Evaluation of amotosalen and UVA pathogen-reduced apheresis platelets after 7-day storage

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Abstract

Background: Amotosalen/UVA pathogen-reduced platelet components (PRPCs) with storage up to 7 days are standard of care in France, Switzerland, and Austria. PRPCs provide effective hemostasis with reduced risk of transfusion-transmitted infections and transfusion-associated graft versus host disease, reduced wastage and improved availability compared with 5-day-stored PCs. This study evaluated the potency of 7-day PRPCs by in vitro characterization and in vivo pharmacokinetic analysis of autologous PCs.

Study Design and Methods: The in vitro characteristics of 7-day-stored apheresis PRPCs suspended in 100% plasma or 65% platelet additive solution (PAS-3)/35% plasma, thrombin generation, and in vivo radiolabeled post-transfusion recovery and survival of 7-day-stored PRPCs suspended in 100% plasma were compared with either 7-day-stored or fresh autologous conventional platelets.

Results: PRPCs after 7 days of storage maintained pH, platelet dose, in vitro physiologic characteristics, and thrombin generation when compared to conventional 7-day PCs. In vivo, the mean post-transfusion survival was 151.4 ± 20.1 h for 7-day PRPCs in 100% plasma (Test) versus 209.6 ± 13.9 h for the fresh autologous platelets (Control), (T–ΔC: 72.3 ± 8.8%; 95% confidence interval [CI]: 68.5, 76.1) and mean 24-h post-transfusion recovery 37.6 ± 8.4% for Test versus 56.8 ± 9.2% for Control (T–ΔC: 66.2 ± 11.2%; 95% CI: 61.3, 71.1).

Discussion: PRPCs collected in both 100% plasma as well as 65% PAS-3/35% plasma and stored for 7 days retained in vitro physiologic characteristics. PRPCs stored in 100% plasma for 7 days retained in vivo survival. Lower in vivo post-radiolabeled autologous platelet recovery is consistent with reported reduced count increments for allogenic transfusion.
1 | INTRODUCTION

Platelet components (PCs) treated with amotosalen and UVA-light pathogen reduction (INTERCEPT Blood System for Platelets; Cerus) were shown in multiple randomized controlled clinical trials to provide effective clinical hemostasis for patients with thrombocytopenia.\(^1\)–\(^7\) Postmarket surveillance data support efficacy in reducing the risk of bacterial sepsis,\(^8\) preventing HIV transmission,\(^9\) and utility in allowing continued platelet collection and distribution in the face of local viral epidemics for which no viral marker tests were available.\(^10\)–\(^11\) Preclinical and postmarket data support the product claims of reducing the risk of a broad-spectrum of pathogen transmission including cytomegalovirus, sepsis, and transfusion-associated graft versus host disease.\(^12\)–\(^18\) Amotosalen–UVA pathogen-reduced PCs (PRPCs) are now routinely transfused in >50 countries and represent all PCs currently transfused in France, Belgium, Switzerland, Iceland, and Kuwait, and the majority of PCs in Austria and other countries, establishing a new standard of care.

The FDA approved PRPCs in December 2014 for the treatment of apheresis platelets collected in 65% PAS-3/35% plasma, and in March 2016 for the storage of apheresis platelets suspended in 100% plasma with storage for up to 5 days. INTERCEPT processing kits for treating ~725,000 PCs were sold in the United States from October 2021 to March 2022, suggesting that the majority (~58%) of US PCs are now PRPCs, assuming an annual collection of ~2.5 million whole blood or apheresis PC equivalents.\(^19\)

In France, Austria, and Switzerland, PRPCs are routinely stored up to 7 days after collection. Postmarket studies have documented clinical efficacy with reduced wastage and increased PC availability when compared with historical 5-day-stored PCs. Furthermore, in routine practice there has been minimal change in RBC, plasma, or platelet usage attributed to the introduction of PRPCs, despite evidence of reduced platelet count increments when compared with untreated conventional platelets.\(^20\)–\(^23\)

