing nominally 500 IU human protein C per container. CEPROTIN 1000 IU is prepared as a powder containing nominally 1000 IU human protein C per container. The product is reconstituted with Sterilised Water for Injections and contains approximately 100 IU/ml human protein C. The currently recommended initial dose of CEPROTIN in the EU is 60 to 80 IU/kg considering the recovery and half-life of the product in the patient.

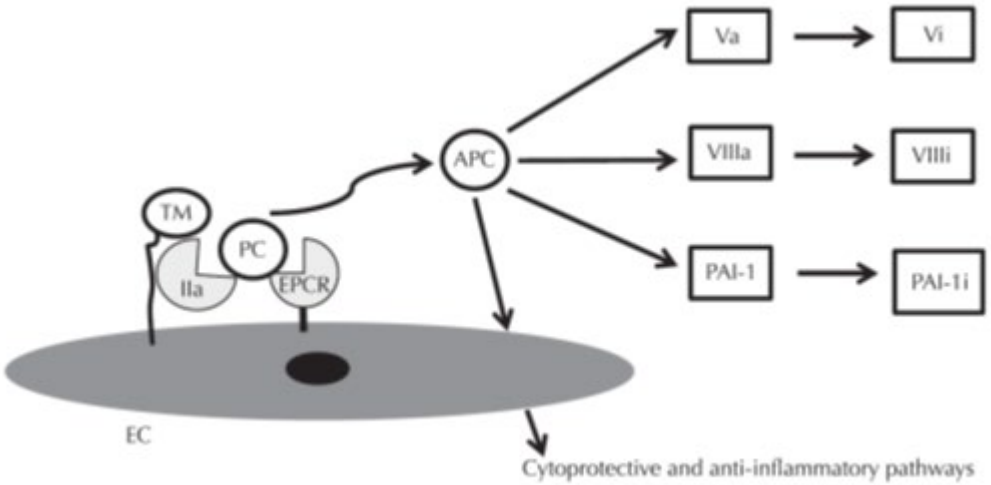
The product is also licensed in the USA with a recommended initial dosing of 100 to 120 IU/kg bodyweight and with 45-60 IU/kg bodyweight every 12 hours for LTP.

Pharmacological classification and Mode of action

Protein C, a vitamin K-dependent zymogen, is converted by the thrombin/thrombomodulin-complex and on the endothelial cell surface to activated protein C (APC), enhanced by the endothelial protein C receptor (EPCR). In the presence of its cofactor protein S (another vitamin K-dependent protein), APC exerts antithrombotic effect by limited proteolysis of the activated forms of factor V (Va) into Vi and factor VIII (VIIIa) into VIIIi, thus leading to a decrease in thrombin formation, which is known as coagulation promoting factor.

In addition, APC displays indirect fibrinolytic properties by binding to plasminogen-activator inhibitor-1 (PAI-1), resulting in an increase in the activity of tissue-type plasminogen activator. Furthermore, because of reduced thrombin generation resulting from inactivation of factors Va and VIIIa, the activation of thrombin activatable fibrinolysis inhibitor (TAFI) is reduced, thus resulting in increased profibrinolytic activity. Protein C also exhibits cytoprotective and anti-inflammatory properties. Biologic roles of protein C are shown in Figure 1.

Figure 1. Biologic roles of protein C



Abbreviations: APC = activated protein C; EC = endothelial cells; EPCR = endothelial protein C receptor; IIa = Thrombin; PAI-1 = plasminogen-activator inhibitor-1; PAI-1i = inactivated plasminogen-activator inhibitor-1; PC = protein C; TM = thrombomodulin; Va = activated forms of factor V; VIIIa = activated forms of factor VIII; Vi = inactivated forms of factor V; VIIIi = inactivated forms of factor VIIIa

Source: Dinarvand P et al, 2019

Current wording for the indication and posology

In the EU, CEPROTIN is indicated in purpura fulminans and coumarin-induced skin necrosis in patients with SCPCD. Furthermore, CEPROTIN is indicated for short-term prophylaxis in patients with SCPCD if one or more of the following conditions are met:

- surgery or invasive therapy is imminent
- while initiating coumarin therapy
- when coumarin therapy alone is not sufficient
- when coumarin therapy is not feasible

The recommended dosing is based on laboratory assessment for each individual case starting with an initial dose of 60 to 80 IU/kg for determination of recovery and half-life. It is recommended to achieve an initial protein C activity of 100% which should be maintained above 25% for the duration of the treatment.

In the case of an acute thrombotic event laboratory measurements should be performed every 6 hours until the patient is stabilised, thereafter twice a day and always immediately before the next injection. It should be kept in mind that the half-life of protein C may be severely shortened in certain clinical conditions such as acute thrombosis with purpura fulminans and skin necrosis (see SmPC).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH is providing an analysis of patients with SCPCD who received long-term prophylactic treatment. Re-analysis of the pivotal study 400101 was performed to address the CHMP position stated in the Scientific Advice letter (EMA/SA/0000050543) and to strengthen the position of LTP in patients with SCPCD. The proposed labeling and the supportive clinical data were presented on 07 December 2021 to the Paul-Ehrlich-Institute (CHMP Rapporteur of CEPROTIN) in a Scientific Advice meeting.

2.1.4. General comments on compliance with GCP

All treatments reported in the RDC (IMAG-039, IMAG-041 and compassionate use) were conducted in accordance with the requirements of the Declaration of Helsinki and the national requirements in the participating countries; however, they were not always conducted in full compliance with the standards of Good Clinical Practice (GCP). Treatment with Protein C Concentrate, which was considered lifesaving, often took priority over meeting GCP standards and complying with the study protocols.

Studies IMAG 098, 400101, 400501, and 400701 were performed in full compliance with GCP standards and with the national requirements of the participating countries.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Conclusion on the non-clinical aspects

This application for a Type II variation to modify the approved therapeutic indication to include long-term prophylaxis in the labeling may result in a significant increase in use; therefore, the MAH is providing an evaluation of environmental impact as per the guideline (EMEA/CHMP/SWP/4447/00 corr 2).

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of Human protein C.

Considering the above data, Human protein C is not expected to pose a risk to the environment as CEPROTIN contains a naturally occurring human protein as the active pharmaceutical ingredient, and that this product is isolated from human blood/plasma, the medicinal product is not expected to pose a risk to the environment. Thus, further studies evaluating the environmental impact of CEPROTIN are not necessary.

2.3. Clinical aspects

2.3.1. Introduction

GCP

Please see above statement with regards to compliance with GCP.

- Tabular overview of clinical studies

Table 1. Overview of Clinical Studies in Congenital PC Deficiency

PK study:

IMAG-098 A Clinical Study on the Pharmacokinetics of Protein C Concentrate (Human) Vapour Heated in Asymptomatic Subjects with Homozygous or Double Heterozygous Congenital Protein C Deficiency	1999-2003	Open-label, non-controlled, non-randomized, multicenter, international (EU, USA) study	To obtain PK data in asymptomatic subjects with homozygous or double heterozygous congenital PC deficiency	13	Single test dose of 80 IU/kg	PK parameters Acute safety in terms of laboratory parameters and Adverse events, including the transmission of viral infection and the development of inhibitors

Overview of Clinical Efficacy Studies with CEPROTIN in Subjects with Severe Congenital PC Deficiency:

Study ID	Design	Study Dates	Objectives	Subjects	Treatment / CEPROTIN Dose	Efficacy endpoints / parameters evaluated
RDC (IMAG-039, IMAG-041, and Compassionate Use) Retrospective Data Collection on the Use of Protein C Concentrate for Treatment of Protein C Deficiency: Clinical Studies IMAG-039 and IMAG-041 and Compassionate Use	Retrospective; open-label, multicenter, international	Subjects were treated between October 1989 and July 1999.	To evaluate the efficacy and safety of CEPROTIN in subjects with protein C deficiency, with or without PF or CISN	79 (42 M / 37 F) subjects: 22 with severe congenital (homozygous or double heterozygous) PC deficiency 57 subjects with simple heterozygous, acquired, other or unknown PC deficiency.	CEPROTIN doses determined by the investigator after evaluating responses to a test dose of 10 IU/kg BW and an initial therapeutic dose of 40 IU/kg BW. Duration: from 1 day to 2,239 days	Regression of skin lesions and dissolution of thrombotic occlusions present at study entry; for short-term and long-term prophylaxis: prevention of thrombotic events and skin lesions during treatment.
400101[a] A Phase 2/3 Clinical Study for the Determination of the Efficacy and Safety of Protein C Concentrate in Subjects with Severe Congenital Protein C Deficiency	Prospective, open-label, non-controlled, non-randomized, 3-part Phase II/III study	Study duration: 1.6 years Date of first enrolment: 22 August 2003 Date of last subject completed: 17 March 2005	To demonstrate that CEPROTIN is safe and effective in subjects with congenital protein C deficiency in the following indications: 1) acute thrombotic episodes; 2) short-term thromboembolic prophylaxis; and 3) long-term prophylactic treatment of acute thrombotic episodes.	18 (9 M / 9 F) subjects with severe congenital PC deficiency enrolled of which 15 (8 M / 7 F) subjects treated	CEPROTIN dose was dictated by the study part that the subject was enrolled in at the time of treatment Duration: 1.6 years	Evaluate whether episodes of PF, CISN (WISN) and/or other thromboembolic events can be treated effectively, effectively with complications, or not treated effectively.

Study ID	Design	Study Dates	Objectives	Subjects	Treatment / CEPROTIN Dose	Efficacy endpoints / parameters evaluated
400501 A Retrospective Study to Capture Dosing and Treatment Outcome Data in Subjects with Severe Congenital Protein C Deficiency Who Were Treated with Protein C Concentrate Under an Emergency IND	Retrospective, open-label, multicenter	Studied period: 7 months Date of first enrolment: June 2005 Date of last subject completed: December 2005	To capture dosing and treatment outcome data for subjects who were treated with CEPROTIN under an Emergency Use IND, as requested by the FDA for consideration of marketing authorisation of CEPROTIN.	11 (6 M / 5 F) subjects with severe congenital PC deficiency requiring treatment with CEPROTIN under an emergency use IND	CEPROTIN dosing was determined for each subject individually by the investigator. Durations on Emergency Use INDs ranged from 21 to 2,134 days.	- Dosage information - Indication of whether dosing was for treatment of acute episode or prophylaxis - Peak and trough levels of Protein C activity - D-Dimer levels during treatment for acute episodes - Time until healing of necrotic and non-necrotic lesions - Time until resolution of vascular thrombi (using vascular imaging) - Additional anticoagulants used - Duration of treatment under Emergency Use IND - Treatment outcome

Study ID	Design	Study Dates	Objectives	Subjects	Treatment / CEPROTIN Dose	Efficacy endpoints / parameters evaluated
400701 CEPROTIN Treatment Registry	Prospective, international, multicenter, open-label, non-interventional, observational, post-authorisation registry	Start of data collection: 23 June 2010 End of data collection: 22 June 2015	To collect and assess data in the real-world situation on the treatment, safety, and treatment outcomes of subjects prescribed and receiving CEPROTIN and participating in the CEPROTIN treatment registry	25 (13 M/12 F) subjects with severe congenital PC deficiency (Of 43 subjects, 25 had severe congenital PC deficiency and 18 had acquired PC deficiency.)	Dosing according to the investigator and local standard of care 3 main categories: - Treatment of acute thrombotic episodes - Short-term replacement (≤3 months) - Long-term Prophylaxis (>3 months) At enrollment: 19/25 subjects on long-term prophylaxis, 2/25 subjects on short-term replacement for surgery. Duration in Registry: 0.9 to 59.9 months	-) Medical diagnoses associated with CEPROTIN treatment -) CEPROTIN treatment regimens -) Relationship between CEPROTIN treatment and treatment outcomes -) Treatment outcomes in different settings (e.g., pregnancy, labor, delivery, surgery, different age groups, pre-existing renal and/or hepatic dysfunction)

Abbreviations: BW = body weight; CISN = coumarin-induced skin necrosis; F = female, FDA = Food and Drug Administration, IND = Investigational New Drug, IU = International Unit(s); M = male; PC = protein C (e.g.: PC deficiency); PF = purpura fulminans; RDC = retrospective data collection; WISN = wafarin-induced skin necrosis

[a] The results of Study 400101 have been published.(Manco-Johnson et al. 2016)

Study 400101: Study designed to meet the different licensing requirements set forth by the EMA and FDA.
Study 400501: Study requested by the FDA for consideration of marketing authorization of CEPROTIN in the USA.

