29 January 2026
EMADOC-1700519818-2488289
Human Medicines Division

# Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

## Ceprotin

Human protein C

Procedure no: EMA/PAM/0000302081

## Note

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

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| Status of this report and steps taken for the assessment | | | | |
|---|---|---|---|---|
| **Current step** | **Description** | **Planned date** | **Actual Date** | **Need for discussion** |
| ☐ | Start of procedure | 13 Oct 2025 | 13 Oct 2025 | ☐ |
| ☐ | CHMP Rapporteur AR | 17 Nov 2025 | 17 Nov 2025 | ☐ |
| ☐ | CHMP members comments | 01 Dec 2025 | N/A | ☐ |
| ☐ | Updated CHMP Rapporteur AR | 04 Dec 2025 | N/A | ☐ |
| ☐ | CHMP adoption of conclusions | 11 Dec 2025 | 11 Dec 2025 | ☐ |
| ☐ | Submission | 23 Dec 2025 | 18 Dec 2025 | ☐ |
| ☐ | Restart | 31 Dec 2025 | 31 Dec 2025 | ☐ |
| ☐ | CHMP Rapporteur AR | 14 Jan 2026 | 09 Jan 2026 | ☐ |
| ☐ | CHMP members comments | 19 Jan 2026 | N/A | ☐ |
| ☐ | Updated CHMP Rapporteur AR | 22 Jan 2026 | N/A | ☐ |
| ☒ | CHMP adoption of conclusions | 29 Jan 2026 | 29 Jan 2026 | ☐ |

## Declarations

☒ The assessor confirms that this assessment does **not** include non-public information, including commercially confidential information (e.g. ASMF, information shared by other competent authorities or organisations, reference to on-going assessments or development plans, etc.), irrespective from which entity was received.

# Table of contents

# 1. Introduction

On 26 September 2025, the MAH submitted a completed paediatric study for CEPROTIN, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

# 2. Scientific discussion

## *2.1. Information on the development program*

The MAH stated that study TAK-662-1501 "An Open-Label, Single-Dose, Phase 1/2 Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Human Protein C (TAK-662) for the Treatment of Congenital Protein C Deficiency in Japanese Subjects Followed by an Extension Part" is a stand-alone study.

TAK-662 was first approved under the brand name of CEPROTIN in July 2001 in EU countries, in March 2007 in the US, and in March 2024 in Japan. In the EU, CEPROTIN is approved for prophylaxis and treatment of purpura fulminans, coumarin-induced skin necrosis and venous thrombotic events in patients with severe congenital protein C deficiency.

## *2.2. Information on the pharmaceutical formulation used in the study*

TAK-662 is a lyophilized, sterile concentrate of human protein C. The protein C content is indicated in IU on the label of each vial. Two vial sizes are available: 500 IU for reconstitution in 5 mL Sterile Water for Injection (sWFI) or 1,000 IU for reconstitution in 10 mL sWFI.

There is no paediatric formulation for CEPROTIN. Dosage varies depending on the patient's condition and the patient's body weight. There is no dose adjustment for the paediatric population. CEPROTIN should be administered at a maximum injection rate of 2 mL per minute. In paediatric patients with a body weight of less than 10 kg, the injection rate should not exceed a rate of 0.2 mL/kg/min.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted a final report for:

- TAK-662-1501: An Open-Label, Single-Dose, Phase 1/2 Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Human Protein C (TAK-662) for the Treatment of Congenital Protein C Deficiency in Japanese Subjects Followed by an Extension Part.

The MAH declares that the study results do not result in any regulatory action and do not require an update of the EU Product Information of CEPROTIN.

### 2.3.2. Clinical study

TAK-662-1501: An Open-Label, Single-Dose, Phase 1/2 Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Human Protein C (TAK-662) for the Treatment of Congenital Protein C Deficiency in Japanese Subjects Followed by an Extension Part.

## Description

TAK-662-1501 was a phase 1/2 open-label, non-randomised, non-controlled, single-dose, multicentre study to evaluate PK, safety, and tolerability of TAK-662 in Japanese subjects with congenital protein C deficiency followed by an extension part.