The therapeutic efficacy of PRPCs stored for 6–7 days is supported by a Phase 3 RCT\(^2\) and by postmarket experience.\(^20\)–\(^25\) Further studies presented in this manuscript support transfusion of PRPCs through 7 days of storage: Phase 1 studies evaluated the post-storage in vitro platelet properties of apheresis PRPCs suspended in 65% PAS-3/35% plasma or 100% plasma (Test) compared to untreated conventional platelets from the same donor (Control) and stored for 7 days; thrombin generation of conventional or PRPCs stored for 7 days in 100% plasma; and a Phase 2 study comparing the in vivo post-infusion radiolabeled recovery and survival of PRPCs suspended in 100% plasma and stored for 7 days, with fresh autologous platelets prepared from platelet-rich plasma (PRP) isolated from whole blood. This manuscript summarizes and integrates the experience with PRPC stored >5 days and was designed to evaluate the hypothesis that single-donor derived PRPCs stored for 7 days retain sufficient function for therapeutic transfusion efficacy.

2 | MATERIALS AND METHODS

2.1 | In vitro study design

Phase 1 in vitro studies were designed as prospective, randomized, open-labeled, paired, controlled, crossover studies of apheresis PCs in 65% PAS-3 (PAS-C)/35% plasma collected on the Amicus separator (Fresenius Kabi), or in 100% plasma collected on the Trima separator (Terumo BCT). The PAS-3 study was performed at Versiti Blood Center of Wisconsin, Dartmouth Hitchcock Medical Center, and New York Blood Center, and the 100% plasma study was performed at Hoxworth Blood Center, and Vitalant Research Institute. Protocols were conducted with institutional review board approval. The population consisted of healthy subjects who met the FDA, AABB, and site/institutional eligibility criteria for autologous apheresis platelet donation and the study inclusion/exclusion criteria.

Each study subject donated a single- or double-apheresis PC during each of two consecutive donation periods. Components were randomized for preparation as untreated Control PCs or Test PRPCs and processed with Small Volume (SV), Large Volume, or Dual Storage (DS) INTERCEPT Platelet Processing sets, the INT100 Illuminator, and compound adsorbing device per the manufacturer’s instructions (Figure 1A). Test platelets were stored in storage containers integral to the pathogen reduction processing sets (Figure 1B). Control platelets were stored in the apheresis manufacturers’ storage containers. All PCs were stored at 22 ± 2°C with agitation and evaluated for in vitro platelet function on Day 0/1 (Input), Day 5, and Day 7 of storage.

The primary endpoints were (i) the proportion of Test PCs with pH\(_{22°C}\) ≥6.2, and (ii) platelet dose of ≥3.0 × 10\(^11\) platelets per PC. Other platelet characteristics were measured as previously described.\(^26\)–\(^34\) Baseline adjusted cell-free lactate dehydrogenase (LDH) was
determined as the proportion (%) of total LDH calculated as follows: supernatant Day 5 or 7 LDH / baseline LDH (Day 0/1)/total LDH, where total LDH was measured after 100% induced cellular lysis by Triton-X treatment.

### 2.2 | Thrombin generation

Thrombin generation of stored Test (INTERCEPT) and Control (untreated) PCs was measured in a separate experiment performed at Cerus Corporation. ABO matched apheresis PCs collected on the Trima apheresis separator suspended in 100% plasma were pooled (Input) and split into two components; one was untreated (Control), and the other was treated with the INTERCEPT SV platelet processing set (Test). Both Test and Control PCs had input platelet doses of 4.7 ± 0.3 × 10^11 platelets and were stored with constant agitation for 7 days at 22 ± 2°C. Samples from six replicates (both Test and Control) were analyzed on Day 1 (Input), Day 5, and Day 7 of storage for thrombin generation capacity in a calibrated automated thrombogram assay (CAT; Stago). Thrombin levels were calibrated against an internal standard (CAT; Stago). Platelet thrombin generation was induced by the Stago PRP-Reagent which includes 5 pM of Tissue Factor and a minimal amount of phospholipid. Lag time, peak height, and endogenous thrombin potential (ETP) were assessed using platelets as the source of phospholipid.

### 2.3 | In vivo study design

The in vivo Phase 2 investigation was a randomized, multi-center, controlled, in vivo study of the recovery and survival of PRPCs suspended in 100% plasma and stored for 7 days before transfusion compared to paired donor fresh autologous platelets. The study was performed at two study sites: Bloodworks Northwest and Hoxworth Blood Center. Subjects donated a single- or double- apheresis PC, which were treated with the INTERCEPT DS set and stored for 7 days from donation (Test; Figure 1A). All females had a negative pregnancy test before any radiolabel infusion. In vitro platelet function was evaluated on Day 0/1 and Day 7 of storage.