2.4. Clinical efficacy

2.4.1. PK characteristics

Table 2: Overview of PK characteristics of Ceprotin in congenital protein C deficiency

	RDC	IMAG-098	400101
Design	Retrospective	Prospective, non-controlled, non-randomized	Prospective, non-randomized
No. of subjects	6[a]-7	13	6
Male **Female**	4 3	6 7	2 4
Asymptomatic subjects **Symptomatic subjects (acute symptoms)**	2 5	13 0	6 0
Age distribution (years) **Subjects aged ≤ 3 years**	0-39 3	1-30 1	3-16 1
Half-life (h)	5.6 [1.1-9.7] (comp) 6.0 [1.4-10.5] (non-comp)	9.9 [4.4-15.8] (comp) 10.0 [4.9-14.7] (non-comp)	ND
Terminal half-life (h)	ND	ND	12.1 [7.8-15.1]
***In vivo* recovery (%)**	41.4 [11.4-87.1][a]	66.8 [25.9-83.2]	ND
Incremental recovery (IU/dL per IU/kg)	1.1 [0.2-2.3]	1.38 [0.5-1.73]	1.5 [1.3-1.6]

Values as median [range]

Abbreviations: comp = compartmental method; h = hour; IU = International Unit; ND = not determined; non-comp = non-compartmental method; PK = pharmacokinetic; RDC = retrospective data collection

[a] In vivo recovery not analyzed for one subject since hematocrit was not available.

As shown in the table above, the median half-life of CEPROTIN in asymptomatic subjects (IMAG-098) was found to be approximately 10 hours. This is supported by findings in the literature (Auberger 1992; Dreyfus et al. 1991; Dreyfus et al. 1995; Hertfelder et al. 2002).

However, the presence of acute symptoms, such as PF, DIC and acute thrombosis, can alter the PK parameters of CEPROTIN, e.g., by accelerating its consumption, reducing its *in vivo* recovery (IVR) and decreasing its half-life. Patients treated during the acute phase of their disease may display much lower increases in PC activity. Half-life values as short as 2 hours have been reported in the literature (Dreyfus et al. 1995). Therefore, coagulation parameters should be checked regularly due to the wide variation in individual responses to the effects of CEPROTIN.

With regard to the PK of CEPROTIN in children, analyses of PK data showed that there is a difference in distribution, metabolism and elimination of CEPROTIN between children and adults. The half-life is shorter and clearance of protein C is faster in younger than in older subjects. This fact must be considered when a dosing regimen for children is determined. Neonates and very young children may require higher doses than adults.

2.4.1. Main study

Study 400101, A Phase 2/3 Clinical Study for the Determination of the Efficacy and Safety of Protein C Concentrate in Subjects with Severe Congenital Protein C Deficiency

Study design and methods

This was a multicenter, open-label, non-randomized, 3-part study evaluating the efficacy and safety of Protein C Concentrate in subjects with severe congenital protein C deficiency at 13 study sites in the United States.

Part 1 of the study evaluated the efficacy and safety of Protein C Concentrate in the on-demand treatment of acute thrombotic episodes, such as PF, CISN, and vascular thrombosis. In subjects presenting with skin lesions, the severity of skin lesions was assessed during screening. In subjects presenting with vascular thrombosis, imaging was used to identify the location and extent of the thrombus. The efficacy of treatment for each episode in Part 1 was rated based on a 4-point scale (excellent, good, fair, and not effective). D-dimers were monitored to determine the resolution of disseminated intravascular coagulation (DIC) in subjects with PF or CISN.

Part 2 of the study evaluated the efficacy and safety of Protein C Concentrate in the short-term prophylaxis of acute thrombotic episodes during surgery, during the postpartum period and for initiation of oral or parenteral anticoagulation therapy. In addition, subjects could enter Part 2 at the discretion of the investigator during transition from parenteral to oral anticoagulant therapy or from oral to parenteral anticoagulant therapy. Subjects who received short-term prophylaxis with Protein C Concentrate for thrombotic complications were evaluated descriptively.

Part 3 of the study was designed to evaluate the efficacy and safety of Protein C Concentrate for long-term prophylactic treatment of acute thrombotic episodes. Originally, subjects were eligible for this part of the study if they: (a) had been treated in Part 1 of this study at least 3 times due to failure of oral or parenteral anticoagulant therapy despite compliance with their prescribed regimen; (b) had a documented contraindication for anticoagulation therapy; or (c) were on long-term prophylaxis treatment with Protein C Concentrate in another study or under emergency use provisions prior to study entry. Originally there was also no time limit for participation in Part 3. Amendment 1 to the Protocol, dated June 21, 2004, stipulated that only subjects less than 6 months of age were permitted to enroll in Part 3, and that the duration of prophylaxis with Protein C Concentrate was limited to a total of 6 months.

Study participants

- Newborn subjects ≤6 months of age: diagnosis of severe congenital protein C deficiency, with documented functional protein C level of <20%. If a genetic diagnosis was not available prior to initiation of Protein C Concentrate treatment, a documented family history of protein C deficiency was required.
- Subjects >6 months of age: confirmed diagnosis of severe congenital protein C deficiency, i.e., by:
    - a genetic analysis of severe congenital protein C deficiency (i.e., homozygous or double heterozygous) OR

- a documented family history of protein C deficiency AND a documented functional protein C level <20% while the subject was in an asymptomatic state and not receiving oral anticoagulation therapy.

Additional Inclusion Criteria for Part 1

- Diagnosis of PF (characteristic cutaneous purpuric lesions involving erythema, induration, and pain) or CISN, and/or
- Diagnosis of acute thromboembolic episode including the determination of thrombus location.

Additional Inclusion Criteria for Part 2

- Subjects requiring treatment with Protein C Concentrate for short-term prophylaxis for surgical procedures, during the postpartum period, or for initiation of oral or parenteral anticoagulation therapy.
- Subjects had to be in an asymptomatic state prior to treatment as defined by the absence of any signs/symptoms of thrombosis (e.g. PF, CISN, or thromboembolic event).

Additional Inclusion Criteria for Part 3

- Infants <6 months of age
- Subject had to be in an asymptomatic state prior to treatment in Part 3 as defined by the absence of any signs/symptoms of thrombosis (e.g. PF, CISN, thromboembolic disease or clinical evidence of DIC).

Treatments

Treatment in Part 1:

Upon presentation with an acute event, the subject was to be infused with Protein C Concentrate at a dose of 120 IU/kg body weight (BW). This initial infusion was to be followed by 3 infusions of 60 IU/kg BW at an interval of every 6h. Doses for all subsequent infusions were to be based on the peak protein C level after the first dose (15±5 minutes after infusion) and were to be given once every 6h. Treatment was to continue until complete resolution of all non-necrotic lesions, healing of necrotic lesions and/or stabilization of thrombi.

Treatment in Part 2:

Surgery

For elective surgery (non-emergency), Protein C Concentrate treatment was to be initiated at 120 IU/kg BW once daily until anticoagulation was successfully discontinued prior to surgery. For emergency surgery, one dose of 100 IU/kg BW was to be given during the anticoagulation reversal period prior to surgery.

A dose of 60 IU/kg BW was to be administered 15 minutes before surgery and once every 6h for the first 24h after the start of surgery. The frequency of infusions was to be reduced to 3 times daily between 24 and 48h, and twice daily from 48h until anticoagulation was initiated (if applicable) and adequate levels were reached. Subsequently, Protein C Concentrate was to be administered once daily at the same dose for an additional 48h before it was discontinued.

Initiation of Anticoagulant Therapy (oral or parenteral)

A dose of 60 IU/kg BW was to be administered upon initiation of anticoagulation, every 6h for the first 24h, and reduced to 3 times daily between 24 and 48h. Infusions were to continue twice daily until 48h after adequate anticoagulation had been achieved (as specified in the study protocol), and once daily for an additional 48h thereafter before it was discontinued.

Short-term Prophylaxis during the Postpartum Period

The initial dose of 80 IU/kg BW was to be administered within 1 hour (h) after delivery. A dose of 60 IU/kg BW was to be administered once every 6h for 4 additional doses (until 24h after delivery), reduced to 3 times daily between 24 and 48h, twice daily from 48h until anticoagulation was initiated and adequate levels were reached, and once daily for an additional 48h thereafter.

Treatment in Part 3:

The dosing regimen was to be established by the investigator based on the subject's prior clinical data including any pharmacokinetic information, with the objective of preventing the trough (pre-infusion) levels from falling below 25% (or 10% for subjects on long-term anticoagulant treatment). The first 3 doses had to be administered at the clinic/hospital. Pre- and 15 minute post-infusion levels were to be determined for all 3 doses, and the dose or frequency of infusions could be adjusted. Once a stable dosing regimen had been established, this was to be applied during home treatment for a maximum of 6 months (as instituted by Amendment 1 of the study protocol). The pre- and post-infusion levels were to be measured at least once every 2 months (±2 weeks) to determine the adequacy of dosing.

If a subject experienced a thrombotic episode during long-term prophylactic treatment or required surgery, the subject was to be admitted to hospital and treated under the provisions of Part 1 or Part 2 of the study until complete resolution of all thrombotic symptoms and DIC.

Objectives

The objective of this study was to demonstrate that Protein C Concentrate is safe and effective in subjects with congenital protein C deficiency in the following indications: 1) for the treatment of acute thrombotic episodes, such as PF, CISN and other vascular thromboembolic events; 2) for short-term thromboembolic prophylaxis during surgical procedures, the postpartum period and the initiation of oral or parenteral anticoagulation; and 3) for long-term prophylactic treatment of acute thrombotic episodes.

Outcomes/endpoints

Primary Endpoint:

Whether episodes of PF, CISN and/or other thromboembolic events were able to be treated effectively, effectively with complications, or not treated effectively.

Secondary Endpoints:

1. Percentage of episodes of PF and thrombotic events in which the efficacy of treatment was rated as excellent, good, fair or none according to a predefined scale (Part 1).
2. Mean and median percent change, from baseline (at presentation) in the number and size of skin lesions of acute episodes of PF treated with Protein C Concentrate at treatment Days 0 6, 14, 28 and at the day of establishment of effective anticoagulation (Part 1).

3. The extent of venous thrombus (extended, retracted and/or canalized, or remained the same) for acute venous thromboembolic episodes at baseline and on treatment Days 2-3 and 4-5 and at the establishment of effective anticoagulation was to be assessed from imaging scans (Part 1).
4. Mean time to normalization of D-dimer levels (as indicator of DIC) for episodes of PF (Part 1).
5. Median number of infusions required, mean and median dose prior to normalization of D-dimer levels, and mean and median dose during the period of the establishment of an oral anticoagulation regimen as well as total dose per episode (Part 1).
6. Percent of infusions per subject that resulted in peak levels within the range of 65 – 300% for protein C (Parts 1 and 2).
7. Percent of infusions per subject that resulted in trough levels of protein C activity of 25% or higher for all subjects treated for acute episodes or short-term prophylaxis (Parts 1 and 2).
8. Percentage of surgical episodes and other treatments, for which Protein C Concentrate was utilized as short-term prophylaxis, that were free of presentations of PF or thromboembolic complications (Part 2).
9. Number of episodes of PF and/or thrombotic episodes while receiving long-term Protein C Concentrate prophylaxis (Part 3).
10. Percentage of subjects presenting with long-term impairment assessed by physical examination at baseline, Months 12 and 24, and at study termination. Mean number of body systems per subject with a long-term impairment at baseline, Months 12 and 24, and study termination. Data on the permanent loss of the limb or organ is reported in the section describing the long-term impairment endpoint (Parts 1, 2 and 3).
11. Number of subjects who develop inhibitors to protein C (Parts 1, 2 and 3).
12. Tabulation of AEs according to seriousness, severity, causality and outcome; number of AEs per subject related to product use that resulted in discontinuation or interruption of treatment (Parts 1, 2 and 3).
13. Pharmacokinetic parameters of protein C in asymptomatic subjects (AUC, terminal half-life, volume of distribution, mean residence time [MRT]) (Parts 1, 2 and 3).