The trial enrolled Japanese patients of any age with a confirmed diagnosis of homozygous or compound heterozygous congenital protein C deficiency for the PK part; and for the extension part, enrolled participants who had participated in the PK part and were:

a) Diagnosed with purpura fulminans (PF), coumarin/warfarin-induced skin necrosis (CISN/WISN), and/or other acute thromboembolic episode for on-demand treatment only.
b) Requiring treatment with CEPROTIN for short-term prophylaxis for surgical procedures.
c) Requiring treatment with CEPROTIN for long-term prophylaxis.

The trial consisted of signing informed consent, a screening period (Day -14 to Day -2 before the administration of CEPROTIN on Day 1), a PK part, and an extension part.

PK part: Once all screening assessments following informed consent were completed and eligibility was confirmed, the participant received a single 80 IU/kg dose of CEPROTIN IV on Day 1. Prior to the IP administration, the participant was admitted to the trial site on Day -1 (hospitalization 1 day earlier [Day -2] was allowed if applicable). For participants with prophylactic treatment that included a protein C ingredient, the IP for PK was administered at least 36 hours after the prophylactic treatment.

From Day 1 to Day 3, participants stayed at the trial site and were followed up for PK and safety before and after the IP administration. The blood sampling for PK was performed immediately prior to infusion and at 30 minutes, and 1, 2, 4, 8, 12, 24, and 36 hours post-infusion; the sampling at 36 hours post-infusion was allowed to be customized by age, especially for feasibility in children. After 7 days from the IP administration (Day 7), the participant had a follow-up visit for the safety assessment. For participants who received prophylactic treatment that included a protein C ingredient before the administration of the IP for PK, the blood sampling was to be additionally performed immediately prior to the prophylactic treatment and at 1, 17, and 25 hours post-treatment.

Extension part: The extension part continued until the commercial protein C concentrate was available at each trial site or trial termination. The duration of participant involvement and the trial completion date were determined depending on the trial part and how many times a participant was to be enrolled (on-demand treatment, short-term prophylaxis, and long-term prophylaxis).

### Methods

#### *Study participants*

The target population was Japanese patients.

Inclusion Criteria

Each subject had to meet the following criteria to be eligible for each of the study parts:

*PK part:*

- An understanding, ability, and willingness to fully comply with study procedures and requirements. If the subject was <20 years of age or informed consent was not able to be

obtained from the subject, a parent or legally authorized representative should perform this role.
- Ability to voluntarily provide written, signed, and dated (personally, or via a parent or legally authorized representative if the subject was <20 years of age or informed consent was not able to be obtained from the subject) informed consent, and assent as applicable (only when informed consent was obtained from the subject), to participate in the study.
- Male and female subjects with Japanese nationality.
- A diagnosis of congenital protein C deficiency (homozygous or compound heterozygous).
- Asymptomatic subject.
- Oral anticoagulants allowed to be received.
- Male, or non-pregnant or non-lactating female who was sexually active and who agreed to comply with the applicable contraceptive requirements of this protocol, or females of nonchildbearing potential. A negative pregnancy test at the Screening visit had to be documented.

*Extension part:*

- Subjects who had participated in the PK part of this study (TAK-662-1501).
- An understanding, ability, and willingness to fully comply with study procedures and requirements. If the subject was <20 years of age or informed consent was not able to be obtained from the subject, a parent or legally authorized representative should perform this role.
- Ability to voluntarily provide written, signed, and dated (personally, or via a parent or legally authorized representative if the subject was <20 years of age or informed consent cannot be obtained from the subject) informed consent, and assent as applicable (only when informed consent was obtained from the subject), to participate in the extension part of this study.