Radiolabeling studies were performed using a variation on the BEST method that excludes the RBC depletion and addition of ACD-A steps during the preparation of the apheresis Test platelets for radiolabeling, to minimize the loss of platelets. Validation studies confirmed the absence of increased RBC contamination using this preparation method. Test platelets stored for 7 days, and fresh Control platelets were radiolabeled according to randomization assignment with either 51Cr (sodium radiocromate—Na\textsubscript{2}\textsuperscript{51}CrO\textsubscript{4}) or 111In (indium oxine). Physical recovery of the Test PC aliquots used for radiolabeling after 7-day storage were assessed by comparing the platelet dose at input and immediately before the addition of the radiolabel to assess platelet loss during the radiolabeling process. Radiolabeled Test and Control platelets were combined, enabling simultaneous
administration into the subject through intravenous infusion (4–14 mL) into a peripheral vein.

The subjects had post-infusion blood samples (10–14 mL) collected at 1-h (±15 min), at 2-h (±15 min) post-infusion, and on Days 1, 2, 3, 5 ± 1, 7/8, and 11 ± 1 post-infusion within ±4 h of the initial infusion time (Figure 1C). Post-infusion platelet recovery (%) and survival (h) were estimated using a multiple-hit gamma-function model. Post-infusion blood samples were corrected for plasma-associated radioisotope, spontaneous radiolabel elution, and RBC-associated radioisotope.

The primary endpoints for the Phase 2 study, post-infusion recovery and survival of PRPCs at Day 7, were assessed using the FDA-required criteria: “fresh” autologous platelets, drawn and prepared on day of reinfusion using the BEST method of processing.

2.4 Statistical analysis

Data were summarized using descriptive statistics (e.g., mean, SD, median, minimum, and maximum for continuous data, frequencies, and percentages for categorical data) across all study sites and within each study site (SAS; SAS Institute). A two-sided 95% confidence interval (CI) for the mean for continuous parameters and by frequencies and percentages for categorical data variables was calculated and used to determine statistical significance between Test and Control platelets. Lactate, glucose, ATP, and supernatant LDH were normalized to the platelet content and were calculated using regression analysis. Recovery and survival were calculated from specific activities using the nonlinear multiple-hit regression model using time points greater than 20 h. Comparisons against FDA acceptance criteria were performed as previously described.

The acceptance criteria were: the lower bound of a two-sided 95% CI for the mean treatment difference in post-infusion recovery (Test 0.66 × Control) is ≥0 and in post-infusion survival (Test 0.58 × Control) is ≥0.

Data were graphed in SAS, Microsoft Excel, and/or GraphPad. Summary statistics for in vivo recoveries, in vivo survivals, and in vitro characteristics, were prepared in SAS. Significance threshold was p values of not more than 0.05.

3 RESULTS

3.1 In vitro quality of PRPCs stored for 7 days in 65% PAS-3/35% plasma

Post collection (Day 0/1), Test and Control PCs demonstrated no significant differences (Table S1). Following amotosalen–UVA treatment, the mean (±SD) platelet dose recovery was 87.3 ± 7.1% for Test components. On Day 7, Test components demonstrated no treatment differences compared to Control for pH, volume, platelet count, or platelet dose (compensated for sampling). All (72/72) of the Test units retained pH22°C ≥6.2; 91.7% (66/72) of Test components retained ≥3.0 × 1011 platelets. Test components exhibited lower extracellular glucose, higher lactate levels, and similar total adenosine triphosphate (ATP) compared to Controls (Figure 2E,F,H; Table S1), indicating that active metabolism was maintained up to 7 days of storage. Indices indicative of in vivo viability were maintained. Test components had higher morphology scores on Day 5 (280 ± 27 vs. 266 ± 29) and on Day 7 (265 ± 27 vs. 255 ± 32) than Controls (p < 0.05) with increase on Day 5 (174.8 ± 6.4% vs. 15.7 ± 5.9%, p < 0.05) or no significant changes on Day 7 of storage (p > 0.05) for extent of shape change (ESC) and hypotonic shock response (HSR) scores (Figure 2A–C). Platelet lysis as determined by the baseline adjusted cell-free LDH normalized level of supernatant LDH (%) was lower in the Control group on Day 5 (test: 3.2 ± 2.0%; control 2.0 ± 1.2%, p < 0.05) and similar between Test (4.1 ± 2.3%) and Control (4.3 ± 3.4%) PCs on Day 7, indicating the presence of a modest storage dependent platelet injury for both Test and Control (Figure 2D). On Day 7, P-selectin expression showed that Test (44.6 ± 12.4%) was higher compared to Control (37.4 ± 15.1%, p < 0.05) (Figure 2G).

