

## Abstract

**Introduction:** INTERCEPT™ Plasma (I-FFP) for transfusion is prepared with a photochemical treatment (PCT) system using amotosalen (S-59) and long-wavelength UVA light to inactivate a broad spectrum of blood-borne pathogens. For Phase 3 clinical trials, 6 U.S. blood centers prepared an inventory of ~10,000 I-FFP units by processing ~250 mL whole blood-derived (WB) or apheresis (APH) plasma units using a prototype PCT system. In these trials, I-FFP effectively supported patients with congenital and acquired coagulopathies or TTP. The prototype PCT system has been modified to treat up to 635 mL of plasma in a single PCT process, yielding up to three ~200 mL doses while maintaining pathogen inactivation efficacy. This modified PCT system intended for commercialization was evaluated in process validation studies in 3 European blood centers under routine operating conditions. After processing with the commercial PCT system, the effect on coagulation factor activity and retention was assessed in APH plasma (Blood 2004;104:746a) and, as reported here, in WB plasma.

**Methods:** Whole blood and/or APH plasma units were collected at 3 European blood centers. Three-unit pools (~600 mL) of WB plasma were prepared. APH plasma (~600 mL) was collected using Autopheresis C (Baxter) or MCS+ (Haemonetics) devices. Blood bank personnel processed a total of 96 WB plasma pools and 90 APH plasma units using the commercial PCT system. Baseline and I-FFP plasma samples were collected, frozen below -60°C, and sent to Cerus for assay of factors I (fibrinogen), II, V, VII, VIII, IX, X, XI, and XIII, proteins C (PC) and S (PS), and antithrombin III (AT). Alpha-2 antiplasmin (AP) was assayed by a reference laboratory. Comparative data from a representative subset of I-FFP units prepared for the Phase 3 trials using the prototype PCT system were obtained from samples collected during PCT processing and stored at ≤ -70°C. Retention of activity is expressed as the proportion (%) of pre-treatment (baseline) activity remaining after PCT.

**Results:** Retention of coagulation factor activity in WB and APH I-FFP prepared with the commercial PCT system (Comm) was 72-76% of baseline fibrinogen and FVIII activity, and 80-97% of baseline for factors II, V, VII, IX, X, XI, XIII, PC, PS, AT, and AP (Table 1). Retention of activity in I-FFP prepared with the commercial PCT system was similar to that of I-FFP prepared with the clinical prototype.

**Conclusion:** The PCT system intended for commercialization provides multiple I-FFP doses with a single PCT process. Retention of coagulation factor activity in WB and APH plasma processed with the commercial PCT system was similar to that of I-FFP used in Phase 3 trials to effectively support patients with congenital and acquired coagulopathies or TTP.

**Table 1: Retention of Coagulation Factor Activity in I-FFP**

	Activity (IU/dL) Mean ±SD		Retention (%) in I-FFP Mean ±SD		
	Baseline-WB <sup>a</sup> (n=96)	I-FFP, Comm-WB (n=96)	Comm-WB (n=96)	Comm-APH (n=90)	Clinical Prototype (n=325)
FI	284 ±34	206 ±29	72 ±4	76 ±7	78 ±7
FII	102 ±8	91 ±8	89 ±3	89 ±5	90 ±5
FV	122 ±16	118 ±15	97 ±3	97 ±4	95 ±4
FVII	112 ±15	89 ±12	80 ±3	81 ±4	82 ±5
FVIII	121 ±23	88 ±18	73 ±5	75 ±6	77 ±7
FIX	94 ±10	78 ±8	84 ±3	85 ±4	88 ±6
FX	106 ±10	92 ±9	86 ±2	89 ±4	90 ±3
FXI	93 ±13	79 ±13	85 ±5	88 ±7	90 ±5
FXIII	113 ±14	106 ±12	94 ±3	96 ±6	99 ±3 <sup>c</sup>
AT	95 ±7	91 ±7	96 ±2	95 ±3	92 ±2 <sup>c</sup>
PC	115 ±16	99 ±14	87 ±6	85 ±6	96 ±7 <sup>c</sup>
PS	114 ±15	110 ±15	96 ±4	97 ±7	99 ±6 <sup>c</sup>
AP	96 ±7	79 ±6	83 ±4	83 ±8	90 ±3 <sup>c</sup>

a. F1 in mg/dL; b. Baseline samples from 3-unit WB plasma pool; c. n=34; d. n=14

## Background

Phase 3 clinical trials demonstrated INTERCEPT Plasma retained coagulation factor activity and hemostatic function for the support of patients with congenital and acquired coagulopathies or TTP. More than 19,000 'test' and 'control' plasma units were prepared at 6 U.S. blood centers for Phase 3 clinical trials. Approximately half of these underwent PCT to prepare I-FFP using a prototype processing set (Table 2, Figure 3). Of the I-FFP units, approximately 325 were randomly selected and analyzed for coagulation factor activity (Table 1, Figure 4).