Exclusion Criteria

Subjects who met any of the following criteria were excluded from each of the study parts:

*PK part:*

- Current or recurrent disease that could have affected the action, or disposition of the IP, or clinical or laboratory assessments.
- A body weight less than 8 kg.
- Serious liver dysfunction, judged by the investigator.
- Any thrombosis within 2 weeks prior to administration of the IP.
- Other IP than TAK-662 received within 60 days prior to the administration of the IP.
- Current or relevant history of physical or psychiatric illness, or any medical disorder that might require treatment or made the subject unlikely to fully complete the study, or any condition that presented undue risk from the IP or procedures.
- Current use of any medication (including over-the-counter, herbal, or homeopathic preparations) that could have affected (improved or worsened) the condition being studied or could have affected the action or disposition of the IP, or clinical or laboratory assessment.
- Known or suspected intolerance or hypersensitivity to the IP, closely-related compounds, or any of the stated ingredients.
- Known history of alcohol or other substance abuse within the last year.

- Within 30 days prior to the first dose of IP, a subject had been enrolled in a clinical study (including vaccine studies) that, in the investigator's opinion, might impact this sponsored study.

*Extension part:*

- New serious medical conditions which could have affected patient's safety or treatment had been observed during participation in the PK part of this study (TAK-662-1501).
- Planning to participate in clinical trials of other investigational drugs or medical devices.
- Females of childbearing potential who did not agree to use acceptable contraception.

***Treatments***

*PK part:*

All subjects received a single 80 IU/kg dose of TAK-662, infused over 15 minutes on Day 1. TAK-662 was administered at a maximum injection rate of 2 mL/min except for children with a body weight of <10 kg, where the injection rate did not exceed 0.2 mL/kg/min.

*Extension part:*

In the extension part, 3 different treatment options were provided:

1) On-demand treatment

Upon presentation with an acute event, the subject was infused with a dose of 100-120 IU/kg. The subsequent 3 infusions were administered every 6 hours at a dose of 60-80 IU/kg. Subsequent infusions (45-60 IU/kg) were also continued every 6 or 12 hours until resolution of all non-necrotic lesions and/or stabilization of thrombi (in the case of a thrombotic episode).

2) Short-term prophylaxis

For subjects on anticoagulation therapy who required elective surgery (non-emergency), treatment with TAK-662 was initiated at a dose of 100-120 IU/kg once daily until anticoagulation therapy was successfully switched to TAK-662 prior to surgery. For subjects on anticoagulation therapy who required emergency surgery, vitamin K dosage could be used to reverse anticoagulation therapy due to warfarin, and TAK-622 treatment (100-120 IU/kg) was started. Fifteen minutes prior to surgery, a dose of 60-80 IU/kg was administered. The same dose was continued once every 6 hours for the first 24 hours after surgery began. The frequency of infusions was reduced to 3 times daily between 24 and 48 hours, and twice daily after 48 hours at the same dose (45-60 IU/kg). Treatment with TAK-662 continued twice daily until anticoagulation therapy was initiated (if applicable) and the investigator determined that an adequate level of anticoagulation was achieved.

3) Long-term prophylaxis

A dose of 45-60 IU/kg was to be administered upon initiation of long-term prophylaxis twice daily. The dose was to be adjusted by referring to the latest protein C activity at the investigator's discretion.

***Objectives***

The primary objective of the trial was to measure the PK parameters of CEPROTIN in asymptomatic participants with homozygous or compound heterozygous congenital protein C deficiency in Japanese participants.

The secondary objectives of the trial were:

- To assess the safety profile of CEPROTIN.
- To assess the efficacy of CEPROTIN in the extension part for (a) on-demand treatment such as for PF, CISN/WISN, and other vascular thromboembolic events; (b) short-term thromboembolic prophylaxis during surgical procedures; and (c) long-term prophylactic treatment of acute thrombotic episodes.

***Outcomes/endpoints***

Primary endpoints

- Protein C activity
- PK parameters including but not limited to terminal half-life ($t_{1/2}$), incremental recovery (IR), in-vivo recovery (IVR), area under the curve (AUC), maximum concentration ($C_{max}$), and minimum time to reach maximum concentration ($t_{max}$)

Secondary endpoints

*Safety endpoint*

- The primary variable for safety assessment was the number of subjects with treatment-related adverse experiences.

Other safety endpoint

- Body temperature, blood pressure, and pulse rate were monitored before and after the IP administration, and the last prophylactic treatment (if applicable) prior to the test dose.