Sample size

Due to the small number of subjects with this disorder, no minimum sample size was specified for this study. The expected number of subjects to be enrolled was approximately 15 to 20 over 2 years. Part 1 was expected to treat 15 to 30 acute thromboembolic events. Part 2 was expected to involve 5 to 10 subjects with severe congenital Protein C deficiency. The sample size for Part 3 was expected to be very small.

Total: 18 patients enrolled of which 3 did not receive study drug

Part 1: 11 subjects analysed for (primary and secondary) efficacy and safety

Part 2: 3 subjects analysed for efficacy and safety

Part 3: 8 subjects analysed for efficacy and safety

Randomisation

It was planned not to randomize study subjects.

Blinding (masking)

The trial was uncontrolled and hence unblinded.

Statistical methods

The MAH set out to estimate the likelihood of the observed configuration under the assumption that there is no difference between the two modalities (On Demand (OD) and Prophylaxis) in the rates of these events. The calculated probability of the observed configuration indicates that it is highly unlikely to have occurred if there was no difference between OD and Prophylaxis.

Primary and secondary endpoints for Study Part 3

Subjects in the prospective study were planned to be treated for episodes of purpura fulminans, Coumarin-induced skin necrosis and/or other vascular thromboembolic events. Treatment of these episodes and of episodes in the historical control (see Section 14.0 in version 2 of the protocol, dated April 1, 2003) were planned be evaluated as effective, effective with complications, and not effective for skin lesions and other vascular thromboembolic events separately. The treatment of 1 episode (treatment course) was planned to may be comprised of 1 or more treatment modalities. The following definitions were planned to apply (skin lesions/other vascular thromboembolic events):

Individual treatment modality (drug/drug combination, dose, frequency):

1. Effective: stabilization and regression of skin lesions/stabilization of thrombi

2. Effective with complications: effective treatment caused an adverse drug reaction interfering with the treatment regimen (resulted in change of dose or frequency of dosing) or forcing discontinuation of treatment or introducing pathogenic viral infection

3. Not effective: All other

Treatment course (sequence of treatment modalities):

1. Not effective: The final treatment modality was ineffective and/or the subject was not discharged on a stable anticoagulation regimen

2. Effective with complications: The final treatment modality was effective (possibly with complications) and the subject was discharged on a stable anticoagulation regimen, but 1 or more of the treatment modalities were effective with complications.

3. Effective: The final treatment modality was effective and the subject was discharged on a stable anticoagulation regimen. Ineffective treatment modalities are disregarded, because in the historical control they may have been applied before the proper diagnosis of Protein C deficiency was available (e.g. antibiotics for presumed sepsis).

Episodes of purpura fulminans or thrombotic events, which receive treatment that is not specified in the study protocol, will nevertheless be rated according to the primary efficacy endpoint. Analysis of efficacy both including and excluding these episodes will be conducted.

The secondary endpoint addressed by Study Part 3 was planned to be: The number of episodes of purpura fulminans and/or thrombotic episodes while receiving long-term Protein C Concentrate prophylaxis.

Analysis of the Primary Endpoint

The comparison to historical controls was planned to be separate for skin lesions and other vascular thromboembolic events and was planned to be performed in a hierarchical testing design. First, effectiveness regarding skin lesions was planned to be compared in those episodes where subjects presented with purpura fulminans and/or Coumarin-induced skin necrosis. Only if this comparison would not be statistically significant, a second comparison regarding other vascular thromboembolic events was planned to be performed using the episodes with these symptoms. In this manner, no adjustment of the type I error was planned to be necessary, because a type I error can only occur in 1 of the 2 comparisons while all treated episodes are accounted for in the analysis of the primary endpoint.

The overall type I error would not be controlled across the analyses of the two endpoints following the approach described in the protocol and the study report. However, the null hypothesis corresponding to the comparison of skin lesions could be formally rejected and thus according to a hierarchical testing approach one could proceed to testing other vascular thromboembolic events (at full level alpha) while controlling the overall type I error rate.

The null hypothesis of no difference between the episodes of purpura fulminans, Coumarin-induced skin necrosis, and/or other vascular thromboembolic events in the prospective study and the historical controls was planned to be tested at the 5% level of overall statistical significance against a 2-sided alternative. Both individual hypothesis tests were planned to use the 5% level of significance, because the second test was planned to only be performed, if the first was not significant.

The evaluation of treatment (effective, effective with complications, and not effective) for skin lesions/other vascular thromboembolic events was planned to be analysed as ordered categorical data using the exact Wilcoxon rank sum test as implemented in StatXact 534 or SAS version 8.235. Exact mid-p values were planned to be reported to avoid conservativeness due to the discrete distributions.

Acute thrombotic episodes treated with FFP prior to treatment with Protein C Concentrate were planned to be reported, but not included for this formal comparison. These would have been treatments for subjects newly diagnosed at a center that has not been qualified for participation at the time of presentation of a new subject with an initial acute thrombotic episode.

Since more than 1 episode per subject were planned to be evaluated, a supplemental analysis was planned to consider subjects' first episodes only.

Multiplicity

A hierarchical testing design was planned to be used to avoid multiple testing. Skin lesions as the lead symptom of the disease were planned to be compared in a first statistical hypothesis test and other vascular thromboembolic events were planned to be analysed only if the first test was not significant.

Results

Participant flow

Not applicable.

Recruitment

No information provided.

Conduct of the study

No information provided.

Baseline data

Table 3: Baseline characteristics

Variable	Part 1	Part	Part 3
Gender:			
Female (n)	7	3	5
Male (n)	4	0	3
Race			
Caucasian (n)	11	3	5
Black (n)			1
Asian (n)			2
Age (Mean in years)	10.5 (0.0 – 25.7)	9.9	4.7 (0.0 – 21.7)
Height (Mean in cm)	121.0 (50.0 – 175.3)	120.3	90.0 (50.0 – 175.0)
Weight (Mean in kg)	32.0 (2.9-74.4)	30.8	16.9 (2.9 -68.0)
Protein C Deficiency			
Mild	0	0	0
Moderate	0	0	0
Severe	11	3	8
Protein C Genetic Analysis			
Homozygous	3	0	1
Double Heterozygous	6	2	5
Unknown	2	1	2

Numbers analysed, Outcomes and estimation

Part 1: Treatment of Acute Episodes of PF/CISN or Thromboembolic Events

A total of 24 episodes of PF/CISN or vascular thrombotic events in 11 subjects were treated with CEPROTIN in Part 1.

For the primary efficacy analysis, the treatment of episodes of PF/CISN and/or other vascular thromboembolic events was rated as *effective*, *effective with complications*, or *not effective* according to the primary efficacy rating scale. The primary efficacy ratings in this study were compared to those in an historical control group who were treated with conventional treatments other than CEPROTIN (e.g., FFP). Of 19 episodes of PF/CISN (7 severe, 11 moderate, 1 mild) treated with CEPROTIN, 18 (94.7%) were rated as *effective*, and 1 (5.3%) was rated as *effective with complications*; none of the PF/CISN episodes treated with CEPROTIN was rated as *not effective*. When compared with the efficacy ratings for 23 episodes of PF/CISN treated with conventional therapy (historical control group), the analysis showed that subjects with severe congenital PC deficiency were more effectively treated with CEPROTIN than with

other treatment modalities such as FFP or conventional anticoagulants (p=0.0032) (CSR 400101, Section 11.4.1.1).

In a secondary efficacy rating, 13 (68.4%) of 19 episodes of PF/CISN treated with CEPROTIN were rated as *excellent*, 4 (21.1%) were rated as *good*, and 2 (10.5%) episodes of severe PF/CISN were rated as *fair*; all were rated as *effective*. Four (80%) of 5 episodes of venous thrombosis had treatment ratings of *excellent*, while 1 (20%) was rated as *good*. When the secondary treatment ratings were combined for all 24 PF/CISN episodes and thrombotic events, 70.8% of the treatment episodes were rated as *excellent*, 20.8% were rated as *good*, and 8.3% were rated as *fair*. These results support the findings of the primary efficacy analysis (CSR 400101, Table 14.2.1-4).

CEPROTIN also proved effective in reducing the size and number of skin lesions. As expected, the change in size and number of necrotic lesions after treatment with CEPROTIN was slower than for non-necrotic lesions. While non-necrotic skin lesions healed over a 12-day period, necrotic skin lesions healed over a 52-day period of CEPROTIN treatment (CSR 400101, Section 11.4.1.2.2).

Part 2: Short-Term Prophylaxis

Three subjects entered Part 2 of the study for a total of 7 times for short-term prophylaxis treatment with study product. All 3 subjects entered Part 2 for initiation of anticoagulation therapy, and 2 of the subjects entered Part 2 also for surgical procedures. All 7 of the short-term prophylaxis treatments were free of complications of PF/CISN or thromboembolic events (CSR 400101, Table 14.2.2-6).

Part 3: Long-Term Prophylaxis

Eight subjects entered Study 400101 Part 3 for long-term prophylactic treatment with study product. The mean number of exposure days to on-site infusions was 14.1 (median 7.5), the mean number of exposure days to home infusions was 192.6 (median 183.0). The total mean volume administered was 182.9 mL (median 97.8 mL) for on-site infusions and 2,648.1 mL (median 3,000.6 mL) for home infusions.

Of the 8 subjects who entered Part 3 for a total of 10 times for long-term prophylactic treatment with CEPROTIN, 4 subjects actually received long-term prophylactic treatment in Part 3, and also received on-demand treatment at different times during the study. The number of days on long-term prophylactic treatment in these 4 subjects ranged from 42 to 338. No episodes of PF/CISN occurred in these subjects during the total of 915 days of prophylactic treatment with CEPROTIN. However, the same 4 subjects experienced 13 episodes of PF/CISN during 660 days while they were on on-demand treatment and did not receive product (Table 4).

Table 4. Study 400101: Summary of Monthly Rates of Episodes of PF/CISN and/or Thrombosis for Subjects Who Were On-Demand and Received Long - term Prophylactic Treatment

	On-Demand Treatment[a]			Long-Term Prophylactic Treatment		
Subject ID	# of Episodes	Number of Days Not Receiving Study Drug	Monthly Rate of Episodes[b]	# of Episodes	Number of Days Receiving Prophylactic Treatment	Monthly Rate of Episodes
	6	323	0.565	0	42	0.000
	2	246	0.247	0	198	0.000
	4	19	6.404	0	337	0.000
	1	72	0.422	0	338	0.000
Total	13	660		0	915	
Mean Rate			1.910			0.000
Minimum Rate			0.247			0.000
Maximum Rate			6.404			0.000
Median Rate			0.494			0.000
95% CI[c]			(0.247, 6.404)			(0.000, 0.000)

Abbreviations: PF=purpura fulminans; CISN=coumarin-induced skin necrosis; 95% CI=95% confidence interval
[a] On-demand is time in study when subjects were not receiving Protein C Concentrate and were not enrolled in Study Part 3.
[b] The denominator for the rate of episodes while subjects were on-demand is based on number of days subjects were not receiving Protein C Concentrate.
[c] 95% confidence intervals for the median are based on distribution-free methods in SAS proc univariate, option=CIPCTLDF, and as described in Zar, J. (1999), Biostatistical Analysis, 4th edition, p.543. The resulting confidence interval for median rates while subjects were on-demand provided 87% coverage.

Source: CSR 400101 Table 14.2.3-1

The number of episodes of PF/CISN and/or vascular thromboembolic events that occurred in all subjects in the study, whether they were treated on-demand or receiving long-term prophylactic treatment under Part 3 is summarized in Table 5. Three subjects were on-demand for the entire duration of the study. The total number of episodes of PF/CISN or vascular thromboembolic events that occurred during 1634 days of prophylaxis treatment for all subjects was zero. In comparison, a total of 31 episodes of PF/CISN or thrombosis were observed in 3687 days of not receiving study product while subjects were receiving treatment on-demand. Thus, the median rate of episodes during on-demand treatment was 0.24 per month (or approximately 3 episodes per year). The number of episodes that occurred while subjects were receiving treatment on-demand ranged from 0 to 6, including the additional episodes that were not treated with study product). Monthly rates of episodes of PF/CISN or vascular thromboembolic events while subjects were on-demand ranged from 0 to 6.4, with a median rate of 0.24 episodes per month and a 95% confidence interval for the median ranging from 0 to 0.57 episodes per month.