An improved PCT system has been developed for commercialization (Table 2, Figure 2). Processing with this improved system is less time-consuming. It is able to treat up to 635 mL of plasma and yield up to three ~200 mL doses of INTERCEPT Plasma with a single treatment.

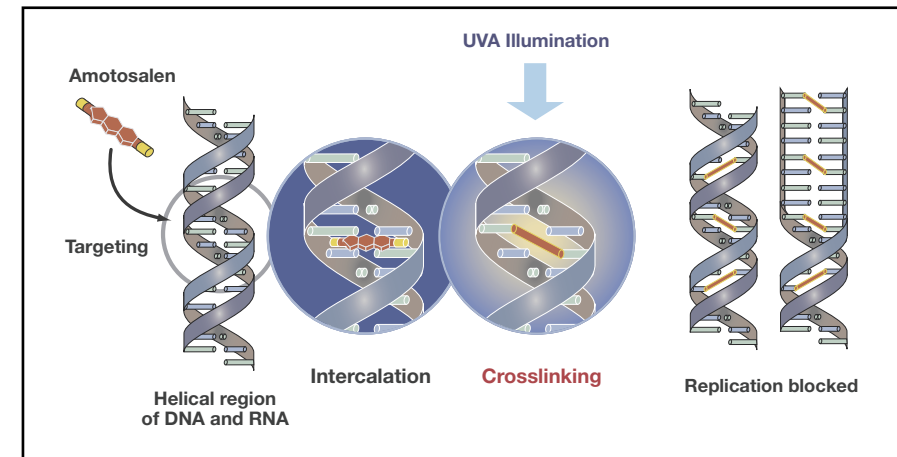
**Table 2: Comparison of Prototype and Improved INTERCEPT Plasma PCT System**

	Improved Set	Prototype Set
Volume plasma to be treated	~600 mL	~250 mL
Units illuminated at one time	2	1
Removal of residual amotosalen by CAD	flow through, ~20 min. on average	1 hr on platelet shaker
Sterile connections required	1	3
Plasma doses produced	up to 3 doses	1 dose

## Introduction

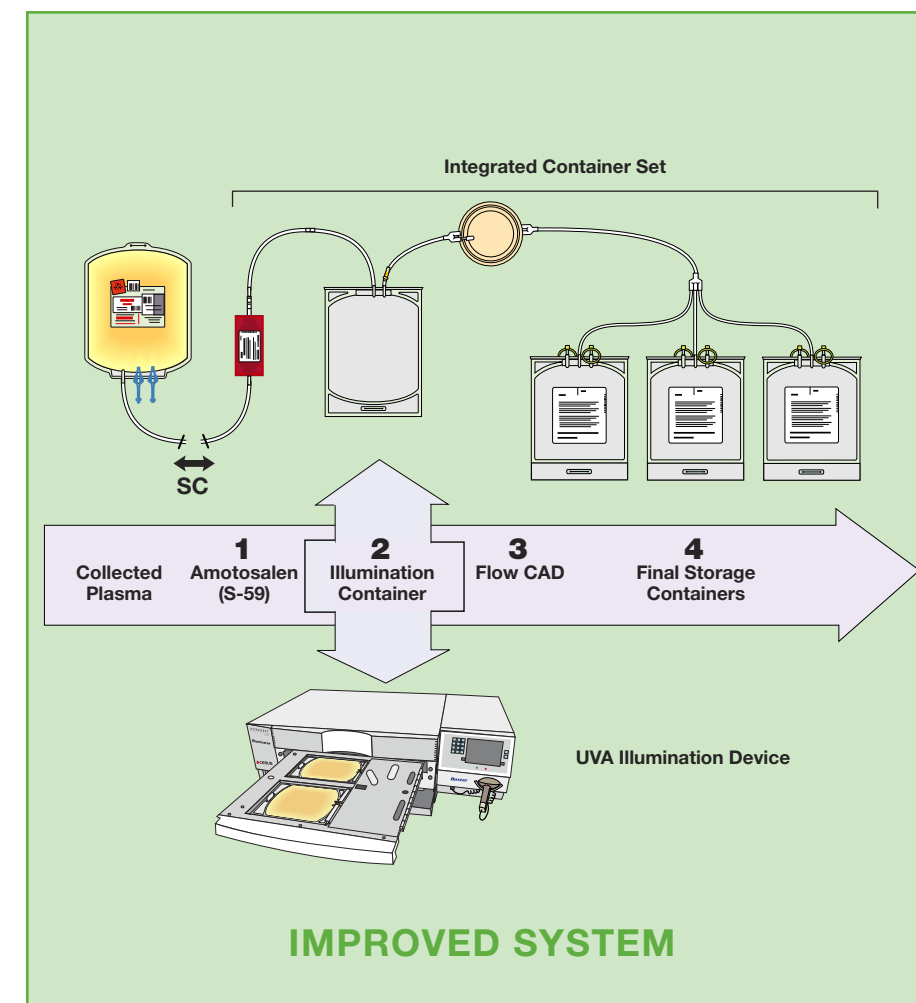
### Figure 1 (at right): Helinx™ Technology