*Efficacy endpoints (Extension part)*

On-demand treatment:

- The treatment of episodes of PF/CISN/WISN and/or other vascular thromboembolic events were rated as effective, effective with complications, or not effective when it was determined that the next infusion was unnecessary according to the efficacy rating scale.

Short-term prophylaxis:

- Percentage of surgical episodes during short-term prophylaxis, for which TAK-662 was utilized as short-term prophylaxis, that was free of presentations of PF or thromboembolic complications.

Long-term prophylaxis:

- Number and rate of episodes of PF and/or thrombotic episodes during long-term prophylaxis.

***Sample size***

The targeted number of patients was set to 3 or more in consideration of feasibility and the study's entry criteria based on the opinions of specialists in Japan.

***Randomisation and blinding (masking)***

Not applicable.

### *Statistical Methods*

Descriptive statistics, including N (sample size), n (available data), mean, standard deviation (SD), coefficient of variation (CV%), median, minimum, and maximum values were used to summarize both PK concentrations and PK parameters data. Geometric mean and geometric coefficient of variation (geometric CV%) were computed for PK parameters where applicable. Only minimum, median and maximum were presented for $t_{max}$, where $t_{max}$ was described as time after ending infusion. Two datasets of the above summaries were created:

- PK analysis dataset 1, which included all protein C levels and associated PK parameters, irrespective of whether they were flagged.
- PK analysis dataset 2, which included only non-flagged data.

Efficacy outcomes (on-demand therapy, short-term prophylaxis, long-term prophylaxis) were summarized using descriptive statistics.

Analysis sets:

The PK Analysis Set included all study participants who received at least 1 dose of TAK-662 and had a sufficient number of quantifiable blood levels of TAK-662 collected post-dose, without important protocol deviations/violations or events thought to substantially affect the PK.

The Safety Analysis Set included all enrolled subjects who received at least 1 dose of TAK-662. A subject was considered enrolled in the study once the informed consent/assent had been obtained and the subject met all of the study eligibility criteria. To analyse safety in the extension part, the Safety Analysis Set in the extension part was used. This was defined as all study subjects who received at least 1 dose of TAK-662 in the extension part.

The Efficacy Analysis Set included all study participants who received at least 1 dose of TAK-662 in the extension part.

## Results

### *Recruitment, participant flow and numbers analysed*

The study enrolled a total of 5 participants from 4 sites in Japan. All 5 participants (100%) were included in the PK analysis set, in the SAS, and in the efficacy analysis set.

PK part: All 5 participants included in the PK part received the PK dose of CEPROTIN.

Extension part: All 5 participants who completed the PK part signed the ICF of the extension part and received treatment with CEPROTIN.

- Four participants received CEPROTIN for on-demand treatment: Two participants received treatment for 2 episodes each, one participant for 8 episodes, and one participant for 7 episodes.
- One participant received CEPROTIN for the short-term prophylaxis of one surgical procedure.
- None of the participants received CEPROTIN for long-term prophylaxis.

***Baseline data***

All 5 subjects enrolled in the PK part were Japanese and 4 (80.0%) of these were male. The median age was 15.0 years, and the median body weight was 20.50kg. Three study participants were <18 years of age (Table 1).

