1. SYNOPSIS

Name of Sponsor/Company: Baxter Innovations GmbH	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Investigational Product: Prothromplex Total	Volume:	
Name of Active Ingredient: Human prothrombin complex factors (Factors II, VII, IX, X)	Page:	

Title of Study:

An international, multi-center, prospective, open-label, non-randomized, uncontrolled study to assess the efficacy and safety of prothromplex total in oral anticoagulant reversal in patients with acquired prothrombin complex coagulation factors (II, VII, IX, X) deficiency

Study Sites:

[redacted] Dr. Med. [redacted] Austria

[redacted] Dr. [redacted] Hungary

[redacted] . Dr. [redacted]
Hungary

[redacted]
Dr.
Dr. [redacted] Hungary

[redacted] Dr. [redacted], Austria

[redacted] . Dr. [redacted], Austria

Publication (reference): None

Study Period: **Initiation:** 2010 July 09 **Completion:** 2012 April 07 **Duration:** 21 months	**Study Phase:** Phase 4

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Study Purpose and Objectives:

Study Purpose:

To assess the efficacy and safety of Prothromplex Total as a treatment for the immediate reversal of oral anticoagulant therapy with vitamin K antagonists in subjects with acquired prothrombin complex coagulation factors (II, VII, IX, X) deficiency

Primary Objective:

- To evaluate the efficacy of Prothromplex Total in reversing the effects of oral anticoagulant therapy with respect to normalization of increased international normalized ratio (INR)

Secondary Objectives:

- To collect information on the shortening of prothrombin time (PT)
- To assess in-vivo recovery of clotting factors II, VII, IX and X at 30 ± 5 minutes after administration of Prothromplex Total
- To assess safety of Prothromplex Total when administered to subjects with acquired coagulopathy due to treatment with oral anticoagulants, with respect to clinically observed adverse drug reactions (ADRs) and coagulation markers

Exploratory Objectives:

- To assess hemostatic efficacy of Prothromplex Total in:
  - Treatment of acute bleeding due to oral anticoagulants
  - Prevention of excessive bleeding during interventional procedures

Study Design:

This was a Phase 4, prospective, non-randomized, uncontrolled study to assess the efficacy and safety of Prothromplex Total (Prothrombin Complex Concentrate; PCC) in approximately 50 evaluable subjects

Number of subjects

Planned: 60 were to have been enrolled to obtain approximately 50 evaluable subjects
Analyzed: 62 enrolled and 61 received at least one infusion

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Diagnosis and main criteria for inclusion:

Subjects who met **ALL** of the following criteria were eligible for this study:

- Subject was at least 18 years of age at enrollment with acquired prothrombin complex coagulation factor (II, VII, IX, X) deficiency, due to oral anticoagulation with vitamin K antagonists (e.g. coumarin, warfarin), requiring reversal of oral anticoagulation for urgent surgery, invasive procedure or acute bleeding episode
- Subject provided written informed consent
- Subject had INR ≥ 2.0 at screening
- Subject must have been on stable doses of anticoagulant or had a known history of stable INR for at least 72 hours prior to screening
- Subject was willing and able to comply with the requirements of the protocol

Exclusion Criteria:

Subject who met **ANY** of the following criteria were not eligible for this study:

- Subject had laboratory and/or clinical symptoms which were clearly indicative of disseminated intravascular coagulation (DIC)
- Subject had been treated with whole blood, fresh frozen plasma (FFP), or platelets within 6 hours prior to study enrollment
- Subject had a hypersensitivity to PCC constituents (including heparin-induced thrombocytopenia)
- Subject had blood loss of ≥ 5 units of blood
- Subject had known congenital Protein C, Protein S, or Antithrombin deficiency, or hereditary bleeding disorder
- Subject had a life expectancy of < 3 months
- Subject had been on oral anticoagulant treatment for a period of < 4 weeks for the treatment of a thrombotic event such as deep vein thrombosis or pulmonary embolism
- Subject had an acute ischemic cardiovascular disorder

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- Subject had or was suspected to have sepsis
- Subject had acute or chronic liver failure (hepatic cirrhosis Child-PUGH score C)
- Subject had renal failure and was undergoing dialysis
- Subject had participated in another clinical study involving an investigational product (IP) or device within 30 days prior to study enrollment or was scheduled to participate in another clinical study involving an IP or device during the course of this study

Investigational Product, dose and mode of administration, and batch number:

IP: Prothromplex Total is provided as a lyophilized powder with solvent (water for injection) for reconstitution. Each vial nominally contains 600 IU Prothromplex Total (human coagulation factors: II – 600 IU; VII – 500 IU; IX – 600 IU; and X – 600 IU). Dosing was based on INR measurements performed at the local laboratory prior to initiating treatment according to the following:

INR	Dose (IU/kg Factor IX)
2.0-3.9	25
4.0-6.0	35
> 6.0	50

If required, additional doses of Prothromplex Total could be administered at any time at the discretion of the investigator based on clinical presentation or on the results of prior INR measurements performed at the local laboratory. If administration of Prothromplex Total was based on the INR results, the IP was dosed according to the table above.