Table 5. Study 400101: Summary of Monthly Rates of Episodes of PF/CISN and/or Thrombosis for All Subjects

	On-Demand Treatment[a]			Long-Term Prophylactic Treatment		
Subject ID	# of Episodes	Number of Days Not Receiving Study Drug	Monthly Rate of Episodes[b]	# of Episodes	Number of Days Receiving Prophylactic Treatment	Monthly Rate of Episodes
	6	323	0.565	0	42	0.000
	3	399	0.229	NA	NA	NA
	6	102	1.789	NA	NA	NA
	2	246	0.247	0	198	0.000
	1	486	0.063	NA	NA	NA
	0	525	0.000	NA	NA	NA
	4	19	6.404	0	337	0.000
	0	330	0.000	NA	NA	NA
	1	373	0.082	NA	NA	NA
	4	366	0.332	NA	NA	NA
	NA	NA	NA	0	289	0.000
	NA	NA	NA	0	178	0.000
	NA	NA	NA	0	178	0.000
	1	72	0.422	0	338	0.000
	NA	NA	NA	0	73	0.000
	3	196	0.466	NA	NA	NA
	0	162	0.000	NA	NA	NA
	0	88	0.000	NA	NA	NA
Total	31	3687		0	1634	
Mean Rate			0.757			0.000
Minimum Rate			0.000			0.000
Maximum Rate			6.404			0.000
Median Rate			0.238			0.000
95% CI[d]			(0.000, 0.565)			(0.000, 0.000)

Abbreviations: PF=purpura fulminans; CISN=coumarin-induced skin necrosis; 95% CI=95% confidence interval
[a] On-demand is time in study when subjects were not receiving Protein C Concentrate and were not enrolled in Study Part 3.
[b] The denominator for the rate of episodes while subjects were on-demand is based on number of days subjects were not receiving Protein C Concentrate.
[c] Subject entered Part 1 at birth, and entered Part 3 directly thereafter. Therefore, this subject spent no time on-demand.
[d] 95% confidence intervals for the median are based on distribution-free methods in SAS proc univariate, option=CIPCTLDF, and as described in Zar, J. (1999), Biostatistical Analysis, 4th edition, p.543.
Source: CSR 400101 Table 14.2.3-2

The time to first episode treated in Part 1 after exiting from long-term prophylaxis treatment ranged from 12 to 32 days (Table 6).

Table 6. Time to First Episode of PF/CISN and/or Thrombosis For Subjects Who Transitioned Off Long-Term Prophylaxis Treatment

Subject ID	Date of Exit from Part 3	Date of 1st Episode treated in Part 1	Time to 1st Episode (days) (a)
	2003	2004	32
	2004	2004	28
	2004	2004	12
	2004	2004	21
Mean			23.3
Median			24.5

Study 400101 Post-hoc Randomization Test for Null Hypothesis of Same Frequency

The 18 subjects shown in Table 4 were analysed in a post-hoc randomization test of the null hypothesis of the same frequency while treated on demand versus prophylactically against the alternative hypothesis of a higher frequency during on-demand treatment. The estimated one-sided p-value for the randomization test is 7.5E-9 < 0.001, should indicate that there is a strong evidence based on the observed data against the null hypothesis that the frequency of PF/CISN and/or thrombosis is the same between on-demand and prophylaxis treatments, and thus in favour of a lower frequency on prophylaxis (Table 6).

Table 7. Study 400101: Analysis of Frequency of PF/CISN and/or Thrombosis by a Randomization Test

ID	On-demand/ Prophylaxis	On-demand		Prophylaxis		Probability under H0
		Events	Days	Events	Days	
	both	6	329	0	42	0.48380
	both	2	248	0	198	0.30864
	both	4	23	0	337	0.00001
	both	1	73	0	338	0.17762
	either	18	3045		718	0.02192

p-value (one-sided) = 7.5E-9 < 0.001
p-value (two-sided) = 2*7.5E-9 < 0.001
Abbreviations: CISN = coumarin-induced skin necrosis; PF = purpura fulminans
Source: Protein C 400101 Post-hoc Randomization Test

Long-Term Impairment

No major changes in long-term impairment were observed in terms of visual impairments and amputations for subjects treated with study product. One subject shifted from abnormal neurological status at baseline to improved status at end of study. These results show that deterioration in long-term impairment status did not occur while subjects were treated with CEPROTIN.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 8. Summary of Efficacy for trial 400101

Title: A Phase 2/3 Clinical Study for the Determination of the Efficacy and Safety of Protein C Concentrate in Subjects with Severe Congenital Protein C Deficiency			
Study identifier	400101		
Design	multicenter, open-label, non-randomized, 3-part study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	1 year and 7 months not applicable> not applicable	
Hypothesis	Superiority		
Treatments groups	On-demand	CEPROTIN n=14	
	Prophylaxis	CEPROTIN n=8	
Endpoints and definitions	Endpoint	Efficacy	Frequency of PF/CISN and/or Thrombosis
Database lock	Date not provided		
Results and Analysis			
Analysis description	**Post-hoc Analysis**		
Analysis population and time point description	Per protocol		

Descriptive statistics and estimate variability	Treatment group	On-demand	Prophylaxis
	Number of subject	14	8
	Monthly Rate of Episodes (Mean)	0.757	0.000
	Monthly Rate of Episodes (Median)	0.238	0.000
	95% CI	(0.000, 0.565)	(0.000,0.000)
Descriptive statistics and estimate variability	Treatment group	On-demand	Prophylaxis
	Number of subject	4 (the same as for prophylaxis)	4 (the same as for on-demand)
	Monthly Rate of Episodes (Mean)	1.910	0.000
	Monthly Rate of Episodes (Median)	0.494	0.000
	95% CI	(0.000, 6.404)	(0.000,0.000)

Effect estimate per comparison	Monthly Rate of Episodes	On-demand versus Prophylaxis	On-demand versus Prophylaxis
		Post-hoc Randomization Test for Null Hypothesis of Same Frequency	Post-hoc Randomization Test for Null Hypothesis of Same Frequency
		p-value (one-sided) = 7.5E-9 < 0.001	p-value (two-sided) = 2*7.5E-9 < 0.001

Supportive studies

Retrospective data

The RDC (retrospective data collection) of studies IMAG-039 and IMAG-041, and compassionate use was based on the procedures of study IMAG-039 and was designed to provide a comprehensive evaluation of the use of CEPROTIN from October 1989 to July 1999 in the US, Canada, and Europe. The investigational centres that had used CEPROTIN for IMAG-039, IMAG-041 and under compassionate use provisions, were contacted and consent for monitoring of the data was obtained from the subjects. Monitoring was subsequently conducted in these centres by collecting and verifying information against the source documentation in the medical records of the subjects. Complete data could not be collected for all subjects since the data spanned a period of almost 10 years (i.e., 1989-1999) and included compassionate use data for which the recording and monitoring requirements were not as rigorous. However, the data of 79 subjects (22 with severe congenital PC deficiency and 57 with simple heterozygous, acquired, other or unknown PC deficiency) were compiled and analysed.

Outcome of long-term prophylactic treatment

Nine subjects, of which 8 were homozygous and 1 was double heterozygous, received long-term prophylactic treatment for a period of up to 8 years. The efficacy of CEPROTIN was rated excellent in 7 subjects. The remaining 2 subjects were not evaluated by the investigator (Table 8). Home treatment was established for 6 subjects. Three subjects who received long-term prophylaxis under compassionate use provisions initially received the product by IV infusion, but were later switched to subcutaneous infusion following independent decisions made by the investigators (Table 9).

Table 9. RDC Dataset I: Outcome of Treatment with CEPROTIN for Long-Term Prophylaxis in Subjects with Severe Congenital PC Deficiency

Subject ID	Method of Manufacture (Method I or II)[a]	Duration of Treatment (DD/MM/YY)	Investigator`s Evaluation of Overall Success
Homozygous	I/II	93 - ongoing[b]	Excellent
Homozygous	I/II	92 - ongoing[b]	Excellent
Homozygous	II	95 - ongoing[b]	Excellent
Homozygous	I/II	92 - ongoing[b]	Excellent
Homozygous	I	89 –92 intermittent	Excellent
Homozygous	II	95 –95 97 - ongoing[b]	Excellent
Homozygous	I/II	92 - ongoing[b]	Excellent
Homozygous	II	95 - 96 96 - ongoing[b]	Not evaluated
Double Heterozygous	II	98 - ongoing[b]	Not evaluated

Source: CSR RDC, Section IV.11.4.1.1.3, Table 11.4.1.1.3
[a] Method I refers to Protein C Concentrate manufactured prior to 1992. Method II refers to CEPROTIN (Protein C Concentrate) manufactured according to the method used since 1992. In 1992, the manufacturing process was modified to include a second viral inactivation step as well as other changes in the chromatography purification steps. Key differences between the current and previous methods (Method I and Method II) are summarized in Table 2 of the Summary of Biopharmaceutic Studies (Module 2.7.1).
[b] Ongoing at the time of the clinical study report. The date of the report is 16 November 2000.

Narratives of the 9 subjects who received long-term prophylaxis are available.

In most cases, the selection and timing of the dose used for each individual subject was determined by the investigator on the basis of the clinical status of the subject rather than on the basis of protocol-specified individual PK data. For treatment of acute thrombotic episodes, the dose, replacement frequency and the duration of treatment depended on the severity of PC deficiency as well as the location and extent of thrombosis. The determination of dose based on clinical status was necessary either because the frequent blood sampling required for individual PK data could not be achieved in many subjects (particularly in neonates and infants) or because the product was administered in a life-threatening situation. A number of investigators used doses of 100 IU per kg BW every 6 h during the acute phase of thrombosis. After the clinical symptoms regressed, the frequency of CEPROTIN administrations was generally reduced to once per day (CSR RDC, Section IV.10.2.2).

Study 400501

A total of 11 subjects (6 male and 5 female) were enrolled at 10 study sites in the US. All subjects had a diagnosis of severe congenital PC deficiency. Age ranged from 2.1 years to 23.8 years (CSR 400501, Table 16.2.4-1). No efficacy analyses were carried out in this study. Only subject data listings are available.

Treatment Outcome

There were 28 acute episodes reported, in which the time to resolution ranged from 0 to 46 days. The treatment outcome for these episodes was considered effective in all cases except one (PF/CISN and

vascular thrombus). Subjects developed PF/CISN when not being treated with CEPROTIN. Initiation of therapy with CEPROTIN resolved PF/CISN in all subjects. Some subjects developed PF/CISN while on anticoagulation therapy. However, these episodes were also resolved upon treatment with CEPROTIN (CSR 400501, Table 16.2.6-3, Table 16.2.6-5).

Dosage Information

For acute episodes, the doses varied from 75 to 4040 IU per administration and the weight-adjusted doses from 28.85 IU/kg BW to 186.77 IU/kg BW. For prophylactic episodes, the doses varied from 112 to 4040 IU per administration and from 19.46 IU/kg BW to 291.67 IU/kg BW (CSR 400501, Table 16.2.5).

A listing of additional anticoagulants, anti-platelets, and systemic thrombolytics given to 11 subjects during the entire treatment period with CEPROTIN is shown in CSR 400501, Table 16.2.10-1, Table 16.2.10-2. Some subjects did not tolerate anticoagulant treatment and were maintained on prophylactic doses of CEPROTIN (Table 16.2.6-5, Table 16.2.6-6).

Study 400701 CEPROTIN Treatment Registry

Study design and methodology

The study was designed as a prospective, international, multi-center, open-label, noninterventional, observational post-authorization registry under normal clinical care. Some retrospective, historical data were also collected. Participants were identified in collaboration with hemophilia treatment centers and thrombosis centers known to have subjects with severe congenital protein C deficiency, as well as with centers that used CEPROTIN in emergent care situations (for severe acquired protein C deficiency [SAPCD]). Being a non-interventional registry study, there were no required predefined visits, medical tests, laboratory tests and/or procedures or interventions during the registry's duration. All data collected in this registry originate from patient medical records documenting routine patient care. Both new users and current (prevalent) users of CEPROTIN were included in the registry.

The registry was conducted at participating centers in Austria, Germany, Italy, the Netherlands, the United Kingdom and the United States of America.

Study participants

Patients with congenital protein C deficiency as well as those with acquired protein C deficiency treated with CEPROTIN.

