UCSF Medical Center

UCSF Transfusion Service will be introducing pathogen-reduced; psoralen-treated platelets on November 8, 2017. We will be phasing in these new platelets into our inventory based on available supply from our blood supplier. *Initially, only 1-2 products will be available per day. Pediatric BMT patients will be the first recipients of psoralen-treated platelets. Providers should continue to order platelets as usual; they should not place special orders for psoralen-treated platelets.* Blood Bank will triage platelet orders and as inventory ramps up, make this product available to other higher risk patients.The following points supported the decision by the Transfusion Committee to adopt these new platelet products. The Transfusion Committee has reviewed the contraindications and warnings and has determined that this product is safe and effective for all patients

The Traditional Approach to Blood Safety Is *Reactive*

- Blood is tested for a limited number of pathogens with current testing methods
- New pathogens continue to emerge, and tests for all new pathogens do not currently exist
- Bacterial contamination is the leading transfusion-transmitted infection and can lead to sepsis and/or death
- Transfusion reactions including sepsis may be under recognized and underreported

PATHOGEN REDUCTION (or PSORALEN TREATMENT) is a *Proactive* Approach to Blood Safety

- Reduces the risk of transfusion-transmitted infection (TTI), including sepsis, in platelet recipients
- Pathogen reduction via psoralen and UVA light treatment is effective in mitigating cytomegalovirus (CMV) and is a proactive approach to reducing the risk of CMV transmission
- Like irradiation, the psoralen/UVA light treatment pathogen reduction process inactivates T cells in platelets and reduces risk of transfusion-associated graft-versus-host disease (TA-GVHD)
- Platelets that have been pathogen reduced by psoralen treatment and UVA do not need to be irradiated. The AABB standard 5.19.3.1 for irradiation of blood products considers the FDA-approved method of pathogen reduction equivalent to irradiation[1]

PATHOGEN REDUCTION has a Strong History of Development and Routine Use

- INTERCEPT® treated platelets can be used for all standard indications in adults & children, with no exclusions.[2]
- Extensive European hemovigilance programs include data on platelets that have undergone psoralen/UVA pathogen reduction prior to transfusion in various patient populations[15-18] showing no unexpected adverse events reported across multiple age ranges including neonates, infants, children and adults across multiple disease states
- >12 years of routine use in >100 centers in multiple countries outside the US with >4 million processing sets distributed for use in pathogen reduction
- Extensive preclinical toxicology program was conducted per FDA product safety standards on the specific psoralen used in the psoralen/UVA light treatment pathogen reduction process. To date, no documented sensitivity to this psoralen known as amotosalen has been reported
- Robust clinical studies were conducted in the US showing effectiveness and safety[2-14]
- Pathogen-reduced, psoralen-treated platelets were approved by the FDA in December 2014 and are in routine use in > 50 US hospitals, including large tertiary care centers, Cancer Centers and Childrens Hospitals

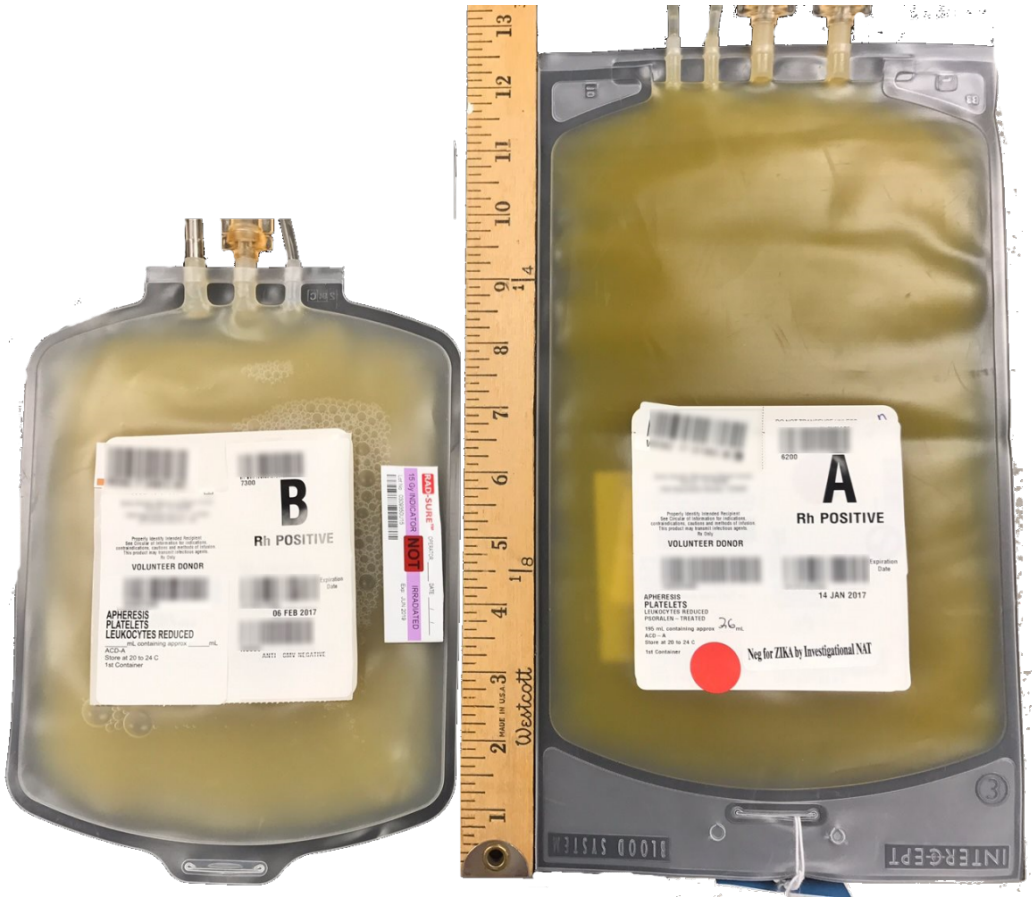
PSORALEN-TREATED PLATELET ADMINISTRATION

- Platelet dosing & volume of psoralen-treated platelets are the same as conventional platelet products
- Pre-medication and hang time for psoralen-treated platelets are the same as conventional platelet products
- Patients may receive both conventional platelets & psoralen-treated platelets
- Psoralen-treated platelets can be transfused in the same line as conventional platelets

PSORALEN-TREATED PLATELET BAG APPEARANCE

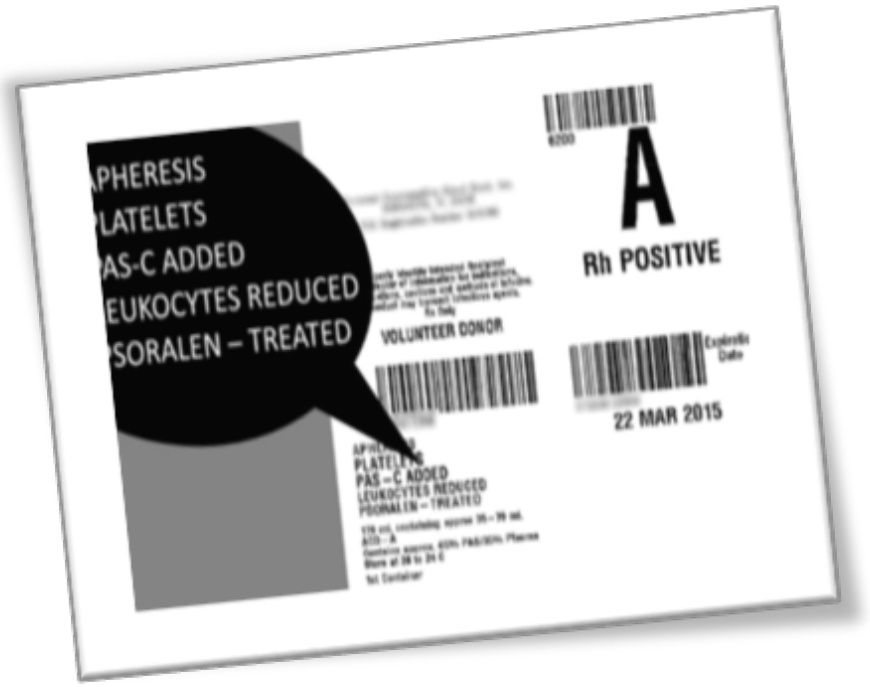
- The new psoralen-treated platelet bags are 2.8 inches longer than conventional platelet products
- INTERCEPT Blood System is embossed across the top of the bag
- All psoralen-treated platelets are leukoreduced

CONVENTIONAL PLATELET **PSORALEN-TREATED PLATELET**

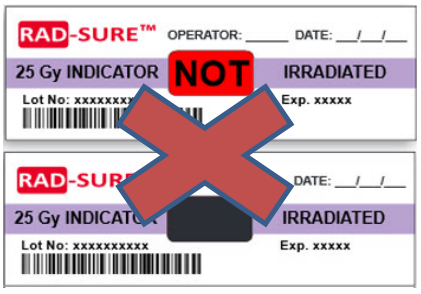


PSORALEN-TREATED PLATELET LABEL

- Labeled as **APHERESIS PLATELETS LEUKOCYTES REDUCED**
- Key words to look for on the new platelet labels - **PSORALEN-TREATED** which indicates that this product has undergone the psoralen + UVA light treatment process to inactivate pathogens



- Although psoralen-treated platelets are not labeled as “CMV negative”, they are considered equivalent to CMV seronegative platelets, as the pathogen inactivation process inactivates many infectious agents, including CMV
- Psoralen treated platelets will not require irradiation. The AABB standard 5.19.3.1 for irradiation of blood products considers the FDA-approved psoralen-treated method of pathogen reduction equivalent to irradiation.[1]
- As the psoralen-treated platelets do not require irradiation there will NOT be a Rad-Sure™ sticker on the bag



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Additional information, including detailed Q and A, clinical trials data, product information and package insert are available on the Clinical Labs online Laboratory Manual.

UCSF Medical Center
Institute for Nursing Excellence

PRACTICE REMINDER

Psoralen-Treated (Pathogen Inactivated) Platelets

UCSF Medical Center blood bank is phasing in new psoralen-treated, pathogen inactivated, platelets into our inventory, with the goal of fully adopting this new product house-wide.

Why?

Bacterial contamination is the leading transfusion-transmitted infection and can lead to sepsis and/or death. Platelets are stored at room temperature making this blood product type more susceptible to bacterial growth.

Transfusion reactions, including sepsis, may be under-recognized and underreported.

What?

Pathogen-reduction via psoralen treatment inactivates many infectious agents, including viruses, bacteria, and parasites.

Psoralen-treatment is effective in mitigating Cytomegalovirus (CMV), and inactivates T cells, therefore these platelets do not require CMV testing, and do not need to be irradiated. **Psoralen-treatment is equivalent to CMV negative and irradiated.**

Who?

Pediatric BMT patients will be the first recipients of psoralen-treated platelets. Initially, only 1-2 products will be available per day, but as inventory ramps up, this product will be available to other higher risk, and eventually all, patients.

How?

Administration

Psoralen-treated platelets are administered in the same way as conventional platelets; the blood product medication administration (BPMA) process is not affected, and can be administered back-to-back with conventional product.

Platelet dosing, volume, pre-medication and hang-time of the new psoralen-treated platelets are the same as conventional products.

Appearance

Psoralen-treated platelets come in a bag that is 2.8 inches longer than conventional platelets, are lighter in color than conventional platelets, and INTERCEPT Blood System is embossed across the top of the bag.

Additional Questions?

Blood Product Transfusion/Administration (General) Nursing Procedure

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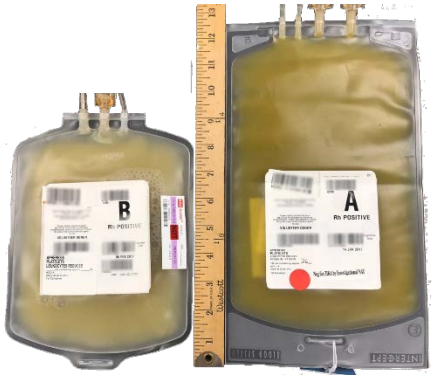

INTERCEPT® Blood System FAQs – US Only –16May2017

The following FAQs are intended as a document to guide in answering key questions.

It is important that the FDA-approved INTERCEPT Blood System Package Inserts be adhered to and read thoroughly.

Question	
What are the possible advantages of INTERCEPT treated products compared to conventional products?	• **INTERCEPT Platelets provide Hospitals a *transfusion-ready* product that delivers significant clinical benefits to patients**, including reduced risk due to sepsis/bacteremia, TA-GVHD, and transfusion-transmitted infections (e.g., emerging pathogens). • **INTERCEPT pathogen reduction (PR)/INTERCEPT Platelets provides:** o **Broad spectrum, comprehensive inactivation** against established and emerging pathogens (bacteria, viruses, protozoans), as well as T-cells. In addition to bacteria, PR has the ability to proactively mitigate risk due to emerging pathogens such as Zika, Babesia, chikungunya and dengue. Recently, FDA release a guidance to mitigate risk against transfusion-transmission due to Zika; per the guidance, pathogen reduction can be used in place of Zika testing for platelet and plasma components (FDA Zika Guidance for Industry February 2016). o **Avoidance of cost and complexity of bacterial detection.** Avoid cost and complexity of implementing and managing secondary bacterial testing or double bacterial culture in the hospital setting. Since INTERCEPT Platelets do not require primary bacterial culture, Hospitals may potentially receive units sooner (with potential effective shelf-life of ~4 days versus ~3 days for conventional). See PR/secondary bacterial testing question on page 4 of this document for further detail. o **Avoidance of gamma irradiation.** Potential avoidance of cost and/or labor due to performing irradiation and maintaining equipment ("Standards for Blood Banks and Transfusion Services," *AABB, 30th edition*, 2015; see section below on ability to replace irradiation) o **Outpatient reimbursement** HCPCS codes have been granted by CMS to allow for outpatient INTERCEPT Platelet and Plasma product billing/payment in the hospital outpatient setting.
Can INTERCEPT Platelets be used for any indication?	• INTERCEPT Platelets can be used according to US standard of care across broad patient populations. • It is contraindicated for patients with a history of hypersensitivity reaction to amotosalen or other psoralens. • It is contraindicated for preparation of platelet components intended for neonatal patients treated with phototherapy devices that emit a peak energy wavelength less than 425 nm, or have a lower bound of the emission bandwidth <375 nm. Note that the American Academy of Pediatrics-Clinical Practice Guidelines state that the recommended spectrum for intensive phototherapy is 430 – 490 nm; this is outside the bounds of the contraindication language. All devices currently marketed in the US are compliant. • For more information related to clinical studies, indications, and contraindications, please contact the Cerus MSL team.
Can you comment on ethical/logistical issues around dual inventories (i.e. pathogen reduced, conventional)?	• The movement to a 100% pathogen-reduced supply of platelets and plasma in the hospital blood bank will likely be a transition as hospital adoption and supply increases. Historically, multiple platelet inventories have existed in the form of irradiated and/or CMV-tested products. INTERCEPT-treated products can be stocked and made available in a similar fashion, as is currently the case in many hospitals transfusing INTERCEPT Platelets today.

Question	
	• Hospitals may consider providing PR-products to its most vulnerable populations (i.e. heme/onc, pediatrics). The most vulnerable patients require more safety against low-titers of bacteria that can colonize implanted devices like central lines as well as the coverage for other pathogens like emerging viruses, all of which are mitigated via pathogen reduced products.
Can you comment on the safety of amotosalen?	The safety of the INTERCEPT pathogen reduction process, which utilizes amotosalen (a psoralen compound), has been demonstrated in several in vitro and in vivo studies as described by the package inserts. • Amotosalen demonstrated no indication of an increased toxicological risk when using INTERCEPT Platelets as demonstrated by toxicity studies in rats and dogs that received doses of at least 10,000-fold the anticipated clinical exposure from 300mL of INTERCEPT Platelets (Ciaravino V et al., Transfusion, 2003; Ciaravino V et al., Human and Experimental Toxicology, 2001). • No evidence of reproductive or developmental toxicities was observed when dosing neonatal rats with amotosalen (Ciaravino V et al., Transfusion, 2009). • No evidence of carcinogenicity after repeated dosing with amotosalen at doses ~1200 times the daily human exposure from a single 300mL INTERCEPT Platelet transfusion (Tice RR et al., Mutation Research, 2007).
Who is currently using INTERCEPT?	• In the US, over 45 blood collection establishments have signed agreements for use of INTERCEPT pathogen reduction. More than 60 US hospitals are now transfusing INTERCEPT Platelets, including several large academic medical centers, cancer centers, children's hospitals, military/VA hospitals and community/critical care access hospitals. NIH and the Mayo clinic are among the hospitals that are currently transitioning to using 100% pathogen-reduced platelets. For a complete list, go to: https://intercept-usa.com/implement-intercept/us-customer-list • INTERCEPT has been used throughout Europe and other countries for over ten years, with kits sold to produce over 4,000,000 INTERCEPT Platelet and Plasma units. • Active hemovigilance studies conducted by Cerus covering 4,076 patients receiving 19,175 INTERCEPT Platelet transfusions have been described (Knutson et al., Vox Sanguinis, 2015). • Independent, mandated national hemovigilance programs in France and Switzerland have also been conducted since 2006, in which over 380,000 INTERCEPT Platelet units have been transfused in routine settings with no reported transfusion-transmitted infections (TTIs) or sepsis-related fatalities, acute respiratory distress syndrome (ARDS), or TA-GVHD to-date.
Is there any experience/data related to pediatric populations?	• A hemovigilance program (21 centers, 11 countries) spanning 7 years, over which 4,067 patients received pathogen reduced platelets, demonstrated similar incidence of adverse events between pathogen-reduced and conventional platelets in pediatric (N=242) and neonatal (N=46) patients (Knutson et al., Vox Sang., 2015). • In a French hemovigilance program, 699 patients, of which 54 were children and infants, received INTERCEPT-treated platelets in place of gamma irradiated platelets for prevention of TA-GVHD and in place of CMV serology tested platelets. No cases of transfusion-related sepsis or TA-GVHD were reported (Cazenave et al., Transfusion, 2011).
What about the contraindication on wavelength for phototherapy?	• The INTERCEPT Package Insert states the following: Contraindicated for preparation of platelet components intended for neonatal patients treated with phototherapy devices that emit a peak energy wavelength less than 425 nm, or have a lower bound of the emission bandwidth <375 nm, due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.

Question	
	• It is important to note that virtually no currently marketed phototherapy devices fall within the bounds of the contraindication language. The American Academy of Pediatrics-Clinical Practice Guidelines state that the recommended spectrum for intensive phototherapy is 430 – 490 nm, this is outside the bounds of the contraindication language.
Can you provide information on the difference in corrected count increment (CCI) with INTERCEPT? Can you comment on hemostatic efficacy?	• Lower CCIs have been reported with pathogen-reduced platelets, for example, in the US Phase 3 SPRINT study conducted in hematology/oncology patients (McCullough et al., Blood, 2004). • However, a lack of correlation between CCI and increased bleeding has also been demonstrated: o In the SPRINT study (refer to Package Insert), no significant differences were found between all three grades of bleeding when comparing pathogen-reduced versus conventional platelets. o Slichter et al. reported in the PLADO study that there was no significant difference in bleeding between patients receiving low, medium, and high conventional platelet doses; also, the number of red cell transfusions did not differ between the 3 platelet dose groups (Slichter et al., NEJM, 2010). • Multi-year hemovigilance (French, Swiss, Austrian) programs have demonstrated no significant increase in the use of RBCs (indirect measure of bleeding) with INTERCEPT Platelets. • A review of 9 clinical trials concluded no difference in clinically significant or severe bleeding, or red cell transfusion requirements between standard and pathogen-reduced platelets (Butler et al., The Cochrane Library, 2013). • Meta-analysis of 5 randomized controlled trials demonstrated no difference in bleeding tendency with INTERCEPT-treated platelets versus conventional platelets (Cid J. Vox Sang. 2012).
What about utilization of platelets? Does it increase with PR?	• Studies have demonstrated no increased utilization of platelet components when using INTERCEPT Platelets, including a study in which the efficacy and safety of pathogen reduced platelets were assessed via active hemovigilance surveillance. As part of the study, platelet, red blood cell and plasma component utilization were measured before and after the adoption of pathogen reduction. Approximately 1,700 patients each, in the control and test periods, were evaluated, and included cardiac surgery (~40%), hematology-oncology (~27%) and pediatric/neonate (~9%) patient subgroups. The authors concluded that platelet, red blood cell and plasma component utilization, and the occurrence of transfusion-related adverse events were comparable between control and test periods (Amato M. Vox Sang. 2016).
Can you speak to the Acute Respiratory Distress Syndrome (ARDS) listed as the adverse reaction when using INTERCEPT Platelets?	• In the SPRINT study, an increased incidence of ARDs was reported in patients receiving INTERCEPT-treated platelets (n=5/318) versus conventional platelets (n=0/318). • In a subsequent reanalysis of the SPRINT study, conducted by an independent blinded expert panel, no difference was found between treated and untreated groups with regard to acute lung injury (ALI), including ARDs. It was determined by the expert panel that the original discrepancy was likely due to differences in diagnosis criteria used for ALI across study sites. (Corash et al., Blood, 2011; Snyder et al., Transfusion, 2005). • Also, in the SPRINT study, no increased frequencies of other high grade (3 or 4) respiratory adverse events were reported with INTERCEPT Platelets. Additionally, mortality was lower for recipients of INTERCEPT-treated platelets versus conventional platelets (refer to Package Insert). • National hemovigilance programs have not identified increased risk of ARDS associated with the transfusion of INTERCEPT Platelets (Swiss, French Annual HV Reports). Nevertheless, as with all platelet transfusions, patients should be monitored for

Question	
	signs and symptoms of ARDS.
Can INTERCEPT replace irradiation of platelets for prevention of TA-GVHD?	• As of March 2016, per AABB's 30th edition of Standards for Blood Banks and Transfusion Services (BBTS Standards) section 5.19.3.1, "Methods known to prevent transfusion-associated graft-vs-host disease shall be used, and include either irradiation or the use of a pathogen reduction technology that is known to inactivate residual leukocytes and is cleared or approved by the FDA or Competent Authority." • The use of pathogen reduction in place of irradiation is supported by extensive data, including: o Ability to achieve a 4 log reduction of T-Cells with INTERCEPT pathogen reduction. o Demonstrated reduction of viable T-cells with INTERCEPT treatment (Corash et al., Bone Marrow Transplant, 2004). o A high density of DNA modification in platelets (~1 adduct per 83 base pairs) with INTERCEPT treatment is indicative of a sufficient frequency to ensure inactivation of most genes; the frequency of DNA modification with gamma irradiation is much lower (~1 strand-break per 37,000 base pairs) (Lin et al., Haematologica, 2010). o In an *in vitro* study, cytokine production was substantially inhibited in the sample treated with INTERCEPT (Hei et al., Transfusion, 1999), indicating inactivation of white blood cells. o In an *in vivo* murine transfusion model, mice receiving untreated splenic leukocytes developed TA-GVHD, while mice infused with irradiated or INTERCEPT-treated splenic leukocytes remained healthy and did not develop TA-GVHD. (Grass et al., Blood, 1999). o An active hemovigilance program (21 centers, 11 countries), spanning 7 years over which 4,067 patients received pathogen reduced platelets, demonstrated no cases of TA-GVHD (Knutson et al., Vox Sang, 2015).
Can INTERCEPT replace bacterial detection, including secondary bacterial testing?	• Yes. Per AABB's Standards for Blood Banks and Transfusion Services, 30th Ed, **"**The blood bank/transfusion service shall have methods to detect bacteria or use pathogen reduction technology in all platelet components."
How does INTERCEPT "fit" in relation to the FDA Draft Guidance on bacterial risk control strategies?	• Though not final, FDA released revised draft guidance in March 2016: "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion." Per the draft guidance, the hospital transfusion service has a choice of using: • Pathogen-reduced platelets -- no further bacterial testing measures necessary for 5-day platelets. • Conventional platelets, already negative in primary bacterial testing -- must perform secondary testing at day 4 and 5 (within 24 hours of transfusion) per methods in guidance document (i.e. point of issue or rapid testing).
What are the advantages of INTERCEPT Platelets vs. culture/secondary bacterial testing?	• INTERCEPT Platelets provide Hospitals a *transfusion-ready* product; the hospital/transfusion service would not need to implement new technology (i.e. secondary bacterial testing). The blood collection center performs the pathogen reduction procedure; no further measures would be necessary at the hospital, per the FDA draft guidance for 5 day platelets. Conversely, secondary bacterial testing introduces an entirely new test and process to Hospitals requiring the need for training, new SOPs, personnel, inventory logistics, FDA registration, etc. • INTERCEPT offers broad protection; in addition to a host of clinically relevant bacteria, INTERCEPT also inactivates viruses and

Question	
	protozoans, including certain emerging pathogens, and T-cells. Secondary bacterial testing and bacterial culture are only able to screen for bacterial contamination. • Avoidance of secondary bacterial testing with INTERCEPT Platelets also means that there would be no need to re-test (and re-label) within 24 hours of transfusion, thereby avoiding safety/compliance risks (i.e. inadvertently "pulling" quarantined non-tested or unit with expired results for transfusion). • With INTERCEPT pathogen reduction, the whole unit is inactivated, thus avoiding the risk of sampling error which can be present with testing (culture or secondary bacterial testing). • Depending on blood center practices, hospitals may be able to obtain fresher platelets due to the possibility for early release of pathogen reduced platelets with avoidance of primary bacterial culture. • INTERCEPT Platelets can be redistributed or consigned, depending on Blood Center policy. Conversely, Blood Centers have expressed the inability to sell secondary bacterial tested/relabeled platelets via consignment to hospitals; in this scenario, the hospital may bear the financial burden for unused units.
Can INTERCEPT replace CMV testing? Is an INTERCEPT-treated product considered "CMV safe"?	• AABB Standard 5.19.2 is fairly broad ("CMV-negative components should be provided…" for specific populations). • INTERCEPT demonstrates inactivation of CMV in platelets in PAS-3 and platelets in 100% plasma at ≥ 4.9 pfu/mL, and ≥ 4.2 pfu/mL log reduction, respectively. • Substantial data supports the use of INTERCEPT for inactivation of CMV: o INTERCEPT treatment of platelet concentrates prevented transfusion-transmitted CMV in an immune-compromised mouse model (Jordan et al., Transfusion, 2004; Lin, Seminars in Hematology, 2001). o In an *in vitro* study, no cell-free or cell-associated CMV was detected in a viral cell culture assay following INTERCEPT treatment, while CMV was detected in solely leukoreduced components (Roback et al., Transfusion,2007a; Roback et al., Blood, 2007b).
What is the shelf-life for INTERCEPT platelets per the approved label?	• INTERCEPT Platelets are approved with a 5-day shelf life.
Can INTERCEPT help reduce outdating/minimize platelet expiry and waste?	• Since INTERCEPT Platelets do not require primary bacterial culture, Hospitals may receive platelet units sooner (with potential effective shelf-life of ~4 days versus ~3 days for conventional). Platelet outdate rate and associated waste can be significantly reduced with the gain in effective shelf-life. • Expiry and waste is also indirectly reduced overall by the ability to re-distribute/consign platelets if not transfused, with PR-treated products.

INTERCEPT Blood System for Platelets and Plasma

There is no pathogen inactivation process that has been shown to eliminate all pathogens. Certain non-enveloped viruses (e.g. HAV, HEV, B19, and poliovirus) and Bacillus cereus spores have demonstrated resistance to the INTERCEPT process.

CONTRAINDICATIONS

Contraindicated for preparation of plasma or platelet components intended for patients with a history of hypersensitivity reaction to amotosalen or other psoralens. Contraindicated for preparation of plasma or platelet components intended for neonatal patients treated with phototherapy devices that emit peak wavelengths less than 425 nm, or have a lower bound of the emission bandwidth <375 nm, due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.

WARNINGS AND PRECAUTIONS

Only INTERCEPT Processing Sets for plasma or platelet components are approved for use in the INTERCEPT Blood System. Use only the INT100 Illuminator for UVA illumination of amotosalen-treated plasma or platelet components. No other source of UVA light may be used. Please refer to the Operator's Manual for the INT100 Illuminator. Discard any plasma or platelet components not exposed to the complete INT100 illumination process. Tubing components and container ports of the INTERCEPT Blood System for Plasma and Platelets contain polyvinyl chloride (PVC). Di(2-ethlhexyl)phthalate (DEHP) is known to be released from PVC medical devices, and increased leaching can occur with extended storage or increased surface area contact. Blood components will be in contact with PVC for a brief period of time (approx. 15 minutes) during processing. The risks associated with DEHP released into the blood components must be weighed against the benefits of therapeutic transfusion.

PLATELETS

INTERCEPT processed platelets may cause the following adverse reaction: *Acute Respiratory Distress Syndrome* (ARDS). An increased incidence of ARDS was reported in a randomized trial for recipients of INTERCEPT processed platelets, 5/318 (1.6%), compared to recipients of conventional platelet components (0/327). Monitor patients for signs and symptoms of ARDS.

PLASMA

Amotosalen-treated plasma may cause the following adverse reaction: *Cardiac Events.* In a randomized controlled trial of therapeutic plasma exchange (TPE) for TTP, five patients treated with INTERCEPT Blood System processed plasma and none with conventional plasma had adverse events in the cardiac system organ class (SOC) reported. These events included angina pectoris (n=3), cardiac arrest (n=1), bradycardia (n=1), tachycardia (n=1) and sinus arrhythmia (n=1). None of these events resulted in documented myocardial infarction or death. Monitor patients for signs and symptoms of cardiac events during TPE for TTP.

Rx only.

QUESTIONS AND ANSWERS ABOUT PATHOGEN-REDUCED APHERESIS PLATELET COMPONENTS

Prepared by the AABB Pathogen Inactivation Technology Review Work Group

The Food and Drug Administration (FDA) has approved pathogen inactivation (PI) technologies that can be employed as an additional safety measure to help maintain a safe blood supply. The FDA has approved the INTERCEPT Blood System (Cerus Corp, Concord, CA) for pathogen reduction of 1) apheresis platelets stored in plasma and platelet additive solution (PAS) and 2) plasma. The FDA has also approved an additional pathogen-reduced plasma product, Octaplas (Octapharma, Vienna, Austria) that uses a solvent/detergent method. This document focuses solely on pathogen-reduced platelets treated using the INTERCEPT Blood System method.

What is pathogen reduction or pathogen inactivation?

PI is the process of treating the blood component soon after collection in order to inactivate any remaining infectious agents. Although the technology is termed pathogen inactivation, the components themselves are referred to as being pathogen reduced. The INTERCEPT method to produce pathogen-reduced platelets uses a chemical agent (amotosalen) that is activated by ultraviolet A (UVA) light to bind nucleic acids so that DNA cannot replicate and thus the cell cannot replicate. Because of the general nature of the inactivation technology, the process is effective against many infectious agents, including viruses, bacteria, parasites, and protozoa. The extent of the inactivation, and thus the effectiveness to prevent transfusion-transmitted infections, varies among different microbes. Red cells and platelets do not have nucleic acids and do not replicate. Lymphocytes do have nucleic acids; therefore, their proliferation is prevented by PI treatment.

What are the benefits of PI technology to patients?

The use of the technology may be expected to 1) materially reduce the risk of transfusion-transmitted infections for patients, 2) eliminate the need for serologic testing for cytomegalovirus (CMV) and production of CMV-reduced-risk components, and 3) eliminate the need for irradiation to prevent transfusion-associated graft-vs-host disease (TA-GVHD). The technology has been shown to inactivate meaningful titers of key viruses including human immunodeficiency virus, bacteria known to contaminate platelets, and parasites including those that cause malaria, babesiosis, and Chagas disease. In recent guidance documents, the FDA has indicated that the technology may be used to protect recipients from bacterial contamination and Zika virus infection. European studies have shown that there have been no cases of bacterial sepsis among patients receiving INTERCEPT platelets. INTERCEPT platelet components may be stored in plasma or PAS. PAS storage has been shown to reduce the frequency of allergic reactions among platelet recipients because there is 65% less plasma in the transfused component.

What should I expect from pathogen-reduced platelets?
A platelet component retains its original color and appearance after being treated using the INTERCEPT method. However, platelets stored in PAS have a lighter color than those stored in plasma. The FDA has approved a 5-day shelf life for INTERCEPT platelet components.

Summary of clinical evidence for efficacy of pathogen-reduced platelets: Evidence of the clinical efficacy of pathogen-reduced platelets comes from published studies and from European hemovigilance data from two countries in which universal pathogen reduction for platelets has been adopted (Belgium and Switzerland) and one country (France) in which universal pathogen reduction has been adopted at one regional blood center. A Cochrane review published in 2013 analyzed the results of 10 trials comparing pathogen-reduced platelets with standard platelets in hematology/oncology and stem cell transplant patients given prophylactic platelet transfusions to prevent bleeding. Nine trials assessed INTERCEPT technology in 1422 total participants, of whom 675 received INTERCEPT platelet transfusions.

Mortality and bleeding: The Cochrane meta-analysis demonstrated no differences in mortality, clinically significant bleeding, or severe bleeding between patient groups receiving INTERCEPT platelets and those receiving standard platelets. The outcome of "any bleeding" (ie, bleeding that includes clinically insignificant bleeding) was statistically different when analyzed using a fixed-effect model (favoring standard platelets) but was not statistically different between treatment arms when analyzed using a random-effect model.

The Italian Platelet Technology Assessment Study (IPTAS) was not included in the Cochrane review. In this randomized controlled trial, there was no significant difference in absolute risk of grade ≥2 bleeding (22.0% INTERCEPT vs 15.9% standard platelets, p=0.16) or in mortality. Other studies of PI for platelets are ongoing.

Corrected count increments and dosage: The Cochrane review showed that corrected count increments (CCIs) at 1 hour and 24 hours were statistically significantly lower after INTERCEPT platelet transfusions compared to standard platelets. The relative risk of platelet refractoriness (defined as low CCIs in two successive transfusions in four studies but defined as also including the presence of platelet antibodies in another study) was 2.74-fold higher with INTERCEPT platelets compared to standard platelets. Patients receiving INTERCEPT platelets required 7% more platelet transfusions and the transfusion interval between multiple INTERCEPT platelet transfusions was shorter than with standard platelets.

Reports of septic transfusion reactions from platelet transfusion: In Switzerland, no cases of sepsis due to INTERCEPT platelet transfusions have been reported to the Swiss hemovigilance system, during 130,800 pathogen-reduced platelet transfusions from 2011-2014. In Belgium, more than 150,000 pathogen-reduced platelet products have been transfused since 2009. None of the transfusions resulted in transfusion-transmitted bacterial infections (TTBIs). For comparison, in the same period, four TTBIs were reported in approximately 186,000 standard platelet transfusions in the Flanders region of Belgium. In France in the 9-year interval from 2007-2015, there were no reported TTBI cases in the region that transfused only INTERCEPT platelets. In contrast, there were 47 cases, including nine fatalities, in parts of France that transfused standard platelets.

Reports of transfusion-related acute lung injury: According to the Swissmedic Hemovigilance reporting, the incidence of transfusion-related acute lung injury was 1:30,000 after transfusion of standard platelets, compared with 1:24,000 after transfusion with INTERCEPT platelets—essentially no difference.

What are the theoretical risks and limitations of this technology to patients?

Psoralen toxicity: In order for platelets to undergo the INTERCEPT method, a psoralen (amotosalen, previously called S-59) is added in conjunction with UVA light exposure. Although the amotosalen is mostly removed using a compound adsorption device, this creates concern for toxicity in transfusion recipients. However, in-vitro data, animal data, and European hemovigilance data show that the dose of amotosalen in INTERCEPT components is safe. The INTERCEPT method is contraindicated for preparation of platelet components intended for patients with a history of hypersensitivity reaction to amotosalen or other psoralens.

Acute respiratory distress syndrome: A warning/precaution in the INTERCEPT package insert notes the risk of acute respiratory distress syndrome, which occurred in a randomized trial involving adults. However, a published reanalysis of the data, sponsored by Cerus, did not confirm this association and hemovigilance systems have not reported an increased risk. A more rigorous evaluation by an ongoing Phase IV postmarketing trial in the United States is actively evaluating this risk.