3.2 In vitro quality of PRPCs stored for 7 days in 100% plasma

Post-collection and pre-treatment (Day 0/1), the Test and Control components demonstrated no significant differences (Table S2). Following amotosalen–UVA treatment, the mean ± SD platelet dose recovery was 84.9 ± 4.4%. After 7 days of storage, 100% (68/68) of Test units had pH22°C ≥6.2; 92.6% (63/68) of Test components retained ≥3.0 × 1011 platelets. Test PCs demonstrated no treatment differences for pH, component volume, or dose. Platelet count was decreased (p < 0.05) in Test PCs (Table S2) due to processing dilution and losses. Test components contained comparable normalized extracellular glucose, lactate, and ATP compared to Controls (Figure 2E,F,H; Table S2) indicating that metabolism was maintained. Indices indicative of in vivo viability were maintained for morphology, while small differences were noted for ESC and HSR (p < 0.05) (Figure 2A–C). Test PCs had higher baseline adjusted proportional LDH on Day 5 but not on Day
7 (Figure 2D). P-selectin expression increased for both Test and Control PCs between Day 5 and Day 7; although Test components showed a significant increase in on Days 5 (21.4 ± 8.8% vs. 15.8 ± 11.9%) and 7 (30.6 ± 11.7% vs. 22.9 ± 17.2%) compared to Controls (Figure 2G).

3.3 | Thrombin generation with PRPCs stored for 7 days in 100% plasma

The ETP was measured to determine the total amount of thrombin generated by a platelet sample following stimulation. Test PCs and untreated Control PCs suspended in 100% plasma had similar ETP, peak thrombin levels, and lag time at input, Day 5, and Day 7 ($p > 0.05$) (Figure 3).

3.4 | In vivo recovery and survival of PRPCs stored for 7 days in 100% plasma

On Day 7 of storage, all Test PCs had pH$_{22°C}$ ≥ 6.2, and platelet active metabolism and viability were maintained in components through 7 days of storage (Table 1). Mean in vitro physical recovery of the Test PC aliquots used for radiolabeling was 84%, indicating the samples used for radiolabeling were representative of the entire Test PC platelet population and platelet populations were not biased by the radiolabeling process.

In vivo platelet survival (expressed as mean lifespan) and post-transfusion recovery were assessed for Test and fresh autologous Control platelets using the $^{51}$Cr and $^{111}$In dual-labeling technique. Post-infusion blood samples were corrected for plasma-associated radioisotope, spontaneous in vitro elution, and the RBC-associated...
**Table 1** *In vitro* analysis for PRPCs stored for 7 days in 100% plasma prior to radiolabeling

| Indices                                      | Mean ± SD [range] |
|----------------------------------------------|-------------------|
| **Input* (Day 0/1) (n = 23)**                | Day 7 (n = 23)    |
| pH$_{22^\circ C}$                            | 7.4 ± 0.1 [7.2–7.7] | 7.1 ± 0.2 [6.8–7.3] |
| Platelet dose$^b$ ($\times 10^{11}$ platelets) | 4.4 ± 0.5 [3.3–5.2] | 3.7 ± 0.5 [2.1–4.6] |
| Component volume (mL)                         | 336 ± 18 [302–367] | 330 ± 20 [276–362] |
| Platelet count ($\times 10^3$ cells/μL)       | 1311 ± 190 [1015–1624] | 1133 ± 176 [661–1401] |
| P-selectin (CD62P, %)                         | 14.4 ± 9.9 [1.1–37.9] | 52.2 ± 16.5 [17.6–75.4] |
| Total ATP (nmol/$\times 10^8$ platelets)      | 4.3 ± 1.3 [2.1–6.5] | 3.5 ± 1.7 [0.6–7.2] |
| Supernatant LDH activity (U/$\times 10^{12}$ platelets) | 104 ± 24 [69–162] | 217 ± 90 [114–440] |
| Baseline adjusted LDH as a % of total LDH$^c$ | N/D               | 4.4 ± 2.9 [1.5–12.4] |
| Supernatant glucose (mmol/$10^{12}$ platelets) | N/D               | 11.2 ± 4.4 [6.9–23.8] |
| Supernatant lactate (mmol/$10^{12}$ platelets) | N/D               | 11.1 ± 2.8$^d$ [7.2–19.6] |
| Extent of shape change (%)                    | N/D               | 16.8 ± 5.5 [6.7–31.1] |
| Hypotonic shock response (%)                  | N/D               | 48.6 ± 16.9 [22.4–78.2] |
| Morphology score                              | N/D               | 324 ± 22 [291–370] |