**Table 1.** Demographics and Other Baseline Characteristics

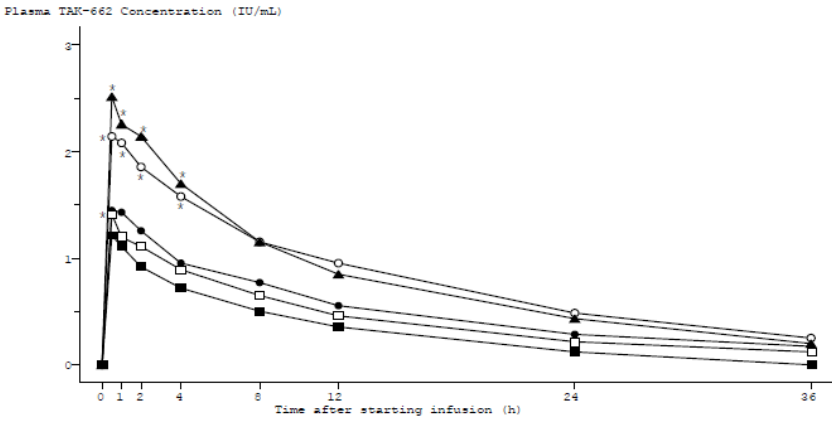
| Subject ID | Sex/ Age/ Race | Height at Screening Visit (cm) | Weight at Screening Visit (kg) | Date of Protein C Deficiency Diagnosis | Functional Protein C Level at Diagnosis | Genetic Confirmation Obtained?/Date/ Underlying Diagnosis/Mutation | Resistant to APC?/ Factor Type | Prophylactic Treatment Received? |
|---|---|---|---|---|---|---|---|---|
| | | | | 2018 | 11 | Yes/ 2018/ DOUBLE HETEROZYGOUS/ | No/ | No |
| | | | | 1994 | 10 | Yes/ 2017/ DOUBLE HETEROZYGOUS/ | No/ | Yes |
| | | | | 2011 | 10 | Yes/ 2011/ DOUBLE HETEROZYGOUS/ | Unknown / | No |
| | | | | 2006 | 10 | Yes/ 2007/ DOUBLE HETEROZYGOUS/ | Unknown / | No |
| | | | | 2001 | 1.7 | Yes/ 2013/ HOMOZYGOUS/ | No/ | No |

The median duration of diagnosed protein C deficiency was 15.50 years (range 3.3-27.4 years). At diagnosis, the mean (SD) functional protein C level was 8.54% (±3.848%). The number of subjects who had received prophylactic treatment was 1 (20.0%). The number of subjects who experienced thrombotic complications or skin necrosis were 5 (100.0%). Of these, the most frequently observed episodes were PF in 5 (100.0%) subjects and thrombotic complication in 2 (40.0%) subjects.

***Clinical Pharmacology***

Graphic displays of TAK-662 level-time profiles by subject are provided in Figure 1 below:

**Figure 1.** TAK-662 Level-Time Profile of PK Analysis Dataset 1 by Subject

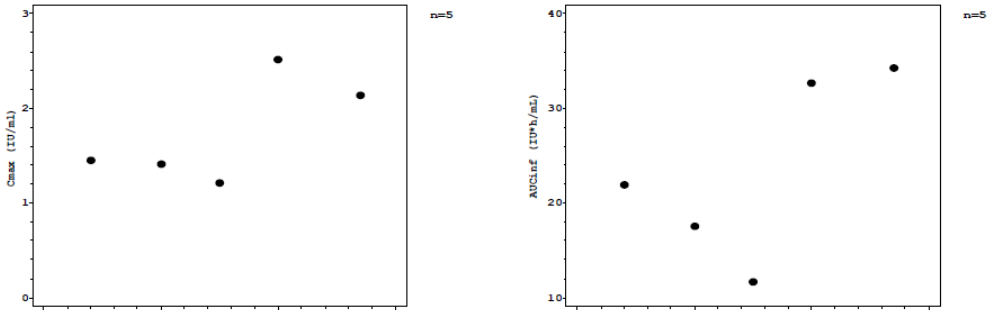



Source: Figure 11.1_CSR

PK parameters of TAK-662 were derived using non-compartmental analysis (NCA) methods. In the PK analysis set, the median (range) terminal phase half-life was 11.6 (7.68-13.0) hours. The median (range) time to maximum concentration was 0.53 (0.43-0.60) hours. The geometric mean (geometric CV%) of the maximum concentration was 1.679 IU/mL (31.7%). Medians (range) of in vivo recovery and incremental recovery were 87.4% (62.2%-147%) and 0.0171 (0.0143-0.0298) (IU/mL)/(IU/kg), respectively. Geometric means (geometric CV%) of clearance and volume of distribution were 3.868 mL/kg/h (47.1%) and 57.93 mL/kg (33.7%), respectively. The geometric mean (geometric CV%) of mean residence time was 14.98 hours (20.8%). The geometric mean (geometric CV%) of area under the curve from time zero to infinite time was 21.88 IU*h/mL (47.1%).