Di(2-ethylhexyl)phthalate exposure: The risks associated with di(2-ethylhexyl)phthalate (DEHP) released into the blood components must be weighed against the benefits of therapeutic transfusion. The FDA reviewed issues related to DEHP and released the following notices in 2001 "Safety Assessment of Di(2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices" and 2002 FDA Public Health Notification: PVC Devices Containing the Plasticizer DEHP.

Phototherapy: The INTERCEPT method is contraindicated for preparation of platelet components intended for neonatal patients treated with phototherapy devices that emit a peak energy wavelength less than 425 nm, or have a lower bound of the emission bandwidth <375 nm, due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.

How is this component different from the platelet components already in use?

A wide array of platelet components is currently available for use in the United States, including apheresis platelets stored in plasma, apheresis platelets stored in PAS, whole-blood-derived platelets, and prestorage pooled whole-blood-derived platelets. INTERCEPT apheresis platelets can be stored in plasma or PAS. The components are all approved by the FDA to deliver a therapeutic platelet dose.

Are there alternative safety measures to achieve similar goals?
Although there are no other broad-spectrum alternatives to pathogen-reduced platelets, there are targeted alternatives for specific safety threats, including direct testing for infectious agents. All infectious disease screening tests on donor blood with the exception of bacterial culturing are performed in the same fashion for apheresis platelet donors whether or not the component is pathogen reduced. Other measures that achieve safety objectives similar to PI include serologic testing and/or leukocyte reduction to mitigate transfusion-transmitted CMV and gamma irradiation to prevent TA-GVHD. CMV testing and gamma irradiation can be replaced by PI technology.

Bacteria: Primary bacteria testing of platelets, currently performed by culture system, is the initial testing to detect the presence of bacterial contamination. The two culture systems for primary testing approved by the FDA for use in the United States are BacT/ALERT (bioMerieux, Marcy l'Etoile, France) and Enhanced Bacteria Detection System (eBDS; Pall Corporation, Port Washington, NY). The FDA has also introduced the terminology of secondary bacterial testing. Secondary testing of platelets refers to the use of any additional test to detect the presence of bacterial contamination in a unit that previously showed no bacterial contamination on initial testing. Secondary testing can be conducted using a culture-based method or a rapid bacteria detection device (point-of-release test). Current FDA-approved rapid tests are the Platelet PGD Test System (Verax Biomedical, Marlborough, MA), which has also received an additional "safety measure" claim from the FDA, and BacTx Bacterial Detection Kit for Platelets (Immunetics, Boston, MA). Platelets that have been pathogen reduced do not need to be tested for bacterial contamination by either primary or secondary testing.

Zika virus: The February 2016 FDA guidance document regarding the risk of Zika virus in donated blood recommended that in areas with active Zika virus transmission, 1) whole blood and blood components for transfusion be obtained from areas of the United States without active transmission, or 2) blood establishments may continue collecting and preparing platelets and plasma if an FDA-approved pathogen reduction device is in use, or 3) all blood components (including Red Blood Cells) may be used if an FDA-licensed blood screening test for Zika is in use. In addition, the FDA noted that use of an investigational donor screening test under an investigational new drug application may be permitted in situations where approved technologies are unavailable. The August 2016 FDA guidance document on this subject recommends that all blood products be tested for Zika virus using an investigational nucleic acid amplification test, or when available, a licensed test, and continues to allow use of pathogen-reduced platelets as an alternative to testing.

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[March 2017]

INTERCEPT® Blood System for Platelets –Small Volume (SV) Processing Set

Rx Only
Caution: US Federal law restricts this device to sale by or on the order of a licensed healthcare practitioner

March 10, 2016

INTENDED USE

The INTERCEPT Blood System for platelets is intended to be used for *ex vivo* preparation of pathogen-reduced Amicus apheresis platelet components suspended in 65% PAS-3/35% plasma, and Trima apheresis platelet components suspended in 100% plasma, in order to reduce the risk of transfusion-transmitted infection (TTI), including sepsis, and to potentially reduce the risk of transfusion-associated graft versus host disease (TA-GVHD).

DEVICE DESCRIPTION

The INTERCEPT Blood System for platelets, SV Processing Set, contains a sterile, non-pyrogenic, single-use, integrated, fluid path platelet processing set (INT2110) comprised of four key components (See Table 1) and an ultraviolet (UVA) illumination device (INT100) for the *ex vivo* preparation and storage of pathogen reduced apheresis platelet components. The INT100 is a microprocessor controlled device designed to deliver a controlled amount of UVA light, wavelength 320 to 400 nm, to up to two illumination containers simultaneously. The device is programmed to be able to control, deliver, record and store intensity and duration of light dose for each cycle.

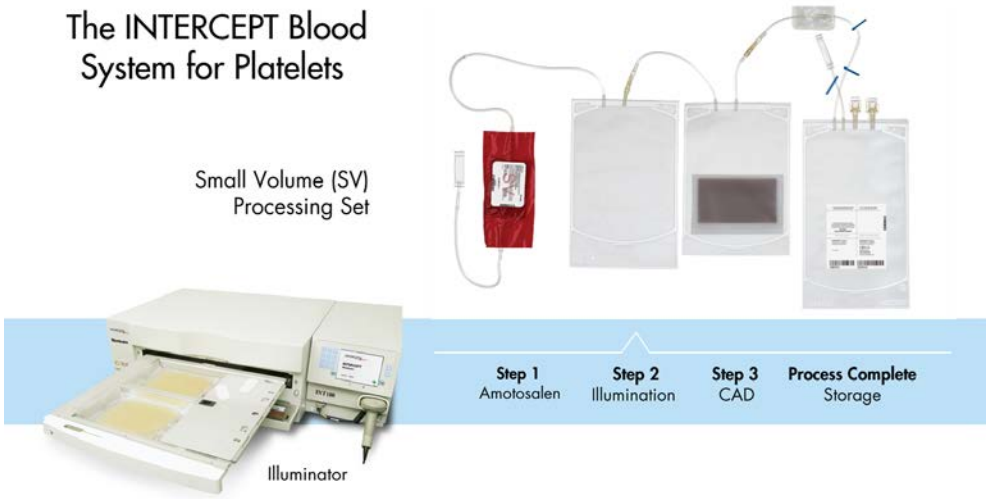
Table 1 Components of the INTERCEPT Platelet SV Processing Set (INT2110)

Component	Description
Amotosalen (S-59, psoralen derivative) solution container	15 mL, 3 mM amotosalen in 0.924% NaCl packaged in a 20 mL, flexible, heat-sealed plastic container, with an integral light-protective overwrap and sleeve
Illumination container	Heat-sealed, plastic bag
Compound Adsorption Device (CAD)	Immobilized beads (wafer) in mesh pouch
Platelet storage containers	One platelet storage bag – 1300 mL storage capacity

The operating principle for the INTERCEPT Blood System for platelets is illustrated below (Figure 1). Platelets collected by apheresis in a container are sterile connected to the Platelet SV Processing Set [INT2110]. The platelets flow through the amotosalen container into the illumination container. The illumination container is placed into the INT100 illumination device for UVA treatment while being mixed with horizontal agitation. Inactivation of potential pathogen or leukocyte contaminants in platelet components is achieved through a photochemical treatment process. Amotosalen (S-59, psoralen derivative), a chemical capable of binding to nucleic acids is added to platelets. UVA illumination (320 – 400 nm wavelengths) of amotosalen-treated platelet components induces covalent cross-linking of any nucleic acids to which amotosalen is bound; thereby, preventing further replication.[1] Treated platelets are then transferred to the CAD container to reduce the levels of residual amotosalen and free photoproducts. Finally, the platelet components are transferred through the in-line

filter to the storage container for use or storage at 20-24°C with continuous agitation for up to 5 days from the time of collection.

Figure 1 INTERCEPT Blood System for Platelets and Treatment Process



DEVICE PERFORMANCE

The INTERCEPT Blood System inactivates a broad spectrum of enveloped and non-enveloped viruses, Gram-positive and Gram-negative bacteria, spirochetes, parasites and leukocytes.[2-22] There is no pathogen inactivation process that has been shown to eliminate all pathogens. Certain non-enveloped viruses (e.g., HAV, HEV, B19, and poliovirus) and *Bacillus cereus* spores have demonstrated resistance to the INTERCEPT process.

Table 2 Viral Reduction (Enveloped)[4-14]

Pathogen	Platelets in PAS-3 Log_{10} Reduction (pfu/mL)[a]	Platelets in 100% Plasma Log_{10} Reduction(pfu/mL)[a]
HIV-1 IIIB, cell-associated	≥5.4	≥ 4.7
HIV-I IIIB, cell-free	≥5.6	[d]
HIV-1 Z84 (clinical isolate)	≥3.3	[d]
HIV-2 CLB-20 (clinical isolate)	≥2.4	[d]
DHBV[b]	≥4.8	≥4.3
BVDV[c]	≥4.4	>3.3
HTLV-I	4.7	[d]
HTLV-II	≥5.1	[d]
West Nile virus (WNV)	≥5.7	>3.7
Cytomegalovirus (CMV)	≥4.9	[d]
Pseudorabies virus (model for CMV)	[d]	≥4.2
Chikungunya virus (CHIKV)	≥5.7	>6.5
Dengue virus (DENV)	≥4.3	3.6
Influenza A virus	≥5.9	[d]

[a] Based on input titer and post-treatment titer in 1 mL, data obtained in platelets in PAS-3 or plasma components unless otherwise noted
[b] DHBV model virus for HBV
[c] BVDV model virus for HCV
[d] = Not tested

Table 3 Viral Reduction (Non-Enveloped)[4,17]

Pathogen	Platelets in PAS-3 Log_{10} Reduction (pfu/mL)[a]	Platelets in 100% Plasma Log_{10} Reduction (pfu/mL)[a]
Calicivirus (model non-enveloped virus)	2.1	0.9
Adenovirus	≥4.9	≥5.3
Blue tongue virus (model non-enveloped virus)	4.4	[b]

[a] Based on input titer and post-treatment titer in 1 mL, data obtained in platelet components in PAS-3 or plasma components unless otherwise noted
[b] = Not tested

Table 4 Bacterial Reduction [15,16]

Pathogen	Platelets in PAS-3 Log_{10} Reduction (cfu/mL)[a]	Platelets in 100% Plasma Log_{10} Reduction (cfu/mL)[a]
Gram-Negative Bacteria		
Klebsiella pneumoniae	5.8	5.9
Escherichia coli	≥6.3	>5.9
Serratia marcescens	≥6.7[c]	>7.1
Pseudomonas aeruginosa	≥3.9	≥6.8
Salmonella choleriaesuis	6.2	>5.9
Enterobacter cloacae	5.5	≥6.0
Yersinia enterocolitica	≥5.9	>6.3
Gram-Positive Bacteria		
Staphylococcus epidermidis	≥6.1	>6.1
Staphylococcus aureus	≥5.4	≥6.1
Listeria monocytogenes	≥6.3[c]	>6.6
Corynebacterium minutissimum	≥5.3	>6.4
Streptococcus pyogenes	≥6.8 [c]	>6.1
Bacillus cereus (vegetative)	≥5.5	≥5.6
Bacillus cereus (spore forming)	3.7 [c]	[d]
Anaerobic Gram-Positive Bacteria and Spirochete Bacteria		
Bifidobacterium adolescentis	≥6.0	[d]
Propionibacterium acnes	≥6.5	>6.7
Clostridium perfringens (vegetative)	≥6.5	>6.0
Lactobacillus species	≥6.4	>6.1

Treponema pallidum	≥6.4	[b]
Borrelia burgdorferi	≥6.8	[b]

[a] Based on input titer and post-treatment titer in 1 mL, data obtained in platelet components in PAS-3 or plasma components unless otherwise noted
[b] Study in progress
[c] Based on culture of full platelet unit (300 mL)
[d] = Not tested

Table 5 Protozoa Reduction[19-21]

Pathogen	Platelets in PAS-3 Log_{10} Reduction (pfu or cfu/mL)[a]	Platelets in 100% Plasma Log_{10} Reduction (pfu or cfu/mL)[a]
Plasmodium falciparum	≥5.6	[c]
Babesia microti	≥4.9	[c]
Trypanosoma cruzi	≥5.3	>5.5
Leishmania mexicana (metacyclic promastigote stage)	≥5.0	[b]

[a] Based on input titer and post-treatment titer in 1 mL, data obtained in platelet components in PAS-3 or plasma components unless otherwise noted
[b] = Not tested
[c] = Study in progress

The INTERCEPT process for platelets reduces a broad spectrum of bacteria by > 4 log_{10} (Table 4) to lower the risk of microbial contamination of blood components.[21] Bacterial spores are resistant to inactivation by the INTERCEPT Blood System for platelets.

Contaminating T cell activity is reduced by the INTERCEPT treatment, potentially lowering the risk of transfusion-associated graft versus host disease (TA-GVHD).[22-27] Using a limiting dilution assay (LDA), platelets processed with the INTERCEPT Blood System exhibited a 4 log_{10} reduction of viable T-cells. Using a DNA modification assay, platelets processed with the INTERCEPT Blood System demonstrated an average of one amotosalen adduct every 83 base pairs in leukocytes.

In vitro Characterization of Platelet Components Processed with the INTERCEPT Blood System.

In vitro platelet function characteristics were evaluated in prospective, randomized, paired, controlled, *in vitro* studies in healthy subjects of INTERCEPT apheresis platelet components compared to unprocessed (control) platelet components. Each study subject donated a single- or double-apheresis platelet component, during each of the two donation periods. Components from the platelet donations were randomized to produce INTERCEPT processed platelet components or control platelet components. *In vitro* platelet function of the platelet components was evaluated on day 5 after apheresis donation. The physical and metabolic characteristics for evaluation included: component volume platelet count, platelet volume (MPV), $pH_{22°C}$, pO_2, pCO_2, HCO_3, morphology, supernatant LDH activity, P-selectin, total ATP, extent of shape change, hypotonic shock response, supernatant glucose, and supernatant lactate. Trima platelets suspended in 100% plasma were evaluated further.

1. Storage in 65% PAS-3/35% Plasma:

63 single-dose and double-dose Amicus platelet collections containing 2.9 - 8.0×10^{11} platelets in PAS-3 treated with the INTERCEPT Blood System for platelets and stored for 5 days retained presumptively therapeutically effective platelet doses (mean of 3.7 x 10^{11} platelets and lower bound of the 95% confidence interval (CI) for the proportion of INTERCEPT processed platelet components retaining >3.0×10^{11} platelets was 78.3%) with an average dose recovery after INTERCEPT treatment of 91.19% (95% CI: 89.7%-92.7%), and with retention of adequate in vitro metabolic and functional properties (Table 6).

Table 6 *In Vitro* Platelet Function Characteristics of INTERCEPT (I) and Control (C) Platelets in PAS-3 After 5 Days of Storage (Mean +/- SD (median) [range]; n=63)

	INTERCEPT	**Control**	**95% CI for Treatment Difference (I-C)**	**INTERCEPT within ± 20% of Control, # / N (%)**
Platelet Component Characteristics				
Component volume (mL)	279±74 (327) [162-382]	288±74 (317) [152-400]	-14.4 to -3.7*	60/63 (95.2%)
Platelet count (×10^3/µl)	1383±341(1368) [717-2002]	1482±375 (1408) [730-2250]	-148.1to -51.0*	53/63 (84.1%)
Platelet dose (×10^{11} cells/unit)	3.7±0.8 (3.5) [2.5-6.1]	4.0±0.6 (3.9) [2.3-5.5]	-0.5 to -0.2*	51/63 (81.0%)
MPV (fL)[1]	8.1±0.8 (8.1) [6.7-10.6]	8.1±0.9 (8.0) [6.7-10.4]	-0.1 to 0.2	58/58 (100%)
Indices of Platelet Metabolism				
pH at 22°C	7.02±0.11(7.04) [6.78-7.20]	7.03±0.12 (7.03) [6.73-7.25]	-0.04 to 0.02	63/63 (100%)†
pO_2 (mm Hg)	130±21(134) [66-168]	124±20 (128) [70-154]	-1.0 to 13.2	39/63 (61.9%)
pCO_2 (mm Hg)	20±6 (20) [10-32]	24±6 (24) [13-35]	-4.4 to -2.4*	36/63 (57.1%)
HCO_3^- (mmol/L)[2]	3.2±1.1 (3.1) [1.0-5.3]	3.8±1.3 (4.0) [2.0-7.0]	-0.9 to -0.3*	23/60 (38.3%)
Supernatant glucose (mg/dL)[3]	21.5±24.0 (18.5) [0.0-127.8]	15.5±23.3 (2.0) [0.0-120.6]	1.2 to 10.9*	29/61 (47.5%)
Supernatant lactate (mmol/L)	11±2 (11) [7-15]	12±3 (13) [7-19]	-1.99 to -0.82*	43/63 (68.3%)
Total ATP (nmol/10^8 Plts)	4.70±1.95 (4.20) [1.07-9.39]	4.47±1.72 (4.28) [1.20-10.25]	-0.22 to 0.70	24/63 (38.1%)
Indices Correlating with In Vivo Recovery, Survival and Function				
Morphology	257±47 (249) [176-360]	251±45 (246) [186-360]	-3.1 to 14.6	52/63 (82.5%)
Extent of Shape Change (ESC; %)	12.2±8.1 (12.3) [1.0-49.0]	11.9±9.1 (10.1) [0.0-32.6]	-2.1 to 2.7	12/63 (19.0%)
Hypotonic Shock Response (HSR; %)	28±18 (28) [0-56]	30±19 (30) [0-62]	-4.8 to 1.9	32/63 (50.8%)
Indices of Granular and Cytoplasmic Content Retention				
LDH activity (IU/L)	149±92 (118) [10-581]	142±83 (115) [60-460]	-10.9 to 26.4	29/63 (46.0%)
LDH (IU/10^{12} Plts)	110±54 (100) [8-329]	97±49 (82) [35-270]	0.1 to 25.8*	19/63 (30.2%)

P-selectin (%)[4]	36.98±16.22 (31.75) [7.93-83.31]	33.70±13.96 (29.76) [9.28-74.47]	0.21 to 6.35*	19/60 (31.7%)

[1]n=58; [2]n=60; [3]n=61; [4]n=60

* Statistically significant difference ($p<0.05$) between INTERCEPT and Control

†The analysis criterion is ≥ 6.2 for $pH_{22°C}$.

***2. Storage in 100% Plasma*:**

a. 67 single-dose and double-dose Trima platelet collections suspended in 100% plasma containing 3.1- 7.9×10^{11} platelets in 100% plasma treated with the INTERCEPT Blood System for platelets and stored for 5 days showed a mean platelet dose of 3.5×10^{11} platelets (the lower bound of the 95% CI for the proportion of INTERCEPT processed platelet components retaining $>3.0\times10^{11}$ platelets/component was 67.6%) with an average dose recovery after INTERCEPT treatment of 86.7% (95% CI: 85.7%-87.7%). *In vitro* results are included in Table 7.

Table 7 *In Vitro* Platelet Function Characteristics of INTERCEPT (I) and Control (C) Platelets in 100% Plasma After 5 Days of Storage (Mean +/- SD (median) [range]; n=67)

	INTERCEPT	**Control**	**95% CI for Treatment Difference (I-C)**	**INTERCEPT within ± 20% of Control, # / N (%)**
Platelet Component Characteristics				
Component volume (mL)	280.8±70.2 [1] [183.5-365.1]	289.9±69.6 [198.4-378.2]	-14.4 to -4.0*	65/67 (97.0%)
Platelet count ($\times10^3$/µl)	1313±254 [1] [795-1955]	1420±261 [883-1941]	-148 to -69*	57/66 (86.4%)
Platelet dose ($\times10^{11}$ cells/unit)	3.5±0.7 [1] [2.4-5.2]	4.0±0.6 [2.9-5.1]	-0.5 to -0.3*	56/66 (84.8%)
MPV (fL)[1]	7.3±1.0 [5.9-10.4]	7.4±0.9 [6.0-11.4]	-0.3 to -0.0*	64/65 (98.5%)
Indices of Platelet Metabolism				
pH at 22°C	7.2±0.3[1] [5.7-7.5]	7.4±0.1 [7.1-7.6]	-0.3 to -0.2*	66/67 (98.5%)†
pO_2 (mm Hg)	131±17[1] [69-175]	121±18 [56-158]	4 to 16*	48/67 (71.6%)
pCO_2 (mm Hg)	31±7[1] [19-46]	30±5 [20-43]	0 to 2*	60/67 (89.6%)
HCO_3^- (mmol/L)	7.6±2.7[1] [0.3-13.0]	11.3±2.0 [7.0-17.0]	-4.4 to -3.2*	15/66 (22.7%)
Supernatant glucose (mg/dL)	225±54[1] [104-481]	268±52 [183-510]	-54 to -32*	40/66 (60.6%)
Supernatant lactate (mmol/L)	11.2±3.9[1] [5.8-26.6]	8.3±2.1 [4.6-13.9]	2.1 to 3.7*	21/66 (31.8%)
Total ATP ($nmol/10^8$ Plts)	4.6±1.4[1] [0.8-7.8]	5.0±2.0 [1.4-13.1]	-0.8 to 0.1	31/66 (47%)
Indices Correlating with In Vivo Recovery, Survival and Function				
Morphology	307±39[1] [203-367]	299±42 [185-366]	-4 to 21	53/66 (80.3%)

Extent of Shape Change (ESC; %)	23.1±5.0[1] [13.2-34.2]	26.9±5.1 [16.3-39.5]	-4.7 to -3.2*	51/66 (77.3%)
Hypotonic Shock Response (HSR; %)	59±9[1] [40-83]	58±10 [36-82]	-2 to 3	54/66 (81.8%)
Indices of Granular and Cytoplasmic Content Retention				
LDH activity (IU/L)	169±56[2] [76 – 483]	141±28 [62 – 277]	16 to 42*	40/67 (59.7%)
LDH (IU/10^{12} Plts)	130±4[1] [55-307]	102±27 [49-252]	20 to 36*	28/66 (42.4%)
P-selectin (%)	20.5±8.5[1] [3.8-44.6]	14.3±6.1 [2.4-35.4]	4.6 to 7.8*	19/66 (28.8%)

[1] n=66; [2] Value for one sample on Day 6

* Statistically significant difference ($p<0.05$) between INTERCEPT and Control

†The analysis criterion is ≥ 6.2 for $pH_{22°C}$.

b. 260 single-dose and double-dose Trima apheresis platelet collections suspended in 100% plasma containing platelet doses of 3.0 to 7.7×10^{11} platelets in 270 to 417 mL plasma with platelet count ranging from 963×10^3 to 1891×0^3 platelets/µL, and stored for 5 days were evaluated for $pH_{22°C}$, platelet dose, and platelet dose recovery. Day 5 INTERCEPT Trima platelet components in 100% plasma contained, on average, 3.6×10^{11} platelets in 313 mL total volume with a lower bound of the 95% CI for the proportion of INTERCEPT processed platelet components retaining $>3.0\times10^{11}$ platelets of 85%. The dose and volume recovery post- INTERCEPT process were 86.5 ±5.0% and 92.6 ±1.8% (95% CI for dose recovery: 85.9%-87.1% and 95% CI for volume recovery: 92.4%-92.8%), respectively. Summary of evaluation criteria for $pH_{22°C}$, platelet dose, and platelet dose recovery are provided in Table 8 by INTERCEPT processing set.

Table 8 ***Evaluation Criteria of INTERCEPT Trima Platelet Components Suspended in 100% Plasma by Processing Set***

Test	Recommended Threshold and Criterion	INTERCEPT Processing Set	Proportion of INTERCEPT Components Meeting Threshold (#/N, [%])	1-Sided 95% CI
Day 5 $pH_{22°C}$	≥ 6.2	SV	24/24 [100%]	≥88.3%
		LV	9/9 [100%]	≥71.7%
		DS	230/231 [99.6%]	≥98.0%
Day 5 Dose	≥ 3.0×10^{11}	SV	21/24 [87.5%]	≥70.8%
		LV	6/7 [85.7%]	≥47.9%
		DS	195/219 [89.0%]	≥84.9%
Dose Recovery	≥ 85%	SV	23/24 [95.8%]	≥81.7%
		LV	4/9 [44.4%]	≥16.9%
		DS	127/225 [56.4%]	≥50.7%
	≥ 80%	SV	24/24 [100%]	≥88.3%
		LV	9/9 [100%]	≥71.7%
		DS	212/225 [94.2%]	≥91.0%

The proportion of platelet units of the SV set containing a platelet dose ≥ 3.0 x 10^{11} platelets on Day 5 was 87.5% (21 out of 24) and the lower bound of the 95% CI for the proportion of units containing a platelet dose ≥ 3.0 x 10^{11} platelets was 70.8%.

The combined overall results of the two in vitro studies described above show that INTERCEPT Trima platelets suspended in 100% plasma retain presumptively therapeutically effective mean platelet doses, with retention of adequate in vitro metabolic and functional properties.

CONTRAINDICATIONS

- Contraindicated for preparation of platelet components intended for patients with a history of hypersensitivity reaction to amotosalen or other psoralens.

- Contraindicated for preparation of platelet components intended for neonatal patients treated with phototherapy devices that emit a peak energy wavelength less than 425 nm, or have a lower bound of the emission bandwidth <375 nm, due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.

  Note: Information about these contraindications needs to be included in the labeling provided with transfusable platelets prepared using the INTERCEPT Blood System for platelets.

WARNINGS AND PRECAUTIONS

- Only INTERCEPT Processing Sets for platelets are approved for use with the INTERCEPT Blood System. Use only the INTERCEPT INT100 Illuminator for UVA illumination of amotosalen-treated platelet components. No other source of UVA light may be used. Please refer to the Operator's Manual for the INT100 Illuminator. Discard any platelet components not exposed to the complete INT100 illumination process.

- Tubing components and container ports of the INTERCEPT Blood System contain polyvinyl chloride (PVC). Di(2-ethylhexyl)phthalate (DEHP) is known to be released from PVC medical devices, and increased leaching can occur with extended storage or increased surface area contact. Blood components will be in contact with PVC for a brief period of time (approx. 15 minutes) during processing. The risks associated with DEHP released to into the blood components must be weighed against the benefits of therapeutic transfusion.

- Pulmonary events: Acute Respiratory Distress Syndrome (ARDS)

  INTERCEPT processed platelets may cause the following adverse reaction: *Acute Respiratory Distress Syndrome (ARDS)*

  An increased incidence of ARDS was reported in a randomized trial for recipients of INTERCEPT processed platelets, 5/318 (1.6%), compared to recipients of conventional platelet components (0/327).[28] Monitor patients for signs and symptoms of ARDS.

  Note: Information about these Warnings and Precautions needs to be included in the labeling provided with transfusable platelets prepared using the INTERCEPT Blood System for Platelets.

INSTRUCTIONS FOR USE

Initial Setup

Equipment Provided: One (1) INT2110 Small Volume Processing Set
Equipment Available Separately: INTERCEPT INT100 Illuminator
Equipment Required But Not Provided: Sterile Connecting Device (SCD), Tube Sealer, Flatbed Agitator, Manual Tube Clamp (e.g., Hemostat)

- **INTERCEPT Processing Sets for platelets are for single use only. Do not reuse sets or components of sets.**

- This process is designed to be a functionally closed system. Treatment with INTERCEPT Blood System does not replace applicable standards for processing in open and closed systems.

Blood Collection

Leukocyte reduced platelets collected by apheresis are used. Refer to **Table 9** for specifications of the platelet products which are used with this processing set.

Table 9 Platelet Collection and Processing Specifications for INTERCEPT Small Volume Processing Set

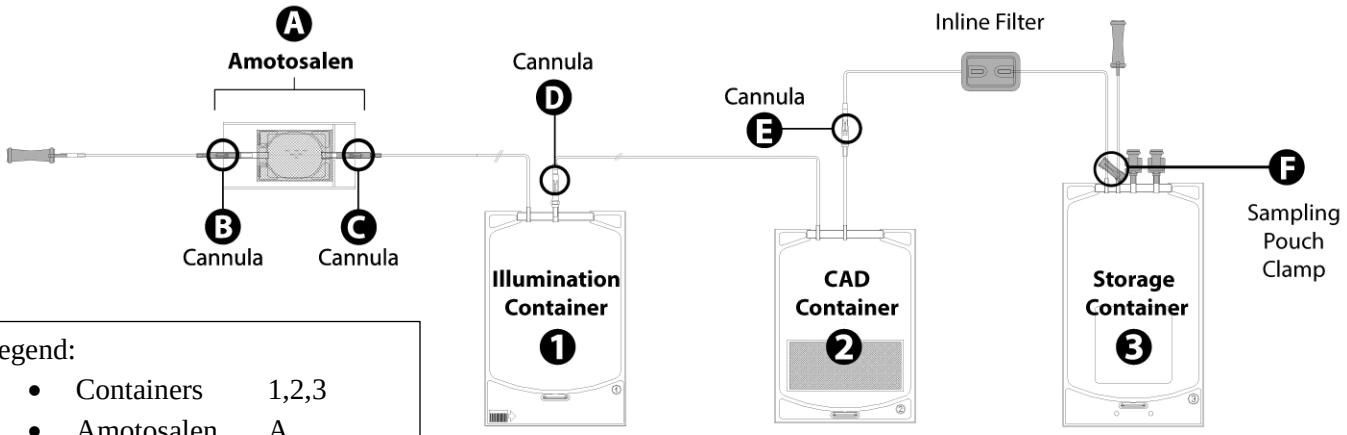
	Platelets in PAS-3	Platelets in 100% Plasma
Collection Specifications		
Platelet Source	Amicus Apheresis	Trima Apheresis
Suspension Medium	PAS-3 and plasma (32-47%)	100% Plasma
Platelet Input Volume	255-325 mL	270-325 mL
Platelet Dose	$2.9\text{-}5.0 \times 10^{11}$	$3.0 – 5.0 \times 10^{11}$
Platelet Count	$0.9 – 2.0 \times 10^{9}$/mL	$0.9 – 2.0 \times 10^{9}$/mL
RBC Content	$< 4 \times 10^{6}$ RBC/mL	$< 4 \times 10^{6}$ RBC/mL
Processing Specifications		
Number of Storage Bags	1	1
CAD Time	4-16 Hrs	12-24 Hrs
Maximum Storage	5 Days	5 Days

Platelet Processing

Platelets must be exposed to UVA light within 24 hours after collection.

Refer to **Figure 2** for labeling and identification of set components.

Figure 2 INTERCEPT Small Volume Processing Set



Legend:

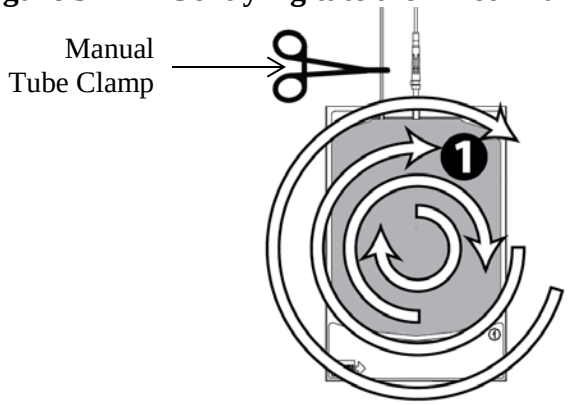
- Containers 1,2,3
- Amotosalen A
- Cannulae B,C,D,E
- Clamp F

I. Amotosalen Addition

NOTE: Amotosalen in contact with skin may result in photosensitization in the presence of ultraviolet light. If skin exposure occurs, flush exposed skin with water.

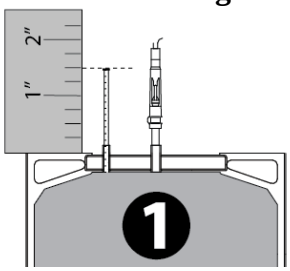
1. Remove set from package. Unwrap only illumination container (❶) from organizer.
2. Weld tubing from platelet collection container to amotosalen container (Ⓐ) tubing using SCD.
3. Label storage container (❸) using appropriate donation identification.
4. Hang platelet collection container and break cannula (Ⓒ) below amotosalen container (Ⓐ) to let amotosalen flow into illumination container (❶); visually verify amotosalen is present.
5. Break cannula (Ⓑ) above amotosalen container (Ⓐ) to let platelets flow through amotosalen container (Ⓐ) into illumination container (❶).
6. Ensure the platelets drain completely from initial platelet collection container into illumination container (❶) by expressing air from the illumination container (❶) into amotosalen container (Ⓐ).
7. When air is removed and platelets have fully drained back through tubing into illumination container (❶), manually clamp tubing above illumination container. Mix illumination container thoroughly by gentle agitation to ensure complete mixing of amotosalen and platelets (**Figure 3**).

Figure 3 Gently Agitate the Filled Illumination Container



8. Open manual tube clamp and express a small amount of platelet and amotosalen mixture into tubing, filling about 1.5 inches of tubing. Close manual clamp.
9. Seal tubing between illumination container (❶) and amotosalen container (Ⓐ) within the 1.5 inches of tubing (See **Figure 4**).

Figure 4 Heat Seal Filled Tubing Within 1.5 Inches



10. Remove and discard empty platelet collection container, amotosalen container (Ⓐ) and excess tubing.

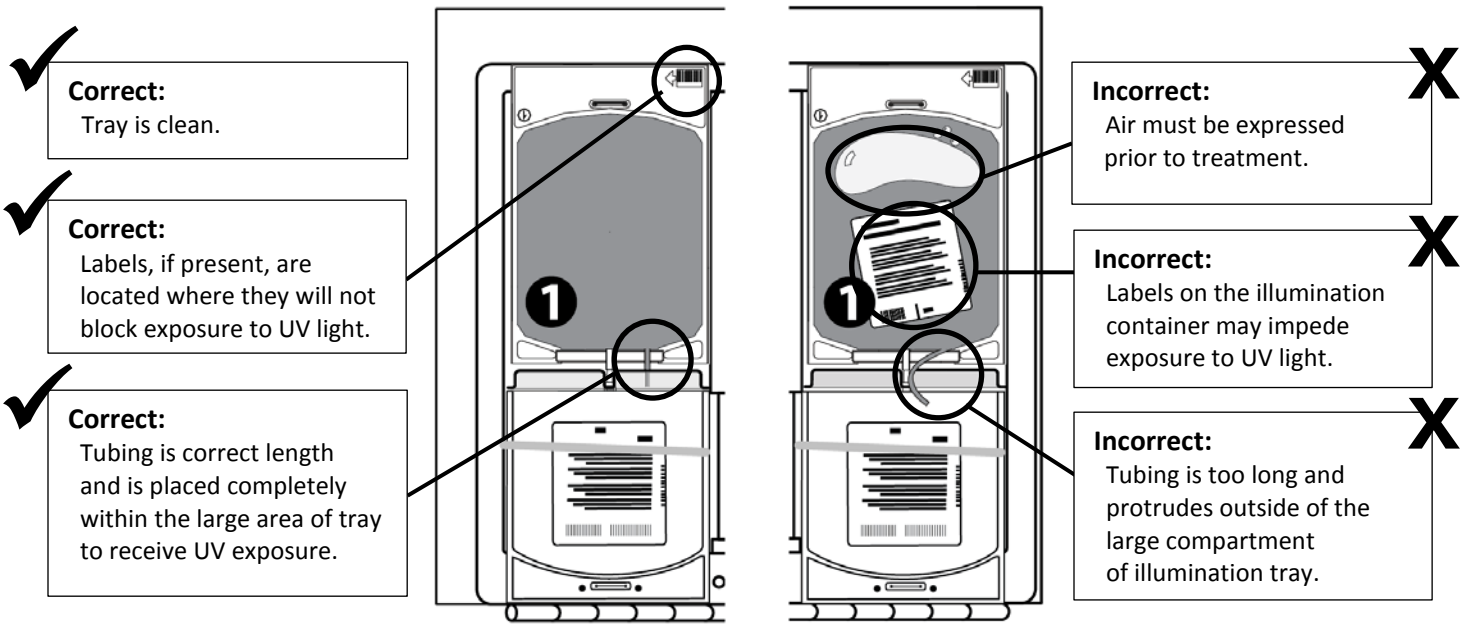
II. Illumination

Refer to INT100 Illuminator Operator's Manual for detailed instructions.