Planned: There was no minimum pre-specified sample size.

All 43 eligible subjects at 24 participating sites were enrolled and analyzed in the registry.

Objective

The overall objective was to collect and assess data in the real-world situation on the treatment, safety, and treatment outcomes of subjects prescribed, receiving, and participating in the CEPROTIN treatment registry.

Primary Objectives included:

1. To identify medical diagnoses associated with subjects receiving CEPROTIN
2. To record CEPROTIN treatment regimens categorized by medical diagnosis

3. To assess the safety of CEPROTIN based on incidence of all serious adverse events (SAEs), related SAEs, and related non-serious adverse events (AEs)

Secondary objectives of the study included:

1. To examine relationships between CEPROTIN treatment and treatment outcomes: evidence of halting or reversal of coagulopathy or thrombosis, endorgan damage (including brain, lung, liver, kidney and other relevant affected organs), limb sparing, length of hospital stay (LOS), and mortality
2. To record information on CEPROTIN use and treatment outcomes in:
    - Pregnancy, labor and delivery
    - Surgery and invasive procedures
    - Different age groups
    - Pre-existing renal and/or hepatic dysfunction

Results

Efficacy of CEPROTIN treatment was collected both retrospectively and prospectively.

Patient characteristics

Twenty-five subjects diagnosed with severe congenital PC deficiency were enrolled in the registry. Subjects were evenly distributed by gender (13 subjects [52.0%] were male and 12 [48.0%] were female). Nearly one-half (48%) of the subjects were children between the ages of 2 and 12 years. The median duration of participation was 39.7 months (range: 0.9 to 59.9 months) with a total of 80.9 subject-years on-study at the time of the final analysis. Most subjects (19/25) received long-term prophylaxis. These subjects participated for a median of 40.2 months (range: 24.0-56.1 months) in the registry (mean ± SD: 40.2 ± 9.41 months).

Subjects were diagnosed with severe congenital PC deficiency at a median age of 0.0 years (range: 0.0 to 19.9 years) and entered the study at a median age of 11.1 years (range: 1.3 to 43.7 years) (CSR 400701 Table 12.1 and Table 2.1). Associated medical diagnoses were analyzed and included 16 (47.1%) cases of PF in 16 subjects (rated severe in 13 subjects and moderate in 3 subjects). There were 18 (52.9%) cases of thromboembolic disorders: 3 severe DIC, 2 severe PE, 5 DVT (2 moderate and 3 severe), 1 severe arterial thromboembolism, 3 severe macrovascular thrombosis, and 4 severe cases of thromboembolic episodes that did not fall into any of the categories mentioned above. No subjects presented with CISN (CSR 400701, Table 12.2).

Among the 25 subjects with severe congenital PC deficiency, blindness and PF were each reported in 15 subjects (60.0%), thromboembolic disease in 18 subjects (72.0%), stroke in 11 subjects (44.0%), thrombophilia in 4 subjects (16.0%), renal failure/dysfunction in 3 subjects (12.0%), PE in 2 subjects (8.0%), amputation in 1 subject (4.0%), and mesenteric thrombosis in 1 subject (4.0%). Eight subjects (32.0%) had conditions that fell within the category of "other". No subjects had a history of myocardial infarction. Within the category of thromboembolic disease, there were 18 subjects with the disease; DVT (in 9/18 subjects) and DIC (in 3/18 subjects) were the most frequently reported conditions (CSR 400701, Table 13).

Efficacy

Historical Administration of CEPROTIN

Most subjects (88.0%) had received treatment with CEPROTIN prior to enrollment. Of 84 historical CEPROTIN administrations, 41.7% were required for acute treatment, 20.2% for short-term replacement due to surgery, 29.8% for long-term prophylaxis, and 8.3% for other reasons. No historical treatments

were given for short-term replacement of PC during pregnancy or the peri-partum period. Of these 84 historical administrations of CEPROTIN, 88.1% were considered effective in the prevention of coagulopathy and thrombosis, 67.9% halted/reversed thrombosis, 42.9% halted/reversed coagulopathy, 13.1% halted/reversed end organ damage, 9.5% resulted in limb sparing (data was missing for 4 cases; treatment outcomes were not mutually exclusive).

Relapse was reported in 3 (12.0%) subjects and these were all subjects with severe congenital PC deficiency. Remission, seen in 21 subjects lasted a median of 3.0 years (range: 0.3 to 19.9). Transition to anticoagulant therapy was successful in 8 (32.0%) subjects assessed (CSR 400701, Table 5.1, Table 6.1).

Administration of CEPROTIN during the Registry Study

At enrollment, 21/25 (84.0%) of subjects were receiving CEPROTIN, which was required for long-term prophylaxis in 90.5% (19 subjects) and for short-term replacement due to surgery in 9.5%. (Only 3/25 [12.0%] subjects received newly prescribed CEPROTIN after enrollment in the registry.) CEPROTIN was administered IV in 61.9% of subjects and subcutaneously in 38.1% subjects at enrollment (Table 7).

Table 10. CEPROTIN Usage at Enrollment Subjects with Congenital PC Deficiency in Study 400701

	Congenital Protein C Deficiency	
Current CEPROTIN Usage	N=25	(%)
Yes (n,%)	21	(84.0%)
No (n,%)	4	(16.0%)
Reason For Administration	N=21	(%)
Short Term Replacement - Surgery (n,%)	2	(9.5%)
Long Term Prophylaxis (n, %)	19	(90.5%)
Current Route of Administration	N=21	(%)
Intravenous (n,%)	13	(61.9%)
Subcutaneous (n,%)	8	(38.1%)

Source: CSR 400701 Table 5.2.1

Dosing at enrollment in subjects with severe congenital PC deficiency was variable (45 IU/kg in 1 subject, 80 IU/kg in 1 subject, 100 IU/kg in 2 subjects, 120 IU/kg in 1 subject, and "other" in 16 subjects), as was the frequency of administration (5 subjects were dosed every other day, 3 were dosed three times a week, 2 were dosed twice a week, 1 was dosed every 12 h, 1 was dosed once a week and 8 were dosed as "other" indicating various other times). Dosing and frequency of administration at the time of analysis were similar to that at enrollment (CSR 400701, Table 5.2.1).

In the subjects receiving long-term prophylactic treatment (19 of 25 subjects), who received a total of 195 infusions, the dose during the study was 45 IU/kg for 37 (19.0%) infusions, 60 IU/kg for 18 (9.2%) infusions, 80 IU/kg for 17 (8.7%) infusions, 100 IU/kg for 5 (2.6%) infusions, 120 IU/kg for 2 (1.0%) infusions and "other" for the remaining 116 (59.5%) infusions. Of these 195 infusions, 36 (18.5%) were administered daily, 13 (6.7%) every 12 h, 2 (1.0%) every 6 h, 2 (1.0%) every 8 h, 7 (3.6%) every other day, 5 (2.6%) twice a week, and 7 (3.6%) infusions were administered three times a week. For the rest, other administration frequencies were used (Table 11).

Table 11. CEPROTIN Usage During Study[a] Subjects with Congenital PC Deficiency Subjects with Long-term Prophylaxis in Study 400701

	Congenital Protein C Deficiency (N= 25)	
Subjects with Long Term Prophylaxis	(N=19)	
Current CEPROTIN Dose (IU/kg)[a]	195	
45	37	(19.0%)
60	18	(9.2%)
80	17	(8.7%)
100	5	(2.6%)
120	2	(1.0%)
Other	116	(59.5%)
Current Frequency of CEPROTIN (n,%)	195	
Initial Dose (n,%)	22	(11.3%)
Every 4 Hours (n,%)	0	(0.0%)
Every 6 Hours (n,%)	2	(1.0%)
Every 8 Hours (n,%)[b]	2	(1.0%)
Every 12 Hours (n,%)	13	(6.7%)
Daily (n,%)[b]	36	(18.5%)
Every Other Day (n,%)[b]	7	(3.6%)
Once a Week (n,%)	0	(0.0%)
Twice a Week (n,%)	5	(2.6%)
Three Times a Week (n,%)	7	(3.6%)
Other (n,%)	101	(51.8%)

[a] Subjects will receive CEPROTIN multiple times, each administration is shown in the table so subjects will appear more than once.
[b] Every 8 hours, daily and every other day were originally collected within other on the CRF but have been recategorized due to a high frequency in these groups.
Source: CSR 400701 Table 5.2.1 and Table 5.3

In subjects with severe congenital PC deficiency, a total of 147 anticoagulation therapies were documented in 22 subjects, of which 51.7% were with enoxaparin sodium and 25.2% were with warfarin, largely given once or twice daily. Twenty subjects received at least one concomitant medication; the medications most frequently used were paracetamol (in 48.0% of subjects), lovenox (32.0%), morphine and warfarin (24.0% each), ibuprofen and enoxaparin (in 20.0% each), and alteplase, levicetarem, coumadin, and amoxicillin (in 16% each) (CSR 400701, Table 10.1, Table 14).

PC activity levels during the study were available in 18 subjects with severe congenital PC deficiency. In subjects who received short-term replacement, 6 assays results were recorded for 2 subjects with a median PC activity level of 172.5% (range: 48.0% to 198.0%). All 6 assays were taken after the first CEPROTIN treatment date for each subject. Fourteen subjects who received long-term prophylaxis with CEPROTIN had a total of 201 assay results available, with a median PC activity level of 41.0% (range: 1.0% to 191.0%) (CSR 400701, Table 15).

Outcome

Acute treatment

Of 25 acute episodes, 22 (88%) resulted in recovery, 2 (8.0%) displayed improvement and 1 (4.0%) was unchanged; there was no instance of an acute episode worsening when CEPROTIN was administered. With respect to specific treatment outcomes, 7 (28.0%) CEPROTIN administrations were reported to have resulted in halting/reversal of coagulopathy and 21 (84.0%) resulted in halting/reversal of thrombosis (CSR 400701 Table 6.2).

Short-Term Replacement

A total of 28 surgeries/invasive procedures were performed during the study in 13 subjects with severe congenital PC deficiency. Short-term replacement with CEPROTIN was administered for 23 (82.1%) of these surgeries/procedures. (There were no short-term replacements during pregnancy or the peri-partum period.) All administrations of CEPROTIN for short-term replacement for surgery/invasive procedures were considered effective in the prevention of coagulopathy and thrombosis (CSR 400701 Table 6.2, Table 16).

Literature

The MAH provided a collection of publications reporting about long-term treatment with CEPROTIN in patients with severe congenital PC deficiency (Table 12). The clinical benefits In the treatment of lesions and their further prevention were documented. No product-related side effects were reported. The most common reasons for discontinuing CEPROTIN therapy and starting oral anticoagulation were problems with the venous access. However, episodes of bleeding or recurrent purpura occurred in all patients who received oral anticoagulation. CEPROTIN therapy had to be reinstated in most of these children, either as needed to control symptoms, or on a long-term prophylactic schedule, alone or in addition to oral anticoagulation. If CEPROTIN is given prophylactically in addition to oral anticoagulation, twice weekly administration appeared to be sufficient. After the acute phase, trough levels of PC activity lower than 0.25 IU/mL may be sufficient to prevent recurrent thrombosis.

The authors also point out that one of the advantages of replacement therapy with CEPROTIN compared with FFP is the possibility of home treatment, which allows a near-normal lifestyle. Patients and parents may choose the timing of the injections to suit their convenience. The availability of various access devices has made home treatment feasible for patients who would otherwise be hospitalized for long periods of time.

