CSL Behring

Efficacy and Safety of a Four-Factor Prothrombin Complex Concentrate in Patients on Vitamin K Antagonists Presenting With Major Bleeding: A Randomized, Plasma-Controlled, Phase IIIb Study

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HIGHLIGHTS

4F-PCC:

- is an effective and safe alternative to plasma for urgent VKA therapy reversal in major bleeding events
- demonstrated superiority to plasma, with **62.2% having rapid INR reduction**
- demonstrated noninferiority to plasma; **72.4% achieved effective hemostasis**, versus 65.4% receiving plasma

INTRODUCTION

Rapid vitamin K antagonist (VKA) reversal via **prompt restoration of vitamin K-dependent coagulation factors is needed** to manage acute hemorrhage

4F-PCC or plasma efficacy and safety comparisons for urgent VKA reversal in patients experiencing major bleeding events

STUDY CHARACTERISTICS

Objective
4F-PCC compared with plasma for urgent VKA reversal in acute major bleeding

Study design
Randomized, open-label, noninferiority Phase 3b trial

Patient population
≥18 years of age (US and Europe)

Endpoints

Coprimary endpoints
- Effective hemostasis: Excellent or good rating >24 hours from infusion
- INR correction: Rapid INR reduction (≤1.3)

Secondary endpoint
- Time to INR correction

Safety endpoint
- Records of adverse and serious adverse events

RESULTS

The intention-to-treat efficacy (ITT-E) population comprised 202 patients (4F-PCC, n=98; plasma, n=104).

72.4%

72.4% achieved hemostatic efficacy with 4F-PCC versus 65.4% receiving plasma, demonstrating noninferiority (difference, 7.1% [95% CI, –5.8 to 19.9])

62.2%

62.2% of 4F-PCC patients experienced a **rapid INR reduction** compared to 9.6% of plasma-treated patients, demonstrating **4F-PCC superiority** to plasma

Coagulation factors were **higher in the 4F-PCC group** from 0.5 to 3 hours after infusion start (*P*<0.02)

Figure 1. Effective hemostasis (ITT-E population)

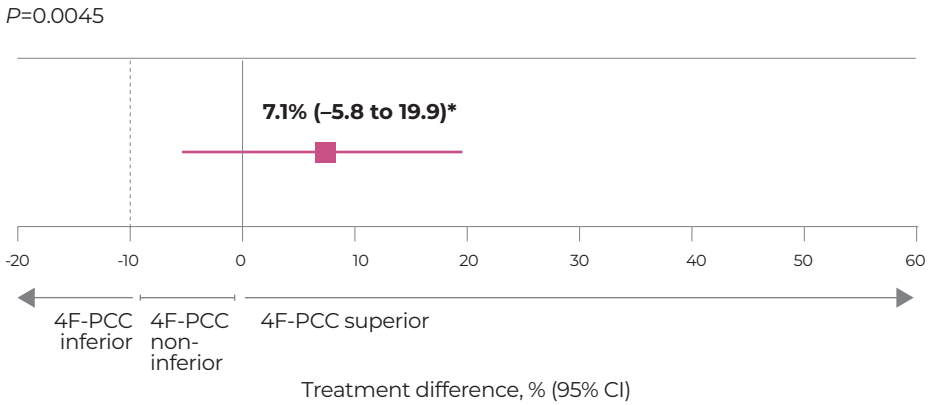
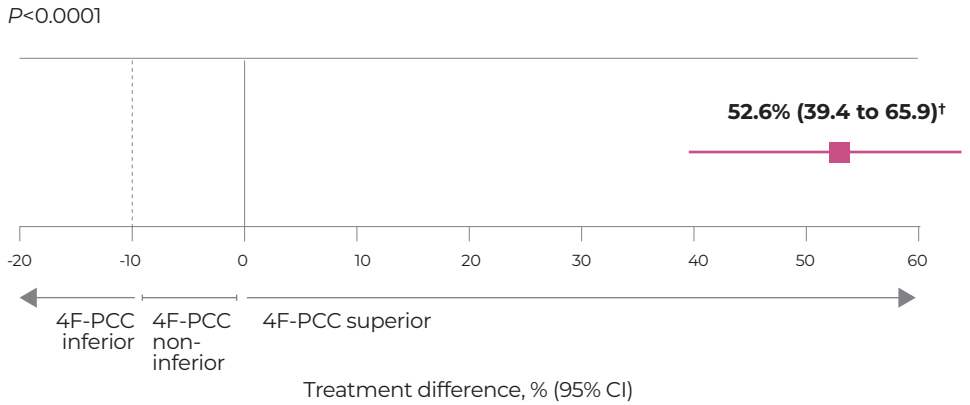


Figure 2. Rapid INR reduction (ITT-E population)*



*4F-PCC noninferior to plasma: lower limit of 95% CI more than –10% Farrington-Manning P-value for noninferiority *P*=0.0045 rejecting null hypothesis of inferiority of 4F-PCC.