Helinx Technology for plasma consists of amotosalen HCl, a psoralen molecule, and illumination with 3.0 J/cm<sup>2</sup> ultraviolet A (UVA) light treatment. The amotosalen compound penetrates cellular and nuclear membranes and intercalates into the helical regions of DNA and RNA. Covalent crosslinks to the nucleic acid base pairs form upon exposure to UVA light, blocking DNA and RNA replication. This process inactivates white blood cells and pathogens, rendering them unable to cause disease, while retaining the function of plasma, which does not require nucleic acid replication for therapeutic efficacy.



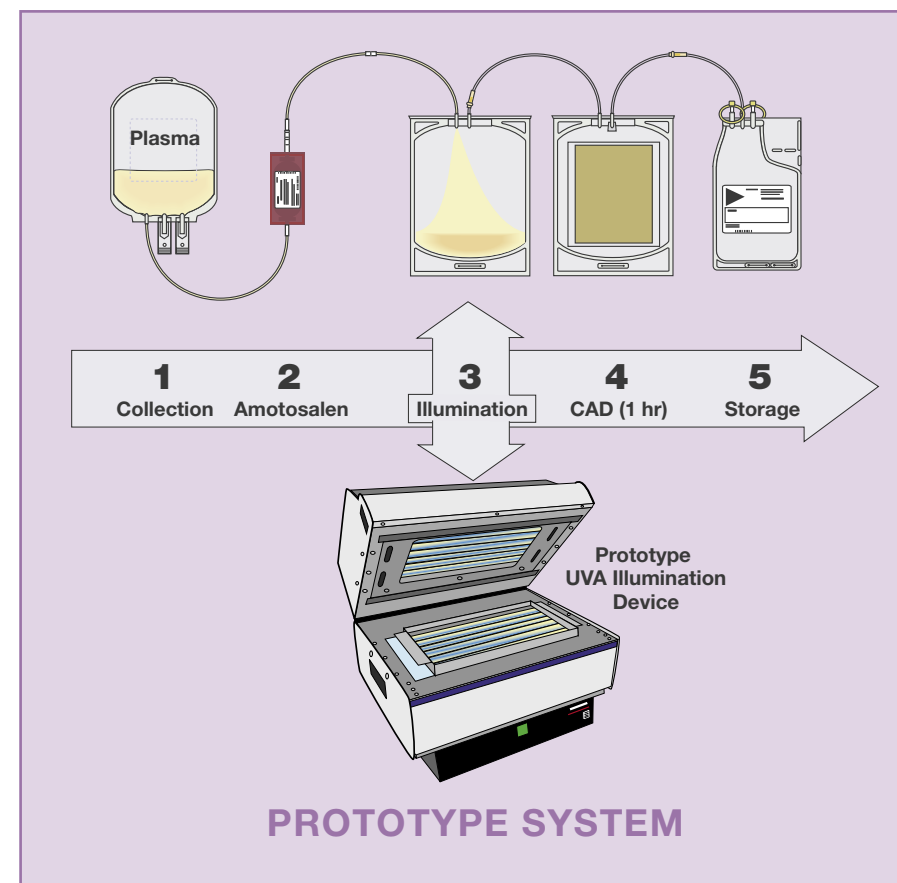
### Figure 2: Improved INTERCEPT Blood System™ for Plasma

The collected plasma is sterile connected to the PCT set (1 through 4). Amotosalen (1) is added by gravity flow and the plasma is illuminated with UVA light (2). Residual amotosalen and its photoproducts are reduced to low levels using a flow-through compound adsorption device (CAD) (3) during transfer to the storage containers (4).



### Figure 3: Prototype INTERCEPT Blood System for Plasma

The amotosalen container (2) was sterile docked to the collection container (1) and the illumination container (3). After addition of amotosalen (2) by gravity flow, and removal of the plasma and amotosalen containers, the plasma was illuminated with UVA light (3). Residual amotosalen and its photoproducts were reduced to low levels during a 1-hour incubation with shaking (60cycles/min) using an enclosed loose-bead compound adsorption device (4). After the 1-hour incubation, the treated plasma was transferred to a single storage container (5).