Mode of Administration: Intravenous infusion

Batch numbers: VNP5K002-01; VNP5K002-02; VNP5L010-03

Duration of treatment: Subjects received at least one infusion of Prothromplex Total (additional infusions at the discretion of the investigator with the aim of normalizing INR) and were followed for a minimum of 15 days

Reference therapy, mode of administration, and batch number:

Reference Therapy(ies): Not applicable

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Mode of Administration: Not applicable

Batch number(s): Not applicable

Criteria for evaluation

Primary Efficacy Endpoint:

- Proportion of subjects who achieved normalization of INR to ≤ 1.3 within 30 ± 5 minutes after administration of Prothromplex Total

Secondary Efficacy Endpoints:

- Number of doses required to achieve normalization of INR
- Shortening of PT (expressed as percent of normal coagulation activity)
- In-vivo recovery of clotting factors II, VII, IX and X at 30 ± 5 minutes after administration of Prothromplex Total

Secondary Safety Endpoints:

- ADRs
- Markers of coagulation (fibrinogen, D-dimer, protein C activity, antithrombin activity, coagulation factor activities for factors II, VII, IX and X)

Exploratory Endpoint:

- Hemostatic efficacy rating in subjects undergoing interventional procedures and in subjects with acute bleeding

Statistical Methods:

The primary endpoint was analyzed by point estimate and 95% Clopper-Pearson confidence interval (CI) for the proportion of subjects with INR ≤ 1.3 within 30 ± 5 minutes after the last Prothromplex Total dose.

Analyses for secondary endpoints and the exploratory endpoint included point and interval estimates, histograms, Kaplan-Meier plots, boxplots, and other descriptive statistics.

Safety data were summarized descriptively.

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Summary – Conclusions

A total of 61 patients were infused with Prothromplex Total in this study; 13 of these subjects were treated for acute bleeding episodes and 48 subjects for interventional procedures.

Primary Efficacy Endpoint:

Of the 61 patients who were infused with Prothromplex Total, 59 subjects had data for the primary endpoint and were included in the full analysis (FA) dataset; 58 subjects in the FA dataset fulfilled all inclusion/exclusion criteria and were included in the per protocol (PP) dataset. All 59 subjects (95% CI, 93.9-100.0) in the FA dataset and all 58 subjects (95% CI, 93.8- 100.0) in the PP dataset achieved normalization of INR to ≤ 1.3 within 30 ± 5 minutes after administration of Prothromplex Total.

Secondary Efficacy Endpoints:

All subjects in the FA and PP datasets required only one infusion to achieve normalization of INR to ≤ 1.3. The median INR value 30 minutes after infusion was 1.03 (range, 1.00-1.29) in both the FA and PP datasets. Shortening of PT was reported as a percentage of normal coagulation activity and was similar in the FA and PP datasets. Upon Prothromplex Total infusion, coagulation activity in the FA dataset rapidly increased from a median baseline value of 15.00% (range, 2.00%-46.00%) to 82.50% (range, 60.00%-150.00%) at the 15-minute time point and 84.00% (range, 59.00%-150.00%) at the 30-minute time point. In-vivo recoveries were similar for the FA and PP datasets. In the FA datastet, the median in-vivo recoveries of clotting factors II, VII, IX and X at 30 ± 5 minutes after infusion were 2.03 IU/dL:IU/kg (95% CI, 1.91-2.12 IU/dL:IU/kg), 1.76 IU/dL:IU/kg (95% CI, 1.76-2.29 IU/dL:IU/kg), 1.12 IU/dL:IU/kg (95% CI, 1.05-1.21 IU/dL:IU/kg), and 1.85 IU/dL:IU/kg (95% CI, 1.75-1.95 IU/dL:IU/kg), respectively.

Secondary Safety Endpoints:

The safety analysis set consisted of 61 subjects infused with Prothromplex Total. A total of 66 AEs (33 mild, 28 moderate, and 5 severe) occurred in 24 subjects, 8 of which were considered SAEs (1 mild, 2 moderate, and 5 severe) occurring in 3 subjects. Two subjects experienced treatment-related AEs (ADRs): subject [redacted] had pyrexia (mild) and subject [redacted] had an acute myocardial infarction (severe). Markers of coagulation showed different patterns of change over a 72-hour period following Prothromplex Total administration: antithrombin activities stayed constant within reference range; D-dimer

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and fibrinogen levels shifted over time from mostly within to mostly above reference range; protein C activities shifted from mostly below reference range at baseline to mostly within reference range during the first hour after infusion and then dipped back down.

Exploratory Endpoint:

The overall hemostatic efficacy of Prothromplex Total was assessed in 48 subjects undergoing interventional procedures and 13 subjects treated for acute bleeds. The overall efficacy was rated excellent for all subjects undergoing interventional procedures (100%, n=48/48 in FA dataset and n=47/47 in PP dataset) and for all subjects treated for acute bleeds (100%, n=11/11 in FA dataset and n=11/11 in PP dataset).

Conclusion:

In conclusion, the primary endpoint of this study was met: all subjects treated with Prothromplex Total achieved normalization of INR to ≤ 1.3 within 30 ± 5 minutes of infusion. One infusion of Prothromplex Total was enough for all patients to normalize INR within 30 minutes and for most subjects to normalize coagulation activity within 15 minutes of infusion. Taken together with the low incidence of ADRs, this study confirms that Prothromplex Total is safe and effective in immediately reversing the effects of oral anticoagulant therapy with respect to normalization of increased INR and restoring levels of vitamin K-dependent procoagulants. Additionally, Prothromplex Total treatment of subjects undergoing interventional procedures prevented excessive bleeding and decreased or stopped bleeding in subjects presenting with acute bleeding episodes.

Date of Report: 2012 OCT 22