Abbreviation: N/D, not done.

$^a$Assessed immediately before initiating amotosalen–UVA treatment.

$^b$Corrected for volume loss due to sampling.

$^c$Adjusted for normal plasma LDH levels measured at baseline.

$^d$N = 22.
TABLE 2  Recovery and survival of radiolabeled amotosalen–UVA PRPCs after 7-day storage

|                | Test       | Fresh Control | T-ΔC | % Fresh Control |
|----------------|------------|---------------|------|----------------|
| Recovery (%)   | n = 23     |               |      |                |
| Mean ± SD      | 37.6 ± 8.4 | 56.8 ± 9.2    | 0.1 ± 5.9 | 66.2 ± 11.2    |
| Median         | 37.6       | 57.0          | 0.0   | 66.1           |
| Min to max     | 20.1–52.4  | 39.8–79.7     | −8.8–18.2 | 45.9–101.0     |
| 95% CI for mean| [33.9, 41.2] | [52.8, 60.7] | [−2.5, 2.6] | [61.3, 71.1]   |
| Survival (h)   | n = 23     |               |      |                |
| Mean ± SD      | 151.4 ± 20.1 | 209.6 ± 13.9  | 29.8 ± 18.5 | 72.3 ± 8.8|
| Median         | 155.9      | 209.3         | 32.8  | 72.7           |
| Min to max     | 120.5–187.8 | 181.8–236.7   | −6.5–63.6 | 55.1–88.1     |
| 95% CI for mean| [142.7, 160.0] | [203.6, 215.6] | [21.8, 37.8] | [68.5, 76.1]   |

*For recovery and survival, T-ΔC = (Test endpoint) − (Δ × Control endpoint), where Δ = 0.66 for recovery and 0.58 for survival.

FIGURE 4  Aggregate post-infusion recovery and survival curve of Test and Control platelet components (A) platelet in vivo recovery at 24 h postinfusion for Test and Control. (B) In vivo survival of Test and Control PCs. Data are presented as individual data points and transversal lines depict average ± one standard deviation (n = 23). (C) Post-infusion recovery and survival of Test and Control platelet components using raw data for recovery at each day post-infusion and 95% confidence interval. The data collected on each nominal day were combined for all subjects to generate a composite curve for Test and Control where the day of infusion was Day 0. Data are presented as mean ± one standard deviation (n = 23). Regression analysis (Test r² = .79; Control r² = .80) shows significantly different slopes; Test in vivo recovery = −4.74 (days post infusion) + 36.02 and Control in vivo recovery = −5.82 (days postinfusion) + 54.22 (Test slope − Control slope: p < 0.0004). Test = Amotosalen/UVA treated platelet components. Controls = untreated platelet components [Color figure can be viewed at wileyonlinelibrary.com]
activity by subtracting the Day 11 ± 1 residual counts. Post-infusion samples greater than 20 h were used to calculate the post-infusion recovery and mean lifespan after all radioactive corrections had been made.

Test components stored for 7 days demonstrated a mean post-transfusion survival of 151.4 ± 20.1 versus 209.6 ± 13.9 h for the fresh Control (Table 2; Figure 4B). Test PRPCs stored for 7 days met the FDA criterion for the lower bound of the two-sided 95% CI of the treatment difference for 58% of the Control (21.8, 37.8) and were non-inferior to the fresh Control platelets by this criterion.