NOTE: The inactivation process requires unimpeded light transmission through tray and illumination container. The illumination container and tubing must be within the large compartment of the illuminator tray. Tray must be clean and free from labels or other material (see **Figure 5**). Illumination container should lay flat in order to ensure complete illumination.

NOTE: During illumination, tubing must be held within large compartment of illumination tray (see below).

Figure 5 Proper Way to Load Processing Set Into the Illuminator Tray



III. Agitation with Compound Adsorption Device (CAD)

Do not fold or bend CAD.

1. Unwrap set from organizer.
2. Hang platelets in illumination container (❶), break cannula (Ⓓ) and allow platelets to flow into CAD container (❷).
3. Express air from CAD container (❷) into illumination container (❶). Do not fold or bend CAD.
4. Seal tubing close to inlet port of CAD container (❷).
5. Remove and discard empty illumination container (❶) and excess tubing.
6. Place CAD container (❷) flat on flatbed agitator with attached storage containers for 4-16 hours for Amicus platelets in PAS-3 or 12-24 hours for Trima platelets in 100% plasma. Agitation rate must be at least 60 RPM. Do not stop the process before the minimum time and do not extend the process beyond the maximum allowable time.
7. Do not fold or place storage container (❸), in line filter, or any tubing under CAD container (❷) during agitation.

IV. Transfer to Storage Container

1. Remove platelets from agitator and hang platelets in CAD container (❷).
2. Expel air from platelet sampling pouch into storage container and close clamp (Ⓕ).
3. Break cannula (Ⓔ) at outlet of CAD container (❷) and allow platelets to flow into storage container (❸).
4. Express air from storage container (❸) into CAD container (❷). Clamp tubing above storage container (❸).
5. Ensure appropriate donor identification is attached to the filled platelet storage container (❸).
6. Seal tubing to storage container (❸).
7. Remove and discard empty CAD container (❷) and tubing. Place platelets on platelet agitator.

The INTERCEPT treatment process is now complete.

V. Sampling Platelet Product (optional)

1. Mix INTERCEPT treated platelets by gently agitating platelet storage container.
2. Open clamp (Ⓕ) to platelet sampling pouch and squeeze several times.
3. Allow sampling pouch to fill with platelets. Seal tubing.
4. Remove sample pouch.
5. Transfer sample to appropriate laboratory tube immediately.

STORAGE AND HANDLING

Processing Sets

- Do not use if tamper-evident package has been opened, signs of deterioration are visible, fluid path closures are loose or not intact, cannulae are broken or if there is no fluid in the amotosalen solution container.

- Protect the processing set package and tubing from sharp objects. Discard platelet product if there is a leak in the set during processing.
- Keep processing sets in the light-protective, aluminum foil pouch until time of use. Protect from direct sunlight and strong UVA light source.
- Do not store processing set above 25°C.
- Do not vent.
- Do not freeze.
- Unused processing sets may be stored for up to 20 days at room temperature (18 – 25°C) in the open aluminum foil pouch by folding and securing the open end of the pouch. Record the "Date Opened" and "Use By" date on the foil pouch label in the space provided. The processing sets removed from the aluminum foil pouch must be used within 8 hours.

Platelet Components

- Platelet components processed with the INTERCEPT Blood System must be stored in the platelet storage container provided in the INT2110 processing sets.
- Processed platelet components may be stored at 20-24°C with continuous agitation for up to 5 days from the day of collection.

NONCLINICAL TOXICOLOGY

Nonclinical studies were conducted in mice, rats and dogs to evaluate the potential toxicity of single and repeated exposures to amotosalen, the synthetic psoralen derivative used in the INTERCEPT process to cross-link DNA and RNA. A single, intravenous injection of amotosalen alone resulted in mortality in rats at doses equal to or greater than 100,000-fold the anticipated human clinical exposure from a single transfusion of INTERCEPT processed platelets as compared on a dose per kilogram body weight basis. Lower doses of amotosalen (12,000- or 60,000-fold greater than the anticipated human clinical exposure in dogs and rats, respectively) were not lethal, and resulted in transient clinical signs of toxicity (i.e. piloerection, inactivity, hunched posture and abnormal breathing in rats, and excessive salivation, swelling of the muzzle and eyelids, and non-lethal cardiac arrhythmias in dogs). No target organ toxicities were noted at necropsy.[29]

Animal experiments with amotosalen provided no indication of an increased toxicological risk for the use of platelets treated using the INTERCEPT Blood System. Repeat-dose toxicity studies in rats and dogs dosed by daily intravenous injection for 7 to 28 days with amotosalen, at doses with at least 30,000- and 10,000-fold, respectively, the anticipated clinical exposure from transfusion of 300 mL of INTERCEPT Blood System-processed platelets showed no evidence of toxicity.[29, 30] Transient, minor changes in hematology profiles with no correlating histopathology findings or major organ toxicities were reported in dogs dosed 3 times weekly for 13 weeks with autologous platelets processed with the INTERCEPT Blood System, at a cumulative amotosalen exposure of approximately 115-fold the anticipated clinical exposure following a single transfusion of 300 mL of INTERCEPT processed platelets.

Amotosalen was rapidly eliminated in mice and rats with an initial plasma $t_{1/2}$ of less than 1 hour. There was no evidence of amotosalen accumulation after repeated exposures over periods as long as 13 weeks. The primary route of excretion of amotosalen and its photoproducts was fecal.[29]

No effects on fertility parameters were noted in male or female rats dosed with amotosalen. In studies evaluating the effects of amotosalen dosing of pregnant rats or rabbits on embryo-fetal or peri-postnatal development in pregnant rats and rabbits, and in one study dosing neonatal rats with amotosalen, there was no evidence of teratogenicity, or other reproductive or developmental toxicities.[31]

No evidence of genotoxicity or mutagenicity was observed in the *in vitro* or *in vivo* mutagenicity studies of amotosalen. In transgenic mice heterozygous for the p53 tumor suppressor gene, there was no evidence of carcinogenicity after repeated three times weekly dosing with amotosalen for 6 months at cumulative weekly doses approximately 1200 times the daily human exposure from a single 300 mL transfusion of INTERCEPT Blood System-treated platelets.[32]

CLINICAL STUDIES

The safety and effectiveness of INTERCEPT processed platelets were investigated in 10 controlled clinical studies.[33-42] A total of 844 study subjects received INTERCEPT processed platelets in these clinical studies.

Three trials were conducted in healthy volunteers to measure the viability of INTERCEPT processed platelets and the clearance of residual amotosalen.[33,34] Three studies utilized small doses (15-20 mL) of radiolabelled platelets; and in one study a full therapeutic dose (300 mL) was administered. All platelet components (PCs) were apheresis collections.

The primary endpoint of the three studies with radiolabelled platelets was post-transfusion viability of autologous INTERCEPT processed platelets after 5 days of storage. Autologous platelets from healthy donors prepared with the prototype IBS System (no amotosalen reduction) and stored for 5 days before transfusion demonstrated mean post transfusion recovery 77.8 % of untreated PCs, and mean life span 74.5 % of untreated PCs. Similarly, autologous platelets from healthy donors prepared with the prototype IBS System (with amotosalen reduction) and stored for 5 days before transfusion demonstrated mean post transfusion recovery 84.5 % of untreated PCs and life span 80 % of untreated PCs.

The primary endpoint of the full dose transfusion of INTERCEPT processed platelets was clearance of residual amotosalen. Peak post transfusion amotosalen levels were < 1 ng/ml with clearance kinetics of residual amotosalen median terminal (T_{50} = 6.5 hr) with acceptable tolerability after rapid transfusion of a therapeutic platelet dose.[34]

No clinically relevant adverse events were observed in healthy subjects exposed to small volumes of autologous radiolabeled platelets or after transfusion of 300 mL of autologous INTERCEPT treated platelet components.

A randomized, controlled, double blind, parallel-group study to compare the therapeutic efficacy and safety of INTERCEPT processed apheresis platelet components to conventional apheresis platelet components using a non-inferiority design was conducted in patients requiring 1 or more platelet transfusions to support hypoplastic thrombocytopenia[35]. The study was designed to assess the proportion of patients with Grade 2 bleeding during up to 28 days of platelet transfusion support. A total of 645 patients (318 Test, 327 Reference) received a total of 4719 platelet transfusions (2678 Test, 2041 Reference). There were 186/318 (58.5%) patients in the Test group and 188/327 (57.5%) patients in the Reference group with Grade 2 bleeding. The test result met the efficacy success criteria of the non-inferiority margin of 12.5%. Differences in mean number of transfusions, average interval between transfusions, rates of refractoriness, mean days with Grade 2 bleeding and mean count increment and corrected count increment at 1 and 24 hours were all statistically significantly different favoring the control

group. The targeted platelet transfusion dose was $3.7x10^{11}$. Sixty percent of the subjects in the INTERCEPT processed platelet group received a platelet dose of less than $3x10^{11}$ compared to 36% in the control group. Additionally, subjects in the INTERCEPT processed platelet group received off-protocol transfusions (32 vs. 15%) more often than the control group because of protocol violations. In order to assess whether the platelet dose could have impacted all these efficacy endpoint outcomes, a post-hoc analyses on three different subsets of subjects: subjects who received transfusions dose of platelets $\geq 3x10^{11}$, subjects who received off-protocol transfusions, and subsets who received transfusions dose of platelets $\geq 3x10^{11}$ without any off-protocol transfusions was conducted. In all the three subsets, a statistically significant difference was no longer seen in mean days with Grade 2 bleeding and in the mean number of platelet transfusions. Adjusting the platelet dose per unit to $\geq 3x10^{11}$ may overcome the differences of these outcomes seen in the original study analysis.[36]

There were no differences between treatment groups in the frequencies of Grade 3 and Grade 4 adverse events, serious adverse events, or mortality. Statistically significant differences for increased incidence of four adverse events of Grade 3 and Grade 4 severity were observed among recipients of INTERCEPT processed platelets. These included: pneumonitis not otherwise specified (5 versus 0); ARDS (5 versus 0); hypocalcemia (21 versus 8); and syncope (6 versus 0). A subsequent blinded, retrospective analysis of patients with clinically significant pulmonary adverse events (n = 148) demonstrated no significant increase in incidence of acute lung injury (ALI), including ARDS.[43] However a trend of increased ARDS in the patients receiving INTERCEPT processed platelets remained. The causality of these events remains uncertain and an increased risk of ARDS with the INTERCEPT processed platelets cannot be ruled out.

Another randomized, double-blind, controlled, parallel-group trial was conducted to evaluate the efficacy and safety of apheresis INTERCEPT processed platelets prepared with the commercial INTERCEPT system compared to conventional apheresis PCs. A total of 43 adult hematology-oncology patients with hypoplastic thrombocytopenia (22 Test, 21 Reference) were enrolled at 3 study centers. INTERCEPT treatment was used in place of gamma irradiation for 93% of INTERCEPT PCs for prevention of TA-GVHD. A total of 218 platelet components were transfused (103 Test and 115 Reference). The primary endpoint was the 1-hour platelet count increment. There was no excess treatment related morbidity reported among patients supported with INTERCEPT processed platelet components.

A single-arm, open label safety study of 560 INTERCEPT processed platelet transfusions in 51 adult patients with malignant hematology-oncology disorders, including HSCT was conducted to assess the frequency of acute transfusion reactions.[38] Platelet concentrates were prepared from either apheresis collections or whole blood derived buffy coat platelets, treated with INTERCEPT in place of gamma irradiation, and stored up to 5 days prior to transfusion. The frequency of acute transfusion reactions was 1.6%. This study was small in size and uncontrolled therefore the rate of acute transfusion reactions cannot be compared with that for conventional platelets.

A single-arm, open label observational study to assess acute transfusion reactions using apheresis “double unit” collections ($5\text{-}6 \times 10^{11}$) without gamma irradiation and stored up to 5 days was conducted in 46 adult hematology patients with malignant disorders, including HSCT.[39] A total of 551 INTERCEPT processed platelet transfusions were administered.in a Swiss Red Cross blood center. The frequency of acute transfusion reactions was 2%. This study was small in size and uncontrolled therefore the rate of acute transfusion reactions cannot be compared with that for conventional platelets.

Post-Marketing Studies

Safety data were obtained from three hemovigilance (HV) programs in routine use without patient selection: the Cerus hemovigilance program and the regulatory surveillance programs in France and in Switzerland.[44-57]

The populations monitored in the Cerus hemovigilance studies included 4,067 patients, where 59 patients were under the age of 1 year and 185 patients were 1-18 years of age. 51% of the patients enrolled in these studies were hematology-oncology patients, of which 12% were HSCT patients. Adverse events within 24 hours and serious adverse events within 7 days of platelet transfusion were reported. The frequencies of adverse events attributed to INTERCEPT processed platelet transfusions were not increased compared to conventional platelet transfusions reported in European regulatory hemovigilance programs.

Clinical Experience with Transfusion of INTERCEPT Platelets Suspended in 100% Plasma

Cerus conducted an analysis of the CLI-HV 00079 study to support the current PMA supplement for the use of the INTERCEPT Blood System for platelets suspended in 100% plasma. The final report (CLI-HV 00079-2) included data for 502 INTERCEPT platelet components suspended in 100% plasma. This study was an observational safety study to detect adverse events (AEs) that if imputed as related to the transfusion were classified as transfusion reactions (TR). Adverse events related to failure of hemostasis in thrombocytopenic patients could be reported in this study. Five hundred and two INTERCEPT platelet components were administered to 169 patients. All patients received INTERCEPT platelet components for hematology-oncology related diseases including HSCT (99.4%) or surgery (0.6%).

AEs were observed following transfusion of 5 INTERCEPT components (1.0%) in 4 patients (2.4%). No AEs were classified as "serious" (SAE) following transfusion of INTERCEPT PC. No adverse events related to bleeding or hemostatic failure were reported. The 4 patients who suffered an AE experienced chills (2 patients, 1.2%), pain (1 patient, 0.6%), pyrexia (3 patients, 1.8%) and rash (1 patient, 0.6%). Based on a clinical causality assessment, these AEs were classified as febrile non-hemolytic transfusion reactions with expected signs and symptoms (pyrexia and rash), and HLA antibody associated with lower back pain. The patients recovered from these adverse events on the day of transfusion, no transfusions were interrupted due to any AE or transfusion reaction, and no patients died during the study. The types of AEs were representative of the types of events experienced by patients with transfusion-dependent thrombocytopenia and were consistent with the types of events commonly experienced by patients following transfusion of conventional platelet components according to published data and national hemovigilance programs. No transfusion related acute lung injury (TRALI), transfusion-related sepsis (TRS), or transfusion-associated graft versus host disease (TA-GVHD) were reported. The frequencies of these AEs were comparable to historical data for conventional PCs in 100% plasma.[44-57,58] Transfusions of INTERCEPT PCs were well tolerated during this observational study, and the study provides further clinical data to support the use of the INTERCEPT Blood System with platelets suspended in 100% plasma.

ANSM and Swissmedic Active HV Programs (France and Switzerland)

Since 2009, INTERCEPT processed platelets suspended in PAS-3 (InterSol™) have been monitored in comparison to other types of platelet concentrates (suspended in PAS-3 or in 100% plasma) transfused in France and Switzerland through a national hemovigilance program.[48-57] In Switzerland, INTERCEPT processed platelets were phased into routine use during 2011, accounting for approximately 80% of all platelet concentrates transfused that year, and 100% of platelets produced thereafter. No septic transfusion reactions due to bacterial

contamination of platelets were observed after the introduction of INTERCEPT processed platelets in France or Switzerland. The number of TRALI reported to the HV systems during the years 2009-2013 is small, and the TRALI rates were similar in both groups. There were 6/187,142 TRALI cases per INTERCEPT processed platelet transfusions, for a TRALI rate of 0.33 per 10,000 platelet transfusion, compared to 37/1,109,135 TRALI cases per conventional platelet transfusions, for a rate of 0.32 per 10,000 platelet transfusions. Limitations of the hemovigilance system include data collection that was limited to only transfusion associated AEs (TRALI, TACO, TAD, etc.) as assessed by the reporter.

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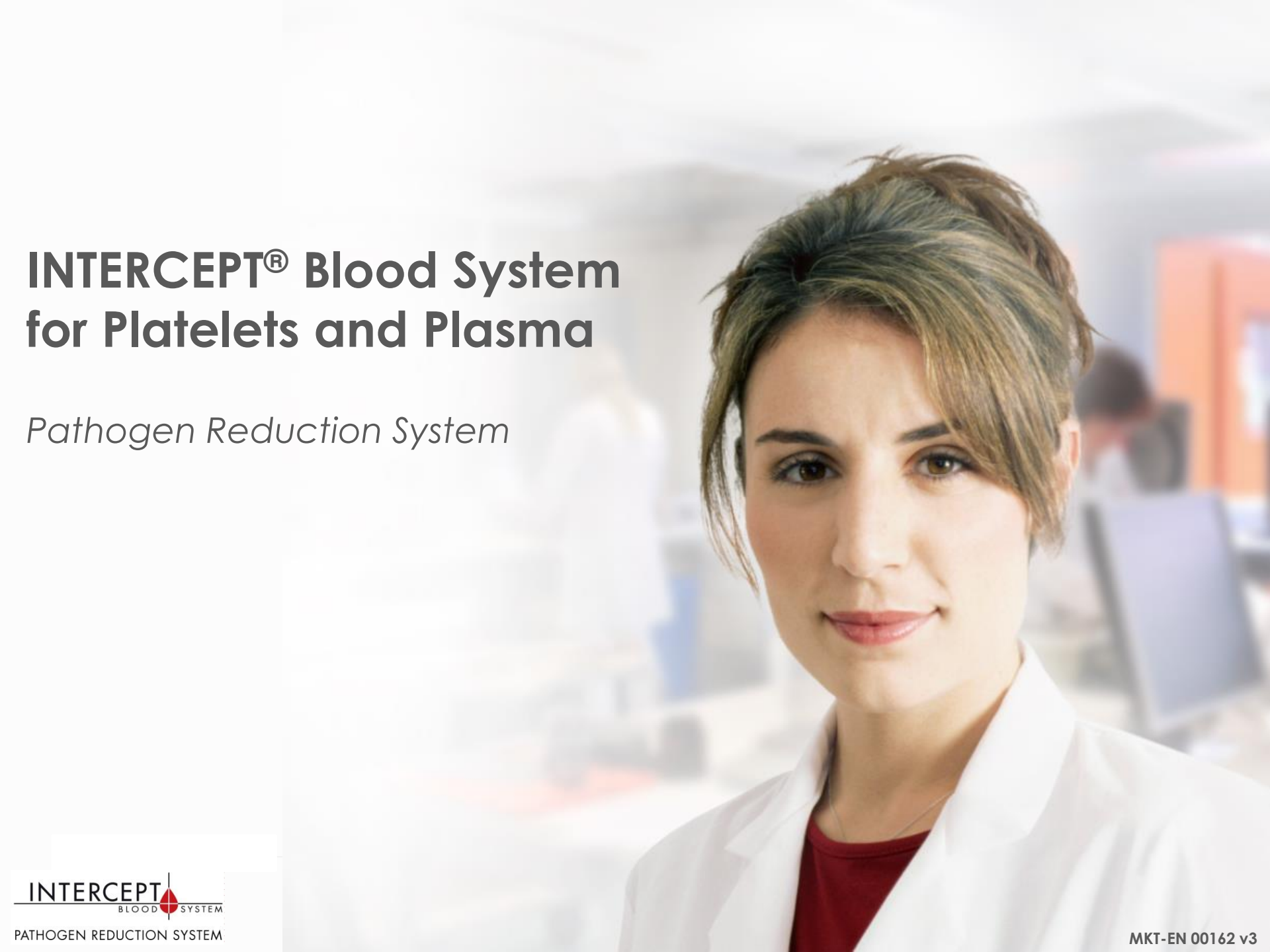
Manufactured for:
Cerus Corporation
2550 Stanwell Drive
Concord, CA 94520 USA

INTERCEPT® Blood System for Platelets and Plasma

Pathogen Reduction System



INTERCEPT BLOOD SYSTEM
PATHOGEN REDUCTION SYSTEM

Warnings and Contraindications

INTERCEPT Blood System for Platelets and Plasma

There is no pathogen inactivation process that has been shown to eliminate all pathogens.

CONTRAINDICATIONS

Contraindicated for preparation of plasma or platelet components intended for patients with a history of hypersensitivity reaction to amotosalen or other psoralens. Contraindicated for preparation of plasma or platelet components intended for neonatal patients treated with phototherapy devices that emit peak wavelengths less than 425 nm, or have a lower bound of the emission bandwidth <375 nm, due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.

WARNINGS AND PRECAUTIONS

Only INTERCEPT Processing Sets for plasma or platelet components are approved for use in the INTERCEPT Blood System. Use only the INT100 Illuminator for UVA illumination of amotosalen-treated plasma or platelet components. No other source of UVA light may be used. Please refer to the Operator's Manual for the INT100 Illuminator. Discard any plasma or platelet components not exposed to the complete INT100 illumination process.

Tubing components and container ports of the INTERCEPT Blood System for Plasma and Platelets contain polyvinyl chloride (PVC). Di(2-ethlhexyl)phthalate (DEHP) is known to be released from PVC medical devices, and increased leaching can occur with extended storage or increased surface area contact. Blood components will be in contact with PVC for a brief period of time (approx. 15 minutes) during processing. The risks associated with DEHP released into the blood components must be weighed against the benefits of therapeutic transfusion.

PLATELETS

INTERCEPT processed platelets may cause the following adverse reaction: *Acute Respiratory Distress Syndrome* (ARDS). An increased incidence of ARDS was reported in a randomized trial for recipients of INTERCEPT processed platelets, 5/318 (1.6%), compared to recipients of conventional platelet components (0/327). Monitor patients for signs and symptoms of ARDS.

PLASMA

Amotosalen-treated plasma may cause the following adverse reaction: *Cardiac Events.* In a randomized controlled trial of therapeutic plasma exchange (TPE) for TTP, five patients treated with INTERCEPT Blood System processed plasma and none with conventional plasma had adverse events in the cardiac system organ class (SOC) reported. These events included angina pectoris (n=3), cardiac arrest (n=1), bradycardia (n=1), tachycardia (n=1) and sinus arrhythmia (n=1). None of these events resulted in documented myocardial infarction or death. Monitor patients for signs and symptoms of cardiac events during TPE for TTP.

INTERCEPT BLOOD SYSTEM

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The Need for Blood Safety

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Current Transfusion-Associated Risks

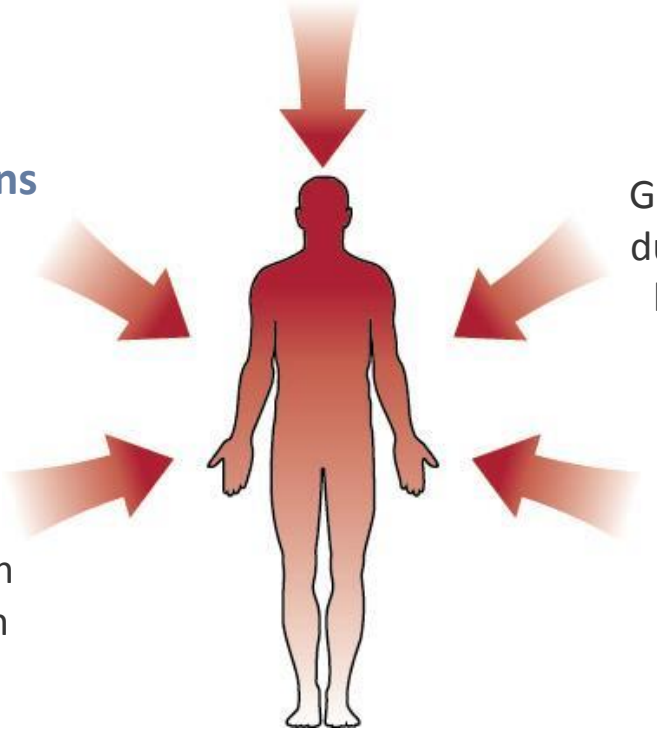
Testing measures have improved blood safety, but residual risks exist

Bacteria

The most frequent transfusion-transmitted infection (TTI)

New and emerging pathogens

A risk that current safety measures cannot eliminate



Screening limitations

Gaps in current defenses exist, due to the window period and limited screening sensitivity

Leukocytes

Residual cells and cytokines can cause harmful post-transfusion reactions such as transfusion-associated graft-versus-host disease (TA-GVHD)

Known pathogens

Routine testing covers only a limited number

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Bacterial Contamination of Platelets

The most frequent TTI

- Despite implementation of interventions to mitigate bacterial contamination and reduce associated adverse events (AEs), **residual risks remain…**
- Several recent studies demonstrate that platelets contaminated with bacteria continue to be transfused.[1–4]

Bacterial Contamination Risk	Clinical Sepsis Risk due to Bacteria	Viral Infectious Risk (HIV/HCV)
 ~1:1,500 Units[1]	 ~1:5,000 Units[5]	 ~1:1,000,000 Units[6]
 ~1:250 Patients[5]	 ~1:1,000 Patients[5]	 ~1:200,000 Patients

[1]Dumont, LJ et al. *Transfusion*. 2010 Mar;50(3):589–99.|[2]Pearce, S et al. *Transfus Med.* 2011 Feb;21(1):25–32.
[3]Murphy, WG et al. *Vox Sang.* 2008 Jul;95(1)13–9. | [4]Walther-Wenke, G et al. *Vox Sang*. 2011 May;100(4):359–66.
[5]Kleinman, S et al. *Transfusion*. 2013 Jul;53(7):1603–18. | [6]Zou, S et al. *Transfusion.* 2010 Jul;50(7):1495–504.

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TA-Sepsis is Often Under Reported

Due to passive vs. active surveillance methods

	Active Surveillance (n=102,988)	Passive Surveillance (n=135,985)	X – Fold Higher Rate by Active vs. Passive
Bacterially Contaminated Units			
Detected	50	2	32.0
Transfused	42	2	27.7
Septic Transfusion Reactions			
Septic Transfusion Reaction	16	2	10.6
Septic Transfusion Reaction with Bactermia	5	1	6.6
Death	1	1	

Jacobs, MR et al. *Clin Infect Dis.* 2008 Apr 15;46(8):1214–20.

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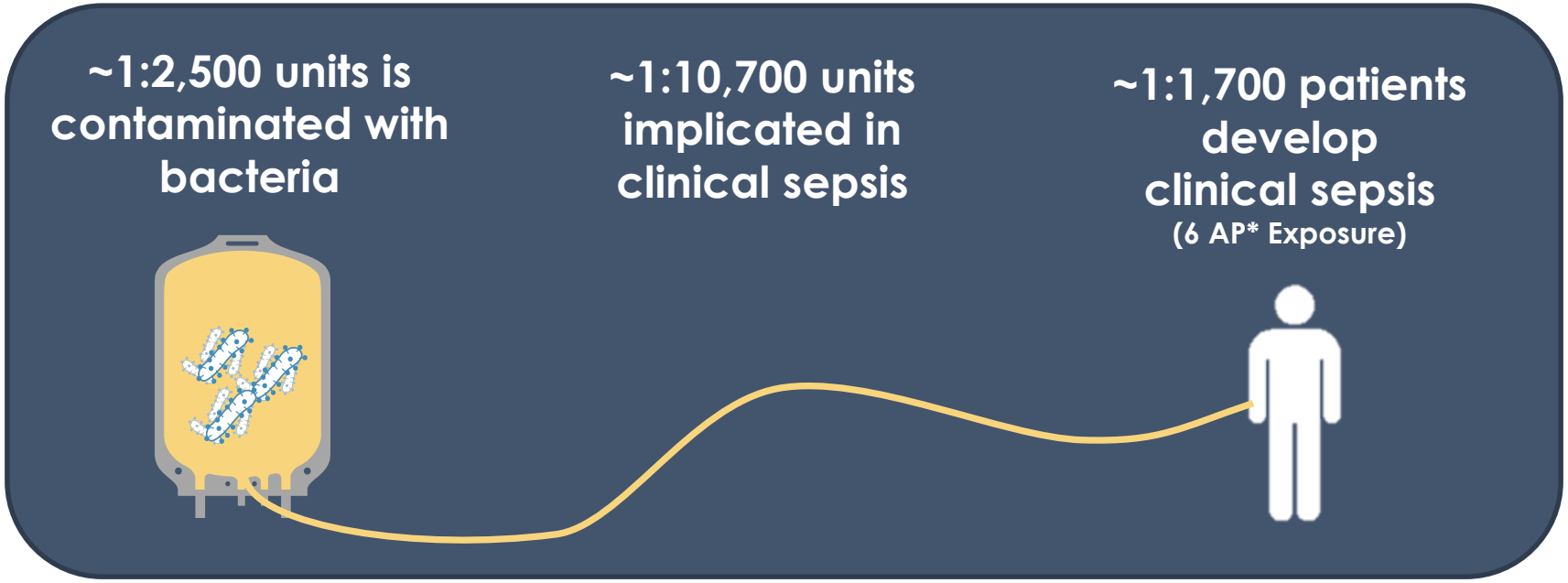
TA-Sepsis is Under Reported

Due to passive vs. active surveillance methods

- Consistent with previous studies, [1–4] the Hong et al. recently demonstrated that platelets contaminated with bacteria continue to be transfused.[5]
- Transfusion-related sepsis is greatly under-reported due to passive vs. active surveillance methods. Patient risk is 10- to 40-fold higher when comparing active vs. passive surveillance. [5]



[1]Dumont, LJ et al. *Transfusion*. 2010 Mar;50(3):589–99.|[2]Pearce, S et al. *Transfus Med*. 2011 Feb;21(1):25–32.
[3]Murphy, WG et al. *Vox Sang*. 2008 Jul;95(1)13–9.
[4]Walther-Wenke, G et al. *Vox Sang*. 2011 May;100(4):359–66.|[5]Hong H, et al. *Blood*. 2016;127(4):496-502.
*Apheresis platelet unit

INTERCEPT BLOOD SYSTEM
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Emerging Pathogens

Risk of spreading pathogens such as chikungunya, dengue, Zika

Chikungunya Cases Spike In New York And New Jersey

Reuters

examiner.com

LIFE/ HEALTH & FITNESS/ DISEASE & ILLNESS

Dengue and chikungunya in the Americas, the U.S. and Florida: 2014

January 3, 2015

SCIENTIFIC AMERICAN™

HEALTH

Zika Virus Threatens U.S. from Abroad

Exclusive: An interactive map, based on data from 50 state health departments, the mosquito-borne disease made its way to America in travelers' bloodst

By Dina Fine Maron on January 26, 2016

Fifth case of chikungunya confirmed in Texas

Hawaii mayor declares state of emergency to address dengue fever outbreak

transmitted to people through bites from mosquitoes of the Aedes species – the same dengue and chikungunya viruses. CBS NEWS

Tweet / Stumble / Email

ND -- Hawaii County Mayor Billy Kenoi has declared a state of ith the growing dengue fever outbreak in the state.

Published On: Thu, Sep 12th, 2013

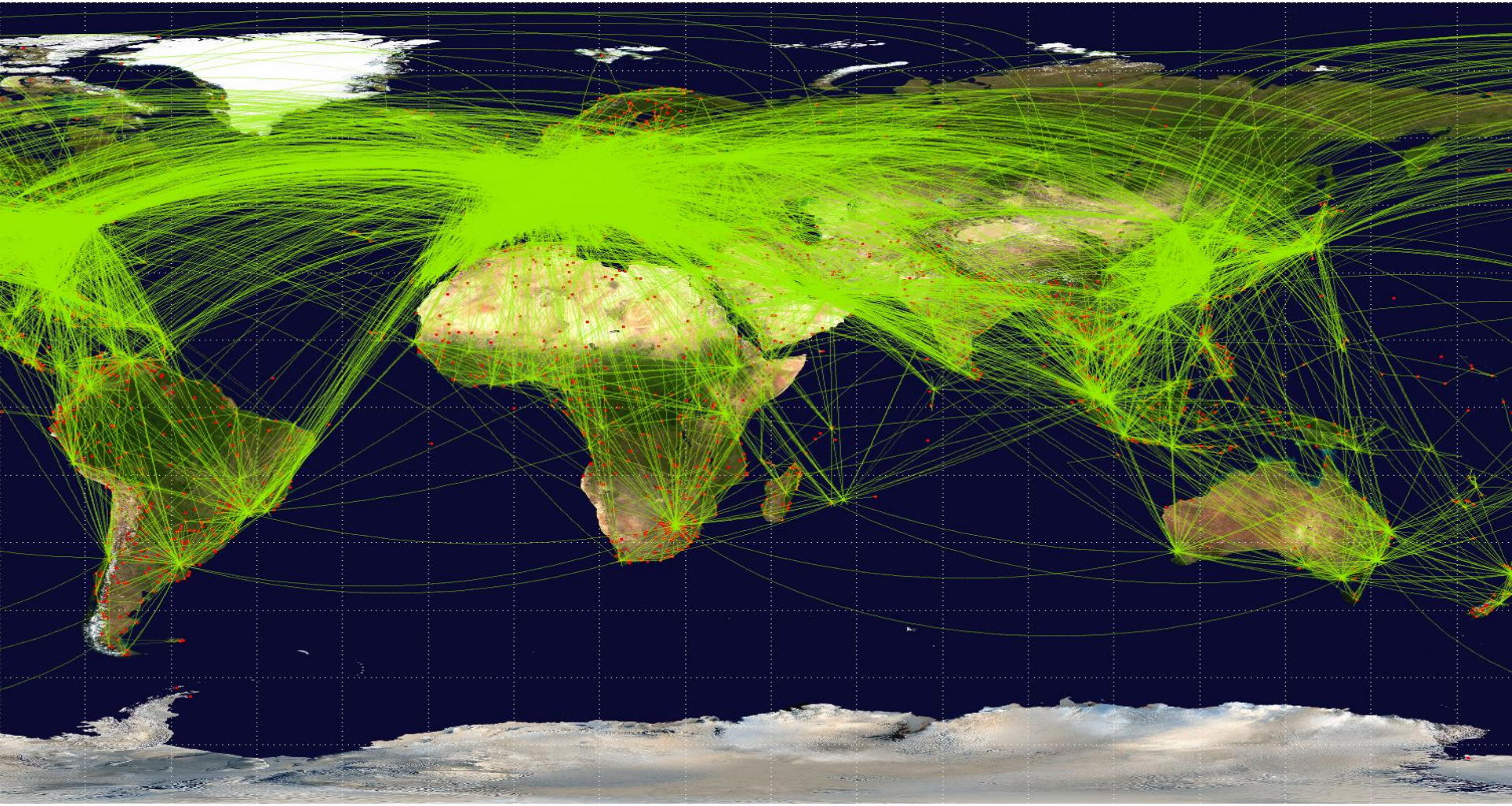
Hometown News / Outbreak News | By Robert Herriman

Florida Blood Bank, OneBlood, Temporarily Suspends Blood Donations From Martin And St. Lucie Counties Due To Dengue Fever

ION SYSTEM

Emerging Pathogens

Global portals of transfusion-transmitted infection – daily air routes



http://openflights.org

INTERCEPT BLOOD SYSTEM

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Emerging Pathogens

Current mitigations

- **No FDA commercially licensed test for donor screening exists.**
- **AABB Bulletin released February 2016: Zika, chikungunya, dengue travel deferrals**
- **Post donation information/illness reporting**
  - Risk still exists with components transfused from asymptomatic donors
- **Stop routine collections, attain components elsewhere**
  - Puerto Rico, Florida due to Dengue (One Blood in 2013)
  - Not ideal for platelets, disruptive due to limited shelf-life and shipping time
- **Pathogen reduction (PR)**
  - FDA approved for arboviruses including chikungunya, dengue, WNV
  - FDA Guidance released February 2016 recommends PR for areas with active transmission of ZIKV
  - WHO Guidance released February 2016 recommends PR for areas with active transmission of ZIKV

*Data for pathogen reduction of Zika by INTERCEPT Blood System, pathogen reduction system, has not been submitted for FDA review.