## Methods

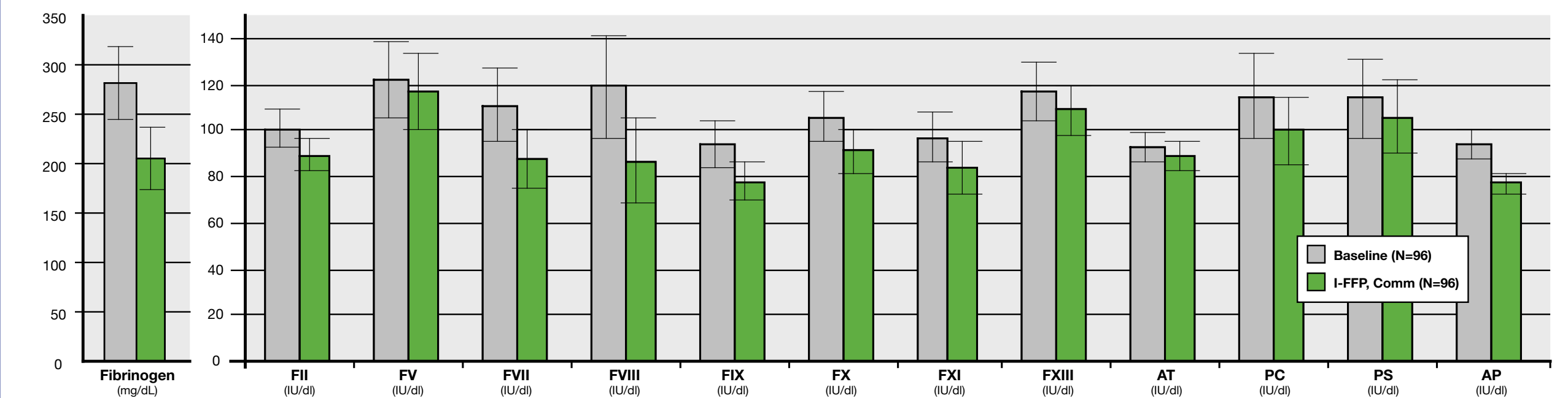
Thirty apheresis plasma units, each approximately 600 mL, were collected at the Haukeland University Hospital (Bergen, Norway), the Institute of Immunology and Transfusion Medicine at the University of Lübeck (Lübeck, Germany), and the Etablissement Français du Sang (Strasbourg, France). The Autopheresis C (Baxter Transfusion Therapies) was used for plasma collection in Bergen and Lübeck, and the Haemonetics MCS+ was used in Strasbourg. Plasma was anticoagulated with half-strength CPD in Bergen and trisodium citrate in both Lübeck and Strasbourg. At the same 3 European blood centers, 30 to 36 whole blood-derived plasma pools, each approximately 600 mL, were prepared by pooling 3 ABO-matched plasma units. The whole blood was anticoagulated in full strength CPD. INTERCEPT Plasma was prepared by blood bank personnel using the improved set. Samples for coagulation testing were collected both before and after PCT. Samples were frozen at < -60°C and shipped on dry ice to Cerus for analysis. Fibrinogen was measured using the Clauss method. Coagulation factors were assayed using PT-based or APTT-based one-stage clotting assays. ATIII was measured using the Stachrome® ATIII assay (Diagnostica Stago, Asnieres-sur-Seine, France). FXIII was measured using the Berichrome FXIII method (Dade Behring, Marburg, Germany). Protein C and Protein S were measured using Staclot® Protein C and Staclot® Protein S assays (Diagnostica Stago). Alpha-2 antiplasmin was sent to Esoterix, Inc. (Aurora, CO) and tested using the Stachrom® Antiplasmin method (Diagnostica Stago).

## Conclusions

- INTERCEPT Plasma can be prepared from whole blood and apheresis plasma collections.
- INTERCEPT Plasma prepared using the improved PCT system maintains coagulation factor activity similar to the plasma prepared for the clinical trials using the prototype PCT system.
- Clinical trials have shown that INTERCEPT Plasma provided sufficient levels of coagulation factor activity for treatment of congenital and acquired coagulopathies and therapeutic plasma exchange for TTP.
- The improved processing system allows production of multiple doses of INTERCEPT Plasma from a single treatment process.

## Results

**Figure 4: Coagulation Factor Activity in Whole Blood-Derived Plasma Before and After PCT (Mean ± SD)**



**Figure 5: Percent Retention of Coagulation Factor Activity (Mean ± SD)**