Scatter plots of $C_{max}$ and $AUC_{inf}$ in relation to subject age are provided in Figure 2 below:

**Figure 2.** Scatter Plots of $C_{max}$ and $AUC_{inf}$ versus Subject Age in PK Analysis Dataset 1 (x axis showing ascending age)




Source: Figure 11.2_CSR.

***Efficacy results***

On-demand treatment

Of 19 acute episodes reported in 4 participants, all treatment effects were rated as effective. The mean (SD) time to resolution of an acute episode for the first episode was 2.00 (0.816) days. The mean (SD) time to resolution of an acute episode for the second and subsequent episodes was 2.00 (1.309) days.

*On-demand treatments in paediatric subjects:*

A Japanese child patient diagnosed with double heterozygous congenital protein C deficiency (functional protein C level at diagnosis: 11%) received CEPROTIN for 8 episodes of on-demand treatment.

A Japanese child patient diagnosed with double heterozygous congenital protein C deficiency (functional protein C level at diagnosis: 10%) received CEPROTIN for 2 episodes of on-demand treatment.

A Japanese adolescent patient diagnosed with double heterozygous congenital protein C deficiency (functional protein C level at diagnosis: 10%) received CEPROTIN for 7 episodes of on-demand treatment.

Short-term prophylaxis

One participant received CEPROTIN for short-term prophylaxis during a surgical procedure. This participant received the first dose of CEPROTIN a day before the surgical procedure and completed the treatment 5 days later, without reports of PF or thromboembolic complications.

***Safety results***

In the PK part, 2 TEAEs were reported in 2 of the 5 (40.0%) study participants. One TEAE was pyrexia and the other was purpura. Each was reported in 1 (20.0%) participant, and both were mild in severity. The event of pyrexia was considered as a treatment-related adverse event.

In the extension part, 12 TEAEs were reported in 4 of the 5 (80.0%) study participants. The only TEAE reported in ≥2 participants was nasopharyngitis (2 participants, 40.0%), and both events were mild in severity. None of the 12 TEAEs were considered as a treatment-related adverse event.

Three SAEs were reported in 2 (40.0%) participants. These were events of dumping syndrome, respiratory syncytial virus infection, and respiratory failure. All SAEs occurred prior to the date of PF diagnosis for the episode of on-demand treatment. None of the SAEs was assessed as being related to CEPROTIN by the investigator or the sponsor and all were resolved.

Throughout the study, no deaths and AEs leading to treatment discontinuation or to trial withdrawal were reported.

## 2.3.3. Discussion on clinical aspects

As part of this Article 46 procedure, the MAH submitted the study report of TAK-662-1501 together with a clinical overview addendum.

TAK-662-1501 was a phase 1/2 open-label, non-randomized, non-controlled, single-dose, multicentre study to evaluate PK, safety, and tolerability of CEPROTIN in Japanese subjects with severe congenital protein C deficiency.

The study enrolled a total of 5 Japanese subjects with a confirmed diagnosis of homozygous or compound heterozygous congenital protein C deficiency. None of the participants discontinued prematurely, and all completed the trial.

The median age of study participants was 15.0 years, and the study included 3 paediatric patients.

PK parameters were derived using non-compartmental methods and showed substantial interindividual variability, which was comparable to previous trials in Western populations. Individual half-lives varied from 7.68 to 13.0 hours, and incremental recoveries ranged from 0.0143 to 0.0298 (IU/mL)/(IU/kg).

During the extension phase, a total of 19 episodes of purpura fulminans (PF), coumarin-induced skin necrosis (CISN) or other vascular thromboembolic events were reported and treated with CEPROTIN in 4 subjects. These included a total of 17 episodes in the three study participants <18 years of age. In addition, one course of short-term prophylaxis for a surgical procedure in an adult patient was analysed. All treatment effects were rated as effective with a mean (SD) time to resolution of acute episodes of 2.00 (0.816) days.