INTERCEPT BLOOD SYSTEM

PATHOGEN REDUCTION SYSTEM

Emerging Pathogens

Current mitigations – Pathogen Reduction

- Per FDA Guidance released 16February2016:

FDA News Release

FDA issues recommendations to reduce the risk for Zika virus blood transmission in the United States

For Immediate Release

February 16, 2016

Release

As a safety measure against the emerging Zika virus outbreak, today the U.S. Food

*In **areas with active Zika virus transmission (http://www.cdc.gov/zika/geo/index.html)**, the FDA recommends that Whole Blood and blood components for transfusion be obtained from areas of the U.S. without active transmission. Blood establishments may continue collecting and preparing platelets and plasma if an FDA-approved, pathogen-reduction device is used. The guidance also recommends blood establishments update donor education materials with information about Zika virus signs and symptoms and ask potentially affected donors to refrain from giving blood.*

area with active Zika virus transmission during the prior three months, and those who have traveled to areas with active transmission of Zika virus during the past four weeks.

*In **areas with active Zika virus transmission (http://www.cdc.gov/zika/geo/index.html)**, the FDA recommends that Whole Blood and blood components for transfusion be obtained from areas of the U.S. without active transmission. Blood establishments may continue collecting and preparing platelets and plasma if an FDA-approved, pathogen-reduction device is used. The guidance also recommends blood establishments update donor education materials with information about Zika virus signs and symptoms and ask potentially affected donors to refrain from giving blood.*

Testing Challenges

Present TTI risk, increased logistics burden to hospitals

- Escaped bacterial detection by early culture[1]
- Point of issue (POI) testing presents significant challenges
  - High false-positive rates can lead to significant product discard rates[2,3]
  - Presents logistic and cost burdens: need for re-testing if not transfused in ≤ 24 hours; repeat testing algorithm for positive POI units[3]
- Reactive approach presents a TTI risk due to emerging pathogens[4]

[1]Benjamin, R et al. *Vox Sanguinis* 2013. | [2]Jacobs MR *et al. Transfusion* 2011;51:2573. | [3]Harm et al. *Transfusion* 2013;843-850.
[4]Kleinman S et al. *Transfusion* 2010, 50 2592-2606

The INTERCEPT® Blood System

pathogen reduction system

Overview

INTERCEPT BLOOD SYSTEM

PATHOGEN REDUCTION SYSTEM

INTERCEPT Blood System
A proactive approach to reducing TTI risk

- **FDA-approved pathogen reduction system**
  - Safety, efficacy demonstrated in prospective clinical trials
  - 10+ Years routine, global use
  - Effective January 1, 2016 – Permanent, hospital outpatient billing codes(P-codes) established for PR-treated platelets and plasma[1]

- **Reduces transfusion-transmitted infectious (TTI) risk through the comprehensive inactivation of viruses, bacteria, and parasites that can be found in plasma and platelet components**[2,3]

- **Potentially lowers the risk of transfusion-associated graft-versus-host disease (TA-GVHD) in platelet units through T-cell inactivation**[3]

There is no pathogen inactivation process that has been shown to eliminate all pathogens. Certain non-enveloped viruses (eg, HAV, HEV, B19 and poliovirus) and *Bacillus cereus* spores have demonstrated resistance to the INTERCEPT process.

1. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Hospital-Outpatient-Regulations-and-Notices-Items/CMS-1633-FC.html?DLPage=1&DLEntries=10&DLSort=2&DLSortDir=descending
2. INTERCEPT Blood System for Plasma [Package Insert]. Concord, CA: Cerus Corporation; 2015.
3. INTERCEPT Blood System for Platelets [Package Insert]. Concord, CA: Cerus Corporation; 2016.

INTERCEPT BLOOD SYSTEM
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INTERCEPT Blood System
Indications for Use

INTERCEPT Platelets[1]

For the *ex vivo* preparation of pathogen-reduced apheresis platelet components in order to:

- Reduce the risk of TTI, including sepsis
- Potentially reduce the risk of TA-GVHD

INTERCEPT Plasma[2]

For the *ex vivo* preparation of pathogen-reduced, whole blood derived or apheresis plasma in order to reduce the risk of TTI

[1]INTERCEPT Blood System for Platelets [Package Insert]. Concord, CA: Cerus Corporation; 2016.
[2]INTERCEPT Blood System for Plasma [Package Insert]. Concord, CA: Cerus Corporation; 2015.

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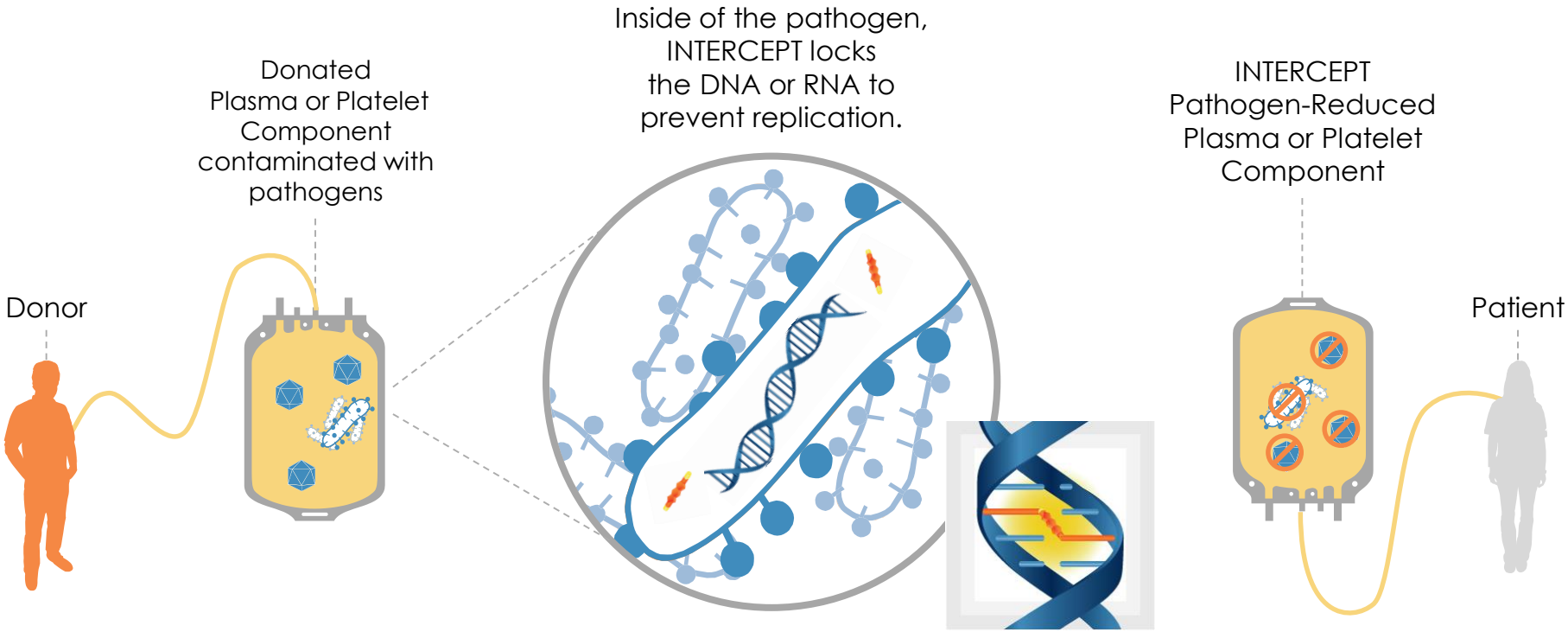
INTERCEPT Blood System

Pathogen reduction system[1,2]



Donated plasma or platelet component(s) may contain harmful agents such as bacteria, viruses, protozoans, and/or white blood cells.

When pathogens are unable to replicate, they are considered "inactivated" and cannot infect patients.

Pathogen-reduced component can then be transfused into the patient

[1]INTERCEPT Blood System for Platelets [Package Insert]. Concord, CA: Cerus Corporation; 2016.
[2]INTERCEPT Blood System for Plasma [Package Insert]. Concord, CA: Cerus Corporation; 2015,

INTERCEPT BLOOD SYSTEM
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Mechanism of Action

Targeting DNA and RNA to prevent pathogen proliferation[1,2]

1 Intercalates Into Regions of DNA and RNA

2 Crosslinks Upon UVA Illumination

3 Blocks Replication, Transcription and Translation

[1]INTERCEPT Blood System for Platelets [Package Insert]. Concord, CA: Cerus Corporation; 2016.
[2]INTERCEPT Blood System for Plasma [Package Insert]. Concord, CA: Cerus Corporation; 2015.

INTERCEPT BLOOD SYSTEM
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Broad Spectrum Inactivation

A proactive approach to reducing TTIs

GRAM-NEGATIVE BACTERIA

*Klebsiella pneumoniae**◊#
*Yersinia enterocolitica**◊#
*Escherichia coli**◊
*Pseudomonas aeruginosa**◊
*Salmonella choleraesuis**◊
*Enterobacter cloacae**◊
*Serratia marcescens**◊
Anaplasma phagocytophilum#

GRAM-POSTIVE BACTERIA

*Staphylococcus epidermidis**◊#
*Staphylococcus aureus**◊
*Streptococcus pyogenes**◊
*Listeria monocytogenes**◊
*Corynebacterium minutissimum**◊
Bacillus cereus (vegetative) *◊
*Lactobacillus species**◊
*Bifidobacterium adolescentis**
*Propionibacterium acnes**◊
*Clostridium perfringens (vegetative)**◊

ENVELOPED VIRUSES

HIV-1*◊#
DHBV (model for HBV)*◊#
BVDV (Model for HCV)*◊#
HTLV-I*#
HTLV-II*#
CMV*
WNV*◊#
Chikungunya*◊#
Dengue*◊
Influenza A*#

NON-ENVELOPED VIRUSES

Bluetongue virus*#
Adenovirus*◊#
Parovirus B19#

PROTOZOA

*Trypanosoma cruzi**◊#
*Plasmodium falciparum**#
*Babesia microti**#

SPIROCHETES

*Treponema pallidum**#
*Borrelia burgdorferi**#

LEUKOCYTES

Human T-Cells*◊#

* pathogen reduced Amicus apheresis platelets in PAS-3
◊ pathogen reduced Trima apheresis platelets in 100% plasma
pathogen reduced plasma

There is no pathogen inactivation process that has been shown to eliminate all pathogens. Certain non-enveloped viruses (e.g., HAV, HEV, B19 and poliovirus) and *Bacillus cereus* spores have demonstrated resistance to the INTERCEPT process. For a full list of pathogens, please refer to package inserts.

INTERCEPT Blood System for Plasma [Package Insert]. Concord, CA: Cerus Corporation; 2015.
INTERCEPT Blood System for Platelets [Package Insert]. Concord, CA: Cerus Corporation; 2016.

INTERCEPT BLOOD SYSTEM
PATHOGEN REDUCTION SYSTEM

Permanent Outpatient Billing Codes

Established for pathogen reduced platelets and plasma

Centers for Medicare & Medicaid Services (CMS) granted Level II codes for pathogen-reduced (PR) platelet and plasma components **allowing hospitals to bill and secure reimbursement in the outpatient treatment setting**

New CY2016 HCPCS P-Code	New HCPCS P-Code Long Descriptor	Final CY 2016 OPPS Payment Amount
P-9070	Plasma , pooled multiple donor, pathogen reduced, frozen, each unit	**$73.08**
P-9071	Plasma (single-donor), pathogen reduced, frozen, each unit	**$72.56**
P-9072	Platelets, pheresis, pathogen reduced, each unit	**$641.85**

HCPCS = Hospital Common Procedure Coding System; P-Code = Permanent Code

https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Hospital-Outpatient-Regulations-and-Notices-Items/CMS-1633-FC.html?DLPage=1&DLEntries=10&DLSort=2&DLSortDir=descending

INTERCEPT BLOOD SYSTEM

PATHOGEN REDUCTION SYSTEM

The INTERCEPT Blood System

For Platelets

INTERCEPT BLOOD SYSTEM

PATHOGEN REDUCTION SYSTEM

INTERCEPT Blood System for Platelets

Proactively defends patients against TTI*

- **First FDA-approved pathogen reduction system for platelets**
  - Safety, efficacy demonstrated in prospective clinical trials
  - 10+ Years routine, global use

- **Reduces transfusion-transmitted infectious (TTI) risk, including sepsis**
  - Broad spectrum of bacteria frequently implicated in TTI
  - Emerging pathogens, such as chikungunya, dengue, *Plasmodium* species.
  - Established threats such as HIV-1, HBV** ,HCV**, WNV

- **Potentially reduce risk of transfusion-associated graft-versus-host disease (TA-GVHD) through reduced contaminating T-cell activity[1]**

- **Approved for use with Amicus apheresis platelets in PAS-3 and Trima apheresis platelets in 100% plasma^**

* There is no pathogen inactivation process that has been shown to eliminate all pathogens. Certain non-enveloped viruses (e.g., HAV, HEV, B19 and poliovirus) and *Bacillus cereus* spores have demonstrated resistance to the INTERCEPT process. ** Pathogen reduction demonstrated for DHBV and BVDV, model viruses for HBV and HCV respectively. ^ Please refer to the package insert for full prescribing information.

INTERCEPT Blood System for Platelets [Package Insert]. Concord, CA: Cerus Corporation; 2016.
[1]FDA Press Release: FDA approves pathogen reduction system to treat platelets. December 19, 2014.

INTERCEPT BLOOD SYSTEM
PATHOGEN REDUCTION SYSTEM

INTERCEPT Blood System for Platelets

Populations studied in clinical trials[1-6]

- Patients with various hematological malignancies (acute myeloid / lymphoid leukemia, lymphoma, multiple myeloma, myelodysplasia, hairy cell leukemia, solid tumors).

- Patients undergoing peripheral blood progenitor cell transplantation or bone marrow transplantation.

[1]INTERCEPT Blood System for Platelets [Package Insert]. Concord, CA: Cerus Corporation; 2016.
[2]McCullough, J et al. *Blood* 2004 Sep;104(5):1534–41.|[3]Janetzko, L et al. *Transfusion* 2005 Sep;45:1443–52.
[4]Slichter, SJ et al. *Transfusion* 2006 Oct;46:731–40.|[5]Schlenke, P et al. *Ann Hematol* 2011 Dec;90(12):1457–65.
[6]Infanti, L et al. *Transfus Apher Sci* 2011 May;45(2):175–181.

INTERCEPT BLOOD SYSTEM
PATHOGEN REDUCTION SYSTEM

Nearly 1000 Subjects Evaluated in Clinical Trials

Primary endpoints met in controlled, randomized studies for the INTERCEPT Blood System for Platelets

Study Description	Primary End Point	Primary End Point Met?
Phase II Randomized, controlled, single-blind, cross-over trial to evaluate the viability of INTERCEPT Platelets, clearance of amotosalen, healthy patients[1] **(n=65)**	Recovery/survival, clearance of amotosalen	✓
Phase II Randomized, controlled, double-blind, cross-over study to evaluate the safety/efficacy of INTERCEPT Platelets, thrombocytopenic patients[2] **(n=32)**	Bleeding time	✓
Phase III Randomized, controlled, double-blind, parallel trial to evaluate the safety/ efficacy of INTERCEPT Platelets, thrombocytopenic patients[3] **(n=645)**	WHO Grade 2 bleeding	✓
Phase III Randomized, controlled, double-blind, parallel trial to evaluate the safety/ efficacy of INTERCEPT Platelets, thrombocytopenic patients[4] **(n=43)**	1-Hour CCI	✓
Observational Single-arm, uncontrolled, open label study evaluating the safety of INTERCEPT in routine setting[5] **(n=51)**	Frequency of acute transfusion reactions was 1.6%	
Observational Single-arm, uncontrolled, open label study evaluating the safety of INTERCEPT routine setting[6] **(n=46)**	Frequency of acute transfusion reactions was 2%	
Observational Single-arm, uncontrolled, open label study evaluating the safety of INTERCEPT, routine setting[7] **(n=169)**	Frequency of acute transfusion reactions was 2.4%	

[1]Snyder, E et al. *Transfusion.* 2004 Dec;44(12):1732–40.|[2]Slichter SJ et al. *Transfusion.* 2006 May;46(5):731–40.
[3]McCullough et al. *Blood.* Sep 2004;104(5):1534–41.|[4]Janetzko et al. *Transfusion.* 2005 Sep;45(9):1443–52.
[5]Schlenke P et al. *Ann Hematol.* 2011 Dec;90(12):1457–65.|[6] Infanti L et al. *Transfus Apher Sci.* 2011 Oct;45(2):175–81.
[7] INTERCEPT Blood System for Platelets [Package Insert]. Concord, CA; Cerus Corporation. 2016.

INTERCEPT BLOOD SYSTEM
PATHOGEN REDUCTION SYSTEM

Hemovigilance Programs

Demonstrated safety in routine use

>300,000 INTERCEPT Platelets Evaluated in Routine Use

	French National Hemovigilance[1]	Swiss National Hemovigilance[2]	Multicenter Cerus HV[3]
# INTERCEPT Platelets Transfusions	**180,782**	**130,843**	**19,175**
# Patients Receiving INTERCEPT Platelets	~30,000	~20,000	4,067
INTERCEPT ATR Rate	~0.3%[4]	~0.3%[5]	~0.6%
Conventional ATR Rate	~0.3%[4]	~0.4%[5]	NA

[1]French National Agency for Medicine and Health Product Safety/ANSM, Hemovigilance Activity Reports, 2006 - 2014.
[2]SwissMedic Haemovigilance Annual Reports, 2010 - 2014. | [3]Knutson F et al. Vox Sanguinis 2015.
[4]French National Agency for Medicine and Health Product Safety/ANSM, Hemovigilance Activity Reports, 2009-2011.
[5]SwissMedic Haemovigilance Annual Report 2014; conventional : 2008-2010, INTERCEPT: 2011-2014.

INTERCEPT BLOOD SYSTEM
PATHOGEN REDUCTION SYSTEM

Demonstrated Sepsis Prevention

With routine use of INTERCEPT platelet units

- Hemovigilance (HV) programs provide a comprehensive view of transfusions and potential adverse events.
  - 300,000+ INTERCEPT platelet units have been transfused in French and Swiss national HV programs
  - No reported TTIs and sepsis-related fatalities to-date

HV Program	Conventional Platelets		INTERCEPT Platelets	
	Platelet Units Transfused	TTIs (Fatalities)	Platelet Units Transfused	TTIs
France 2006–2014[1,2]	2,299,334	49 (8)	180,762	0
Switzerland 2010–2014[1,3]	36,500	1 (0)	130,843	0
Total	**2,335,834**	**50 (8)**	**311,605**	**0**

[1] Sweeney J, Lozano M. *Platelet Transfusion Therapy*. Bethesda: AABB Press, 2013.
[2] French National Agency for Medicine and Health Product Safety/ANSM, *Hemovigilance Activity Reports*, 2012–2014.
[3] SwissMedic *Haemovigilance Annual Reports*, 2010–2014.

INTERCEPT BLOOD SYSTEM
PATHOGEN REDUCTION SYSTEM

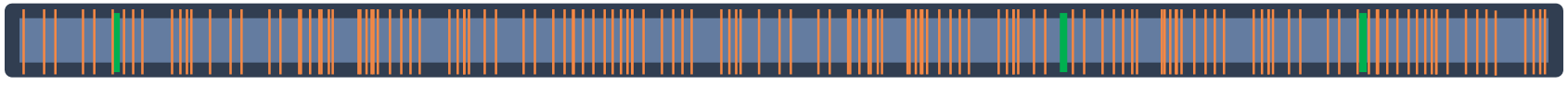
Reduction of T-Cells

To a level that potentially reduces the risk of TA-GVHD[1]

- INTERCEPT processed platelets exhibited a 4 $\log_{10}$ reduction of viable T-cells.[2]
- DNA modification assay in components processed with the INTERCEPT Blood System demonstrated high DNA modification densities to help ensure inactivation of most genes:

Gamma irradiation 1:37,000 strand-break: base pair

INTERCEPT Platelets 1:83[3,4] amotosalen adduct formed: base pair



Animation courtesy of AuBuchon, JK.

[1]FDA Press Release: *FDA approves pathogen reduction system to treat platelets*. December 19, 2014. | [2]INTERCEPT Blood System for Platelets [Package Insert]. Concord, CA: Cerus Corporation; 2016. | [3]Grass, JA et al. *Blood*. 1998 Mar 15;91(6):2180-8. | [4]Setlow, RB, Setlow, JK. *Effect of radiation on polynucleotides*. Baldwin, ML, Jeffries, LC (eds). *Irradiation of blood components*. Bethesda, MD. AABB, 1992 p1.

INTERCEPT BLOOD SYSTEM

PATHOGEN REDUCTION SYSTEM

No Reports of TA-GVHD in Routine Use

With INTERCEPT treated platelets

- Longitudinal studies conducted in 21 centers, across 11 countries over 7-years in broad patient populations
  - Large proportion of hematology/oncology patients
- 97% of Platelet components (PCs) were not treated with gamma irradiation

Study	PCs	Patients	Intervention	Outcome	Timing
HV1	5,106	651	INTERCEPT PCs	Safety	2003–2005
HV2	7,437	1,400	INTERCEPT PCs	Safety	2005–2007
HV3	6,632	2,016	INTERCEPT PCs	Safety	2006–2010
Total	**19,175**	**4,067**	**INTERCEPT PCs**	**Safety**	**2003–2010**

Knutson, F et al. *Vox Sang*. 2015 May 15. doi:10.1111/vox.12287. [Epub ahead of print]

The INTERCEPT Blood System

For Plasma

INTERCEPT BLOOD SYSTEM

PATHOGEN REDUCTION SYSTEM

INTERCEPT Blood System for Plasma

A proactive approach for blood centers to reduce TTI risk*

- **Reduces transfusion-transmitted infection (TTI) risk[1]**
  - Broad spectrum inactivation with ≥4 log reduction for most pathogens
  - Emerging pathogens, such as chikungunya, *Plasmodium* species
  - Established threats such as HIV-1, HBV**, HCV**, WNV

- **Approved for use with whole blood derived or apheresis plasma[1]**

* There is no pathogen inactivation process that has been shown to eliminate all pathogens. Certain non-enveloped viruses (e.g., HAV, HEV, B19 and poliovirus) and *Bacillus cereus* spores have demonstrated resistance to the INTERCEPT process. ** Pathogen reduction demonstrated for DHBV and BVDV, model viruses for HBV and HCV respectively.

[1]INTERCEPT Blood System for Plasma [Package Insert]. Concord, CA: Cerus Corporation; 2015.

INTERCEPT BLOOD SYSTEM
PATHOGEN REDUCTION SYSTEM

INTERCEPT Blood System for Plasma

Populations studied in clinical trials[1]

- Acquired coagulation factor deficiencies[1,2]
- Congenital coagulation factor deficiencies [1,3]
- Those undergoing therapeutic plasma exchange (TPE) due to thrombotic thrombocytopenic purpura (TTP)[1,4]
- Those undergoing liver transplantation[1,5]

[1]INTERCEPT Blood System for Plasma [Package Insert]. Concord, CA: Cerus Corporation; 2015.|[2]Mintz, PD et al. *Blood*. 2006 May1;107(9):3753-60.
[3]de Alarcon, P et al. *Transfusion* 2005 Aug;45(8):1382-72.|[4]Mintz, PD et al. *Transfusion* 2006 Oct;46(10):1693-704.
[5] Cinqualbre, J et al. *Vox Sang* 2012 103(Supplement 1):247-48.

INTERCEPT BLOOD SYSTEM
PATHOGEN REDUCTION SYSTEM

INTERCEPT Blood System for Plasma

Demonstrated safety, efficacy in routine use

- Hemovigilance (HV) programs - a comprehensive view of transfusions and potential adverse events.
- HV programs tracking the ***routine use of >200,000 INTERCEPT Plasma***[1] units in Europe have demonstrated therapeutic efficacy with an adverse event profile consistent with untreated plasma.[2-4]

Year	Product	Plasma Units	Acute Transfusion Reactions per 1,000 Units
2009	Untreated Plasma	348,725	0.55
	INTERCEPT Plasma	**22,933**	**0.52**
2010	Untreated Plasma	329,757	0.59
	INTERCEPT Plasma	**52,692**	**0.47**
2011	Untreated Plasma	311,482	0.31
	INTERCEPT Plasma	**68,440**	**0.31**

[1] Subset HV data shown above, French HV data.
[2] INTERCEPT Blood System for Plasma [Package Insert]. Concord, CA: Cerus Corporation; 2015.
[3] Cazenave JP et al. *Transfusion* 2010;50:1210-1219. | [3]Bost V et al. *Vox Sanguinis* 2013;104:337-341.
[4]Afssaps Rapport Annuel Hemovigilance 2009-2011.

INTERCEPT BLOOD SYSTEM
PATHOGEN REDUCTION SYSTEM

Safety, Efficacy Evaluated in Prospective Trials

Studies met primary endpoints for the INTERCEPT Blood System for Plasma[1]

Study Design*	Primary Result(s)	Primary Endpoint Met?
Phase I Randomized, single-blind, crossover with healthy subjects **(N=15)**	**Comparable coagulation factor levels** attained between test and control FFP.[2]	✓
Phase II Randomized, single-blind, crossover with healthy subjects, warfarin anticoagulated **(N=27)**	**Comparable prothrombin time and FVII kinetics** between test and control FFP.[2]	✓
Phase II Randomized, double-blind, parallel group, multiple coagulation deficiencies **(N=13)**	INTERCEPT plasma was **safe and well tolerated by patients impaired with hepatic function. Comparable hemostatic activity attained** between test and control FFP.[3]	✓
Phase IIIa Open label, single arm, congenital coagulation deficiencies **(N=34)**	**Comparable recovery, pharmacokinetic performance, and PT/PTT** attained between test and control FFP.[3]	✓
Phase IIIb Randomized, double-blind, parallel group, acquired coagulation deficiencies **(N=121)**	**Comparable coagulation responses and clinical hemostasis** were attained between test and control FFP.[4]	✓
Phase IIIc Randomized, double-blind, parallel group, thrombotic thrombocytopenic purpura (TTP) **(N=35)**	**Remission rates, time to remission, relapse rates, and time to relapse, as well as number of TPE and volume of FFP required were comparable** between INTERCEPT Plasma and conventional FFP.[5]	✓

*Sample size (N) is the total of test and control patient samples.

[1]INTERCEPT Blood System for Plasma [Package Insert]. Concord, CA: Cerus Corporation; 2015.
[2]Hambleton, J et al. *Transfusion.* 2002 Oct;42(10):1302–7. | [3]de Alarcon, P et al. *Transfusion.* 2005 Aug; 45(8):1362–72.
[4]Mintz, PD et al. *Blood.* 2006 May 1;107(9):3753–60. | [5]Mintz PD et al. *Transfusion.* 2006 Oct;46(10):1693-704.

INTERCEPT BLOOD SYSTEM
PATHOGEN REDUCTION SYSTEM

INTERCEPT Blood System for Plasma

Effective at retaining plasma coagulation function

- INTERCEPT Plasma maintains hemostatic potency, as shown by the retained activity of key coagulation factors.

Factor	Untreated Plasma	INTERCEPT Plasma
Global Coagulation Parameters		
Prothrombin Time (seconds)	13.1	14.4
Activated Partial Thromboplastin Time (aPTT) (seconds)	24.2	27.0
Coagulation Factors and Proteins of the Hemostatic System		
Fibrinogen (mg/dL)	2.91	2.43
Factor II (IU/mL)	1.03	0.93
Factor V (IU/mL)	0.91	0.82
Factor VII (IU/mL)	0.99	0.81
Factor VIII (IU/mL)	0.91	0.73
Factor IX (IU/mL)	1.12	0.93
Factor X (IU/mL)	0.95	0.83
Factor XI (IU/mL)	1.02	0.90
vWF Ristocetin Cofactor Activity	1.01	0.97

Data shown is for whole blood derived plasma frozen within 24 hours. For apheresis plasma, please see package insert. The INTERCEPT Blood System for Plasma Package Insert, 2015.

INTERCEPT BLOOD SYSTEM

PATHOGEN REDUCTION SYSTEM

INTERCEPT Blood System for Plasma

Effective at retaining plasma coagulation function

- INTERCEPT Plasma maintains hemostatic potency, as shown by the retained activity of key coagulation factors.

Factor	Untreated Plasma	INTERCEPT Plasma
Anticoagulant Proteins		
Antithrombin III	**0.98**	**0.93**
Protein C (IU/mL)	**0.95**	**0.86**
Protein S (IU/mL)	**1.08**	**1.04**
Proteins of the Fibrinolytic System		
Alpha-2-plasmin inhibitor (IU/mL)	**1.00**	**0.85**
Markers of Coagulation Activation		
Thrombin-Antithrombin Complexes (µg/L)	**2.4**	**2.3**
Factor VIIa (ng/mL)	**<3.6**	**<3.6**

Data shown is for whole blood derived plasma frozen within 24 hours. For apheresis plasma, please see package insert.
The INTERCEPT Blood System for Plasma Package Insert, 2015.

INTERCEPT BLOOD SYSTEM
PATHOGEN REDUCTION SYSTEM

The INTERCEPT Blood System
Operational Efficiencies

INTERCEPT BLOOD SYSTEM

PATHOGEN REDUCTION SYSTEM

INTERCEPT Blood System

Operational and cost efficiencies

Improved clinical outcomes

The INTERCEPT Blood System for Platelets reduces TTI risk, including sepsis.[1] It also potentially reduces the risk of TA-GVHD.[1] This can result in reduced costs associated with treatment, re-calls and follow-up investigations.[2]

Avoidance of cost and complexity of bacterial testing

INTERCEPT offers the potential to replace or avoid bacterial detection methods, including point of issue testing, with its ability to reduce the risk of bacterial contamination of platelets and sepsis.[1] This enables hospitals to avoid costs associated with bacterial testing, labor and platelet waste due to potential false positive results.

Improved platelet availability, decreased wastage

INTERCEPT allows for immediate accessibility of platelet units. Early platelet unit receipt provides added flexibility for managing inventory, and enables hospitals to attain fresher platelets.

Permanent outpatient billing codes assigned

Effective January 1, 2016 CMS has granted permanent billing codes for pathogen reduced platelets and plasma components allowing hospitals to bill and secure reimbursement in the outpatient treatment setting.

[1]INTERCEPT Blood System for Platelets [Package Insert]. Concord, CA: Cerus Corporation; 2016.
[2]Berger K, et al. *Onkologie* 2013;36:53–59.

INTERCEPT BLOOD SYSTEM
PATHOGEN REDUCTION SYSTEM

Pathogen inactivation of platelets with a photochemical treatment with amotosalen HCl and ultraviolet light: process used in the SPRINT trial

Alvaro Pineda, Jeffrey McCullough, Richard J. Benjamin, Ritchard Cable, Ronald G. Strauss, Edwin Burgstaler, Seth Porter, Lily Lin, Peyton Metzel, and Maureen G. Conlan for the SPRINT Study Group

BACKGROUND: A photochemical treatment (PCT) system has been developed to inactivate a broad spectrum of pathogens and white blood cells in platelet (PLT) products. The system comprises PLT additive solution (PAS III), amotosalen HCl, a compound adsorption device (CAD), a microprocessor-controlled ultraviolet A light source, and a commercially assembled system of interconnected plastic containers.

STUDY DESIGN AND METHODS: A clinical prototype of the PCT system was used in a large, randomized, controlled, double-blind, Phase III clinical trial (SPRINT) that compared the efficacy and safety of PCT apheresis PLTs to untreated apheresis PLTs. The ability of multiple users was assessed in a blood center setting to perform the PCT and meet target process specifications.

RESULTS: Each parameter was evaluated for 2237 to 2855 PCT PLT products. PCT requirements with respect to mean PLT dose, volume, and plasma content were met. Transfused PCT PLT products contained a mean of $3.6 \times 10^{11} \pm 0.7 \times 10^{11}$ PLTs. The clinical process, which included trial-specific samples, resulted in a mean PLT loss of $0.8 \times 10^{11} \pm 0.6 \times 10^{11}$ PLTs per product. CAD treatment effectively reduced the amotosalen concentration from a mean of 31.9 ± 5.3 μmol per L after illumination to a mean of 0.41 ± 0.56 μmol per L after CAD. In general, there was little variation between sites for any parameter.

CONCLUSIONS: The PCT process was successfully implemented by 12 blood centers in the United States to produce PCT PLTs used in a prospective, randomized trial where therapeutic efficacy of PCT PLTs was demonstrated. Process control was achieved under blood bank operating conditions.

The risk of transfusion-transmitted clinically significant blood-borne infection continues to have relevance despite improvements in donor health screening and laboratory testing for markers of disease transmission. Although a reduction of known transfusion-transmitted major viral infections has been achieved with improved donor health screening,[1] laboratory testing,[2] and recently, the introduction of nucleic acid testing (NAT),[3] bacterial contamination of platelets (PLTs) resulting in transfusion-associated sepsis continues to occur.[4,5] Although bacterial culture of PLT products has recently been introduced in the United States, experience in Europe suggests that bacterially contaminated products will continue to be transfused.[5,6] Additionally, there is no logistically feasible process for culture of poststorage pooled random donor PLTs. Furthermore, there is the risk of transmitting other pathogens such as emerging viral and protozoal agents for which effective testing lags behind their initial recognition as pathogens,[7] and even NAT does not eliminate the risk of disease transmission.[8]

ABBREVIATIONS: CAD = compound adsorption device; PCT = photochemical treatment.

From the Mayo Clinic, Rochester, Minnesota; the University of Minnesota, Minneapolis, Minnesota; Brigham and Women's Hospital, Boston, Massachusetts; the American Red Cross Blood Services, Farmington, Connecticut; the DeGowin Blood Center, University of Iowa, Iowa City, Iowa; Cerus Corp., Concord, California; and Transfusion Therapies, Baxter Healthcare Corp., Round Lake, Illinois.

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TRANSFUSION 2006;46:562-571.

Most approaches used to reduce the risk of transmitting blood-borne infections presently rely on techniques that apply only to known pathogens. Some screen donors nonspecifically and result in exclusion of otherwise suitable donors. More importantly, these procedures are not effective against unknown or emerging pathogen contamination and no strategies are in place to prevent transmission of infections from known but rare pathogens such as *Trypanosoma cruzi*,[9] *Borrelia burgdorferi*,[10] or malaria.[11] Accordingly, a different strategy has been developed, aimed at inactivating a broad spectrum of pathogens. This strategy has already been successfully applied to pooled plasma derivatives.[12] More recently, pathogen inactivation methods have been developed and applied to cellular blood components as well as plasma.[13,14]

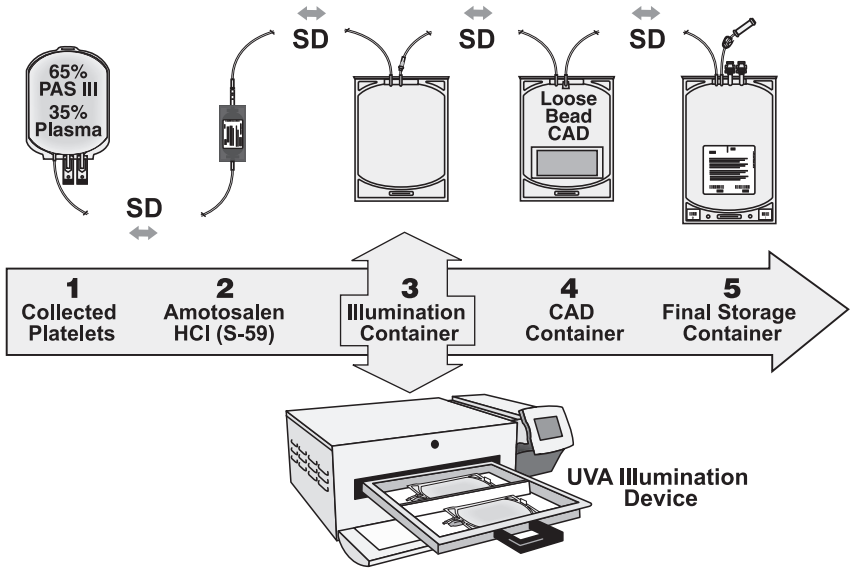


Fig. 1. Representation of the clinical prototype of the processing set and UVA illuminator used for PCT in the SPRINT trial. The device consists of a pouch containing 15 mL of 3 mmol per L amotosalen HCl, a microprocessor-controlled illumination device, a CAD, and a set of plastic containers connected by sterile connection. In the commercial version of the processing set, the plastic containers are preconnected, requiring only one sterile connection to the amotosalen pouch.