Table 12. Overview of Published Studies for Long-term Prophylaxis

Reference	Subjects (n)	Diagnosis	Duration of prophylaxis	Dosing#
Dreyfus et al. 1991	1 neonate (male)*	homozygous PC deficiency and PF	8 months	SD: 20 U/kg every 6 h. TD: 150,000 IU
Dreyfus et al. 1995	9 infants (3 male, 6 female)	Severe congenital PC deficiency and life-threatening PF and/or thrombosis associated with DIC	22 days to 3 years	Mean SD: 46.7 ± 25 IU/kg;, TD: 15,000 – 950,000 IU
Minford et al. 1996	1 neonate (female)*	homozygous PC deficiency and PF	3 years	SD: 40 IU/kg 3 times per day**
Müller et al. 1996	1 neonate (female)*	homozygous PC deficiency and PF	8 months	SD: 40 IU/kg 3 times per day,

				MD: 500 IU once daily
Sanz-Rodriguez et al. 1999	1 neonate (female)*	homozygous PC deficiency, PF+DIC	>12 months	SD: 80 IU/kg every 12 h, MD: 80 IU/kg twice weekly **
Mathias et al. 2004	2 neonates (female)	homozygous PC deficiency and PF	3 years (both), ongoing	SD: 50 IU/kg 3 times daily (both), MD: 200 IU/kg twice daily (patient 1) and 100 IU/kg (patient 2) **
Fernandez-Burriel 2005	1 preterm neonate (male)	type I/II compound PC deficiency with neonatal PF-like syndrome and ophthalmologic complications	3 years, ongoing	SD: 80 IU/kg every 12 h **
Tcheng et al 2008	2 neonates (female, sisters)	Severe type I PC deficiency and PF	>6 years for both patients and ongoing	MD: 85 resp. 90 IU/kg 3 times a week
Goldenberg and Manco-Johnson, 2008	20-year-old woman	severe PC deficiency and congenital blindness	2 years, ongoing	3 times a week (+ low-dose warfarin)
Goldenberg and Manco-Johnson, 2008	3 children	severe/moderately severe genetic PC deficiency	long-term	not specified
de Kort et al., 2011	1 neonate (male)	severe PC deficiency and PF (on feet and scalp, blindness)	>1 year	SD: 180 IU/kg 3 times daily, MD: 90 IU/kg 4 times daily**
Minford et al., 2014	14 subjects	severe PC deficiency (all cases presented during the neonatal period)	10 patients ≥ 2 years; 7 patients ≥ 5 years; 3 patients ≥ 10 years (i.e., 10 years, 11 years, 17 years)	Ceprotin prophylaxis (+Warfarin in 5 patients)**
Piccini et al., 2014	1 neonate (female)	Severe PC deficiency (homozygous), PF and blindness	~50 days	SD: 100 IU/kg twice daily**
Boey et al., 2016	18-year-old woman	compound heterozygote PC deficiency with proximal left leg DVT	~2 years	MD: 100 U/kg/week (+Warfain), MD: 90 U/kg/week (+Rivaroxaban)**
Shah et al., 2016	1 female term infant	progressive PF and laboratory evidence of DIC	~40 months	SD: 100 IU/kg every 6 h (+Heparin)**
Kung et al., 2017	2 patients (sister and younger brother)	homozygous PC deficiency and PF	~11 years (sister)	MD: Ceprotin i.v. (sister) MD: Ceprotin s.c. (brother)
Pöschl et al., 2021	1 male preterm infant	compound heterozygous PC deficiency	12,5 years	SD: 120 IU/kg every 6 h, MD:60 IU/kg every 12 h **

TD=total dose; Maintenance dose=MD; Starting dose=SD

*Also included in Dreyfus et al. 1995

**Switch to subcutaneous infusion (s.c.)

dose regimen only specified for intravenous route

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Clinical efficacy of long-term prophylactic treatment with CEPROTIN in subjects with severe congenital protein C deficiency was investigated in one prospective, multicenter, open-label, non-randomized phase 2/3 study (400101). Supportive information on the use of CEPROTIN in this indication derives from retrospective data (RDC), one registry study (400701) and published data.

The pivotal study 400101 was divided in three parts for on-demand treatment of acute episodes (part 1), short-term prophylaxis (part 2) and long-term prophylaxis (part 3).

A total of 24 episodes of PF/CISN or vascular thrombotic events in 11 subjects were treated with CEPROTIN in Part 1. Three subjects entered Part 2 of the study for a total of 7 times for short-term prophylaxis treatment with study product (initiation of anticoagulation therapy, for surgical procedures). Eight subjects with a mean age of 4.7 years entered Part 3 for long-term prophylactic treatment with study product for a treatment period of 42 to 338 days. The dosing regimen for long-term prophylaxis was based on the investigator's decision guided by Protein C activity levels preventing the trough levels from falling below 25% (or 10% for subjects on long-term anticoagulant treatment).

The retrospective data collection (Studies IMAG-039 and IMAG-041 and Compassionate Use) included 9 subjects, of which 8 were homozygous and 1 was double heterozygous, receiving long-term prophylactic treatment for a period of up to 8 years. The selection and timing of the dose used for each individual subject was determined by the investigator on the basis of the clinical status of the subject.

In the registry study 19 patients with severe congenital protein C deficiency and a median age of 11.1 years (range 1.3 to 43.7) were enrolled to receive long-term prophylaxis with CEPROTIN. The according dosing regimen also highly varied. The subjects on long-term prophylaxis participated for a median of 40.2 months.

The cases of 39 patients suffering from severe congenital PC deficiency were described in 17 publications. Most of the subjects had homozygous PC deficiency. There were also some cases with compound heterozygous PC deficiency. Most of the patients were neonates or very young infants displaying severe lesions of PF up to ophthalmologic complications including blindness and DIC. Long-term prophylactic treatment was introduced with regard to individual requirements.

Efficacy data and additional analyses

In study 400101 the outcome of the eight subjects on long-term prophylaxis is rated as excellent since no event of PF/CISN and/or thrombosis occurred. Four subjects had both periods of on-demand and prophylaxis experiencing 6, 4, 2 and 1 event while on on-demand treatment. A post-hoc reanalysis delivered significant results with regard to the non-occurrence of events during prophylaxis. Previously, it has been discussed whether the patient population in the different parts is comparable due to different inclusion criteria. For the inclusion in part 1 the presence of PF/CISN or thromboembolic events is a prerequisite. In part 3 patients should be asymptomatic. However, important differences of the included patients per part can be ruled out with regard to the baseline characteristics and the performed switching between parts. A further descriptive analysis shows a quite similar time frame between stopping long-term prophylaxis and the occurrence of the first episode. Even if the patient number is very small (n=4), this demonstrates that long-term prophylactic treatment with Protein C Concentrate is effective in preventing thrombotic events by long-term treatment of subjects with severe protein C deficiency.

In the retrospective data collection of 9 subjects, efficacy of CEPROTIN for long-term treatment was rated excellent in 7 subjects who were evaluated by the investigator. Dosing regimen (dose selection, timing) highly varied between individuals since it was based on the decision of the investigator according to PC activity levels. Sometimes long-term prophylaxis with CEPROTIN was combined with anticoagulation therapy. This data contribute to the supportive evidence that CEPROTIN is effective in long-term prophylaxis.

The registry study does not provide outcome data for the 19 subjects on long-term prophylaxis with CEPROTIN. Their dosing regimens highly varied and most of the patients received anticoagulation therapies (enoxaparin sodium or warfarin). The available PC activity levels showed a broad range. Therefore, additional information is requested for these patients in the registry on long-term prophylactic treatment, which would be useful to characterise efficacy in older patients (age ranging between 1.3 to 43.7 years in the recruited population). These data are expected in the submission of PSUR.

In the publications, CEPROTIN was efficacious in the treatment of lesions and prevented the development of lesions during its following long-term administration. In general, no side effects of CEPROTIN treatment were reported. Since CEPROTIN prophylaxis requires frequent intravenous administration there was often a switch to oral anticoagulation, which does not appear to be fully effective in the prevention of thromboembolic events in severe PC deficiency. Thus, often oral anticoagulation was combined with CEPROTIN treatment. Regarding the individual requirements and the various treatment regimen for CEPROTIN prophylaxis, it is recognised that CEPROTIN is dosed according to laboratory measurements of the Protein C activity and the individual need judged by the treating physician. In this connection, the publications state that trough levels of PC activity can be lower than usual for effective long-term prophylaxis. In addition, it is reported that CEPROTIN administration can be reduced to twice per week in the combination with oral anticoagulation. Section 4.2 of the SmPC recommends the following posology for long term prophylaxis: "For the long-term prophylactic treatment, a dose of 45 to 60 IU/kg every 12 hours is recommended. Measurement of the protein C activity should be performed to ensure trough levels of 25% or more. Dose or frequency of infusions should be adjusted accordingly." Subcutaneously administered PC concentrate was described as tool for the long-term prophylactic treatment. Since no preclinical and/or clinical study data (especially no bioavailability data) are available for the subcutaneous route, this tool of administration should only be used in exceptional situations (see SmPC) and no recommendations can be made for long-term prophylactic treatment.

2.4.3. Conclusions on the clinical efficacy

The overall evidence currently available indicates benefit for CEPROTIN in the long-term prophylaxis of congenital severe protein C deficiency and supports the sought extension of indication.

In the pivotal study and RDC dataset efficacy of CEPROTIN was rated excellent in long-term prophylactic treatment in patients with SCPCD based on investigator`s evaluation. Exposure was limited to 6 months in the pivotal 400101 trial as per study design but much longer periods of prophylactic treatment are supported by the RDC dataset and various publications. Knowledge on the natural course of disease enables contextualisation of these data, thus overcoming the limited sample size and concluding for a positive effect of treatment sustained over time. This is reinforced by data collected in 4 out of 8 patients from study 400101 who received both on-demand and long-term schedule with CEPROTIN, demonstrating benefit in terms of prevention of events achieved with sustained therapy.

Therefore, the extension of indication from short-term prophylaxis to prophylaxis is agreed.

2.5. Clinical safety

Introduction

The assessment of the safety of CEPROTIN in this application is based on data from all clinical studies conducted by the sponsor, in both the congenital and acquired PC deficiency indications.

Table 13 : Overview of Clinical Safety Studies with CEPROTIN: Studies in Severe Congenital PC Deficiency (symptomatic or asymptomatic subjects)

Study ID	Design	No. of Subjects, Age and Sex	Safety Parameters Evaluated
RDC (IMAG-039, IMAG-041, and Compassionate Use) Retrospective Data Collection on the Use of Protein C Concentrate for Treatment of Protein C (PC) Deficiency: Clinical Studies IMAG-039 and IMAG-041 and Compassionate Use	RDC; open-label, multi-center, international	79 (42 M/37 F) subjects aged 0 (newborn) to 39 years	AEs, viral safety (HBV, HCV, HIV-1), development of inhibitory anti-protein C antibodies and anti-murine IgG, vital signs
IMAG-098 A Clinical Study on the Pharmacokinetics of Protein C Concentrate (Human) Vapor Heated in Asymptomatic Subjects with Homozygous or Double Heterozygous Congenital PC Deficiency	Prospective, open-label, non-controlled, non-randomized, multi-center, international	13 (6 M/ 7 F) subjects aged 1 to 30 years, minimum body weight: 8 kg	AEs, viral safety (ALT, HIV-1/2, HAV, HBV, HCV, PVB19), development of inhibitory anti-protein C antibodies and anti-murine IgG, blood counts, vital signs
400101 A Phase 2/3 Clinical Study for the Determination of the Efficacy and Safety of Protein C Concentrate in Subjects with Severe Congenital Protein C Deficiency	Prospective, open-label, non-controlled, non-randomized, 3-part study	15 (8 M/ 7 F) subjects aged 0 to 25.7 years	AEs, viral safety (ALT, HIV-1/2, HAV, HBV, HCV, PVB19), development of inhibitory anti-protein C antibodies and anti-murine IgG, blood counts, vital signs, parameters indicating thrombophilia, D-dimer levels, PT, aPTT, TAT complexes
400501 A Retrospective Study to Capture Dosing and Treatment Outcome Data in Subjects with Severe Congenital Protein C Deficiency Who Were Treated with Protein C Concentrate Under an Emergency IND	Retrospective data collection	11 (6 M/ 5 F) subjects aged 2.1 to 23.8 years	Treatment-related AEs
Treatment Registry 400701	Prospective, international, multi-center, open-label, non-interventional, observational post-authorization registry	25 (13 M/12 F) aged 1.3 to 43.7 years (Of a total of 43 subjects, 25 had severe congenital PC deficiency and 18 had acquired PC deficiency)	SAEs, related SAEs and related non-serious AEs, laboratory data

Abbreviations: AE = adverse event, ALT = alanine aminotransferase, aPTT = activated partial thromboplastin time, F = female, HAV = hepatitis A virus, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV-1/2 = human immunodeficiency virus types 1 and 2, IgG = immunoglobulin G, IND = investigational new drug, M = male, PT = prothrombin time, RDC = retrospective data collection, TAT = thrombin-antithrombin, PC = protein C, PVB19 = parvovirus B19, SAE = serious adverse event.