*INR ≤1.3 at 0.5 h after end of infusion. †4F-PCC noninferior to plasma: lower limit of 95% CI more than –10% Farrington-Manning P-value for noninferiority *P*<0.0001 rejecting null hypothesis of inferiority of 4F-PCC; 4F-PCC superior to plasma: lower limit of 95% CI >0.

RESULTS

INR correction was **more rapid with 4F-PCC**, with **69%** reaching an INR ≤1.3 at 1 hour post-infusion, compared to none in the plasma group.

Figure 3. Time to INR correction (ITT-E population)

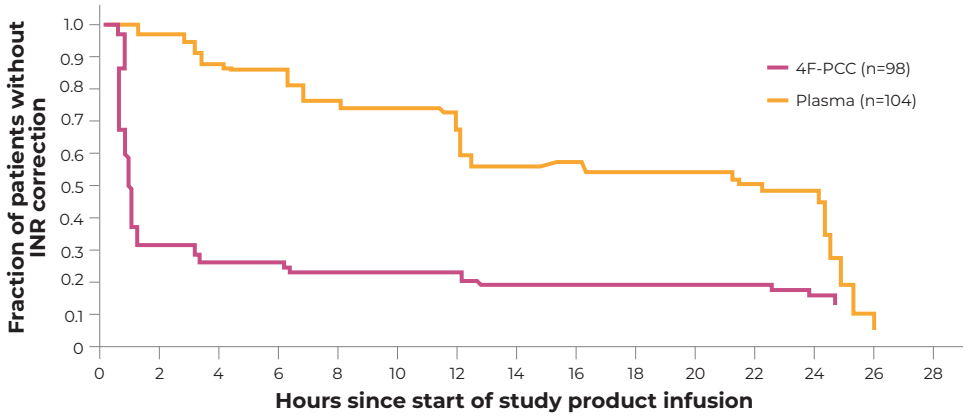
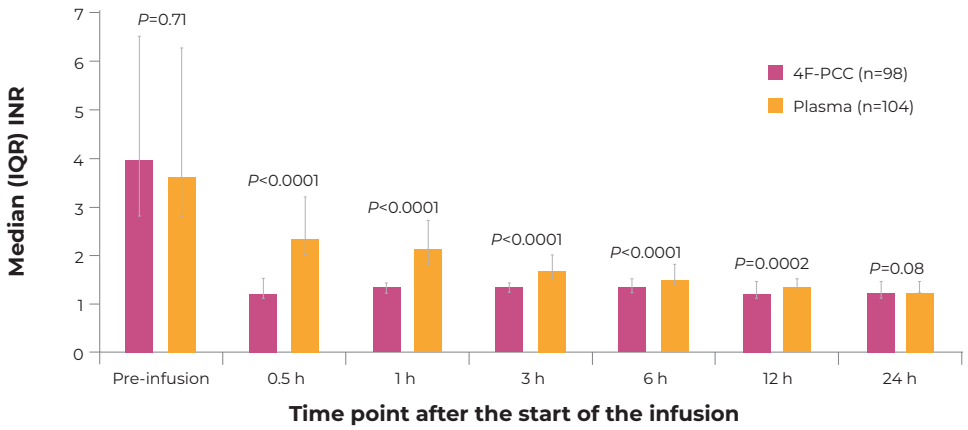


Figure 4. Median INR by time point (ITT-E population)



Both groups had **similar safety profiles** including adverse events, serious adverse events, thromboembolic events, and deaths.

Table. Summary of AEs (ITT-S population)

AE	No. (%) of patients	
	4F-PCC (n=103)	Plasma (n=109)
Any nonserious AE*	66 (64.1)	71 (65.1)
Related AE†	10 (9.7)	23 (21.1)
AE leading to treatment discontinuation	0	3 (2.8)
Serious AE*	32 (31.1)	26 (23.9)
Related serious AE†	2 (1.9)	4 (3.7)
AEs of interest		
Deaths to Day 30	6 (5.8)	5 (4.6)
Deaths to Day 45	10 (9.7)	5 (4.6)
Related deaths (to Day 45)‡	1 (1.0)	0
Thromboembolic AE	8 (7.8)	7 (6.4)
Related thromboembolic AE†	4 (3.9)	3 (2.8)
Fluid overload or similar cardiac event	5 (4.9)	14 (12.8)
Related fluid overload or similar cardiac event†	0	7 (6.4)

*Defined in Table XIV in the online-only Data Supplement.
†Defined as events for which there was a relationship to study treatment in the opinion of the investigator. AEs with missing relationship were considered treatment related.
‡As assessed by the Safety Adjudication Board; no deaths in either group were classified as related by an investigator.

ITT-E population: all patients from the ITT population who had received any portion of study product, who presented with acute major bleeding, and who had an INR >1.3 before infusion with study product.

ITT-S population: all patients from the ITT population who had received any portion of the study product.

Abbreviations
4F-PCC: four-factor prothrombin complex concentrate; AE: adverse event; INR: international normalized ratio; IQR: interquartile ratio; ITT-E: intention-to-treat efficacy; ITT-S: intention-to-treat safety; VKA: vitamin K antagonist.

Reference
Sarode R, Milling TJ Jr, Refaai MA, et al. *Circulation*. 2013;128(11):1234-1243.

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