This article reports on a photochemical treatment (PCT) system for pathogen inactivation of apheresis PLT products. The system consists of a PLT additive solution (PAS III), amotosalen HCl, a compound adsorption device (CAD), a microprocessor-controlled ultraviolet A (UVA) light source, and a commercially assembled set of interconnected plastic containers, collectively known as the INTERCEPT Blood System for PLTs (Baxter Healthcare Corp., Round Lake, IL; and Cerus Corp., Concord, CA).[15-17] This system has been demonstrated to result in pathogen inactivation of a broad spectrum of pathogens, including viruses,[18] bacteria,[19] and protozoa,[20] as well as contaminating white blood cells.[21] A clinical prototype of this system (Fig. 1) was used to process apheresis PLTs for a randomized, controlled, double-blind, Phase III clinical trial (SPRINT) that compared the efficacy and safety of PCT PLTs, given for up to two 28-day treatment cycles, to conventional non–pathogen-inactivated control PLTs.[22] The implementation of the pathogen inactivation process used in this large multicenter study was informative about the reproducibility of the PCT process for the production of multiple PLT doses. The ability of blood centers to perform the process and meet target specifications are the subject of this report.

MATERIALS AND METHODS

Study design and study sites

Eligible patients were randomly assigned to receive PCT or conventional untreated (control) apheresis PLT transfusions for up to 28 days. Patients who continued to require or resumed PLT transfusion support were eligible to participate in a second cycle of PLT transfusion support maintaining the same treatment assignment as in the first cycle.[22] Study PLT products for transfusion were collected and processed locally at each of the participating study sites. Personnel at local blood center processing sites were thoroughly trained on the PCT process and had to pass a validation study (i.e., demonstrate competence) before study initiation. The validation study included steps to ensure that each study site could collect, photochemically treat, and store PCT products that would meet the study and regulatory guidelines for transfusible apheresis PLT products. Required criteria for PLT products before PCT included achieving a volume (255-325 mL), PLT yield (2.5×10^{11}-6.0×10^{11}), and plasma content (32%-47%; including the additional 15 mL of amotosalen, the plasma content requirement before illumination was 30%-45%). Required criteria for the PLT product following PCT before issue for transfusion included PLT dose; targeted transfused PLT dose was 3.7×10^{11} or greater. The study protocol was approved by all study sites' institutional review boards before initiating any protocol-related activities. Twelve study sites (listed in the Acknowledgments) participated in the study and manufactured PCT PLTs for transfusion to study patients.

Plateletpheresis

Each site used a standard technique to collect a single dose of apheresis PLTs for both PCT and control PLT prod-

ucts on a blood cell separator (Amicus, software version 2.41, Baxter Healthcare Corp.) with either single- or double-needle kits. PLT donors were screened with accepted AABB standards,[23] and PLT products were tested according to standard practice.[24] Target PLT dose at collection for control PLTs was per the sites' standard operating procedures. After collection, control PLTs were processed and stored in 100 percent autologous plasma at 22 ± 2°C according to standard site procedures.

A target yield of 4.1×10^{11} PLTs, or 10 percent above the standard single dose collection of the study site, was recommended for PLTs that were to undergo PCT. The actual target was determined during validation procedures at each site before initiating the study. The storage volume setting for PCT PLTs was reduced to 110 mL for each procedure to compensate for the subsequent addition of 180 mL of PAS III. One of the two PL-2410 storage containers that were part of the Amicus kit was heat-sealed and removed for PLT product storage post-PCT.

PLT products prepared for PCT

Addition of PAS III to PLT products. PAS III (Baxter Healthcare Corp.) was manually added to each PLT product immediately after collection. PAS III was supplied as 180 mL of sterile solution in a PL-2411 plastic container. The composition of PAS III was 4.42 g per L sodium acetate, 3.18 g per L trisodium citrate, 1.05 g per L monosodium phosphate dihydrate, 3.82 g per L disodium phosphate dihydrate, and 4.52 g per L sodium chloride in water. The osmolality of PAS III was 300 ± 10 mOsm per L and pH level was 7.2.

The PAS III container was sterile docked to the PLT storage container with a sterile tubing welder (Models SCD-312 and SCD-201, Terumo Medical Corp., Elkton, MD). The PAS III was drained into the PLTs that were in approximately 110 mL of plasma, the air pushed was back into the empty PAS III container, the PAS III container was heat sealed and removed, and the PLT product was mixed with the PAS III by gentle manual agitation. Final product volumes were determined by the formula

$$\text{Weight after PAS III addition} \div 1.01\ \text{g/mL}.$$

The acceptable range for the final PLT product volume was 255 to 325 mL. Percentage of PLT-rich plasma after PCT (i.e., with the addition of 15 mL of amotosalen) was determined by the formula

$$[(\text{Final product volume} - 180\ \text{mL PAS III}) \div \text{Final product volume} + 15] \times 100.$$

The acceptable range was 30 to 45 percent in plasma.

The standard procedure was to store the PCT PLT product in a single storage bag. Two sites had difficulty in maintaining acceptable pH after 5 days of storage. At those sites, an additional storage bag (a stand-alone 1-L PL-2410 container, Baxter Healthcare Corp.) was sterile docked after addition of PAS III, and the product was split equally between the two storage bags.

After addition of PAS III to the PLT product, PLTs had a static rest period of 2 hours at room temperature without agitation. After the static rest, the PLT products were placed in a standard PLT agitator, at 22 ± 2°C for a minimum of 6 hours before initiation of PCT. PCT was initiated within 24 hours of PLT collection.

PCT and amotosalen reduction. Amotosalen HCl (S-59) was supplied in pliable plastic (PL-2411) pouches with two tubing extensions (Baxter Corp.). The pouches were individually packaged in opaque plastic overwraps. The composition of amotosalen was 15.2 ± 1.5 mg amotosalen in 15 mL of sterile 0.9 percent sodium chloride. Addition of 15 mL of amotosalen to 285 mL of PLT product resulted in a final amotosalen concentration of 150 µmol per L. Because the volume of the PCT product could range from 255 to 325 mL, the amotosalen concentration could range from 120 to 180 µmol per L.

PCT was performed between 8 and 24 hours after collection. The amotosalen pouch was sterile docked to the PLT collection container with one of the tubing extensions. The other tubing extension was sterile docked to a 1-L PL-2410 plastic illumination container (Baxter Healthcare Corp.). The PLT product was then drained through the amotosalen pouch into the illumination container. During the trial, the procedure was changed to improve mixing consistency of the preillumination samples, so that once the product had completely drained, the containers were inverted, draining the amotosalen PLT product back into the original PLT storage container and then draining the product back into the illumination container to ensure that a representative preillumination sample could be collected. Air was expressed from the illumination container. A preillumination amotosalen sample was obtained from a tubing segment or by sterile-docked sample pouch. The amotosalen PLT product was weighed (and divided by 1.01 to convert grams to milliliters) to determine preillumination volume.

The UVA illuminator (Baxter Healthcare Corp.) was a microprocessor-controlled device that controlled the UVA illumination and had a built-in shaker to agitate the PLT product during illumination. The device was set to the "apheresis platelets" setting to deliver a 3.0 J per cm^2 UVA (320-400 nm) treatment. The device contained two illumination chambers: either one or two PLT products could be illuminated simultaneously. The instrument monitored the UVA dose delivered; when the appropriate dose was delivered, the device stopped the illumination. A digital screen displayed the illumination time, temperature, and illumination pass or fail for each chamber. Each UVA treatment took approximately 4 minutes. UVA illuminators were installed, tested, and maintained by the study sponsor (Baxter Healthcare Corp.) at each processing site.

Study monitors verified that standard operating procedures were in place, the equipment was validated, staff was trained, quality control measures and quality inventory monitoring were in place, and cGMP policies were being followed. The instrument performed self-checks each time it was turned on and a sponsor-trained study site technician performed periodic quality checks per sponsor guidelines.

After illumination, the PLT product was sterile docked to the inlet tubing extension on the CAD container. The purpose of the CAD was to reduce residual amotosalen and free amotosalen photoproducts in the PLT product. The CAD (Baxter Healthcare Corp.) consisted of 2.5 ± 0.1 g of resin beads (Dowex L-493) contained within a medical grade 35-µm polyester mesh pouch inside a 1-L PL-2410 plastic container. The PL-2410 plastic container had an additional polyester mesh filter over the outlet port to prevent beads or particles from leaving the container. The containers were inspected for loose beads or ruptured pouch before and during use. The CAD container had two tubing extensions, an outlet and an inlet with a sample pouch for postillumination sampling.

After gentle mixing, the PLT product was drained from the illumination container into the CAD container. A postillumination sample was collected in the sample pouch or from a tubing segment. The CAD container was then placed on a PLT agitator (22 ± 2°C) for 6 to 8 hours. After CAD treatment, the PLT product was transferred to the PL-2410 plastic PLT storage container saved from the collection process or to a prepackaged single PL-2410 plastic storage container. The CAD container was sterile connected to the final storage container and the PLTs were drained into the storage container. A post-CAD sample was obtained from a tubing segment. The product was weighed and converted to milliliters by dividing by 1.01 g per mL for the final product volume. At the two sites that encountered difficulty in maintaining pH at Day 5, an additional PL-2410 plastic storage container was sterile docked and the product was equally distributed between the two storage containers. The final products were labeled and placed on PLT shakers at 22 ± 2°C until issue.

Just before issue for transfusion, a sample of the PLT product was obtained for PLT count with a sample pouch. The percentage of PLT loss was determined from the difference between the PLT yield after collection and PLT dose at issue:

$$[(\text{PLT dose at issue} \div \text{PLT yield at collection}) \times 100].$$

Product volume loss could be monitored by comparing product volume measurements after PAS III addition, after amotosalen addition, and after CAD treatment. Measurements of sample volumes were imprecise, however, and residual volumes in containers and tubing due to multiple transfers were not accounted for, making the sources of loss difficult to establish precisely.

Storage and secondary processing of PLT products

Both PCT and control PLT products were stored under standard storage conditions at 22 ± 2°C at all sites. Standard PLT agitators were used. Some sites reduced the volume of the products, as clinically warranted, before issue with their site's standard procedures. Gamma irradiation of both PCT and control PLT products was performed at time of issue, as clinically indicated, with each study sites' standard procedures.

PLT product samples

Samples for amotosalen quantitation were collected before illumination, after illumination, and after CAD for all PCT PLT products whether or not they were transfused. Samples were not obtained from control PLT products. Samples were placed in the dark and frozen at 15°C within 2 hours. All samples were sent to central laboratories (PPD, Richmond, VA; and Cerus Corp.), and a random subset of approximately 48 percent of PCT PLT products produced was analyzed for amotosalen concentrations by high-performance liquid chromatography. Samples were approximately equally distributed across study sites (percentage of units produced) and across time.

Samples for PLT count and calculation of PLT yield were obtained from PCT-designated PLT products after collection, with a sampling pouch, and after PCT at time of issue for transfusion to determine PLT loss due to PCT. Samples for PLT count were obtained from control PLT products only at time of issue for transfusion. Each site used its standard automated counter for PLT counts. At five sites, different counters were used for preparation and issue, because different centers performed those functions. At issue for transfusion, a PLT sample was obtained with a sample pouch for potential bacterial culture from both PCT and control PLT products; samples were stored for possible culture at 1 to 6°C. Approximate estimated volume loss for all of the above-described samples was 8.5 mL for PCT and 4.0 mL for control PLTs.

Data management

Case report forms and source documents were maintained on PCT and control units. These forms gave details on the processing procedures. Research product inventories and final disposition records on PCT and control products were also maintained. Study monitors reviewed these documents on a regular basis, to the extent the blinding process would allow. Inventory and disposition records of the research items (amotosalen, illumination containers, CAD, etc.) were maintained and monitored.

Statistical analysis

Unless specified, all PLT units manufactured throughout both cycles of the study were included in the analyses,

regardless of whether or not the PLT product was transfused. Missing data were not estimated or carried forward in any analysis. Descriptive statistics (including mean, standard deviation, median, minimum, and maximum) and the percentage of products that fell outside of the target ranges were summarized, for all processing sites combined and for each individual site. Parameters analyzed included: PLT yield at time of collection, PLT dose at time of transfusion, PLT loss, PCT product volume, amotosalen concentration before and after illumination and after CAD treatment, and duration of CAD incubation. To test for treatment difference, two-way analysis of variance was used to test for continuous variables, with treatment group and processing site being included as the main effects. The two-sided Fisher's exact test was used to compare the treatment difference for categorical data.

RESULTS

PCT PLT product characteristics

To support the 318 patients transfused in the PCT arm in Cycle 1 and the 52 patients transfused in the PCT arm in Cycle 2 of the study, 4896 PCT PLT products were manufactured at 12 sites. Sixty-four percent of manufactured PCT PLT products were transfused. The primary reasons for PCT products not being transfused were absence of clinical need and outdating. 2715 PCT PLT products (2678 transfusion episodes) were transfused in Cycle 1 and 394 (390 transfusion episodes) were transfused in Cycle 2. Overall PCT PLT product characteristics are presented in Table 1 and by study site in Table 2. Mean pre-PCT PLT yield at the time of collection for transfused products was $4.4 \times 10^{11} \pm 0.7 \times 10^{11}$ PLTs (range, 2.0×10^{11}-7.2×10^{11} PLTs), within the target range of 2.5×10^{11}-6.0×10^{11} PLTs; 1.0 percent of products were outside the target range. The mean PLT dose at the time of issue was $3.6 \times 10^{11} \pm 0.7 \times 10^{11}$ PLTs (range, 1.2×10^{11}-7.1×10^{11} PLTs). Mean values by site ranged between 3.2×10^{11} and 3.9×10^{11}. There were no significant differences in mean PCT PLT dose transfused between sites (Table 2). Approximately 20 percent of all PCT PLT products produced (and 21% of all PCT PLT products transfused) contained fewer than 3.0×10^{11} PLTs. Mean PLT loss due to PCT, sampling, and storage was $0.8 \times 10^{11} \pm 0.6 \times 10^{11}$ PLTs (range, -1.4×10^{11} to 3.6×10^{11} PLTs). This represents a mean overall PLT loss of 18 percent, ranging from 12 to 27 percent by site.

Post-PAS III product volume was the product volume after PAS III was added but before addition of amotosalen. The mean volume was 294 ± 7.3 mL (range, 262-331 mL), within the target range of 255 to 325 mL; 0.1 percent of products were outside the target range. The mean plasma content, the percentage of plasma in the PLT product after addition of amotosalen, was 36.9 ± 1.5 percent (range, 29.6%-43.1%), within the target range of 30 to 45 percent; less than 0.1 percent of products were outside the target range.

Control PLT product characteristics

The 327 patients in the control arm in Cycle 1 received transfusions with 2092 control PLT products (2041 transfusion episodes), and the 39 patients in the control arm in Cycle 2 received transfusions with 250 control PLT products (245 transfusion episodes). Data for control PLT products were only collected for transfused products. The mean PLT dose at issue for all transfused control products in both cycles was $3.9 \times 10^{11} \pm 0.8 \times 10^{11}$ PLTs (n = 2237). There were no significant differences in mean control PLT dose transfused between sites; mean doses ranged from 3.5×10^{9} to 4.6×10^{9} per L PLTs. Twelve percent of all transfused control products contained fewer than 3.0×10^{11} PLTs. PLT yields at the time of collection were not obtained for control PLT products.

Amotosalen concentrations in PCT PLT products

Mean amotosalen concentrations before illumination, after illumination, and after CAD treatment are presented in Table 1 and by study site in Table 3. The mean preillu-

TABLE 1. PLT product processing and PCT results

Parameter	Target value (range)	Total number of units analyzed*	Mean result (range)	Number of units (%) out of range
PLT yield/product ($\times 10^{11}$) at time of collection	4.0 (2.5-6.0)	2850	4.4 ± 0.7 (2.0-7.2)	28 (1)
Volume of unit (mL) before addition of amotosalen	285 (255-325)	2855	294 ± 7.3 (262-331)	3 (0.1)
Plasma content (%) after addition of amotosalen	35 (30-45)	2854	36.9 ± 1.5 (29.6-43.1)	1 (<0.1)
Length of CAD treatment (hr)	6 (6-8)	2854	6.5 ± 0.6 (5.0-13.8)	25 (0.9)
Amotosalen before illumination (μmol/L)	150 (120-180)	2330	133.7 ± 13.1 (39.7-223.6)	247 (10.6)
Amotosalen after illumination (μmol/L)	31.5 (14.4-54)	2315	31.9 ± 5.3 (11.6-61.1)	4 (0.2)
Amotosalen after CAD (μM)	Mean ≤ 0.5	2237	0.41 ± 0.56 (0.17-15.03)	NA†

* Only transfused PCT units (n = 3109) were tested. Not all transfused units had samples available for assay.
† NA = not applicable.

TABLE 2. PCT product characteristics

	PLT yield at collect		PLT does at issue		PLT loss		PCT product volumes			
	Number of products	PLT count ($\times10^{11}$)	Number of products	PLT count ($\times10^{11}$)	Number of products	PLT count ($\times10^{11}$)	Number of products	After PAS III, before amotosalen addition (mL)	Number of products	Plasma content after amotosalen addition (%)
Target site		4.0 (2.5-6.0)		NA*		NA		285 (255-325)		35 (30-45)
1	240	4.2 ± 0.6	240	3.6 ± 0.5	240	0.6 ± 0.3	240	295 ± 4.9	240	37.0 ± 1.0
2	461	4.5 ± 0.8	456	3.9 ± 0.8	456	0.6 ± 0.4	461	296 ± 6.4	461	37.3 ± 1.3
3	748	4.4 ± 0.6	705	3.4 ± 0.6	705	1.1 ± 0.4	747	291 ± 5.8	747	36.2 ± 1.2
4	293	4.6 ± 0.6	289	3.6 ± 0.6	289	0.9 ± 0.4	293	299 ± 3.3	293	37.9 ± 0.6
5	100	4.2 ± 0.7	99	3.2 ± 0.7	99	1.0 ± 0.5	100	294 ± 5.3	100	36.8 ± 1.1
6	92	4.1 ± 1.0	91	3.7 ± 0.9	91	0.5 ± 0.8	92	300 ± 4.5	92	38.2 ± 0.9
7	261	4.4 ± 0.7	258	3.8 ± 0.8	258	0.6 ± 0.7	261	292 ± 4.4	261	36.6 ± 0.9
8	154	4.2 ± 0.7	154	3.3 ± 0.8	154	0.9 ± 0.6	154	287 ± 8.1	154	35.4 ± 1.7
9	53	4.4 ± 0.5	53	3.6 ± 0.5	53	0.7 ± 0.5	53	291 ± 6.0	52	36.3 ± 1.2
10	77	4.5 ± 0.6	78	3.3 ± 0.7	77	1.2 ± 0.6	78	291 ± 6.5	78	36.2 ± 1.4
11	286	4.1 ± 0.7	290	3.5 ± 0.8	285	0.6 ± 0.6	291	301 ± 7.5	291	38.3 ± 1.4
12	85	4.6 ± 0.8	85	3.7 ± 0.7	85	0.9 ± 0.6	85	285 ± 4.1	85	35.0 ± 0.8
Total	2850	4.4 ± 0.7	2798	3.6 ± 0.7	2792	0.8 ± 0.6	2855	294 ± 7.3	2854	36.9 ± 1.5

* NA = not applicable.

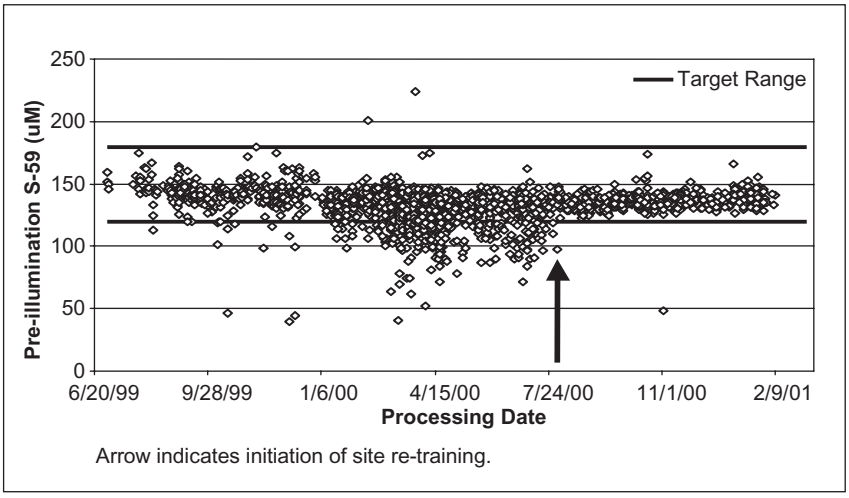
TABLE 3. Amotosalen concentrations in PCT PLT products

	Number of products	Before illumination (μmol/L)	Number of products	After illumination, before CAD (μmol/L)	Number of products	After CAD (μmol/L)
Target site		120-180		14.4-54.0		≤0.5
1	294	137.9 ± 9.1	291	32.3 ± 4.7	269	0.37 ± 0.09
2	331	136.0 ± 14.2	330	31.1 ± 6.4	328	0.33 ± 0.09
3	325	137.6 ± 11.1	327	32.8 ± 6.3	323	0.37 ± 0.24
4	245	130.0 ± 14.2	243	32.4 ± 4.3	233	0.41 ± 0.11
5	143	129.5 ± 17.1	143	31.3 ± 4.7	141	0.58 ± 0.41
6	141	134.8 ± 11.5	141	32.9 ± 4.0	140	0.37 ± 0.07
7	226	133.4 ± 8.3	224	30.8 ± 4.8	213	0.35 ± 0.08
8	279	122.8 ± 15.7	279	30.9 ± 4.5	274	0.48 ± 0.90
9	93	137.5 ± 7.0	93	32.1 ± 4.0	86	0.40 ± 0.31
10	74	138.2 ± 6.9	74	30.6 ± 5.7	73	0.33 ± 0.11
11	121	135.6 ± 8.6	113	33.9 ± 5.3	103	0.79 ± 1.98
12	58	137.1 ± 5.2	57	34.7 ± 4.6	54	0.39 ± 0.09
Total	2330	133.7 ± 13.1	2315	31.9 ± 5.3	2237	0.41 ± 0.56

mination amotosalen concentration was 133.7 ± 13.1 μmol per L (range, 39.7-223.6 μmol/L), within the target range of 120 to 180 μmol per L; 10.6 percent of values were outside the target range. It was determined retrospectively that most, if not all, of the out-of-range values were artifacts due to erroneous sampling procedures. After retraining and correction of the sampling procedures, the mean preillumination amotosalen concentration values were higher and less variable, 138.0 ± 4.8 μmol per L (Fig. 2A).

The mean postillumination amotosalen concentration was 31.9 ± 5.3 μmol per L (range, 11.6-61.1 μmol/L), within the target range of 14.4 to 54.0 μmol/L; 4 units (0.2%) had values outside the target range (Fig. 2B). Three were 11.6 μmol per L and one was 61.1 μmol per L. Neither of these values significantly affect pathogen inactivation. By the fundamentals of photochemistry, the expected postillumination amotosalen concentrations could only be obtained from expected preillumination amotosalen values. The consistency in the postillumination values throughout the entire trial period demonstrated the appropriateness of the photochemical reaction and further supported the finding that the lower than expected preillumination values were the result of erroneous sampling procedures.

The mean post-CAD amotosalen concentration was 0.41 ± 0.56 μmol per L (range, 0.17-15.03 μmol/L), within the target of ≤0.5 μmol per L. At two sites, the mean post-CAD amotosalen concentration was higher than the target range (0.58 ± 0.41 and 0.79 ± 1.98 μmol/L). The median for these two sites, however, was 0.50 and 0.39 μmol per L, respectively. The higher mean values were the result of a



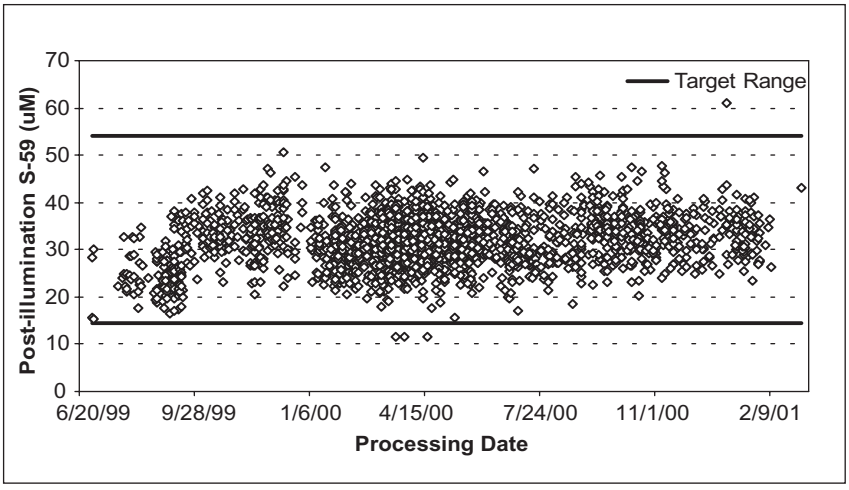


Fig. 2. (A) Amotosalen (S-59) concentrations before illumination as a function of processing date. The lower than expected preillumination amotosalen concentrations before retraining were artifacts due to erroneous sampling procedures. The arrow indicates the date for site retraining. After retraining, a new procedure for the addition and mixing of amotosalen with PLT concentrate was instituted to ensure representative sampling. Subsequently, values for the preillumination amotosalen concentrations were more consistent and values falling outside the target range were rare. (B) Amotosalen concentrations after illumination as a function of processing date. Only 4 of a total of 2315 samples assayed had postillumination amotosalen concentration slightly outside of the target range. These values were not likely to affect pathogen inactivation.

small number of outliers observed. Mean duration of CAD treatment was 6.5 ± 0.6 hours (range, 5.0-13.8 hr), within the target range of 6 to 8 hours; 0.9 percent of values were outside the target range.

Secondary processing

Volume reduction was performed, as clinically indicated, at the time of issue for transfusion. It was performed at eight study sites for 6.9 percent of transfused PCT PLT products and 8.4 percent of control products.

PLT storage duration

The mean PLT age at issue for transfusion for all transfused PLT products was 3.5 ± 1.2 days for PCT products (n = 3082) and 3.6 ± 1.2 days for control products (n = 2335; $p < 0.01$). Gamma irradiation was performed on 99.8 percent of PLT products transfused (n = 3103, 99.8 % PCT; and n = 2340, 99.9% control PLT products).

DISCUSSION

This report summarizes the experience of 12 US blood centers in performing the PCT process for apheresis PLTs with amotosalen and UVA light under blood bank conditions in the context of a clinical trial and with a clinical prototype of the device. PLT products produced were used to support thrombocytopenic patients in a Phase III trial of safety and efficacy. Critical parameters were measured to assess the ability of the sites to produce PLTs within the target ranges established for the process that had been demonstrated to result in pathogen inactivation while preserving PLT function.

Extensive laboratory studies have defined the critical characteristics of materials and processes needed to obtain successful pathogen inactivation through PCT of human PLT concentrates.[15-17] To obtain the desired level of pathogen inactivation and retain PLT functionality, the plasma content in the PLT suspension medium is diluted with PAS III to obtain an approximate plasma:PAS III volume ratio of 35 percent:65 percent after amotosalen addition. The active nucleic acid cross-linking agent, amotosalen, is added to obtain a final concentration range of 120 to 180 µmol per L. UV light is applied to the PLT-PAS III-amotosalen mixture with a 3.0 J per cm^2 treatment, such that the free amotosalen concentration is reduced, through photoconversion, to 12 to 30 percent of its original concentration. The residual amotosalen level after photoconversion is indicative that sufficient UVA energy has been applied to the system to effect pathogen inactivation. Toxicology

studies in animals[25-27] and clinical studies in humans[22,28] have provided no indication of any detrimental effects of amotosalen. Nonetheless, an amotosalen reduction device (CAD) has been incorporated into the PCT system to reduce levels of unreacted amotosalen and free photoproducts. Laboratory validation studies, performed by Cerus Corp., demonstrated that within 6 to 8 hours of CAD treatment, amotosalen concentrations were reduced to approximately 0.5 µmol per L.

Design of the PCT system, the manufacture of amotosalen formulations, and the target ranges for measurable endpoints were established for the clinical trial based on the above-mentioned laboratory studies coupled with the practical operation of PLT apheresis and the needs of clinical practice. Thus, the amotosalen containers were manufactured to contain 15 mL of a 3 mmol per L solution such that upon addition to 285 mL of PLT product in plasma-PAS III, a final concentration of 150 µmol per L would be obtained. The range of allowable PLT product volumes required for the process was based on the design requirement for a working amotosalen concentration range of 120 to 180 µmol per L (the validated range for pathogen inactivation) in the final PLT unit. At the time the study was performed, standard AABB practice required that 75 percent of the PLT components derived from apheresis procedures contain a dose of 3×10^{11} or more PLTs.[23] Because the PCT process results in PLT loss, the target for PLT collection yield for PCT PLTs was set to 4.1×10^{11} or 10 percent greater than the target collection yield for control PLTs.

The results demonstrated that the PCT PLT units prepared for the study satisfied the salient target ranges established for the process. No more than 1 percent of the PLT products analyzed had values outside of the target ranges for PLT yield at time of collection, volume of the unit before amotosalen addition, plasma content, duration of CAD treatment, and postillumination amotosalen concentration. In addition, the mean post-CAD amotosalen concentration was below the 0.5 µmol per L target. Except for one site with several outliers (Site 11), there was little variation between sites. The only measured parameter with a frequency of out-of-target values greater than 1 percent was the preillumination amotosalen concentration (10.6% out-of-target range). In contrast, postillumination amotosalen concentrations exhibited a low frequency (0.2%) of out-of-range values. By the fundamentals of photochemistry, photoconversion of amotosalen is dependent on the concentration of amotosalen and the applied dose of UVA light. At a constant UVA light dose, and controlled unit volume and plasma content, expected postillumination concentrations could only be obtained from expected preillumination values. Because of the discrepancy in the consistency of the results obtained with preillumination (Fig. 2A) and postillumination (Fig. 2B) amotosalen values during the trial, the adequacy of presample mixing following amotosalen addition was questioned. Nine of 12 sites were retrained to assure adequate mixing before collection of the preillumination sample. Following retraining (as shown by the arrow in Fig. 2A), there was improved consistency in preillumination amotosalen concentration values, with only rare values falling below the target range. Improvements obtained after retraining revealed that the initial clinical site method used for preillumination sample collection yielded samples that frequently were not representative of the actual PLT-amotosalen mixture in the illumination container. The postillumination data, as shown in Fig. 2B, indicate that amotosalen addition occurred appropriately. Despite erroneous sampling for the preillumination sample, complete mixing occurred during the illumination process and that photoconversion had occurred reliably.

The aggregate processing data pertaining to the preparation of PCT PLT products at 12 trial sites indicate that all sites were capable of performing the process established for pathogen inactivation in PLT products suspended in 35 percent plasma and 65 percent PAS III with 150 µmol per L amotosalen and a 3 J per cm^2 UVA treatment. The process capability evaluation of postillumination amotosalen concentration values indicates that 99.93 percent of the time the process was capable of producing amotosalen concentrations within the target range.

The mean PLT dose for all transfused PCT PLT products (3.6×10^{11}) was lower than the mean PLT dose for transfused control products (3.9×10^{11}, $p < 0.01$), and a greater proportion of transfused PCT PLTs (21%) than control PLTs (12%) failed to meet the FDA recommended dose[29] of 3.0×10^{11} or greater ($p < 0.01$), although the overall mean and the mean for each site met the minimum target dose at issue. There was little variation between sites. Mean PLT loss associated with the PCT process, and any secondary processing performed, was $0.8 \pm 0.6 \times 10^{11}$ PLTs. When expressed as a percentage of the PLT yield at collection, the mean losses at each site due to treatment, sampling, and storage ranged from 12 to 27 percent, with an overall mean loss of 18 percent. Some variation in PLT loss between sites was observed (range, 0.5×10^{11}-1.2×10^{11} PLTs). Causes of PLT loss fall into three main categories: 1) study-related (sample collection); 2) blood center process–related (PLT counting error, storage, and secondary processing); and 3) PCT-related (volume losses during transfers). PLT loss for control PLTs was not documented, so a comparison of PLT loss in PCT and control PLT products was not performed. PLT counting errors may be related to the use of different automated counters for measuring pre- and posttreatment yields. Five of the 12 sites used different counters for pre- and posttreatment samples. In all five sites the posttreatment counter was a Coulter counter that has been reported to give the lowest PLT counts in PLT products.[30,31] The highest PLT loss was

encountered in two of the sites with different counters. With the mean from each site, the five sites with different counters had a mean PLT loss of 0.9×10^{11} PLTs versus the seven sites with the same type of counter with a mean PLT loss of 0.8×10^{11} PLTs.

The PCT system used in this study was a clinical prototype that required numerous sterile connections of the individual components, manual addition of PAS III to the PLT product, a loose-bead CAD within a mesh pouch, and a prototype of the illuminator. Subsequent improvements that have been made to the system include automated addition of PAS III, an integrated set of disposables requiring a single sterile connection, an immobilized-bead (wafer) CAD for improved safety, and improvements to the illuminator increasing ease of use and documenting illumination. A commercial prototype of the improved system was employed in a small confirmatory trial of PCT apheresis PLTs in Europe.[32] Results of that study showed improved processing parameters and comparable safety and efficacy for PCT and control patients. A total of 204 PCT PLT products were prepared for that trial. Mean PLT loss was 16.4 percent, for a mean PLT loss of 0.65×10^{11} PLTs. The overall 16.4 percent PLT loss included loss due to clinical trial samples, including three amotosalen concentration samples, and PLT count and bacterial culture samples. Hervig and Aksnes[33] have reported PLT loss of 10.7 percent in validation studies of PCT buffy-coat PLTs ($n = 35$) where additional clinical trial samples were not required. In a nonclinical trial setting, it should be possible to maintain PLT loss due to PCT processing alone at less than 10 to 12 percent.

The results demonstrate that the performance of the PCT process with the clinical disposables during the conduct of the SPRINT Phase III clinical trial conformed to the target ranges for the key parameters of the PLT products that were established in laboratory studies. The PCT process was successfully conducted at 12 treatment sites under blood center conditions on nearly 4900 PLT products with the clinical prototype of the system.