Patient exposure

Extent of Exposure to Protein C Concentrate across clinical studies (Table 14).

Table 14. Cumulative exposure to Protein C across clinical studies (1989 – 2015)

Study ID	**Number of subjects treated with Protein C**
Severe congenital Protein C deficiency	
Study RDC (IMAG-039, IMAG-041 and Compassionate Use)	22
Study IMAG-098	13
Study 400101	15
Study 400501	11
Study 400701	25
Total	**86**
Acquired Protein C deficiency	
Study RDC (IMAG-039, IMAG-041 and Compassionate Use)	57
Study IMAG-103	9
Study IMAG-112	30
Discontinuation due to AES	Discontinuation due to AES
Study 400701	118
Total	**308**

Adverse events

A review of all the reported AEs in the clinical studies shows the following:

Of a total of 146 subjects enrolled in clinical studies with CEPROTIN in the indication of congenital PC deficiency, 10 (6.8%) subjects died. All deaths were considered unrelated to the study drug. Of a total of 825 reported AEs, 6 (0.7%) were considered to be related to the study drug. These were itching, rash, and light-headedness, which occurred in one subject in Study IMAG-098, and abdominal pain, pain in extremity, and PF, which occurred in one subject in Study 400701; all 6 related AEs occurred in two subjects in two studies (Study IMAG-098, Study 400701). Two of the related AEs were serious (abdominal pain, pain in extremity).

Of a total of 164 subjects enrolled in clinical studies, treated with either CEPROTIN or placebo (albumin) in the indication of bacterial sepsis/septic shock and/or PF, 37 (22.6%) subjects died. No deaths were considered to be related to the study drug. Of a total of 56 reported AEs, 23 were serious and 33 were non-serious. All 23 SAEs were considered unrelated to the study drug. In Study IMAG-112, one moderate AE, skin rash, was deemed related to the albumin infusion. No other related AEs were reported in the sepsis/PF studies.

Study 400101

Protein C was found to be effective for both short- and long-term prophylaxis. A total of 15 subjects were exposed to protein C. Eight subjects were studied for LTP. The median number of exposure days for these 8 patients was: 7.5 for on-site infusions and 183 for home infusions. None of the AEs was related to study drug or resulted in withdrawal from the study. No protein C inhibitory antibodies were detected.

Serious adverse event/deaths/other significant events

Deaths

In congenital PC deficiency, 10 (6.8%) subjects died of a total of 143 subjects treated with CEPROTIN: 8 deaths were reported in the RDC (IMAG-039, IMAG-041, compassionate use), 1 death was reported in Study 400101, and 1 death was reported in Treatment Registry 400701. All deaths were considered unrelated to the study drug. Among the patients included in the literature review on congenital PC deficiency, one death occurred (see Summary of Clinical Efficacy [Module 2.7.3], Section 3.1.2.2.2, Case Report 9) (Dreyfus et al. 1995). In acquired PC deficiency (Section 5.2.2), 37 (22.6%) subjects died of a total of 164 subjects treated with either CEPROTIN or placebo (albumin) in the indication of bacterial sepsis/septic shock and/or PF: 5/12 subjects died in Study IMAG-103, 9/40 died in Study IMAG-112, 21/94 died in Study CEPROTIN-D-001, and 2 died in Treatment Registry 400701. No deaths were considered related to the administration of the study drug.

Serious AEs

A comparison of serious and non-serious AEs cannot be made across all the studies in the indication of congenital PC deficiency, as no distinction was made in the RDC of studies IMAG-039, IMAG-041 and compassionate use between serious and non-serious AEs (although 4 severe AEs were reported in 4 subjects in the RDC, i.e., abdominal pain, migraine headache, tachycardia (> 300 beats per minute), and ablation of second toe on the right and left foot). All AEs in the RDC were considered unrelated to the study drug. In Study IMAG-098, 52 SAEs occurred in 9 subjects; in Study 400101 there were 35 SAEs. None of these SAEs were attributed to the study drug. In Treatment Registry 400701, 39 of 111 AEs in subjects with severe congenital PC deficiency were serious and occurred in 13 subjects. A total of 3 AEs were considered possibly related to CEPROTIN by the investigator; two of these AEs were SAEs. All 3 related AEs occurred in one subject and were as follows: abdominal pain (SAE), pain in extremity (SAE), and PF (non-serious AE) xi. It should be noted that in all 3 events the dose was increased and CEPROTIN was not discontinued. Related AEs occurred in one subject and were as follows: abdominal pain (SAE), pain in extremity (SAE), and PF (non-serious AE) xi. It should be noted that in all 3 events the dose was increased and CEPROTIN was not discontinued.

Of a total of 56 AEs reported in the four studies in bacterial sepsis/septic shock and/or PF, 23 were serious and 33 were non-serious. All 23 SAEs were considered unrelated to the study drug. In Studies IMAG-103 and IMAG-112, most SAEs were deaths: Five deaths occurred in Study IMAG-103 and 9 deaths occurred in Study IMAG-112. These were attributable to septic shock or bacterial sepsis.

Laboratory findings

PC inhibitory antibodies

Assessment of PC inhibitory antibodies was only performed during clinical studies on congenital PC deficiency. There have been no reports describing the development of an inhibitor against protein C in subjects with PC deficiency following administration of CEPROTIN. The determination of inhibitory antibodies against protein C was based on the chromogenic assay to determine protein C activity.

Anti-Murine Antibodies

During the manufacturing process, protein C is isolated by immunoaffinity chromatography using a murine anti-human protein C monoclonal antibody. As CEPROTIN may therefore, theoretically, contain traces of mouse protein as a result of this stage of the process, anti-murine antibodies were assessed during clinical studies.

Anti-murine antibodies were determined in study IMAG-103 in acquired protein C deficiency and in studies RDC (IMAG-039, IMAG-041, and compassionate use), IMAG-098, and 400101 in congenital protein C deficiency. One positive test result for anti-murine antibodies was reported in study RDC. However, this test result was below the upper limit of 200 ng/mL of the ELISA test system used. No AEs (other than this low titre) occurred in this subject, who received a total of 51 doses of CEPROTIN (22,883 IU) over a treatment period of 15 months.

Viral Safety

No subjects showed positive shifts for HAV.

Two positive hepatitis B markers were detected throughout the study courses of RDC (IMAG-039, IMAG-041, compassionate use) and IMAG-098. However, these positive shifts are not likely to be due to CEPROTIN. No subjects showed positive shifts for HCV.

While no transmission of PVB19 could be confirmed in study IMAG-103 and in the studies with congenital protein C deficiency, 6 subjects in study IMAG-112 seroconverted for PVB19. However, all 6 subjects had received non-virus inactivated blood products (FFP, plasma, whole blood, packed cells, erythrocytes, and thrombocytes) in addition to CEPROTIN. A transmission of PVB19 through CEPROTIN is very unlikely, given the drug product's safety profile.

In study IMAG-098, 7 subjects tested positive for PVB19-IgG antibodies at study entry, indicating that infection had occurred at some point prior to study entry. Six subjects were negative for PVB19-IgG at study entry, but 3 of them tested positive for PVB19-Immunoglobulin M (IgM) antibodies, indicating that a recent infection had occurred prior to study entry. Two subjects changed from negative to positive according to the PCR test method during the observation period. However, both of these subjects already had a positive result for PVB19 antibody at study entry (one positive result for PVB19-IgM and one for PVB19-IgG). No viral transmission was determined to have occurred in study IMAG-098 during the 3-month follow-up period.

In study 400101, one subject tested negative for PVB19-IgG at baseline, but was positive for IgG at all following assessments. The subject was negative for PVB19-IgM at all assessments. PCR for PVB19 nucleic acid was negative 6 months after initial treatment with the study product. The investigator determined that the occurrence of the positive PVB19-IgG result did not coincide with any of the clinical symptoms expected with an active infection by PVB19, and therefore did not report this event as an AE.

No subjects showed positive shifts for HIV-1/-2.

Safety in special populations

No studies evaluating the use during pregnancy/lactation have been performed.

In addition, there are not clinical data in patients with renal and/or hepatic impairment and in the elderly.

Safety related to drug-drug interactions and other interactions

No studies investigation evaluating drug interactions have been performed. No interactions with other drug products are currently known. In the absence of incompatibility studies, CEPROTIN should not be mixed with other medicinal products.

In patients starting treatment with oral anticoagulants belonging to the class of vitamin K antagonists (e.g., warfarin, coumarin), a transient hypercoagulable state may arise before the desired anticoagulant effect becomes apparent. This transient effect may be explained by the fact that protein C, itself a vitamin K-dependent plasma protein, has a shorter half-life than most of the vitamin K-dependent proteins (i.e., II, IX and X). Subsequently, in the initial phase of treatment, the activity of PC is more rapidly suppressed than that of the procoagulant factors. For this reason, if the patient is switched to oral anticoagulants, protein C replacement must be continued until stable anticoagulation is obtained. CISN can occur in any patient during the initiation of oral anticoagulant therapy, but individuals with severe PC deficiency are particularly at risk (Broekmans 1985; Broekmans et al. 1983; Nazarian et al. 2009; Stewart 2010; Vigano'D'Angelo et al. 1986).

Discontinuation due to adverse events

There were no withdrawals due to AEs.

Post marketing experience

The post-marketing experience with CEPROTIN is based on Periodic Safety Update Reports (PSURs)/Periodic Benefit-Risk Evaluation Reports (PBRERs), covering the period from the International Birth Date (IBD) of CEPROTIN (16 July 2001) until 31 July 2021.

CEPROTIN was first approved on 16 July 2001 in the European Union (EU) through a centralised procedure. As of 31 July 2021, CEPROTIN has approved licenses in 40 countries: Australia, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Russia, Saudi Arabia, Slovakia, Slovenia, South Africa, Spain, Sweden, Switzerland, Turkey, UK, the United Arab Emirates, and the United States of America (USA).

Cumulative Subject Exposure from Marketing Experience

Due to the large number of parameters taken into account to calculate the daily dose and the duration of treatment for CEPROTIN, the best estimate of patient exposure is the number of units sold worldwide. The average daily treatments calculated in International Units (IU), are based upon the recommended dose of 60 - 80 IU/kg BW, a BW of 30 - 40 kg for an average individual, and on the assumption that a considerable proportion of subjects will be at child age. Based on the above methodology, the cumulative patient exposure can be estimated to be 437,188,650 IU (i.e., the number of units sold), corresponding to approximately 174,875 daily treatments cumulatively.

Adverse Drug Reactions Reported in the Post-Marketing Experience

The following adverse reactions have been reported in the post-marketing experience, listed by MedDRA System Organ Class (SOC):

- Psychiatric Disorders: Restlessness
- Skin and Subcutaneous Tissue Disorders: Hyperhidrosis

- General Disorders and Administration Site Conditions: Injection site reaction

2.5.1. Discussion on clinical safety

Patients have been sufficiently exposed to protein C.

The rates of AEs across clinical studies vary due to differences in the patient's disease status, duration and other factors. Overall, however, reports of related AEs are extremely rare and uncritical (one case of skin rash to the placebo in IMAG-112) and one subject displaying 3 related AEs (itching, rash, and light-headedness) in Study IMAG-098. As with any intravenous product allergic type hypersensitivity reactions are possible. The following ADRs have been reported in the post-marketing experience and the frequency of these ADRs is not known: restlessness, hyperhidrosis and injection site reaction.

No certain safety issues have been identified with regard to prophylactic treatment. Furthermore, no specific safety data are available for CEPROTIN in the combination with anticoagulation therapy.

Based on the revision of all available data in patients with severe protein C deficiency undergoing long-term prophylaxis, it is noted that catheter thrombosis represented the most common reason for drug discontinuation. This is an expected complication of central catheterization which is required in the youngest ages. However, it is noted that in several occasions, intravenous therapy was switched to subcutaneous drug administration, which is identified as exceptional mode of administration in the current SmPC (section 4.2).

The presentation of SAE including the fatal case showed a high rate of SAE due to deaths in acquired protein C deficiency. This observation is consistent with the underlying disease of bacterial sepsis/septic shock. All these cases were considered unrelated to the study drug.

Overall, no clinically relevant dose-related changes have been observed for laboratory parameter. There is no evidence for viral transmission.