Throughout the study, CEPROTIN was well-tolerated without indications of potential age-related differences. No deaths or AEs leading to treatment discontinuation or to study withdrawal were reported. The only adverse event that was assessed by an investigator as related to treatment was a case of mild pyrexia, which was reported in one of the adult study subjects in the PK part of the study. In response to a request for additional information, the MAH (who also acted as the sponsor of the study) clarified that this classification remains questionable and that the totality of available data do not provide sufficient evidence to consider pyrexia as an ADR. Consequently, it has been agreed with the MAH that there is no need to update section 4.8 of the EU SmPC.

In essence, the newly submitted data from a small group of Japanese patients with severe congenital protein C deficiency further supports the favourable safety profile and efficacy of CEPROTIN in the on-demand treatment of acute thrombotic episodes and short-term prophylaxis.

# 3. Rapporteur's overall conclusion and recommendation

Final data of study TAK-662-1501 do not change the favourable benefit risk profile of CEPROTIN in its approved indication and no regulatory actions are required.

☒ **Fulfilled.**

# 4. Request for supplementary information

Based on the data submitted, the MAH should address the following question as part of this procedure:

1. The adverse event of pyrexia reported in study TAK-662-1501 was deemed to be related to treatment (as e.g. mentioned on page 84 of the final clinical study report) However, pyrexia is not currently mentioned in section 4.8 of the CEPROTIN SmPC. Therefore, the declared dispensable update of the EU Product Information requires additional justification.

The timetable is a 30-day response timetable with clock stop.

## MAH responses to Request for supplementary information

1. The adverse event of pyrexia reported in study TAK-662-1501 was deemed to be related to treatment (as e.g. mentioned on page 84 of the final clinical study report) However, pyrexia is not currently mentioned in section 4.8 of the CEPROTIN SmPC. Therefore, the declared dispensable update of the EU Product Information requires additional justification.

**MAH's response:**

A total of 10 studies has investigated Ceprotin: IMAG-039, IMAG-041, IMAG-098, 400101, 400501, 400701, IMAG-103, IMAG-112, CEPROTIN-D-001, and TAK 662-1501. Among these, three studies (400101, 400701, and TAK 662-1501) reported event PT pyrexia. The events in 400101 and 400701 were assessed as unrelated to treatment, while the event in TAK 662-1501 was considered related by investigator. Additionally, RDC-IMAG-039/041 reported event PT fever, deemed unrelated, and Ceprotin-D-001 reported event PT minor transient increase in body temperature assessed as improbable.

Key study descriptions:

- 400101: Phase 2/3 study evaluating efficacy and safety of Protein C Concentrate in severe congenital Protein C deficiency.
- 400701: CEPROTIN Treatment Registry.
- TAK 662-1501: Open-label, single-dose Phase 1/2 study in Japanese subjects, with one event of pyrexia reported in the pharmacokinetic cohort.
- RDC-IMAG-039/041: Retrospective data collection on Protein C Concentrate use.
- Ceprotin-D-001: Retrospective study on Ceprotin for purpura fulminans.

In summary, pyrexia was considered related to Ceprotin in only one subject from one study (TAK 662-1501), specifically in one out of five subjects in the pharmacokinetic phase. Current data does not include sufficient evidence supporting a causal relationship; hence, pyrexia is not considered as an ADR.

**Assessment of MAH's response:**

The MAH discussed the event of mild pyrexia reported in study TAK-662-1501 in the context of the totality of available reports of the PTs 'pyrexia', 'fever', or 'increase in body temperature' and reaches the conclusion that the currently available data does not provide sufficient evidence supporting a causal relationship. Indeed, the report from study TAK-662-1501 appears to be the only AE (of a total of 5 reports) that has been considered related by the investigator. In addition, the submitted study report lacks any additional information that would allow the investigator's classification to be further assessed. Consequently, the sponsor's divergent classification is acknowledged, and it is agreed that the totality of available data does not provide sufficient evidence to consider pyrexia as an ADR.

**Issue considered resolved.**