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Therapeutic efficacy and safety of platelets treated with a photochemical process for pathogen inactivation: the SPRINT Trial

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We report a transfusion trial of platelets photochemically treated for pathogen inactivation using the synthetic psoralen amotosalen HCl. Patients with thrombocytopenia were randomly assigned to receive either photochemically treated (PCT) or conventional (control) platelets for up to 28 days. The primary end point was the proportion of patients with World Health Organization (WHO) grade 2 bleeding during the period of platelet support. A total of 645 patients (318 PCT and 327 control) were evaluated. The primary end point, the incidence of grade 2 bleeding (58.5% PCT versus 57.5% control), and the secondary end point, the incidence of grade 3 or 4 bleeding (4.1% PCT versus 6.1% control), were equivalent between the 2 groups ($P = .001$ by noninferiority). The mean 1-hour posttransfusion platelet corrected count increment (CCI) (11.1×10^3 PCT versus 16.0×10^3 control), average number of days to next platelet transfusion (1.9 PCT versus 2.4 control), and number of platelet transfusions (8.4 PCT versus 6.2 control) were different ($P < .001$). Transfusion reactions were fewer following PCT platelets (3.0% PCT versus 4.4% control; $P = .02$). The incidence of grade 2 bleeding was equivalent for PCT and conventional platelets, although posttransfusion platelet count increments and days to next transfusion were decreased for PCT compared with conventional platelets. (Blood. 2004;104: 1534-1541)

Introduction

More stringent donor selection and increased laboratory testing have been extremely effective in improving the safety of the US blood supply.[1-6] However, transmission of some infections still occurs because the present approach is limited to specific known pathogens, is not effective against bacterial contamination,[7-9] does not test for all pathogens,[10] fails to prevent transmission of cytomegalovirus (CMV) despite testing,[11] and tests for new pathogens, such as West Nile virus,[12] can only be implemented after the new agent is identified. With increasing globalization, previously localized transfusion-transmitted infections such as malaria, trypanosomiasis, or babesiosis are now becoming more widespread. Therefore, strategies have been developed to treat the blood components in a way that will inactivate viruses, bacteria, protozoa, and contaminating leukocytes but retain therapeutic efficacy of the components.[13-17]

Amotosalen HCl, formerly designated S-59, is a synthetic psoralen compound that intercalates into helical regions of DNA or RNA and on illumination with ultraviolet A (UVA) light reacts with pyrimidine bases to form internucleic and intranucleic acid strand cross-links. The photochemical treatment (PCT) inhibits replication of any DNA or RNA. This achieves reduction of a broad range of viruses, bacteria, and protozoa to levels below those likely to transmit infection (Table 1). Extensive toxicology, mutagenicity, carcinogenicity, phototoxicity, and pharmacologic studies established an adequate safety profile for PCT platelets.[24,25] In vitro platelet function of PCT platelets was preserved following up to 7 days of storage.[15,16] Recovery and survival of radiolabeled PCT platelets in healthy subjects were reduced compared with conventional untreated platelets but within acceptable therapeutic ranges.[26] PCT and conventional untreated platelets resulted in comparable correction of prolonged bleeding times in patients with thrombocytopenia.[27] A randomized, controlled, double-blind, parallel group phase 3 study in 103 patients with thrombocytopenia of PCT buffy coat platelets demonstrated that 1-hour platelet count increments

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Table 1. Inactivation of pathogens in platelet concentrates after photochemical treatment with amotosalen and UVA light

Pathogen	Log-reduction in organisms
Enveloped viruses	
HIV (cell-free)	> 6.2
HIV (cell-associated)	> 6.1
CMV	> 5.9
Hepatitis B virus	> 5.5
Hepatitis C virus	> 4.5
Duck hepatitis B virus	> 6.2
Bovine viral diarrhea virus	> 6.0
Human T-cell leukemia virus type I/II	4.7/5.1
West Nile virus	> 6.0
Nonenveloped viruses	
Blue tongue	6.1-6.4
Parvovirus B19*	4.0-4.9
Gram-negative bacteria	
Escherhia coli	> 6.4
Serratia marcescens	> 6.7
Klebsiella pneumoniae	> 5.6
Pseudomonas aeruginosa	4.5
Salmonella choleraesuis	> 6.2
Yersinia enterocolitica	> 5.9
Enterobacter cloacae	5.9
Gram-positive bacteria	
Staphylococcus aureus	6.6
Staphylococcus epidermidis	> 6.6
Streptococcus pyogenes	> 6.8
Listeria monocytogenes	> 6.3
Corynebacterium minutissimum	> 6.3
Bacillus cereus	> 6.0
Gram-positive anaerobic bacteria	
Lactobacillus species	> 6.9
Propionibacterium acnes	> 6.7
Clostridium perfringens	> 7.0
Bifidobacterium adolescentis	> 6.5
Protozoa	
Trypanosoma cruzi	> 5.3
Plasmodium falciparum	> 7.0
Leishmania mexicana	> 5.2

Data are summarized from Lin,[14] Lin et al,[15,16,18] Van Voorhis et al,[19,20] Dupuis et al,[21] Savoor et al,[22] and Sawyer et al.[23]

*Preliminary data; inactivation was performed in 35% B19-infected plasma and 65% PAS III (platelet additive solution III) in the absence of platelets. Studies included a 15- or 30-minute rest between addition of amotosalen and UVA treatment.

were not different for PCT and conventional buffy coat platelets.[28] We now report on a prospective, randomized, controlled, double-blind, parallel group phase 3 study to evaluate the efficacy, as determined by the prevention and treatment of significant bleeding, and safety of PCT apheresis platelets compared with conventional platelets.

Patients, materials, and methods

Patients

Patients were eligible for enrollment if they had thrombocytopenia requiring platelet transfusion support and were at least 6 years of age. Patients were excluded from study participation if they had any factors that could potentially interfere with assessment of the study end points. These exclusion criteria included positive lymphocytotoxic antibody (> 20% panel reactive antibody at screening) or history of clinical refractoriness, history of immune or thrombotic thrombocytopenic purpura or hemolytic uremic syndrome, diagnosis of acute promyelocytic leukemia, recent surgery or psoralen ultraviolet A (PUVA) therapy, interleukin-11 therapy, or participation in another study with pathogen-inactivated blood products. Patients who met all inclusion and exclusion criteria were randomly assigned in a 1:1 ratio to receive all of their platelet transfusions with either PCT or control platelet concentrates for up to 28 days or until transfusion independence (7 days without platelet transfusion) prior to day 28. On completion of the transfusion period, patients entered a 7-day surveillance period to monitor for additional adverse events. The study was approved by each site's institutional review board (IRB), and all patients gave informed consent to participate.

All individuals involved in clinical care and assessment of patients were blinded to study treatment assignment. These individuals included the principal investigator, clinical study coordinators and nurses making hemostatic assessments, clinicians and nurses caring for the patient, and the study sponsor. Blood bank and transfusion service personnel responsible for randomization, collection, processing, and issue of study platelets were not blinded.

End points

The primary efficacy end point was the proportion of patients with grade 2 bleeding, as assessed by using expanded World Health Organization (WHO) criteria (Table 2),[29] on any day during the period of platelet support. Additional secondary efficacy end points included the proportion of patients with WHO grade 3 or 4 bleeding; number of days of WHO grade 2 bleeding; 1- and 24-hour platelet count increments (CIs) and corrected count increments (CCIs); number of days to next platelet transfusion; number of platelet transfusions; incidence of platelet refractoriness; and number of red blood cell (RBC) transfusions. Safety end points included number of platelet transfusion reactions, development of antibody to potential amotosalen neoantigens, and overall safety.

Platelet collection and photochemical treatment

Both PCT and control study platelet transfusions were collected on the Amicus Separator (Baxter Healthcare, Round Lake, IL), which includes process leukoreduction, to attain a targeted average platelet transfusion dose of 3.7×10^{11}. PCT platelets were suspended in 30% to 45% plasma and 70% to 55% platelet additive solution (Intersol; Baxter Healthcare, Deerfield, IL), whereas control platelets were suspended in 100% plasma. Photochemical treatment[15] was performed at each study site within 24 hours of platelet collection by adding 150 μM amotosalen, mixing, and exposing the platelets to 3 J/cm^2 UVA light in an illumination device for 3 to 5 minutes with constant gentle agitation. Following illumination, platelets were transferred to a plastic container with a compound adsorption device (CAD) to reduce the concentration of residual amotosalen and free photoproducts. After adsorption for 6 to 8 hours, PCT platelets were transferred to another container and were stored for up to 5 days according to blood bank standards.[30] All donors and platelet products underwent required blood bank testing.[30] PCT and control platelet concentrates were issued for transfusion in identical plastic containers with identical labeling. Because PCT platelets were manufactured solely for the purpose of the trial, there were occasional inventory shortages that resulted in transfusion of non-PCT platelets to patients randomly assigned to the PCT group ("off-protocol" transfusion) or transfusion of low-dose PCT products that would not otherwise have been transfused to prevent an off-protocol transfusion. Control platelet transfusions not collected on the Amicus Separator were also off-protocol transfusions.

Transfusion strategies

Platelet transfusions were given according to each institution's guidelines either prophylactically to prevent bleeding or therapeutically to treat existing bleeding or prepare for an invasive procedure. The most common threshold for prophylactic transfusions was 10×10^9/L. Each institution's policies determined platelet ABO type, use of irradiation, volume reduction, and HLA matching or cross-matching for donor selection. Patients received conventional red cell products; more than 98% of red cell units were leukocyte reduced and 99% were gamma irradiated in both treatment groups.

Table 2. Expanded WHO bleeding scale used for the hemostatic primary end point

Organ system	Bleeding grade	
	1	2
Mucocutaneous		
Epistaxis	< 1 h in duration	> 1 h in duration
Oropharyngeal	< 1 h in duration	> 1 h in duration
Petechiae/purpura	Localized petechiae of skin or oral mucosa; purpura < 1-inch diameter	Purpura > 1-inch diameter; generalized petechiae or purpura
Gastrointestinal		
Melena	NA	Melanotic stool with positive occult blood
Rectal bleeding/ hematochezia	Occult blood in stool; no visible blood	Visible blood in stool
Hematemesis	NA	Occult or visible blood in vomit or gastric contents
Genitourinary		
Hematuria	< 1+ (slight, trace, small) blood in urine	≥ 2+ (moderate)
Vaginal bleeding, abnormal	Spotting; < 2 saturated pads/d	> 2 saturated pads/d
Bronchopulmonary	NA	Hemoptysis; blood-tinged sputum; bloody bronchopulmonary lavage
Musculoskeletal and soft tissue	NA	Spontaneous hematoma; any joint bleed
Body cavity (pleural, peritoneal, pericardial, retroperitoneal)	NA	RBCs on microscopic examination of any body fluid
Central nervous system	NA	Retinal bleeding without visual impairment
Invasive sites	NA	Any bleeding around a catheter, venipuncture site, or other invasive or surgical site

Grade 3 bleeding requires RBC transfusion; grade 3 body cavity bleeding is grossly bloody body fluid; grade 3 central nervous system (CNS) bleeding is bleeding on computed tomography or magnetic resonance imaging scan without clinical consequence. Grade 4 bleeding is associated with hemodynamic instability (hypotension; > 30 mm Hg decrease in systolic or diastolic blood pressure) or fatal bleeding; grade 4 musculoskeletal bleeding is associated with a permanent debilitating joint change; grade 4 CNS bleeding is CNS bleeding with neurologic symptoms and signs, or retinal bleeding with visual impairment (field deficit). Expanded scale is based on WHO bleeding scale from Miller et al.[29] NA indicates not applicable.

Hemostatic assessments and laboratory evaluation

Hemostatic assessments of 8 potential bleeding sites were performed by trained observers blinded to the treatment assignment. At each assessment, each of the 8 potential bleeding sites was assigned a WHO bleeding grade (Table 2) ranging from 0 (no bleeding) to 4 (life-threatening bleeding). The first hemostatic assessment encompassed the 12 hours preceding the first study platelet transfusion. Subsequent hemostatic assessments were performed daily and for 3 days following the last study platelet transfusion. The overall bleeding grade for each assessment was the highest grade observed for any of the 8 sites assessed. If grade 2 bleeding was observed at any potential bleeding site on any assessment during the transfusion period, the patient met the primary end point. For example, a patient with a 2-inch ecchymosis on day 3 of the transfusion period but no other bleeding events during the transfusion period would have been classified as having experienced grade 2 bleeding and would have met the primary end point of the trial.

The daily platelet count obtained for routine care was used for the study pretransfusion platelet count. The 1-hour and 24-hour posttransfusion platelet counts were obtained 10 minutes to 4 hours and 10 to 24 hours, respectively, following each platelet transfusion. Lymphocytotoxic antibody (LCA) testing to determine study eligibility was performed locally, and patients whose serum reacted with more than 20% of panel cells (PRA) were excluded. Plasma samples for LCA and antibody to amotosalen neoantigen testing were drawn weekly; baseline and end-of-study samples were analyzed at central laboratories for LCA by using standard techniques[31] and for antibodies to potential amotosalen neoantigens by using a validated enzyme-linked immunosorbent assay (ELISA; Cerus, Concord, CA).[28] If the patient became platelet refractory, all samples from the patient were analyzed for LCA, antibody to amotosalen neoantigens, and platelet-specific alloantibodies[32,33] in central laboratories. The CCI, a measure of the response to platelet transfusion that takes into account patient body size as well as transfused platelet dose, was calculated as the difference between the platelet count after transfusion and the platelet count before transfusion, multiplied by the body surface area (in meters squared) and divided by the number of platelets transfused ($\times 10^{-11}$). A patient was considered clinically refractory if the 1-hour CCI was less than 5×10^3 following each of 2 consecutive platelet transfusions. Immunologic refractoriness was defined as clinical refractoriness (2 consecutive CCIs $< 5 \times 10^3$) in the presence of any of the following: LCA (> 20% PRA), platelet-specific alloantibodies, and/or antibody to amotosalen neoantigens.

Adverse events and transfusion reactions

Adverse events were collected from initiation of first study transfusion through the end of the 7-day surveillance period. Adverse event and transfusion reaction severity was assigned on the basis of the most severe symptom or sign present. Reactions to study platelet transfusions were assessed for the 6 hours following each transfusion.

Randomization and statistical methods

A sample size of 300 patients per group was estimated before the start of the study to provide more than 90% power to reject the null hypothesis of inferiority with respect to grade 2 bleeding at a significance level of 0.05. All patients who received at least one study platelet transfusion were included in the analyses. Randomization was stratified by study site.

The study was designed as a noninferiority trial. Differences between treatment groups for the primary end point (the proportion of patients with grade 2 bleeding) and one secondary end point (the proportion of patients with grade 3 or 4 bleeding) were analyzed using one-sided tests of noninferiority with prespecified noninferiority margins of 12.5% and 7%, respectively. All other secondary end points were analyzed for differences between treatment groups. For the primary end point, the test statistic was $(P_T - P_R - 0.125)/(\mathrm{Var}[P_T - P_R])^{1/2}$, where P_T is the observed proportion of patients with grade 2 bleeding in the PCT group, P_R is the observed proportion of patients with grade 2 bleeding in the control group, and $\mathrm{Var}(P_T - P_R)$ is the variance estimated by the maximum likelihood estimate.[34] The one-sided 95% confidence interval for the treatment difference in the proportion used the same estimated variance.

Analysis of variance with treatment and study site in the model was used for continuous variables. Fisher exact test was used for comparison of adverse events. Time to grade 2 bleeding was compared by using the log-rank test. Longitudinal regression analysis was used to adjust platelet count increment and transfusion interval for platelet dose.[35,36] Except for

the tests of noninferiority, all other statistical tests were 2-sided with a significance level of 0.05.

Results

Of the 671 patients randomly assigned, 645 received at least one study platelet transfusion (318 PCT; 327 control) and composed the intention-to-treat (ITT) population. The 26 patients not included in the ITT analyses did not require platelet transfusions before recovery from thrombocytopenia. There were no differences between the groups for sex, age, ethnic origin, diagnosis, or receipt of stem cell transplant (Table 3) or in baseline hematology, chemistry, and coagulation laboratory studies (data not shown).

The proportion of patients completing the transfusion period (89%) and the surveillance period (81%), the mean duration of platelet support (11.8 days PCT versus 10.6 days control), and the proportion of patients achieving and maintaining platelet transfusion independence prior to day 28 (66% PCT versus 70% control) were not different between treatment groups (Table 4).

The primary end point of the trial, the proportion of patients with grade 2 bleeding, was equivalent for the PCT group and control group, both overall, as well as for any of the 8 potential bleeding sites (Table 5). Grade 2 bleeding occurred during the transfusion period in 58.5% of patients in the PCT group compared with 57.5% of patients in the control group. The time to onset of grade 2 bleeding after beginning the study was not significantly different between PCT and control patients, either for the ITT population (Figure 1A, $P = .78$) or for those patients without grade 2 bleeding at study entry (Figure 1B, $P = .91$). Grade 2 bleeding occurred on a mean of 3.2 days in the PCT group as compared with 2.5 days in the control group ($P = .02$) and on a median of 1 day for each group.

The maximum grade of bleeding at any potential bleeding site was grade 2 for most patients. Grade 3 or 4 bleeding occurred in only 4.1% of patients in the PCT group and 6.1% in the control group. There were no statistically significant differences between the groups in grade 3 or 4 bleeding overall or for any of the 8 potential bleeding sites. The most common site of grade 3 or 4 bleeding was the neurologic system (3 of 318, 0.9% PCT versus 6 of 327, 1.8% control).

The 645 patients in this study received a total of 4719 platelet transfusions (2678 PCT; 2041 control) (Table 6). Most units of platelets transfused (91.5% PCT and 95.2% control) were prepared according to study methods ("on-protocol transfusions"). During the study transfusion period, exclusively on-protocol transfusions were received by 68% of patients in the PCT group and 85% of patients in the control group ($P < .01$). Of patients who received any off-protocol transfusions, most

Table 3. Patient characteristics

	PCT; n = 318	Control; n = 327
Sex		
% male	54	51
Age, y		
Mean	47	46
Range	7-85	6-75
% younger than 16 y	2	5
Ethnic origin, %		
White	91	91
African American	3	3
Hispanic	3	3
Other	3	3
Stem cell transplantation, %		
Bone marrow	20	22
Peripheral blood	54	55
Cord blood	2	3
Total	76	80
Source of stem cells, %		
Autologous	64	65
Allogeneic	36	35
Underlying diagnosis, %		
Acute leukemia	29	28
Chronic leukemia	11	11
Lymphoma	24	29
Myelodysplasia	3	2
Plasma cell dyscrasia	20	18
Nonhematopoietic solid tumor	8	8
Other	5	4
WHO grade 2 bleeding at study entry, %	15.7	16.5

All characteristics had $P > .05$, thus showing no differences.

Table 4. Patient participation

	Treatment group		
	PCT, n (%) n = 318	Control, n (%) n = 327	*P*
Completed transfusion period	280 (88)	294 (90)	.53
Reason for not completing transfusion period			
Patient decided to withdraw	8 (2.5)	4 (1.2)	.26
Physician withdrew patient	10 (3.1)	4 (1.2)	.11
Adverse event(s)	0 (0)	0 (0)	—
Lost to follow-up	1 (< 1)	1 (< 1)	—
Death	10 (3.1)	15 (4.6)	.42
Other	9 (2.8)	9 (2.8)	—
Total	38 (11.9)	33 (10.1)	.44
Mean days of platelet support	11.8	10.6	.08
Achieved and maintained platelet independence prior to day 28	210 (66)	230 (70)	.27
Completed surveillance period	248 (78)	273 (84)	.09

— indicates not applicable.

Table 5. Proportion of patients with grade 2 or higher bleeding

	PCT, n (%) n = 318	Control, n (%) n = 327	*P**
Any grade 2 bleeding	186 (58.5)	188 (57.5)	<.01†
Grade 2 bleeding by bleeding site			
Genitourinary	104 (32.7)	103 (31.5)	0.80
Mucocutaneous	82 (25.8)	65 (19.9)	0.08
Invasive sites	69 (21.7)	65 (19.9)	0.63
Gastrointestinal	60 (18.9)	63 (19.3)	0.92
Respiratory	35 (11.0)	28 (8.6)	0.35
Musculoskeletal	15 (4.7)	18 (5.5)	0.72
Body cavity	0 (0.0)	1 (0.3)	1.00
Neurologic	0 (0.0)	0 (0.0)	—
Any grade 3 or 4 bleeding	13 (4.1)	20 (6.1)	<.01‡

— indicates not applicable.

*Fisher exact test was used to calculate the *P* value for each of the 8 potential bleeding sites.

†The *P* value for the overall proportion of patients with grade 2 bleeding was < .01, based on a noninferiority test with a noninferiority margin of 0.125 (one-sided 95% confidence interval of difference: −1, 0.07). By using this method, a *P* value of < .05 indicates that PCT was not inferior to control.

‡The *P* value for any grade 3 or 4 bleeding was < .01, based on a noninferiority test with a noninferiority margin of .07 (one-sided 95% confidence interval of difference: −1, 0.013). By using this method, a *P* value of < .05 indicates that PCT was not inferior to control.

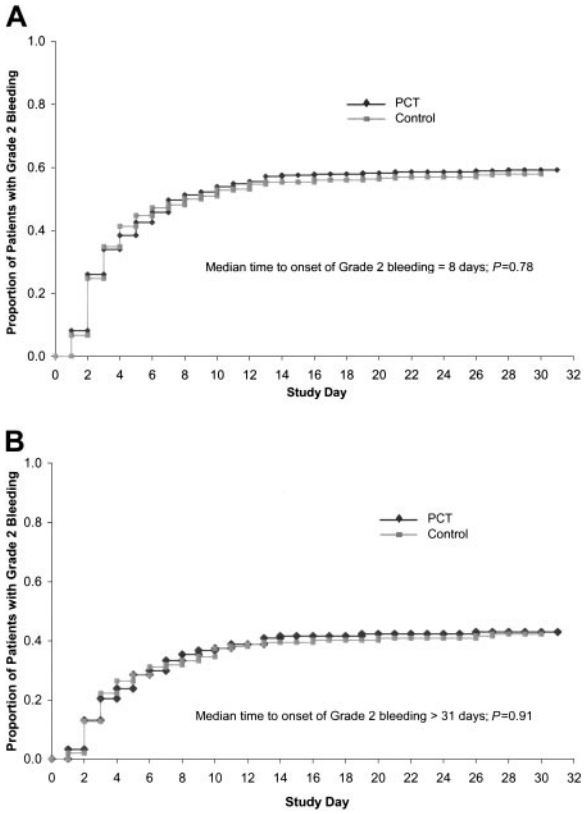

Figure 1. Time to onset of grade 2 bleeding. (A) Time to onset of grade 2 bleeding in ITT population (n = 645). Median time to onset of grade 2 bleeding was 8 days, log rank $P = .78$. (B) Time to onset of grade 2 bleeding in patients with no (grade 0) bleeding at baseline (n = 541). Median time to onset of bleeding more than 31 days, log-rank test $P = .91$.

(53% PCT and 59% control) received only one. The proportion of platelet transfusions that were HLA matched (1.5%), crossmatch compatible (0.2%), volume reduced (7.5%), or irradiated (99.8%) were comparable between the 2 groups. Slightly more PCT transfusions were ABO-matched (with patient pretransplantation blood type) than control transfusions (78.5% versus 75.4%, $P = .01$). Mean platelet storage duration prior to transfusion was 3.4 days for PCT as compared with 3.6 days for control platelets ($P < .01$).

Table 6. Platelet and RBC transfusions during the study

	PCT, n = 318	Control, n = 327	*P*
Platelet transfusions			
Total number	2678	2041	—
Mean number per patient	8.4	6.2	< .001
Mean number per day of platelet support*	0.74	0.65	< .001
Interval between transfusions, d	1.9	2.4	< .001
Platelet dose, $\times 10^{11}$			
Mean average dose	3.7	4.0	< .001
Percentage of platelet doses less than 3.0 $\times 10^{11}$	20	12	< .01
Mean total dose over entire transfusion period	29.4	24.1	.01
Duration of platelet storage, d	3.4	3.6	< .05
RBC transfusions			
Mean number per patient	4.8	4.3	.13
Mean number per day of platelet support*	0.31	0.30	.53

— indicates not applicable.

*Days of platelet support is defined as number of days from the first to the last study platelet transfusion.

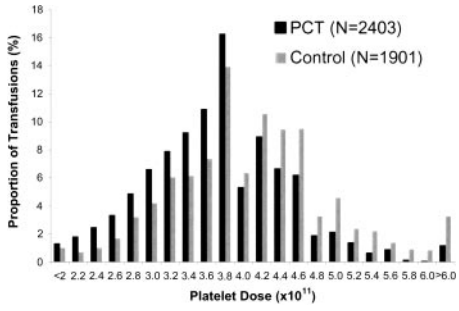

Figure 2. Distribution of transfused platelet doses. A greater proportion of doses were less than 3.0×10^{11} in the PCT group compared with the control group ($P < .01$).

Patients in the PCT group received more platelet transfusions overall (8.4 PCT versus 6.2 control; $P < .001$; Table 6) and more platelet transfusions per day of platelet support (0.74 PCT versus 0.65 control; $P < .001$). These differences may be partially explained by the lower mean dose of platelets per transfusion in the PCT group compared with the control group (3.7×10^{11} PCT versus 4.0×10^{11} control; $P < .001$) and the greater proportion of PCT platelet doses that contained less than 3.0×10^{11} platelets (20% PCT versus 12% control; $P < .01$; Figure 2). Sixty percent of patients in the PCT group received at least one platelet dose less than 3.0×10^{11} compared with 36% of patients in the control group ($P < .01$). However, by using longitudinal linear regression to adjust for platelet dose, when equal doses of PCT and control platelets were given, the 1-hour posttransfusion platelet count was estimated to be 10.4×10^9/L lower for PCT than for control platelets ($P < .001$), and the time to the next transfusion was shorter by 0.4 days for PCT than for control platelets ($P < .001$). Other factors that can affect platelet recovery,[37] such as splenomegaly, fever, sepsis, and amphotericin use were comparable between treatment groups. There was no difference between the groups in the mean number of red blood cell transfusions or the mean number of red blood cell transfusions per day of platelet support (Table 6).

Most transfusions were given for prophylaxis (93.5% PCT versus 90.1% control; $P < .01$); the others were considered to be therapeutic either to treat active bleeding or to prepare for an invasive procedure. Although mean pretransfusion platelet counts were similar for patients in both groups, the mean 1-hour posttransfusion platelet count was lower in the PCT group (36.5×10^9/L PCT versus 49.5×10^9/L control; $P < .001$), as were the mean 1-hour and 24-hour CI and CCI (Table 7).

Platelet clinical refractoriness occurred in 21.4% of PCT as compared with 7.0% of control patients ($P < .001$; Table 8).

Table 7. Mean platelet responses following platelet transfusions

	PCT; n = 318	Control; n = 327
Before transfusion		
Platelet count, $\times 10^9$/L	15.1	15.2
1 h after transfusion		
Platelet count, $\times 10^9$/L	36.5*	49.5
Count increment, $\times 10^9$/L	21.4*	34.1
Corrected count increment, $\times 10^3$	11.1*	16.0
24 h after transfusion		
Platelet count, $\times 10^9$/L	27.9*	36.1
Count increment, $\times 10^9$/L	13.2*	21.5
Corrected count increment, $\times 10^3$	6.7*	10.1

*$P < .001$ compared with control.

Table 8. Refractoriness to platelet transfusions

	PCT	Control	*P*
ITT population, n	318	327	—
Any refractory episode, %*	21.4	7.0	< .001
Any transfusion with CCI less than 5×10, %	27.4	12.7	< .001
Refractory subset of patients, n	68	23	—
Single episode of refractoriness, %	57	65	.63
Refractory to end of study, %	6	9	.64
Immunologic refractoriness†			
LCA and/or platelet alloantibody, %	22	44	.06
Lymphocytotoxic antibodies, %	15	39	.02
Platelet specific alloantibodies, %	12	10	1.00
Antibody to amotosalen neoantigens	0	0	—

— indicates not applicable.

*Episode is 2 consecutive platelet transfusions with 1-hour CCI $< 5 \times 10^3$.

†Immunologic refractoriness, defined as the presence of LCA (> 20% PRA), platelet alloantibodies, and/or antibody to potential amotosalen neoantigens in the presence of 2 consecutive 1-hour CCI less than 5×10^3.

One-hour CCIs less than 5×10^3 were observed with 27.4% of all PCT transfusions and 12.7% of all control platelet transfusions ($P < .001$) and 33.4% of PCT as compared with 12.3% of control platelet transfusions with platelet doses less than 3.0×10^{11} ($P < .001$). Most refractory episodes were transient, involving only a single episode of 2 consecutive 1-hour CCIs less than 5×10^3 (57% PCT versus 65% control). Only 6% of refractory patients in the PCT group and 9% of refractory patients in the control group remained refractory through study completion. Alloimmunization to HLA, platelet-specific antigens, or amotosalen neoantigens as the basis for platelet refractoriness occurred 4.7% of PCT patients as compared with 3.1% of control patients in the ITT population ($P = .31$) and in 22% of PCT patients as compared with 44% of control patients in the refractory subset of patients ($P = .06$). Among refractory patients, LCA was more common in the control group (39%) compared with the PCT group (15%; $P = .02$). Platelet alloantibodies occurred with similar frequency among refractory patients (12% PCT compared with 10% control; $P = 1.00$).

Although there were fewer transfusion reactions following transfusion of PCT platelet units (3.0% PCT versus 4.4% control transfusions; $P = .02$), there was no difference in the proportion of patients who experienced a reaction (16.0% PCT versus 19.3% control; $P = .30$). Reactions were primarily fever, chills, urticaria, or rash. Almost all patients experienced one or more adverse events (Table 9). Adverse events were coded to 898 MedDRA Preferred Terms.[39] The most common adverse events (reported in > 30% of patients in either treatment group), such as hematuria, diarrhea, hypokalemia, rigors, petechiae, epistaxis, fecal occult blood, contusion (bruising), and dermatitis, were consistent with those expected for the patient population enrolled in this study. As expected, with the large number of statistical comparisons performed, there were statistically significant differences between treatment groups for some types of adverse events, but these differences were not considered to be clinically relevant and will be reported in detail separately. Grade 3 or 4 adverse events, those considered by the investigator to be probably or possibly related to study platelet transfusion, and adverse events meeting US Food and Drug Administration (FDA) criteria for serious were not different between the PCT and control groups (Table 9). There were 28 deaths (3.5% PCT versus 5.2% control) during the study, mostly because of infectious or respiratory complications.

Discussion

Despite improvements in the safety of the US blood supply, the public wants transfusion risks to be as close to zero as possible, and political and health policy decisions reflect this goal. As new transfusion-transmitted infectious agents are identified, new tests for these agents may be implemented, but this approach will always have limitations. Inactivation of a broad spectrum of viruses, bacteria, and protozoa in blood products is a promising new strategy to improve blood safety.

The low prevalence of pathogens in blood components precludes a study of the prevention of transfusion-transmitted infection by PCT platelets. Therefore, we studied the effect of PCT on platelet transfusion hemostatic effectiveness rather than transfusion transmissible infections. The trial, the largest one of its kind, evaluated platelet hemostasis as the primary end point while also evaluating the quality and safety of PCT platelets. PCT and control platelets were hemostatically comparable overall and, for each of the 8 potential bleeding sites evaluated, established that PCT platelets were clinically effective. Patients who received PCT platelets had lower platelet count increments following transfusion, received more platelet transfusions, and had a shorter interval between transfusions compared with patients who received conventional apheresis platelets. The lower platelet count increment is partly explained by the lower mean platelet dose in the PCT group and the disproportionate number of transfusions containing doses less than 3.0×10^{11} (Figure 2). The greater proportion of low-dose platelets transfused to the PCT group may have resulted in the greater number of platelet transfusions in the PCT group.[41] Reasons for lower platelet doses in the PCT group primarily reflected clinical trial requirements. These reasons included a clinical prototype of the device was used with a nonintegrated processing set and a prototype CAD; processing loss for PCT platelets was acknowledged; samples taken for amotosalen assay came from PCT but not control; to avoid off-protocol transfusions, low doses of PCT platelets were transfused when a higher dose unit was not available; and because PCT units were produced solely for the purpose of the clinical trial, control units were more readily available, resulting in higher platelet doses. During routine use, it is expected that doses of PCT platelets will be comparable to control platelets. Following completion of this trial, an integrated PCT processing set with an improved CAD was developed and evaluated in a small supplemental trial in Europe. That trial in 43 patients demonstrated no increase in the number of platelet transfusions

Table 9. Adverse events during the study

	PCT, %; n = 318	Control, %; n = 327	*P*
Any adverse event*	99.7	98.2	.12
Grade III or IV adverse event	78.9	78.6	.92
Serious adverse event†	27.0	24.8	.53
Treatment-related adverse event‡	26.4	29.4	.43
Death§	3.5	5.2	.34

*Adverse events were graded I to IV using the National Cancer Institute Common Toxicity Criteria (NCI-CTC)[38] and coded to Preferred Term by using Medical Directory for Regulatory Affairs (MedDRA).[39]

†Serious adverse events were defined by using Food and Drug Administration (FDA) criteria.[40]

‡Treatment-related adverse events were reported as possibly or probably related to the study platelet transfusions by the blinded investigator at each site.

§One patient in each group died of hemorrhage; both deaths involved pulmonary alveolar hemorrhage thought to result from toxicity of the myeloablative preparative regimen.

required to manage patients transfused with PCT platelets for up to 28 days[42]; those results will require confirmation in a larger study.

Another factor accounting for the reduced platelet responses with PCT platelets was a decrease in platelet viability; ie, at equal platelet doses, there was a significant reduction in both platelet increment and days to next transfusion comparing PCT with control platelets. An effect of the PCT process on platelet viability was suggested in previous studies in healthy research subjects and patients.[26,27] As a consequence of the lower platelet count increments in the PCT group, clinical platelet refractoriness occurred more frequently in patients receiving PCT platelets; however, it tended to be transient, persisting to the end of the study in only 6% of PCT and 9% of control refractory patients. Alloimmune platelet refractoriness and the need for HLA-matched platelets were uncommon and were similar in both groups. Among platelet refractory patients, the incidence of LCA was lower in the PCT group, but platelet-specific alloantibodies were similar. Despite the lower platelet count increments, the shorter intervals between platelet transfusions, and the resultant greater number of PCT platelets transfused, the PCT platelets were hemostatically equivalent to the control platelets; therefore, differences in these secondary end points appear to have little effect on product efficacy and patient benefit.

Overall, no unusual toxicities or adverse events were associated with the transfusion of PCT platelets. A companion safety analysis will be reported separately. Although the proportion of patients who experienced a transfusion reaction was similar in the 2 groups, fewer PCT platelet transfusions were associated with a reaction. This could be due to leukocyte inactivation, resulting in less cytokine production during storage of PCT platelets or the reduced volume of plasma in the PCT units.[43] Other adverse events, including hemorrhagic adverse events and death, were not different between the 2 groups of patients.

Photochemically treated platelets were clinically effective in maintaining hemostasis, appear to be associated with an acceptable safety profile, and offer the potential to further reduce the infectious risks of blood transfusion, including those associated with emerging transfusion-transmitted infections.

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Clinical safety of platelets photochemically treated with amotosalen HCl and ultraviolet A light for pathogen inactivation: the SPRINT trial

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BACKGROUND: A photochemical treatment (PCT) method utilizing a novel psoralen, amotosalen HCl, with ultraviolet A illumination has been developed to inactivate viruses, bacteria, protozoa, and white blood cells in platelet (PLT) concentrates. A randomized, controlled, double-blind, Phase III trial (SPRINT) evaluated hemostatic efficacy and safety of PCT apheresis PLTs compared to untreated conventional (control) apheresis PLTs in 645 thrombocytopenic oncology patients requiring PLT transfusion support. Hemostatic equivalency was demonstrated. The proportion of patients with Grade 2 bleeding was not inferior for PCT PLTs.

STUDY DESIGN AND METHODS: To further assess the safety of PCT PLTs, the adverse event (AE) profile of PCT PLTs transfused in the SPRINT trial is reported. Safety assessments included transfusion reactions, AEs, and deaths in patients treated with PCT or control PLTs in the SPRINT trial.

RESULTS: A total of 4719 study PLT transfusions were given (2678 PCT and 2041 control). Transfusion reactions were significantly fewer following transfusion of PCT than control PLTs (3.0% vs. 4.1%; $p = 0.02$). Overall AEs (99.7% PCT vs. 98.2% control), Grade 3 or 4 AEs (79% PCT vs. 79% control), thrombotic AEs (3.8% PCT vs. 3.7% control), and deaths (3.5% PCT vs. 5.2% control) were comparable between treatment groups. Minor hemorrhagic AEs (petechiae [39% PCT vs. 29% control; $p < 0.01$] and fecal occult blood [33% PCT vs. 25% control; $p = 0.03$]) and skin rashes (56% PCT vs. 42% control; $p < 0.001$) were significantly more frequent in the PCT group.