No inhibitor development was detected in any patient treated with CEPROTIN. Development of low titre anti-murine immunoglobulins was observed in one patient without clinical implications.

So far, post-marketing data do not display any safety signals due to CEPROTIN treatment.

2.5.2. Conclusions on clinical safety

Clinical safety has been analysed from the data of all clinical trials. The presented results are considered to be sufficient. No unexpected pattern in the reported adverse events and serious adverse events were observed. The safety data of studies cover subjects < 18 years and adults. No patients developed protein C inhibitory antibodies. Review of the new safety data does not reveal any new significant safety issue. The safety profile of the product remains consistent with the safety profile established during clinical trials and as established in previous evaluations.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted a RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.0 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update, as follows:

- In the next revision of the RMP, please pay more attention to detail. For example, with regard to i) the wording in Table 2 Annex 2 (bleeding episodes is not a safety concern associated with Ceprotin); ii) the section on post-authorisation exposure (no reference to periods without specifying actual times; the term "Number of daily treatments" is ambiguous); and iii) the subsection Pharmaceutical form(s) and strengths in RMP part I, which of course remains applicable for Ceprotin.

The CHMP endorsed the Risk Management Plan version 2.0 with the following content:

Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity to the active substance or to any of the excipients or to mouse protein or heparin
Important potential risks	• Bleeding episodes • Risk of transmission of infectious agents • Inhibitor development • Heparin induced thrombocytopenia
Missing information	• The effects of CEPROTIN on fertility, pregnancy, and lactation have not been established in clinical trials • No clinical data on use of CEPROTIN in patients with renal and/or hepatic impairment • No clinical data on the use of CEPROTIN in patients aged ≥65 years

Pharmacovigilance plan

Not Applicable.

Risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypersensitivity to the active substance or to any of the excipients or to mouse protein or heparin.	**Routine risk minimisation measures:** SmPC Section 4.2; Section 4.3; Section 4.4 and Section 4.8. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Bleeding episodes.	**Routine risk minimisation measures:** SmPC Section 4.4. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Transmission of infectious agents	**Routine risk minimisation measures:** SmPC Section 4.8. **Additional risk minimisation measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance**
	None.	**activities:** None.
Inhibitor development	**Routine risk minimisation measures:** SmPC Section 4.8. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Heparin induced thrombocytopenia (HIT)	**Routine risk minimisation measures:** SmPC Section 4.3 and Section 4.4 **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
The effects of CEPROTIN on fertility, pregnancy and lactation have not been established in clinical trials	**Routine risk minimisation measures:** SmPC Section 4.6 **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
No clinical data on use of CEPROTIN in patients with renal and/or hepatic impairment	**Routine risk minimisation measures:** SmPC Section 4.2 and Section 4.4. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
No clinical data on use of CEPROTIN in patients aged ≥ 65	**Routine risk minimisation measures:** None. **Additional risk minimisation measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.
	None.	**Additional pharmacovigilance activities:** None.

The effects of CEPROTIN on fertility, pregnancy and lactation have not been established in clinical trials	**Routine risk minimisation measures:** SmPC Section 4.6 **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
No clinical data on use of CEPROTIN in patients with renal and/or hepatic impairment	**Routine risk minimisation measures:** SmPC Section 4.2 and Section 4.4. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
No clinical data on use of CEPROTIN in patients aged ≥ 65	**Routine risk minimisation measures:** None. **Additional risk minimisation measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2 and 5.1 of the SmPC have been updated. In addition, the MAH took the opportunity to implement minor editorial changes in sections 4.2, and 4.4 in the SmPC and Package Leaflet and to correct the address of the manufacturer of the biological active substance in Annex II following variation EMEA/H/C/000334/IAIN/0126/G.

The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This application is an extension of indication to include long-term prophylaxis (deletion of wording 'short-term' and currently listed conditions) of purpura fulminans and coumarin induced skin necrosis in patients with severe congenital protein C deficiency.

3.1.2. Available therapies and unmet medical need

CEPROTIN is currently the only treatment option available to substitute protein C in severe congenital PC deficiency. Fresh frozen plasma (FFP) is not a real therapeutic alternative since the volume of FFP required to raise protein C to normal levels can lead to fluid overload, especially in children, with the risk of pulmonary edema, hypertension, hyperproteinemia, or proteinuria. Prothrombin complex concentrates (PCCs) contains protein C, but also vitamin K dependent coagulation factors with thromboembolic potential. Liver transplantation has been curative for severe congenital PC deficiency in a few cases. However, it necessitates lifelong immunosuppression and is associated with a potential risk of autoantibody formation against protein C produced by the transplanted organ, due to polymorphism. Long- term anticoagulation with coumarin or heparin derivates has side effects and can often not fully prevent thromboembolic events. Severe congenital PC deficiency being a lifelong condition, long-term prophylaxis with CEPROTIN could prevent thromboembolic complications and overcome the drawbacks of alternative treatment options.

3.1.3. Main clinical studies

Clinical efficacy of long-term prophylactic treatment with CEPROTIN in subjects with severe congenital protein C deficiency was investigated in one prospective, multicenter, open-label, non-randomized phase 2/3 study (400101) which was divided in three parts for on-demand (n=11), short-term (n=3) and long-term treatment (n=8). Supportive information on the use of CEPROTIN in this indication derives from retrospective data (RDC), one registry study (400701) and published data.

3.2. Favourable effects

In 8 subjects of study 400101 no event of PF/CISN and/or thrombosis occurred while on long-term prophylaxis. Four subjects were treated in both parts of on-demand and prophylaxis experiencing 6, 4, 2 and 1 event while on on-demand treatment. A post-hoc reanalysis demonstrated that the non-occurrence of events during prophylaxis. A further descriptive analysis shows a quite similar time frame between stopping long-term prophylaxis and the occurrence of the first episode. The beneficial effects are supported by a registry study, publications and retrospective data. Section 4.2 of the SmPC recommends that if the response to CEPROTIN injection is satisfactory (measured by chromogenic assays), dosing may be gradually reduced to 12 hourly dosing ensuring trough protein C activity >25% (>0.25 IU/ml).

3.3. Uncertainties and limitations about favourable effects

Since SCPCD is a very rare disease, the number of investigated patients was low. In the pivotal study only 8 of 18 included patients were on long-term prophylaxis for a limited time. This study was uncontrolled. The post-hoc analysis of 4 patients participating in both treatment parts of on-demand therapy and long-term prophylaxis has its limitations (e.g. different inclusion criteria). The supportive data comprising literature, retrospective data and a registry study also include a limited number of patients and show a high variation of applied dose regimen. There were several reports of combination with anticoagulation therapy and different requirements of trough levels of PC. Section 4.2 of the SmPC recommends that if the patient is switched to permanent prophylaxis with oral anticoagulants, protein C replacement is to be discontinued only when stable anticoagulation is obtained (see section 4.5). Furthermore, during the initiation of oral anticoagulant therapy it is advisable to start with a low dose and adjust this incrementally, rather than use a standard loading dose. At start of a combination treatment of anticoagulants (especially Vitamin K antagonists) with Protein C, stable activity levels of Protein C above 0.25 IU/ml (chromogenic) should be maintained before starting the anticoagulation. Careful monitoring of the international normalized ratio (INR) is recommended. In the combination of Protein C Concentrate and -anticoagulants, a protein C trough level of about 10% or more is recommended to be maintained.

In addition, as stated in section 4.2 of the SmPC mentions that in patients with combined severe congenital protein C deficiency and with APC resistance, there are limited clinical data to support the

safety and efficacy of CEPROTIN. The safety and efficacy of CEPROTIN in patients with renal and/or hepatic impairment have not been established. Patients with any of these conditions should be monitored more closely.

3.4. Unfavourable effects

No certain side effects have been reported for long-term prophylaxis with CEPROTIN. Safety risks of hypersensitivity, inhibitors, transmissible agents, Heparin induced thrombocytopenia, concurrent anti-coagulation medication are already reflected in section 4.4 of the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

The available safety database of 8 subjects on long-term prophylaxis is very small. The time frame of long-term prophylactic treatment was limited (42-338 days). Dosing was guided by blood levels of protein C and investigator`s decision. The actual administered doses of CEPROTIN have not been provided. No specific safety data are available for CEPROTIN in the combination with anticoagulation therapy.

3.6. Effects Table

Table 15: Effects Table for CEPROTIN (all studies are completed)

Effect	Short description	Unit	On-demand	Long-term	Uncertainties / Strength of evidence	References
Favourable Effects						
Monthly rate of episodes*	* PF/CISN and/or Thrombosis, all patients (n=14, n=8)	Mean (n)	0.757	0.000	Low number of patients, different inclusion criteria	Study 400101
		Median (n)	0.238	0.000		
Monthly rate of episodes*	* PF/CISN and/or Thrombosis, the same 4 patients	Mean (n)	1.910	0.000	Low number of patients, different inclusion criteria	Study 400101
		Median (n)	0.494	0.000		
Unfavourable Effects						
Hypersensitivity					Not reported	
Bleeding					Not reported	

Abbreviations: PF=purpura fulminans; CISN=coumarin-induced skin necrosis

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The proposed extension of indication is supported by a strong pharmacological rationale. CEPROTIN is already approved in severe protein C deficiency for treatment of acute episodes and short-term prophylaxis, and offers the only protein C replacement therapy in a population of patients with a very rare inherited blood disorder for which current alternatives have limited efficacy and/or unsatisfactory safety profile. Available data are numerically limited, including 8 patients from the pivotal trial 400101 and 9 from a retrospective dataset (RDC) which is consistent with the clinical setting. Evidence mainly refer to the paediatric population (small infants and children), as expected given the history of disease. Exposure to therapy was individually based in terms of dose/frequency of administration and length of treatment, limited to 6 months in the pivotal 400101 trial as per study design but much longer periods of prophylactic treatment are available from the RDC dataset and various publications. Given the lack of a proper PK/PD response in the long-term prophylaxis, information on dosage is provided in the SmPC as based on current findings. The effect of treatment (either with or without concomitant anticoagulation) was established based on clinically relevant outcomes (observed prevention of thrombotic events and skin lesions during treatment) and response was rated as excellent in all treated patients, as based on investigator's assessment. Knowledge on the natural course of disease enables contextualisation of these data concluding for a positive effect of treatment sustained over time. Further information has been provided on efficacy as derived from the registry study that would include also an older population and additional information on combination of CEPROTIN with anticoagulants.

No related AEs were reported for patients on long-term prophylaxis with CEPROTIN in the pivotal study. This favourable safety profile is supported by the safety data across all clinical studies.

Unlike the pivotal trial where exposure was limited to 6 months, retrospective data from the RDC and registry study with longer treatment length (up to 8 years) showed that a common cause of drug discontinuation during long-term prophylaxis was catheter thrombosis, which is an expected complication. In several occasions, investigators switched to subcutaneous drug administration, currently contemplated in the SmPC section 4.2 in exceptional circumstances.

Overall, the benefit of no thromboembolic events during prophylaxis outweighs the limitations of a small uncontrolled sample size in the pivotal study. The efficacy of prophylaxis is supported by publications, registry data and retrospective data.

3.7.2. Balance of benefits and risks

The provided data demonstrate that long-term prophylactic treatment with Protein C Concentrate is effective in preventing thrombotic events in subjects with severe protein C deficiency. Prophylactic treatment with CEPROTIN showed a good safety and tolerability. An increased bleeding risk or allergic reactions were not observed.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Ceprotin for this extended indication is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include long-term prophylaxis (deletion of wording 'short-term' and currently listed conditions) of purpura fulminans and coumarin induced skin necrosis in patients with severe congenital protein C deficiency, based on a re-analysis of long-term prophylaxis data from the pivotal Study 400101; a phase 2/3 clinical study undertaken to evaluate PK, safety and efficacy of CEPROTIN in patients with severe congenital PC deficiency for the treatment of acute thrombotic episodes, for short-term thromboembolic prophylaxis and for long-term prophylactic treatment. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated and the Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial changes in sections 4.4 and 4.8 the SmPC and Package Leaflet.
Version 2.0 of the RMP has also been submitted. In addition, MAH took the opportunity to correct the address of the manufacturer of the biological active substance in Annex II following variation EMEA/H/C/000334/IAIN/0126/G.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

4.1. Update of the Product information

4.1.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.