CONCLUSION: The overall safety profile of PCT PLTs was comparable to untreated PLTs.

Extensive donor screening and testing have significantly improved the safety of the blood supply; however, transfusion-transmitted infections continue to be reported.[1-3] A new modality for prevention of transfusion-transmitted infection is pathogen inactivation of the blood component before transfusion. One such method involves treatment of platelets (PLTs) or plasma with a novel synthetic psoralen, amotosalen HCl (S-59), with ultraviolet A (UVA) illumination.[4-7] Amotosalen intercalates into helical regions of DNA and RNA and is crosslinked to pyrimidine bases upon activation with UVA light (320-400 nm), thereby preventing replication of pathogens and white blood cells (WBCs).

The efficacy of PLTs treated with the photochemical process has been demonstrated both in vitro and in vivo.[7,8]

ABBREVIATIONS: AE(s) = adverse event(s); ALI = acute lung injury; ARDS = acute respiratory distress syndrome; ITT = intent-to-treat; NCI-CTC = National Cancer Institute Common Toxicity Criteria; NOS = not otherwise specified; PCT(s) = photochemical treatment(s); SOC(s) = system organ class(es); TBI = total body irradiation.

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Clinical trials in thrombocytopenic patients demonstrated hemostatic and therapeutic efficacy of photochemically treated (PCT) PLTs comparable to untreated PLTs.[9-12] Van Rhenen and colleagues[10] reported comparable PLT count increments and a comparable safety profile for PCT and untreated pooled buffy-coat PLT concentrates in 103 thrombocytopenic oncology patients treated in the euroSPRITE trial. McCullough and colleagues[12] reported that hemostatic efficacy of PCT apheresis PLTs was equivalent to untreated PLTs in 645 patients transfused in the SPRINT trial.

The preclinical safety program evaluated amotosalen and PCT PLTs and plasma with an extensive series of toxicology studies consistent with development of a new pharmaceutical. Studies included acute toxicity, repeated-dose toxicity, reproductive toxicity, phototoxicity, genotoxicity (in vitro and in vivo), carcinogenicity, and safety pharmacology,[13-16] as well as neoantigenicity.[7] No specific organ toxicity, reproductive toxicity, carcinogenicity, or neoantigenicity was observed. Dermal phototoxicity was observed only at 1000 times the clinical exposure with intense UVA illumination. No toxicologically relevant effects were identified in any of these studies that included adult, juvenile, and neonatal animals.

To further assess the safety of PCT PLTs in the clinical setting for patients receiving complex therapies, we analyzed the clinical safety of PCT apheresis PLTs in a population of patients receiving repeated PLT transfusions.

MATERIALS AND METHODS

Study design

The SPRINT trial was a randomized, controlled, double-blind Phase III trial conducted at 12 US study sites to evaluate the safety and hemostatic efficacy of PCT apheresis PLTs in comparison to untreated conventional (control) apheresis PLTs in thrombocytopenic patients requiring multiple PLT transfusions.[12] Eligible patients were randomized in equal numbers to receive all PLT transfusions with either PCT or control PLTs for up to 28 days (transfusion period). Adverse events (AEs) were recorded by study staff, blinded to treatment assignment, during the transfusion period and for an additional 7 days after the last study PLT transfusion (surveillance period). All patients who received at least one study PLT transfusion were included in the intent-to-treat (ITT) analysis of efficacy and safety.

Overall patient safety during the conduct of the trial was overseen by an independent Data and Safety Monitoring Board composed of three experts in transfusion medicine and a statistician. Safety endpoints included PLT transfusion reactions and overall safety (AEs and deaths). The Data and Safety Monitoring Board reviewed all serious AEs and all safety data in aggregate.

Study patients

Patients were eligible for enrollment if they had thrombocytopenia requiring PLT transfusion support and were at least 6 years of age. Patients were excluded from study participation if they had any factors that could potentially interfere with assessment of the study endpoints: positive lymphocytotoxic antibody (>20% panel-reactive antibody at screening) or history of clinical refractoriness to PLTs; history of immune or thrombotic thrombocytopenic purpura or hemolytic uremic syndrome; diagnosis of acute promyelocytic leukemia; recent surgery or psoralen UVA therapy; interleukin-11 therapy; or participation in another study with pathogen-inactivated blood products. The PLT transfusion threshold was selected at physician discretion.

All study patients gave informed consent in conformance with institutional review board policy. The study was conducted according to the tenets of the Declaration of Helsinki and its subsequent revisions.

Study PLT transfusions

PCT and control PLT concentrates were prepared as previously described.[12] Briefly, PLT concentrates were collected on a cell separator (Amicus, Baxter Healthcare Corporation, Round Lake, IL) that included process leukoreduction. PCT PLTs were resuspended in 35 percent donor plasma and 65 percent PAS-III (Baxter Healthcare); control PLTs were resuspended in 100 percent donor plasma. PCT PLTs were PCT with a clinical prototype of a pathogen inactivation system for PLTs (INTERCEPT Blood System, Baxter Healthcare) with 150 μmol per L amotosalen HCl and a 3 J per cm^2 UVA light treatment and then treated for 6 to 8 hour with a loose-bead compound adsorption device to reduce residual amotosalen and unbound amotosalen photoproducts. Both PCT and control PLTs were stored for up to 5 days under standard conditions. To maintain the study blind, PCT and control PLT concentrates were issued for transfusion in identical plastic containers with identical labeling. PLT concentrates were transfused as clinically indicated by the patient's physician.

Study assessments

PLT transfusion reactions, AEs, and deaths. All AEs reported from the start of the first study PLT transfusion through completion of the surveillance period were recorded by study site staff, blinded to patient treatment assignment, and graded in severity by the study site staff on a scale of 1 to 4 with the National Cancer Institute Common Toxicity Criteria (NCI-CTC).[17] Reported AEs were coded by sponsor personnel, also blinded to patient treatment assignment, with the Medical Dictionary for Regulatory Activities (MedDRA), Version 3.3,[18] and sum-

marized by MedDRA Preferred Term (single medical concept) and primary (and when appropriate, also by nonprimary) system organ class (SOC). The SOC provides the broadest level for data categorization in MedDRA (e.g., summarization by anatomical system, body organ, etiology, or purpose). Hemorrhagic and thrombotic AEs were summarized with the MedDRA special search categories across SOCs for these events. AEs were summarized by severity: less severe AEs were summarized as Grade 1 or 2 (low-grade) and more severe AEs were summarized as Grade 3 or 4 (high-grade). The study site also assessed whether an AE met the regulatory requirements for reporting as serious (e.g., life-threatening, resulted in hospitalization, etc.)[19] and classified the relationship of the AE to the study PLT transfusion (probable, possible, or no relationship). Patients were assessed for the occurrence of an acute transfusion reaction during and for up to 6 hours after each study PLT transfusion; reactions were graded with NCI-CTC criteria. Details of all deaths that occurred during the study were reported.

All clinical data were monitored by the sponsor (or their representatives). With the exception of the reanalysis of clinically serious pulmonary AEs described below, however, there was no adjudication of the validity of the AE reporting by an independent panel.

Evaluation of high-grade pulmonary AEs. Because higher frequencies were observed in the PCT group compared to the control group for two high-grade pulmonary AE preferred terms (pneumonitis not otherwise specified [NOS] and acute respiratory distress syndrome [ARDS]), additional analyses of pulmonary AEs were performed. Pulmonary AEs were summarized by MedDRA preferred term and by primary, as well as nonprimary, SOC. All patients who died on study (n = 28; 11 PCT and 17 control) were retrospectively assessed for the presence or absence of ARDS by an independent expert in pulmonary medicine with the objective American-European ARDS Consensus Conference criteria[20] for diagnosis: radiographic presence of bilateral pulmonary infiltrates; PaO_2/FiO_2 ratio of ≤200; and absence of cardiogenic pulmonary edema.

A second, independent reanalysis of a larger subset of patients (n = 148; 78 PCT and 70 control) with potentially clinically serious pulmonary AEs was performed also. Patients for inclusion in this reanalysis were selected, based on AEs reported in the original trial, by an independent blinded expert physicians panel (two pulmonologists and one stem cell transplant hematologist), none of whom participated in the first independent expert review. Data required for assessment of pulmonary outcomes were identified by the panel and collected from original patient medical records by a contract research organization, also blinded to treatment assignment. The panel determined the incidence of clinically serious pulmonary outcomes, overall and by specific respiratory anatomical and disease categories, including acute lung injury (ALI) and ARDS. ARDS was defined as above with the American-European ARDS Consensus Conference criteria, and ALI was defined with the same criteria as for ARDS but with a higher PaO_2/FiO_2 ratio of ≤300 to encompass all patients with any degree of ALI.[20]

Randomization and statistical analysis

Randomization was stratified by study site. Fisher's exact test was used to test for significance of treatment differences for categorical data. Analysis-of-variance with treatment and study site in the model was used for continuous variables. Two-sided *p*-values, with a 0.05 significance level were used.

RESULTS

Patient characteristics and baseline data

The ITT population was composed of 645 patients, 318 randomized to PCT and 327 randomized to control PLTs. There were no differences between treatment groups for mean age, sex, diagnosis, antineoplastic therapy, or baseline characteristics[12] (Table 1). Twenty-three patients

TABLE 1. Demographic and baseline data for ITT population

Patient characteristics and baseline data	Treatment group* PCT (n = 318)	Control (n = 327)	P value
Mean age (years)	47 ± 14	46 ± 15	0.31
Male sex	172 (54)	168 (51)	0.53
Mean body surface area (m^2)	1.95 ± 0.29	1.92 ± 0.31	0.18
PLT transfusion threshold			0.28†
10×10^9/L	194 (61)	196 (60)	
20×10^9/L	88 (28)	80 (25)	
Other	36 (11)	50 (15)	
Diagnosis			0.61†
Acute leukemia	91 (29)	91(28)	
Chronic leukemia	35 (11)	34 (10)	
Lymphoma	76 (24)	96 (29)	
Plasma cell dyscrasia	63 (20)	58 (18)	
Other	53 (17)	48 (15)	
Antineoplastic therapy			0.35†
Stem cell transplant	240 (76)	262 (80)	
Peripheral blood	173 (54)	179 (55)	
Bone marrow	61 (19)	72 (22)	
Cord blood	6 (1.9)	11 (3.4)	
Chemotherapy	66 (21)	59 (18)	
Donor source of stem cells			0.85†
Autologous	154 (64)	171 (65)	
Allogeneic	86 (36)	91 (35)	

* Data are reported as number (%).
† Fisher's exact test comparing the distribution of patients between the treatment groups.

(3.6%) were in the pediatric age category (age, 6-16 years) and 59 patients (9.1%) were in the geriatric age category (age, ≥65 years). There were no clinically significant differences between treatment groups in baseline chemistry, hematology, or coagulation tests or baseline illness (data not shown).

PLT transfusions

The duration of PLT support was comparable between treatment groups: 11.8 days for PCT versus 10.6 days for control ($p = 0.08$). The ITT population received a total of 4719 study PLT transfusions, 2678 in the PCT group and 2041 in the control group. The mean PLT dose was lower in the PCT than in the control group: 3.7×10^{11} versus 4.0×10^{11} PLTs, respectively ($p < 0.001$). The PCT group received more PLT transfusions during the transfusion period than the control group: 8.4 versus 6.2, respectively ($p < 0.01$). This difference in mean number of PLT transfusions may, in part, be related to the lower dose of PCT PLTs transfused.[21]

PLT transfusion reactions

Acute PLT transfusion reactions, during and for up to 6 hours after transfusion, occurred with 3.0 percent of PCT versus 4.4 percent of control transfusions ($p = 0.02$; Table 2). This difference was mainly related to a higher incidence of Grade 1 transfusion reactions in the control versus the PCT group. The incidence of urticaria was significantly less for PCT transfusions (0.4%) than for control transfusions (1.5%, $p < 0.01$). No cases of transfusion-related acute lung injury (TRALI) were reported; however, this was not a prespecified endpoint of this trial.

AEs

Almost all patients experienced at least one AE during the trial. The incidence of serious and treatment-related AEs was comparable between treatment groups (Table 3). Most events were high-grade (Grade 3 or 4), as might be expected in the population studied. The incidence of AEs was generally similar for the pediatric and geriatric populations between treatment groups and similar to the overall population (data not shown).

The most common AEs reported are shown in Table 4 (summarized by MedDRA SOC and preferred term). Among 26 SOCs, there were no differences between treatment groups with two exceptions. A difference between treatment groups for the skin and subcutaneous tissue disorders SOC was due to a higher incidence of Grade 1 or 2 AEs in the PCT group, mostly minor hemorrhagic events (petechiae, contusion, ecchymosis) and low-grade nonspecific skin rashes (dermatitis NOS). A difference between treatment groups for the infections and infestations SOC was due to a greater frequency of low-grade skin rashes (cellulitis, folliculitis, herpes simplex, herpes zoster, skin candida NOS, skin infection NOS, skin papilloma, and tinea pedis), classified as infectious, in the PCT group (11% PCT vs. 5.8% control; $p = 0.02$). The incidences

TABLE 2. Acute PLT transfusion reactions occurring within 6 hours of PLT transfusion

Characteristic	Treatment group* PCT	Control	P value
Patients	n = 318	n = 327	
Any reaction	51 (16)	63 (19)	0.30
Mean number of reactions			
All patients	0.4 ± 1.27	0.4 ± 1.01	0.82
Among patients with reaction	2.5 ± 2.18	2.0 ± 1.44	0.12
Overall grade (NCI CTC)			
Grade 1	20 (6)	37 (11)	0.03
Grade 2	19 (6)	20 (6)	1.00
Grade 3	11 (3)	5 (2)	0.13
Grade 4	1 (0.3)	1 (0.3)	1.00
Transfusions	n = 2678	n = 2041	
Any reaction	81 (3.0)	89 (4.4)	0.02
Overall grade (NCI CTC)			
Grade 1	27 (1.0)	52 (2.6)	<0.001
Grade 2	30 (1.1)	26 (1.3)	0.69
Grade 3	21 (0.8)	10 (0.5)	0.28
Grade 4	3 (0.1)	1 (<0.1)	0.64
Type of reaction			
Rigors	41 (1.5)	36 (1.8)	0.56
Fever	30 (1.1)	17 (0.8)	0.38
Urticaria	12 (0.4)	32 (1.5)	<0.01
Skin rash	8 (0.3)	11 (0.5)	0.25
Bronchospasm	6 (0.2)	2 (0.1)	0.48

* Data are reported as number (%).

TABLE 3. AEs in the ITT population

Characteristic	Treatment group* PCT (n = 318)	Control (n = 327)	P value
Any AE	317 (99.7)	321 (98.2)	0.12
NCI-CTC grade			
Grade 1	16 (5)	17 (5)	1.00
Grade 2	50 (16)	47 (14)	0.66
Grade 3	142 (45)	130 (40)	0.23
Grade 4	109 (34)	127 (39)	0.25
Serious AE	86 (27)	81 (25)	0.53
Treatment-related AE†	84 (26)	96 (29)	0.43
Deaths	11 (3.5)	17 (5.2)	0.34

* Data are reported as number (%).
† Includes events assessed by the investigator as possibly or probably related to study PLT transfusion.

of Grade 3 or 4 infections, and of bacteremia and sepsis, were not different between groups.

Among the 898 preferred terms that were compared, there were significant differences for 11 terms (Table 5), all with a higher incidence in the PCT group. Only three of these were reported with an incidence of greater than 5 percent: petechiae, fecal occult blood positive, and dermatitis NOS.

Grade 3 or 4 AEs. Overall, 79 percent of patients had one or more Grade 3 or 4 events; however, only four preferred terms were reported in more than 10 percent of patients: anemia NOS, febrile neutropenia, thrombocytopenia, and hyperglycemia NOS. There were no differences between treatment groups for Grade 3 or 4 AEs overall, nor were there differences for any SOC (Table 6). Significant differences were observed for four preferred terms, all reported with low frequency but in a greater proportion of patients in the PCT group: hypocalcemia, syncope, pneumonitis NOS, and ARDS. Further investigation revealed incorrect reporting of severity grade by study sites for a number of the AEs of hypocalcemia and syncope. When grade was corrected, no significant differences were observed for hypocalcemia and syncope. Pneumonitis NOS and ARDS were investigated further.

Respiratory, thoracic, and mediastinal disorders AEs. There were no differences in the incidence of AEs (all grades combined; Table 4) or Grade 3 or 4 AEs (Table 6) classified in the respiratory, thoracic, and mediastinal disorders SOC. Significant differences, however, were observed for three preferred terms: pleuritic pain, pneumonitis NOS, and ARDS, all occurring with low frequency and more commonly in the PCT group (Table 5). There were no differences in respiratory AEs analyzed by primary or nonprimary SOC for all grades combined or

TABLE 4. AEs reported in at least 20 percent of patients in either treatment group*

SOC Preferred term	Treatment group† PCT (n = 318)	 Control (n = 327)	 P value
Any AE	317 (99.7)	321 (98.2)	0.12
Blood and lymphatic system disorders	197 (62)	198 (61)	0.75
Anemia NOS	89 (28)	94 (29)	0.86
Febrile neutropenia	72 (23)	65 (20)	0.44
Transfusion reaction	58 (18)	70 (21)	0.33
Cardiac disorders	107 (34)	89 (27)	0.09
Eye disorders	80 (25)	73 (22)	0.41
Gastrointestinal disorders	268 (84)	271 (83)	0.67
Diarrhea NOS	123 (39)	103 (32)	0.06
Vomiting NOS	84 (26)	68 (21)	0.10
General disorders and administration site conditions	257 (81)	266 (81)	0.92
Rigors	111 (35)	101 (31)	0.31
Pyrexia	84 (26)	88 (27)	0.93
Fatigue	77 (24)	65 (20)	0.22
Edema lower limb	64 (20)	53 (16)	0.22
Hepatobiliary disorders	83 (26)	89 (27)	0.79
Infections and infestations	133 (42)	110 (34)	0.04
Investigations	242 (76)	231 (71)	0.13
Fecal occult blood positive	106 (33)	83 (25)	0.03
Blood magnesium decreased	88 (28)	87 (27)	0.79
Metabolism and nutrition disorders	208 (65)	222 (68)	0.51
Hypokalemia	114 (36)	110 (34)	0.56
Hyperglycemia NOS	74 (23)	87 (27)	0.36
Hypocalcemia	69 (22)	57 (17)	0.20
Musculoskeletal, connective tissue, and bone disorders	102 (32)	101 (31)	0.80
Nervous system disorders	193 (61)	175 (54)	0.07
Headache NOS	73 (23)	69 (21)	0.64
Insomnia NEC	72 (23)	59 (18)	0.17
Psychiatric disorders	109 (34)	106 (32)	0.62
Renal and urinary disorders	158 (50)	157 (48)	0.69
Hematuria	118 (37)	135 (41)	0.30
Respiratory, thoracic, and mediastinal disorders	223 (70)	210 (64)	0.11
Epistaxis	106 (33)	103 (32)	0.67
Cough	69 (22)	60 (18)	0.33
Skin and subcutaneous tissue disorders	261 (82)	243 (74)	0.02
Petechiae	124 (39)	94 (29)	<0.01
Contusion	102 (32)	82 (25)	0.06
Dermatitis NOS	99 (31)	67 (21)	<0.01
Surgical and medical procedures	79 (25)	64 (20)	0.13
Vascular disorders	118 (37)	111 (34)	0.41

* Data summarized by MedDRA SOC and preferred term.
† Data are reported as number (%).

TABLE 5. Summary of AEs by MedDRA preferred term significantly different between treatment groups

Preferred term	Treatment group* PCT (n = 318)	Control (n = 327)	P value†
All grades combined			
Petechiae	124 (39)	94 (29)	<0.01
Fecal occult blood positive	106 (33)	83 (25)	0.03
Dermatitis NOS	99 (31)	67 (21)	<0.01
Rash maculopapular	15 (4.7)	6 (1.8)	0.05
Pleuritic pain	12 (3.8)	3 (0.9)	0.03
Muscle cramps	10 (3.1)	2 (0.6)	0.02
Pneumonitis NOS	7 (2.2)	0 (0)	<0.01
Mucosal hemorrhage NOS	5 (1.6)	0 (0)	0.03
ARDS	5 (1.6)	0 (0)	0.03
Grade 3 or 4			
Hypocalcemia	21 (6.6)	8 (2.4)	0.01
Syncope	6 (1.9)	0 (0)	0.01
Pneumonitis NOS	5 (1.6)	0 (0)	0.03
ARDS	5 (1.6)	0 (0)	0.03

* Data are reported as number (%).
† Based on Fisher's exact test.

Grade 3 or 4 events (Table 7). Specifically, there were no differences in the incidence of any Grade 3 or 4 respiratory infection or Grade 3 or 4 pneumonia NOS. Additional investigation revealed that there was inconsistent use of the terms pneumonitis and ARDS for AE reporting among study sites. Review of the patients who died on study (n = 28: 11 PCT and 17 control) by an independent pulmonologist with objective criteria demonstrated that a comparable number of these selected patients in both groups met the criteria for ARDS (73% PCT vs. 71% control; p = 1.00). None of the reported cases of ARDS appeared to represent TRALI.

TABLE 6. Grade 3 or 4 AEs reported in at least 5 percent of patients in either treatment group*

SOC Preferred term	Treatment group† PCT (n = 318)	Control (n = 327)	P value
Any AE	251 (79)	257 (79)	0.92
Blood and lymphatic system disorders	149 (47)	149 (46)	0.75
Anemia NOS	65 (20)	68 (21)	0.92
Febrile neutropenia	69 (22)	61 (19)	0.38
Thrombocytopenia	48 (15)	49 (15)	1.00
Cardiac disorders	30 (9.4)	21 (6.4)	0.19
Gastrointestinal disorders	105 (33)	94 (29)	0.27
Diarrhea NOS	30 (9.4)	23 (7.0)	0.32
Oral mucosal petechiae	21 (6.6)	18 (5.5)	0.62
General disorders and administration site conditions	76 (24)	69 (21)	0.40
Pyrexia	30 (9.4)	21 (6.4)	0.19
Fatigue	18 (5.7)	16 (4.9)	0.73
Mucosal inflammation NOS	16 (5.0)	27 (8.3)	0.12
Hepatobiliary disorders	29 (9.1)	31 (9.5)	0.89
Infections and infestations	77 (24)	77 (24)	0.85
Investigations	83 (26)	74 (23)	0.31
Blood bilirubin increased	18 (5.7)	18 (5.5)	1.00
Blood culture positive	22 (6.9)	21 (6.4)	0.88
Metabolism and nutrition disorders	96 (30)	100 (31)	0.93
Hypokalemia	27 (8.5)	28 (8.6)	1.00
Hyperglycemia NOS	34 (11)	34 (10)	1.00
Hypocalcemia	21 (6.6)	8 (2.4)	0.01
Anorexia	28 (8.8)	30 (9.2)	0.89
Hypophosphatemia	16 (5.0)	17 (5.2)	1.00
Nervous system disorders	28 (8.8)	31 (9.5)	0.79
Psychiatric disorders	24 (7.5)	27 (8.3)	0.77
Renal and urinary disorders	30 (9.4)	27 (8.3)	0.68
Respiratory, thoracic, and mediastinal disorders	63 (20)	63 (19)	0.92
Dyspnea NOS	21 (6.6)	18 (5.5)	0.62
Hypoxia	25 (7.9)	21 (6.4)	0.54
Skin and subcutaneous tissue disorders	37 (12)	33 (10)	0.61
Vascular disorders	42 (13)	46 (14)	0.82
Hypotension NOS	16 (5.0)	14 (4.3)	0.71
Hypertension NOS	20 (6.3)	25 (7.6)	0.54

* Data summarized by MedDRA SOC and preferred term.
† Data are reported as number (%).

TABLE 7. Grade 3 or 4 respiratory AEs reported in more than 1 percent of patients in either treatment group*

SOC Preferred term	Treatment group† PCT (n = 318)	 Control (n = 327)	 P value
Any respiratory AE‡	74 (23)	68 (21)	0.51
Respiratory, thoracic, and mediastinal disorders SOC	63 (20)	63 (19)	0.92
ARDS	5 (1.6)	0 (0)	0.03
Dyspnea NOS	21 (6.6)	18 (5.5)	0.62
Epistaxis	10 (3.1)	4 (1.2)	0.11
Hypoxia	25 (7.9)	21 (6.4)	0.54
Lung infiltration NOS	13 (4.1)	7 (2.1)	0.18
Pharyngeal hemorrhage	6 (1.9)	5 (1.5)	0.77
Pleural effusion	6 (1.9)	9 (2.8)	0.60
Pneumonitis NOS	5 (1.6)	0 (0)	0.03
Pulmonary alveolar hemorrhage	7 (2.2)	7 (2.1)	1.00
Respiratory distress	4 (1.3)	2 (0.6)	0.44
Respiratory failure	5 (1.6)	4 (1.2)	0.75
Tachypnea	5 (1.6)	2 (0.6)	0.28
Cardiac disorders SOC	4 (1.3)	8 (2.5)	0.38
Pulmonary edema	4 (1.3)	6 (1.8)	0.75
Gastrointestinal disorders SOC	9 (2.8)	4 (1.2)	0.17
Sore throat NOS	8 (2.5)	4 (1.2)	0.26
Infections and infestations SOC	23 (7.2)	14 (4.3)	0.13
Lung infection NOS	5 (1.6)	1 (0.3)	0.12
Pneumonia NOS	7 (2.2)	7 (2.1)	1.00

* Data summarized by MedDRA SOC and preferred term.
† Data are reported as number (%).
‡ Includes any event whose primary or nonprimary SOC is respiratory, thoracic, and mediastinal disorders

TABLE 8. Clinically serious pulmonary AEs assessed by independent expert panel reanalysis

Characteristic	Treatment group* PCT (n = 318)	 Control (n = 327)	 P value
Any clinically serious pulmonary AE	55 (17)	45 (14)	0.23
Tracheal bronchial tree	4 (1.3)	2 (0.6)	0.45
Lung parenchyma	55 (17)	45 (14)	0.23
Pneumonitis	39 (12)	32 (10)	0.38
ALI	19 (6.0)	16 (4.9)	0.60
ARDS	12 (3.8)	5 (1.5)	0.09
ALI	7 (2.2)	11 (3.4)	0.48
Pleural space	18 (5.7)	20 (6.1)	0.87

* Data are reported as number (%).

A second larger reanalysis of retrospectively collected pulmonary data for 148 patients (78 PCT and 70 control) with potentially clinically serious pulmonary AEs, as selected and reviewed by the independent expert physicians panel blinded to treatment assignment and with specific diagnostic criteria for ALI, revealed no differences between treatment groups for these events overall or by respiratory anatomical or disease category. Specifically, there were no significant differences observed between treatment groups for pneumonitis, ALI (including both ALI and ARDS), ARDS only, or ALI only (Table 8). Furthermore, the incidence of death among patients with clinically serious pulmonary AEs (Table 9), including the incidence for patients with ARDS, was similar between treatment groups. The incidence of death among patients with ALI was significantly higher for the control group.

Hemorrhagic and thrombotic AEs. Clinical bleeding assessments were conducted on a daily basis with the WHO scale for each patient as part of the primary endpoint determination—the incidence of Grade 2 bleeding.[12] In addition, hemorrhagic AEs were reported as part of the safety assessments with the NCI-CTC scale. Hemorrhagic AEs were reported at least once during the transfusion and surveillance periods in 90 percent of patients in the PCT group versus 85 percent in the control group (Table 10). Most of these events were minor. No significant differences were observed for any SOC with the exception of the skin and subcutaneous tissue disorders SOC; these were mostly Grade 1 or 2 events. The most common hemorrhagic AEs, reported for at least 10 percent of patients in either treatment group, are shown in Table 10. Among the 58 types of hemorrhagic AEs reported, differences in incidence rates were observed for only 3 preferred terms: petechiae, fecal occult blood positive, and mucosal hemorrhage NOS. Although there were differences in the incidence of fecal occult blood positive, there were no differences between the two groups in overt gastrointestinal hemorrhage (36% PCT vs. 36% control; $p = 1.00$) or oral mucosal hemorrhage (28% PCT vs. 24% control; $p = 0.25$). There were no differences in the incidence of mucocutaneous bleeding in other SOCs. For example, hematuria was reported in 39 percent of patients; the incidence was not different between treatment groups and it was almost entirely Grade 1. Hemorrhagic cystitis was observed in only 1.7 percent of patients. Hemorrhagic AEs involving the central nervous system were uncommon; there were two hemorrhagic strokes, one subarachnoid hemorrhage, and one intracranial hemorrhage NOS in the control group, and one subarachnoid hemorrhage in the PCT group. Pulmonary alveolar hemorrhage was reported in 3.1 percent of patients, and pulmonary hemorrhage was reported in 0.6 percent of patients; there were no significant differences between treatment groups. Two of these events (1 PCT and 1 control) resulted in death; these were the only two deaths attributed to hemorrhage in the trial.

Thrombotic AEs were uncommon. The most common event was injection site (catheter-related) thrombo-

TABLE 9. Deaths among patients with clinically serious pulmonary AEs assessed by independent expert panel reanalysis

Characteristic	Treatment group* PCT (n = 78)	Control (n = 70)	P value
Among patients with any clinically serious pulmonary AE	14/55 (25)	17/45 (38)	0.20
Among patients with ARDS or ALI	9/19 (47)	11/16 (69)	0.31
Among patients with ARDS	9/12 (75)	5/5 (100)	0.52
Among patients with ALI	0/7 (0)	6/11 (55)	0.04

* Data are reported as number (%).

TABLE 10. Hemorrhagic AEs reported in at least 5 percent of patients in either treatment group*

SOC Preferred term	Treatment group† PCT (n = 318)	Control (n = 327)	P value
Any hemorrhagic AE	285 (90)	277 (85)	0.08
NCI-CTC Grade 1	147 (46)	164 (50)	0.34
NCI-CTC Grade 2	65 (20)	48 (15)	0.06
NCI-CTC Grade 3	63 (20)	57 (17)	0.48
NCI-CTC Grade 4	10 (3.1)	8 (2.4)	0.64
Eye disorders	27 (8.5)	24 (3.7)	0.64
Gastrointestinal disorders	114 (36)	117 (36)	1.00
Hematemesis	41 (13)	42 (13)	1.00
Mouth hemorrhage	41 (13)	42 (13)	1.00
Oral mucosal petechiae	32 (10)	20 (6.1)	0.08
Rectal hemorrhage	12 (3.8)	17 (5.2)	0.45
General disorders and administration site conditions	55 (17)	44 (14)	0.19
Injection site bruising	20 (6.3)	23 (7.0)	0.75
Hemorrhage NOS	24 (7.5)	16 (4.9)	0.19
Investigations	113 (36)	98 (30)	0.15
Fecal occult blood positive	106 (33)	83 (25)	0.03
Hematuria present	15 (4.7)	20 (6.1)	0.49
Renal and urinary disorders	121 (38)	135 (41)	0.42
Hematuria	118 (37)	135 (41)	0.30
Reproductive system and breast disorders	19 (6.0)	30 (9.2)	0.14
Vaginal hemorrhage	15 (4.7)	24 (7.3)	0.19
Respiratory, thoracic, and mediastinal disorders	132 (42)	125 (38)	0.42
Epistaxis	106 (33)	103 (32)	0.67
Hemoptysis	33 (10)	24 (7.3)	0.21
Pharyngeal hemorrhage	27 (8.5)	19 (5.8)	0.22
Skin and subcutaneous tissue disorders	189 (59)	154 (47)	<0.01
Petechiae	124 (39)	94 (29)	<0.01
Contusion	102 (32)	82 (25)	0.06
Ecchymosis	41 (13)	28 (8.6)	0.10
Purpura NOS	18 (5.7)	9 (2.8)	0.08
Surgical and medical procedures	51 (16)	38 (12)	0.11
Catheter site hemorrhage	42 (13)	32 (9.8)	0.18

* Data summarized by MedDRA SOC and preferred term. Includes any hemorrhagic AE, classified with the MedDRA coding dictionary and special search category for hemorrhage, reported during the transfusion and surveillance periods.
† Data are reported as number (%).

sis in 2.8 percent of PCT patients and 1.8 percent of control patients. Deep vein thrombosis was reported in 1.3 percent of PCT patients and 1.8 percent of control patients.

Skin and subcutaneous tissue disorders AEs. In addition to a greater incidence of hemorrhagic AEs involving the skin and skin rashes (dermatitis NOS) in the PCT group, more low-grade skin infections (folliculitis, cellulitis, herpes simplex, and zoster, etc.) were reported in the PCT group also. These differences were entirely due to a higher incidence of low-grade events; there were no differences for Grade 3 or 4 events. The incidence of all types of skin rashes combined was 56 percent in the PCT group and 42 percent in the control group ($p < 0.001$). The incidence of Grade 3 or 4 skin rashes was much lower (9.8% PCT vs. 5.5% control; $p = 0.05$). A broad spectrum of skin rashes was reported. No between-group differences were noted except for those events reported in Table 5. Specifically, there were no differences between groups for erythematous skin rashes (16% PCT vs. 15% control; $p = 0.75$), the typical rash associated with photosensitization. Furthermore, a photosensitivity reaction was

reported in only one (control) patient. Also, the incidence of skin rashes reported during or within the 6 hours after study PLT transfusions was similar between groups. It was impossible to determine the causality for these rashes because they occurred with high frequency and the population studied had many other possible explanations for skin rash. Multiple antibiotics were used by almost all patients (99%); 85 percent of patients had exposure to diverse chemotherapeutic agents and/or total body irradiation (TBI), and 7 percent of patients also had stem cell transplant–associated graft-versus-host disease (GVHD), which is often manifested with skin rash. There were no differences between groups for any of these risk factors; however, the PCT group showed a trend for greater exposure to TBI (34% PCT vs. 27% control; $p = 0.07$) and PBPC transplant–associated GVHD (9.4% PCT vs. 5.5% control; $p = 0.07$).

Deaths

There were a total of 28 deaths (4.3%): 3.5 percent of PCT patients versus 5.2 percent of control patients died during study participation ($p = 0.34$). Most deaths in both treatment groups were due to complications of chemotherapy and stem cell transplantation or progression of an underlying malignancy.

DISCUSSION

The study population of patients with hematologic and solid tumor malignancies, a large proportion undergoing stem cell transplantation, represented an appropriate population in which to evaluate the therapeutic benefit of PCT PLTs. However, these patients are prone to a large number of toxicities as a result of underlying, frequently advanced, malignancy, as well as complications of conditioning chemotherapy, TBI, GVHD, and numerous concomitant medications. As anticipated in a population of seriously ill oncology patients, nearly all patients reported at least one AE, with 79 percent graded as severe; 6 percent of patients died on study. Overall AEs and deaths were comparable between treatment groups. This population had prolonged pancytopenia, with the expected attendant complications of infections and bleeding, and is a complex population in which to assess the safety of a supportive product, such as PCT PLTs. This was illustrated by the evaluation of ALI for which two AE terms suggested a difference in incidence between treatment groups that was not sustained when more specific criteria for diagnosis were used.

Hemorrhagic and thrombotic AEs were of particular interest since they reflect PLT therapeutic efficacy. Because this trial was designed to evaluate the therapeutic efficacy of PLT transfusions to prevent bleeding, specific methods and criteria for bleeding assessments with use of a scale that reflected efficacy (modified WHO bleeding scale) were used. For evaluation of AEs, a different scale (NCI-CTC) was used and hemorrhagic AEs were reported with this system.

In comparison to other studies, the high proportion of patients with hemorrhagic events may be attributed to the rigorous documentation of bleeding that occurred during the trial, including daily examination of skin and mucous membranes for bleeding as well as daily evaluation of urine and stool for occult blood. These evaluations are not routine in most clinical settings. The overall incidence of hemorrhagic AEs, however, was similar between treatment groups with either the WHO or the NCI-CTC scales. The majority of hemorrhagic AEs in both treatment groups were low-grade and included hematuria, skin bleeding, epistaxis, and fecal occult blood. This is not unexpected because most bleeding associated with thrombocytopenia in the absence of plasma protein coagulopathy or anatomical lesion is mucocutaneous and since the advent of PLT transfusion support, relatively minor.

Hemorrhagic AEs involving the skin and fecal occult blood were more common in the PCT group. These were minor bleeding events (primarily Grade 1), generally did not require specific intervention, and were not associated with an increased incidence of mucocutaneous bleeding in other organ systems (genitourinary) or of progression to higher grade bleeding indicative of generalized hemostatic failure. More severe bleeding (Grades 2-4) was not different between groups. Furthermore, analyses based on the prospectively collected WHO bleeding assessments showed equivalent control of hemostasis for Grades 2 through 4 bleeding.[12]

It is theoretically possible that the PCT process could lead to PLT activation resulting in an increased incidence of thrombotic events. P-selectin, an in vitro indicator of PLT activation, has been observed to be elevated following PCT of PLTs;[4] however, there are no data confirming a correlation between P-selectin levels and clinical thrombosis. The patient population in this study was a high-risk population for thrombotic events due to primary diseases and therapies that are associated with an increased risk of thrombosis in multiple organs. The incidence of thrombosis in this trial was low, mainly related to central venous catheters, and similar between treatment groups. Hence there was no evidence that PCT PLTs had increased thrombogenic potential compared to untreated PLTs in this high-risk population. AEs in the infections and infestations SOC occurred with slightly higher frequency in the PCT group compared to the control group, owing to more low-grade skin rashes classified in the infections SOC. The incidences of high-grade infections, notably bacteremia and sepsis, were comparable between treatment groups. Infections are an expected complication in this population of patients with prolonged severe neutropenia. No

cases of transfusion-attributed bacteremia occurred in this trial.

Skin rashes, mostly low-grade, occurred with greater frequency in the PCT group (56% PCT vs. 42% control; $p < 0.001$). Contributing to these skin rashes may be medications given to these patients or transplant-related GVHD, which occurred with a greater frequency in the PCT group (9%) compared to the control group (6%). Erythematous rashes and photosensitivity, the types of rashes expected if there was toxicity related to amotosalen, were similar between groups.

AEs, overall and Grade 3 or 4, in the respiratory, thoracic, and mediastinal disorders SOC occurred with similar frequency between treatment groups (67%). Because of differences in rates of two specific terms, ARDS (1.6% PCT vs. 0% control; $p = 0.03$) and pneumonitis NOS (2.2% PCT vs. 0% control; $p < 0.01$) however, a supplemental investigation of clinically serious pulmonary AEs was conducted. The discordance between treatment groups for these AEs appeared to be due to inconsistent reporting of the AE of ARDS and the marked specificity of the coding options in the MedDRA coding dictionary. Expert review of patients who died on study, a subset selected because most stem cell transplant patients who develop respiratory failure requiring mechanical ventilation (most of whom have ARDS) progress to death,[22,23] indicated that similar proportions of patients in both treatment groups had objective criteria for ARDS. The disparity in the incidence rates of reported AEs of ARDS and the rate identified with objective criteria illustrates the fact that clinicians do not routinely apply objective criteria to diagnosis of ARDS in routine clinical management of patients.

Reanalysis of a larger subset of patients with potentially clinically serious pulmonary AEs, by an independent blinded expert physicians panel with primary medical records, confirmed that there were no significant differences between treatment groups for the incidence of clinically serious pulmonary AEs, including pneumonitis or ALI (including ARDS).

Fewer transfusions in the PCT group were associated with an acute PLT transfusion reaction than in the control group (3.0% vs. 4.4%, respectively; $p = 0.02$), primarily due to a higher incidence of Grade 1 transfusion reactions in the control group. Although the incidence of acute transfusion reactions has been associated with increased storage duration of the PLT product,[24,25] PCT and control products in this trial had similar storage durations (3.4 vs. 3.6 days, respectively). Most reactions were low-grade and typical of reactions seen with conventional PLT products. Allergic reactions, however, such as urticaria, occurred with lower frequency in the PCT group than control group. This may be attributed to a reduced content of plasma in the PCT PLTs and/or inhibition of cytokine generation by contaminating WBCs;[26,27] both plasma content and cytokines in stored PLT concentrates have been documented to be associated with transfusion reactions.[28,29] No cases of TRALI were reported, although specific criteria for diagnosis and reporting of this event were not provided.

In summary, the safety profile of PCT PLTs appears to be consistent with that of conventional PLTs in this acutely ill patient population. Although there were some significant differences in the frequency of certain AE terms, no trends within SOCs were detected. Because no statistical adjustments for multiple comparisons were made, a certain percentage of significant p values of less than 0.05 would be expected just based on the number of comparisons that were made. These small p values were viewed as hypothesis-generating, rather than confirmation of a proven difference. The MedDRA system is highly granular for specific AE terms, and observed differences require analysis within SOC and across SOC to determine the relevance of the differences. In this study, further investigation of each of these differences did not confirm a trend for a suspected toxicity. These clinical safety data, in conjunction with the preclinical efficacy and safety data[13-16] and clinical efficacy data,[8-12] support the routine use of PCT PLTs for prevention and treatment of bleeding in patients of all ages, including children and the elderly. Although safety was assessed for a relatively short period of time after PCT PLT transfusion, approximately 15 percent of patients had a second cycle of study PLTs, with an interval as long as 190 days after the first cycle. No unusual intercurrent illnesses or AEs were reported in patients with a second exposure. Potential for long-term toxicity of PCT PLTs was not evaluated in this trial. This new class of PLTs has the potential to reduce the rate of transfusion-transmitted infections in PLT recipients.

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A prospective, active haemovigilance study with combined cohort analysis of 19 175 transfusions of platelet components prepared with amotosalen–UVA photochemical treatment

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Vox Sanguinis

Background and Objectives A photochemical treatment process (PCT) utilizing amotosalen and UVA light (INTERCEPT™ Blood System) has been developed for inactivation of viruses, bacteria, parasites and leucocytes that can contaminate blood components intended for transfusion. The objective of this study was to further characterize the safety profile of INTERCEPT-treated platelet components (PCT-PLT) administered across a broad patient population.

Materials and Methods This open-label, observational haemovigilance programme of PCT-PLT transfusions was conducted in 21 centres in 11 countries. All transfusions were monitored for adverse events within 24 h post-transfusion and for serious adverse events (SAEs) up to 7 days post-transfusion. All adverse events were assessed for severity (Grade 0–4), and causal relationship to PCT-PLT transfusion.

Results Over the course of 7 years in the study centres, 4067 patients received 19 175 PCT-PLT transfusions. Adverse events were infrequent, and most were of Grade 1 severity. On a per-transfusion basis, 123 (0·6%) were classified an acute transfusion reaction (ATR) defined as an adverse event related to the transfusion. Among these ATRs, the most common were chills (77, 0·4%) and urticaria (41, 0·2%). Fourteen SAEs were reported, of which 2 were attributed to platelet transfusion (<0·1%). No case of transfusion-related acute lung injury, transfusion-associated graft-versus-host disease, transfusion-transmitted infection or death was attributed to the transfusion of PCT-PLT.

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Conclusion This longitudinal haemovigilance safety programme to monitor PCT-PLT transfusions demonstrated a low rate of ATRs, and a safety profile consistent with that previously reported for conventional platelet components.

Key words: amotosalen, haemovigilance, INTERCEPT, pathogen inactivation, platelets, safety.

Introduction

Since 2002, the INTERCEPT™ Blood System for platelets (Cerus Corporation BV, Amersfoort, the Netherlands), a PCT process that inactivates viruses, bacteria, protozoa and leucocytes potentially contaminating PLT components with amotosalen and low-energy UVA, has been approved for use in Europe through CE Mark registration. Blood centres in Belgium, Italy, Norway and Spain implemented routine production of PCT-PLT in 2003. Adoption of PCT-PLT components has expanded since then and is currently in routine clinical use in more than 100 blood centres in 20 countries. As of September 2014, over 1·23 million PCT-PLTs have been produced for transfusion to patients.

Postmarketing haemovigilance (HV) programmes that monitor adverse events during routine clinical use extend the safety characterization of new products or technologies. HV studies include a greater number and wider demographic spectrum of patients than are feasible in randomized controlled trials [1–3] and provide additional data about the safety profile of these products. The World Health Organization has issued a recommendation for HV programmes specifically in the field of blood transfusion safety to 'identify and prevent occurrence or recurrence of transfusion-related unwanted events' [4]. The European Haemovigilance Network also recommends surveillance for AEs after transfusion of labile blood components [5–7].

After centres began routine production of PCT-PLT, Cerus implemented an Internet-based, active HV programme to prospectively collect additional safety information. In this study, each PCT-PLT transfusion was reported and documented regardless of whether an AE occurred or not. This HV system was largely modelled after the French HV system for documentation of recipient transfusion incidents [8]. The PCT-PLT HV experience has been partially reported previously in two interim reports [9, 10]. This account provides an aggregate analysis of all 19 175 PCT-PLT transfusions occurring under the HV programme to date and includes data for 6632 additional transfusions.

Materials and methods

Study design

This was a prospective, non-randomized, one-arm, observational, HV study documenting all transfused PCT-PLT components (Table 1) in participating centres. Data presented here represent the total HV experience from three studies: HV1 [10], HV2 [9] and HV3 from inception in October 2003 to December 2010. The objective of the study was to determine the proportion of transfusions associated with an acute transfusion reaction (ATR) following administration of PCT-PLT. There were no randomization requirements, no inclusion criteria other than the need for PLT transfusion and no exclusion criteria of patients.

The study was conducted in accordance with the European regulations governing clinical investigations of medical devices and the International Conference on Harmonization Guideline for Good Clinical Practice E6 (CPMP/ICH/135/95). No ethical committee approval or patient consent was required as the system is a CE-marked Class III medical device approved for sale in the European Union, and the study was conducted under existing HV programmes in compliance with country law to monitor the impact of new technologies on blood transfusion practice. Patients received transfusions of PCT-PLT components according to the standard institutional practice. Patient confidentiality was preserved through assignment of a centre-specific study number, and sponsor did not have access to any patient files.

Study report forms

Participating centres used a standardized data capture form to record patient characteristics, primary diagnosis, indication for transfusion and clinical observations of AEs [10]. The data collection form was designed based on HV report forms already in use in Europe [11]. A data and safety monitoring board (DSMB) approved the HV report form before utilization and provided oversight of the study. Trained HV personnel from the blood centres recorded patient characteristics and demographics,

Table 1 INTERCEPT haemovigilance study centres

Country	Transfusion centre	Number of platelet transfusions
Belgium	Mont Godinne	7551
Belgium	Erasme	899
Belgium	Brugge	440
Czech Republic	Prague	4
Germany	Lübeck	77
France	Strasbourg	2048
France	St Etienne	854
France	Rennes	501
France	La Reunion	1950
Iceland	Reykjavik	354
Italy	Pescara	2
Italy	Rome	794
Norway	Bergen	634
Norway	Trondheim	139
Portugal	Lisbon	102
Slovenia	Ljubljana	540
Spain	Madrid RC	382
Spain	Leon	381
Spain	Barcelona	356
Spain	Santiago de Compostela	163
Sweden	Uppsala	1004

platelet component characteristics, transfusion events and AE documentation following the transfusion.

A checklist format was used to capture clinical AE symptoms and signs for each transfusion. The checklist documented the presence of fever, chills, cardiac arrhythmia, hypotension, pruritus, urticaria, skin rash, jaundice, pulmonary oedema, bronchospasm, dyspnoea, tachycardia, respiratory distress, nausea, vomiting, lower back pain, chest pain, abdominal pain and shock. AEs not listed on the checklist, such as refractoriness to platelet transfusion, hypertension, cephalea, pain in the leg, flush, malaise, cyanosis, oxygen desaturation, volume overload and transfusion-related acute lung injury (TRALI), were also recorded. Standardized criteria were used to define transfusion-related sepsis, TRALI [12], transfusion-associated circulatory overload (TACO) and transfusion-associated graft-versus-host disease (TA-GVHD).

Safety monitoring

Patients who received PCT-PLT were monitored for any AE with each transfusion. All AEs within the first 24 h and all serious adverse events (SAEs) within 7 days following each transfusion were recorded.

If an AE occurred after transfusion, additional clinical and biological information was collected to allow diagnosis and assessment of causality and severity. AEs were graded using a 0–4 numerical scale from least to most severe [13]: Grade 0: isolated dysfunction without clinical or biological manifestation; Grade 1: absence of immediate or long-term life-threatening effects; Grade 2: long-term life-threatening effects; Grade 3: immediate life-threatening effects; and Grade 4: death.

The clinical investigator at each site independently assessed the relationship of each AE to the preceding PCT-PLT transfusion. An ATR was defined as an AE possibly related, probably related or related to a PCT-PLT transfusion. SAEs (Grade 2–4 reactions) were reported in greater detail with a narrative for each event. All reported SAEs were reviewed by the appropriate national regulatory authority and by the Cerus Drug Safety Officer.

If an AE was reported, temperature, blood pressure and heart rate were recorded. Abnormal clinical laboratory values, results of diagnostic procedures (chest radiograph) and bacterial cultures from patients and blood component sources were documented on the report form when considered by the physician to be associated with an ATR.

Preparation of test materials

PLTs were collected by apheresis or prepared from whole-blood-derived buffy-coat concentrates according to each centre's standard operating procedures. Briefly, volunteer donors were screened and tested for transfusion-transmitted pathogens according to each centre's procedures, and in compliance with relevant national regulations. All components were leucocyte reduced,

either by filtration (Sepacell™ PLS-5A; Asahi Biomedical, Tokyo, Japan; LRP6; Pall Medical, Portsmouth, UK) or process leucodepletion (Amicus Cell Separator, Fenwal, La Chatre, France, Haemonetics MCS+, Haemonetics, Braintree, MA, USA, or Trima, Terumo BCT, Lakewood, CO, USA). Collections containing $2{\cdot}5–6{\cdot}0 \times 10^{11}$ PLTs were suspended in approximately 35% plasma and 65% Inter-Sol™ (Fenwal, Fresenius-Kabi, Lake Zurich, IL, USA) and treated with amotosalen (nominal final concentration 150 μM) and 3 J/cm^2 UVA (320–400 nm) according to manufacturer's instructions for use. After treatment, PCT-PLTs were stored up to 5 or 7 days under temperature-controlled conditions (22 ± 2°C) before release for transfusion. For HV1, PCT-PLTs were transfused before the expiration period of 5 days. For HV2 and HV3, PCT-PLTs were transfused prior to 5 or 7 day storage depending upon regulations of each country.

Statistical analyses

Data were summarized descriptively by mean, standard deviation, median and range (minimum, maximum) for continuous data or by frequencies and percentages for categorical data, using SAS® version 9.3 (SAS Institute, Cary, NC, USA). All PCT-PLT transfusions administered to a patient were included in the full analysis population, and data were summarized on a per-transfusion basis and a per-patient basis. *P* values for ATR and SAE rates were calculated utilizing the two-sided Fisher's exact test.

The primary assessment of safety was the proportion of PCT-PLT transfusions associated with an ATR. Additionally, patient demographics, primary indication for transfusion, the number of PCT-PLT transfusions received, the characteristics of the PCT-PLT transfused, the AEs reported and the time to first reaction were summarized to characterize the safety profile of PCT-PLT. Among patients with at least one AE reported, the number of transfusions received before the first occurrence was also summarized.

Results

The study population from the culmination of three active HV programmes conducted from October 2003 to December 2010 provided a cohort of 4067 patients transfused with 19 175 PCT-PLT components. Of those, 2016 patients receiving 6632 PCT-PLT transfusions have not been previously reported. The geographic distribution of transfusions is presented (Table 1).

Patient characteristics

The majority of the patient population was male (60%; Table 2). The mean age of the combined cohort was 56·7 years of age (range <1–96) with 94% of patients greater than 18 years of age. The diagnostic indication for platelet transfusion was a haematology disorder (50·1%), or intra- or peri-operative support during surgery (17·5%). Diagnoses other than these accounted for 32% of patients. Of patients being treated for a haematology disorder, 42·4% were receiving conventional chemotherapy and 11·8% received a hematopoietic stem cell transplant (HSCT). The diagnosis was not specified for 19 patients (0·5%).

In the study population, 61·8% had received a blood product prior to the first PCT-PLT transfusion. Among these patients, 5·1% had a history of a transfusion reaction. PCT-PLT transfusions occurred mainly in non-intensive care, inpatient hospital settings. The remaining transfusions were administered in the intensive care unit or in outpatient clinics (Table 2).

Platelet component characteristics

There was a shift over time in the PLT production method used in the participating centres from apheresis collections to whole-blood buffy-coat extraction (Table 3). The majority of centres (97%) elected to use PCT-PLT without γ-irradiation for patients at risk of TA-GVHD based on reported data showing that INTERCEPT effectively inactivates T cells [14]. Additionally, only 1·9% of the units were human leucocyte antigen (HLA) matched (Table 3).

Number of transfusions per-patient

Approximately 56% of patients received multiple transfusions of PCT-PLT during the study. The mean number of transfusions received for each patient for the entire cohort was 4·7 (range 1–156) (Table 4). Of the 4067 patients, 44·1% received only one PCT-PLT transfusion, 27·9% patients received two to three transfusions, and 28·1% patients received four or more transfusions. Platelet usage was greater for patients diagnosed with haematologic disease where the mean number of transfusions per patient was 7·0 (Table 4).

AEs and ATRs following PCT-PLT transfusion

On a per-patient basis, the proportion of patients who experienced any AE, regardless of the grade or cause, was 3·1% (126/4067 patients; Table 5). Of these, 94 patients (2·3% of study population) were classified with an ATR possibly related, probably related or related to PCT-PLT transfusion. Only 13 patients (0·3%) were classified with a SAE; however, all but 2 were judged as unrelated to PCT-PLT and assigned alternative causes for the signs and symptoms by the investigators. No cases of TRALI,

Table 2 Patient and transfusion demographics

	Per-patient basis (N = 4067)	Per-transfusion basis (N = 19 175)
Sex		
Male	2441 (60·0%)	11 467 (59·8%)
Female	1622 (39·9%)	7703 (40·2%)
Unknown	4 (0·1%)	5 (<0·1%)
Age (years)		
Mean (SD)	56·7 (19·9)	
Median	61	
Minimum–Maximum	0–96	
Location of transfusion		
Intensive care unit		2835 (14·8%)
Outpatient		1164 (6·1%)
Regular ward		15 170 (79·1%)
Unknown		6 (<0·1%)
Haematology–Oncology patients	2038 (50·1%)	14 349 (74·8%)
Conventional chemotherapy	1725 (42·4%)	11 898 (62·0%)
Stem cell Transplant	478 (11·8%)	3231 (16·9%)
Surgery patients	710 (17·5%)	1317 (6·9%)
Cardiovascular surgery	593 (14·6%)	1025 (5·3%)
Solid organ transplantation	79 (1·9%)	192 (1·0%)
Other diagnosis	1300 (32·0%)	2856 (14·9%)
Missing diagnosis	19 (0·5%)	653 (3·4%)
History of a previous transfusion		
Yes	2512 (61·8%)	12 771 (66·6%)
No	1176 (28·9%)	5308 (27·7%)
Unknown	378 (9·3%)	1095 (5·7%)
Missing	1 (<0·1%)	1 (<0·1%)
If history of previous transfusion – did they experience an ATR?		
Yes	127 (5·1%)	1338 (10·5%)
No	2272 (90·4%)	11 078 (86·7%)
Unknown	112 (4·5%)	352 (2·8%)
Missing	1 (<0·1%)	3 (<0·1%)

Table 3 PCT-PLT component characteristics

HV study	Patients	Transfusion episodes	% Buffy coat	% Apheresis	% γ-Irradiated	% HLA matched
HV1 [10]	651	5106	8·0	92·0	2·7	3·1
HV2 [9]	1400	7437	35·2	64·8	1·1	2·5
HV3	2016	6632	58·8	41·2	5·3	0·3
Total	4067	19 175	36·1	63·9	3·0	1·9

HLA, human leucocyte antigen; HV, haemovigilance.

TA-GVHD and no deaths due to PCT-PLT transfusions were reported. Additionally, consistent with the rationale for pathogen reduction, no transfusion-transmitted infection occurred.

On a per-transfusion basis, 167 of 19 175 transfusions resulted in an AE (0·9%). Of those, 123 transfusions (0·6%) were classified as ATRs. Only 14 transfusions (0·1%) resulted in SAEs, of which 2 (<0·1%) were classified as ATRs attributed to PCT-PLTs.

Patients with primary haematological disease (n = 2038) demonstrated a greater probability of ATRs (4·3%, $P < 0·001$) than found for the rest of the cohort. However, the rate of SAE experienced by this population was the same (0·3%). Interestingly, cardiovascular surgery

Table 4 Number of transfusion episodes per-patient group[a]

Number of transfusions	Per-patient basis
Total patient population (n = 4067)	
Mean (SD)	4·7 (9·9)
Median	2
Minimum–Maximum	1–156
1	1794 (44·1%)
2	804 (19·8%)
3	328 (8·1%)
≥4	1141 (28·1%)
Paediatric patients (n = 242)	
Mean (SD)	4·6 (8·4%)
Median	2
Minimum–Maximum	1–66
1	109 (45·0%)
2	49 (20·2%)
3	16 (6·6%)
≥4	68 (28·1%)
Neonate patients (n = 46)	
Mean (SD)	2·0 (2·0)
Median	1
Minimum–Maximum	1–9
1	31 (67·4%)
2	8 (17·4%)
≥4	7 (15·2%)
Haematology–Oncology patients (n = 2038)	
Mean (SD)	7·0 (13·1)
Median	3
Minimum–Maximum	1–156
1	649 (31·8%)
2	346 (17·0%)
3	190 (9·3%)
≥4	853 (41·9%)
Cardiovascular patients (n = 593)	
Mean (SD)	1·7 (1·7)
Median	1
Minimum–Maximum	1–24
1	391 (65·9%)
2	116 (19·6%)
3	34 (5·7%)
≥4	52 (8·8%)

[a]One transfusion episode is equivalent to one PCT-PLT component.

patients (n = 593) experienced a lower ATR rate (0·3%, $P < 0·001$) and a similar SAE rate (0·5%, $P = 0·421$) compared to the rest of the patient population.

Paediatric patients (n = 242) experienced a similar ATR rate (3·7%, $P = 0·179$) and SAE rate (0·4%, $P = 0·550$) when compared with adults. No paediatric patient experienced an SAE judged to be related to PCT-PLT. Additionally, the number of PLT transfusions per patient received by paediatric patients was similar to the total study population (Table 4). No AEs occurred in neonate patients under 28 days old (n = 46).

Characteristic of clinical signs and symptoms associated with ATRs

The most common clinical characteristics of ATRs per-patient were chills (1·5%) and urticaria (0·9%) (Table 5). The other reported ATRs were reported in 0·6% or less of patients for each symptom (Table 5). The symptoms observed, their frequencies and the clinical severities were similar in this study as to those reported for conventional PLT [15–23]. Most ATRs were described by investigators as Grade 1 in severity.

On a per-transfusion basis, the most frequently observed ATR symptom was chills reported for 77 of 19 175 transfusions (0·4%). Urticaria was observed after 0·2% of transfusions. Additional signs and symptoms were present with 0·1% or less of transfusions (Table 5).

Cardiac and respiratory events

The subset of AEs specific to the system order class for cardiac disorders and respiratory, thoracic and mediastinal disorders were summarized (Table 5). There were 10 transfusion recipients with cardiac disorder AEs: seven were tachycardia (0·2%) and three were cardiac arrhythmia (<0·1%). The majority of these events were Grade 1 in severity, and consistent with reported observations in transfusion recipients. Adverse events in the respiratory, thoracic and mediastinal disorders categories were present in 22 patients (0·5%) and were most frequently due to dyspnoea (19 patients) (Table 5). Respiratory distress was observed in three patients (<0·1%), and there was 1 case (<0·1%) of bronchospasm. No cases of TRALI or anaphylaxis were reported for haematology–oncology patients within the period of observation despite repeated exposure to PCT-PLT.

Further analysis of the reported AEs in the cardiac and respiratory system organ class revealed classification of six cardiac events (0·1% of patients) and 13 respiratory events (0·3% of patients) as ATRs, the majority of which were Grade 1 (Table 5). Of these, 5 were cases of tachycardia, 1 was a case of arrhythmia, 12 were cases of dyspnoea, and one was a case of bronchospasm.

SAE following platelet transfusion

During the course of the programmes, a total of 13 patients (0·3%) experienced AEs classified as SAEs. Eleven of the 13 SAEs were assessed to be 'unrelated or probably unrelated' to the PCT-PLT transfusion and were attributed to the progression of underlying disease. The remaining 2 SAE were described by the investigator as 'possibly related' to the PCT-PLT transfusion.

Table 5 Clinical characteristics of AE and transfusion reactions

	Per-transfusion basis (n = 19 175)				Per-patient basis (n = 4067)			
	Any AEs	AE attributed to platelets (ATR)	SAE	SAE attributed to platelets	Any AEs	AE attributed to platelets (ATR)	SAE	SAE attributed to platelets
Transfusions with at least one event Signs/Symptoms[a]	167 (0·9%)	123 (0·6%)	14 (0·1%)	2 (<0·1%)	126 (3·1%)	94 (2·3%)	13 (0·3%)	2 (<0·1%)
Fever	40 (0·2%)	26 (0·1%)	3 (<0·1%)	0	36 (0·9%)	23 (0·6%)	3 (0·1%)	0
Chills	99 (0·5%)	77 (0·4%)	4 (<0·1%)	0	76 (1·9%)	59 (1·5%)	3 (0·1%)	0
Pruritus	17 (0·1%)	16 (0·1%)	0	0	15 (0·4%)	14 (0·3%)	0	0
Hypotension	9 (<0·1%)	4 (<0·1%)	6 (<0·1%)	1 (<0·1%)	9 (0·2%)	4 (0·1%)	6 (0·1%)	1 (<0·1%)
Cardiac arrhythmia	3 (<0·1%)	1 (<0·1%)	1 (<0·1%)	0	3 (0·1%)	1 (<0·1%)	1 (<0·1%)	0
Urticaria	43 (0·2%)	41 (0·2%)	1 (<0·1%)	1 (<0·1%)	37 (0·9%)	35 (0·9%)	1 (<0·1%)	1 (<0·1%)
Skin rash	12 (0·1%)	12 (0·1%)	0	0	11 (0·3%)	11 (0·3%)	0	0
Dyspnoea	19 (0·1%)	12 (0·1%)	3 (<0·1%)	0	19 (0·5%)	12 (0·3%)	3 (0·1%)	0
Respiratory distress	3 (<0·1%)	0	3 (<0·1%)	0	3 (0·1%)	0	3 (0·1%)	0
Nausea/vomiting	14 (0·1%)	8 (<0·1%)	3 (<0·1%)	0	11 (0·3%)	6 (0·1%)	2 (<0·1%)	0
Lower back pain	6 (<0·1%)	1 (<0·1%)	0	0	2 (<0·1%)	1 (<0·1%)	0	0
Chest/abdominal pain	3 (<0·1%)	2 (<0·1%)	1 (<0·1%)	1 (<0·1%)	3 (0·1%)	2 (<0·1%)	1 (<0·1%)	1 (<0·1%)
Shock	9 (<0·1%)	1 (<0·1%)	9 (<0·1%)	1 (<0·1%)	8 (0·2%)	1 (<0·1%)	8 (0·2%)	1 (<0·1%)
Bronchospasm	1 (<0·1%)	1 (<0·1%)	1 (<0·1%)	1 (<0·1%)	1 (<0·1%)	1 (<0·1%)	1 (<0·1%)	1 (<0·1%)
Tachycardia	8 (<0·1%)	6 (<0·1%)	1 (<0·1%)	0	7 (0·2%)	5 (0·1%)	1 (<0·1%)	0
Platelet refractoriness	2 (<0·1%)	2 (<0·1%)	0	0	2 (<0·1%)	2 (<0·1%)	0	0
Other	27 (0·1%)	15 (0·1%)	6 (<0·1%)	0	25 (0·6%)	14 (0·3%)	6 (0·1%)	0

ATR, acute transfusion reaction; SAE, serious adverse event; AE, adverse event.

[a]Number of signs/symptoms can exceed number of AE due to multiple observed signs/symptoms per AE.

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Patient 01-464 developed a haemorrhage during mitral valve surgery and was treated with PCT-PLT and methylene blue-treated fresh frozen plasma. He experienced hypotension after the second study transfusion. One day later, the patient experienced a second hypotensive event after receiving a red blood cell transfusion. The investigator attributed the event as an allergic adverse event related to the PLT transfusion. The patient recovered and was released.

Patient 1868 had a history of aortic valve replacement and bypass. The patient experienced urticaria, bronchospasm, hypotension and chest/abdominal pain after a single transfusion of PCT-PLT and required mechanical ventilation. The patient recovered the same day, and the bacterial culture of the platelet container was negative. No device malfunctions were reported during the preparation of the PLTs, and the patient did not receive any additional transfusions. The investigator considered the events 'possibly related' to the PCT-PLT transfusion.

Number of transfusions prior to the first AE

Among the 126 patients who experienced at least one AE, repeated exposure to PCT-PLT did not appear to increase the likelihood of a transfusion reaction (Table 6). The mean number of transfusions before first AE occurrence was 8·3.

Table 6 Number of PCT-PLT transfusions per patient prior to the first AE

Number of transfusions before first AE	Per-patient basis
Total patient population (n = 4067, 126 AE)	
1	37 (0·91%)
2	16 (0·39%)
3	8 (0·20%)
4	9 (0·22%)
5	5 (0·12%)
6–10	22 (0·54%)
11–19	15 (0·37%)
≥20	14 (0·34%)
Mean (SD)	8·3 (14·6)
Median	4
Minimum–Maximum	1–139
Paediatric patients (n = 242, 13 AE)	
1	3 (1·24%)
2	1 (0·41%)
4	1 (0·41%)
6–10	4 (1·65%)
11–19	2 (0·83%)
≥20	2 (0·83%)
Mean (SD)	9·8 (10·1)
Median	6
Minimum–Maximum	1–30
Haematology–Oncology patients (n = 2038, 111 AE)	
1	26 (1·28%)
2	14 (0·69%)
3	8 (0·39%)
4	9 (0·44%)
5	5 (0·25%)
6–10	20 (0·98%)
11–19	15 (0·74%)
≥20	14 (0·69%)
Mean (SD)	9·2 (15·3)
Median	4
Minimum–Maximum	1–139
Cardiovascular patients (n = 593, 3 AE)	
1	2 (0·34%)
6–10	1 (0·17%)
Mean (SD)	2·7 (2·9)
Median	1
Minimum–Maximum	1–6

AE, adverse event.

Discussion

This active HV programme prospectively monitored routine transfusions of 19 175 PCT-PLT components into 4067 recipients. Only 94 patients (2·3%) experienced an ATR during the study (Table 5). On a per-transfusion basis, 123 transfusions (0·6%) were associated with ATRs (Table 5). The active design of this HV programme stipulated that all transfusions were evaluated, allowing for a greater amount of clinical data to be collected for a large patient population. This approach facilitates the detection of unexpected or low-grade AEs.

There are several published reports on the frequency of ATRs for conventional PLTs that can be used as a comparison to determine whether use of PCT-PLTs is associated with an increased risk. Concurrent to this PCT-PLT HV programme, independent national HV programmes in France and Switzerland documented their experience with PLT transfusions [24]. The Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS), later renamed Agence Nationale de Securite du Medicament et des Produits de Sante (ANSM), has published results from an independent, active HV programme which monitors the routine use of blood components in France. Between 2009 and 2012, approximately 250 000 conventional PLT products were transfused each year. ATR frequency was reported to be 102·88 per 20 000 units (0·5%), 527·9 per 100 000 units (0·5%), 443·2 per 100 000 units (0·4%) and 406·1 per 100 000 units (0·4%) for each year, respectively [17–20].

Swissmedic, the Swiss Agency for Therapeutic Products, also reported results from an independent HV surveillance programme on the frequency and severity of transfusion reactions. In 2008, 155 ATRs were observed after 27 669 transfusions (0·6%) [25]. Analysis of the

combined period from 2009 to 2011 documents 223 ATRs per 66 000 transfusions (0·3%) [23]. Based on the data above, there appears to be no increased risk of ATRs after transfusion of PCT-PLTs vs. conventional PLTs.

The French and Swiss programmes also published the results of their experience utilizing PCT-PLT components. The results reported are consistent with the frequency and type of AEs reported here. The French HV programme from 2009 to 2010 documents the rates of ATRs related to PCT-PLT transfusion to be steady at 0·2% (51 of 21 767 transfusions) and 0·2% (34 per 21 897 transfusions) for each year, respectively. Swissmedic also reported their HV experience for the years 2011–2013. The reported rate of ATRs that were related to PCT-PLT transfusion was 0·3% (251 per 95 515 transfusions) [23], again similar to the results described here.

When patient groups are subdivided by diagnosis, differences in ATR rates were observed. The higher ATR rate observed for patients with haematologic disease may be attributed to the increased number of transfusions this population received (Table 4). Similarly, the decreased ATR rate observed for cardiovascular surgery patients may be due to decreased platelet usage in these patients (Table 4). However, importantly the SAE rate for both these populations was not different than observed for the overall population.

Since country-specific HV programmes do not report on a per-patient basis, it is difficult to determine a baseline rate of transfusion reactions per recipient. Some available literature includes the Trial to Reduce Alloimmunization to Platelets (TRAP) study, which examined the incidence of moderate and severe ATRs in 598 patients with acute myeloid leukaemia receiving 8769 PLT transfusions [16]. The study found that 22% of patients experienced at least one ATR. For this programme, when ATRs were evaluated for only haematology–oncology patients, a significantly lower per-patient (4·3%) and per-transfusion (0·8%) ATR rate was observed. It is thought that the use of platelet additive solution (PAS) during the preparation of PCT-PLTs may partially account for the reduction in ATR incidence. The TRAP study did not utilize PAS during platelet preparation.

Consistent with the suggestion above, a study by Cazenave *et al*. [26] found that the AE rate was significantly less from transfusions of PLTs prepared with 65% T-Sol/35% plasma vs. 100% plasma (2·0% vs. 2·9%, $P = 0·0094$). The AE rate was reported to decrease to 1·7% for transfusions additionally treated with PCT ($P = 0·0214$). A recent study by Tobian *et al*. [27] also demonstrated that the ATR rate was lower for PLTs prepared in 65% PASIII/35% plasma than 100% plasma (1·0% vs. 1·8%, respectively). The 604 patients who received 3884 PLT transfusions suspended in 100% plasma experienced 72 ATR, while the 345 patients who received 1194 PLT transfusion containing PASIII experienced only 12 ATR. Therefore, the use of PASIII resulted in a 46% reduction in ATR.

The absence of reports of TRALI associated with platelet transfusion in this HV programme is important in the view of previous observations in the SPRINT trial of ALI in approximately 5% of HSCT patients [12]. The haematology–oncology patients enrolled in this HV programme were repeatedly transfused and observed for all AEs and SAEs following each transfusion (including respiratory symptoms) for 7 days. Under these conditions, it appears highly likely that probable cases of TRALI would be reported given the intensity of the medical intervention required to diagnose and treat TRALI. Additionally, a similar low frequency of TRALI associated with routine use of PLT components has been observed by the French HV system. From 2008 to 2011, only 2 (0·005%, $n = 82\,383$ transfusions) cases of TRALI occurred after PCT-PLT transfusion and 26 (0·003%, $n = 1\,022\,224$ transfusions) were associated with transfusion of conventional PLTs.

In conclusion, we report the combined 7-year results of an active HV programme designed to monitor all PCT-PLT transfusions at participating centres. Incidence of ATR associated with PCT-PLTs was consistent with the per-transfusion ATR rates of conventional PLTs and at the lower range of ATRs reported per-patient. The clinical experience of 4067 patients receiving 19 175 transfusions has demonstrated that PLT components treated with amotosalen and UV light for pathogen reduction were well tolerated in routine clinical practice.

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