Test PRPCs demonstrated a mean 24-h post-transfusion recovery of 37.6 ± 8.4% versus 56.8 ± 9.2% for the fresh Control (>66% recovery of fresh Control platelets) and did not meet the FDA criterion for the lower bound of the two-sided 95% CI of the treatment difference for 66% of the Control (−2.5, 2.6) (Table 2; Figure 4A).

The mean post-infusion recovery for the aggregated data (n = 23) using nominal days were plotted to examine the shape of the Test PC survival curve compared to the Controls (Figure 4C). Both survival curves are approximately linear with a terminal exponential phase, indicative of a predominantly linear senescence-driven clearance process. The Test platelet clearance is significantly less rapid (p < 0.0004) than the control platelet clearance rate (Table S3; Figures S1 and S2).

To evaluate the clinical impact of Test PCs that did not meet the FDA criterion for 24-h post-infusion platelet recovery, a specific analysis of the potential clinical impact of Test PCs with recovery values less than 66% of fresh Controls was performed to estimate the risk to patients of a potential inadequate Cl response. The average post-infusion recovery of components with recovery <66% of the fresh Control was 33.2%, and the average difference from 66% of Control was −5%. Each of these components demonstrated in vitro properties (pH, ATP, morphology score, HSR, and ESC) indicative of therapeutic efficacy, indicating that low recovery did not correlate with poor in vitro characteristics (data not shown).

4 | DISCUSSION

We report the in vitro characteristics of apheresis PRPCs in 65% PAS-3/35% plasma and 100% plasma, containing the range of platelet doses collected in routine practice and stored for 7 days, demonstrated therapeutically sufficient mean platelet dose (>3.0 × 10^{11}) with retention of pH and in vitro metabolic and functional properties consistent with post-transfusion viability. PRPC had similar thrombin generation potential as paired conventional PCs, demonstrating adequate hemostatic capacity potential; and baseline adjusted LDH as a proportion (%) of total LDH, a measure of platelet injury due to leakage or lysis, was increased in Test platelets stored for 5 days and not different (p < 0.05) between Test and Control platelets stored for 7 days. Absolute LDH values were similar on Day 7 of storage to those previously reported with 5-day storage of apheresis platelets in 65% PAS-3/35% plasma\(^{40}\) and 7-day storage in 100% plasma\(^{41}\) (both products that are approved for use in the United States) and lower than historical data for proportional LDH release in whole blood platelets stored for 48 h in plasma.\(^{35}\)

The study met the primary efficacy endpoint for platelet survival in vivo. PRPCs retained >66% mean recovery at 24-h after infusion when compared to fresh autologous Control platelets but did not meet the FDA’s criterion for lower bound of the 95% CI of the treatment difference for post-transfusion recovery (T−66%C = −2.5, 2.6). Normal platelet senescence is a linear process, in contrast to treatment-related damage, that is, random destruction, which results in nonlinear clearance.\(^{42,43}\) The linear clearance of Test platelets with a significantly less steep slope (p < 0.0004) compared to fresh Control platelets after infusion indicates robust survival and normal senescence processes for circulating platelets consistent with minimal random destruction through the end of the Test platelet lifespan. The data suggest that 7-day-stored PRPCs that circulate for >24 h have a lifespan consistent with therapeutic efficacy and a reasonable potency for the transfusion support of thrombocytopenia.

The overall effect of reduced platelet recovery at 24-h would predict decreased post-transfusion platelet count increments in patients, as has been demonstrated with PRPCs, most recently in the study from Basel, Switzerland.\(^{22}\) Clinical data from several large studies showed patients transfused at a threshold platelet count of 10 × 10^{9} platelets/L, a 1-h post-transfusion platelet count increase of ≥10 × 10^{9}/L resulting in a patient platelet count of ≥20 × 10^{9}/L provided adequate hemostasis.\(^{1,40}\) Using data from the current study, 1-h count increments were estimated using the measured radiolabeled recovery data for Test PCs with an assumed average Test PC platelet dose containing 3.0 × 10^{11} platelets. This analysis predicts that the estimated post-transfusion platelet count increment for a patient with a 5-L blood volume under ideal conditions would be 20 × 10^{9}/L, resulting in a post-transfusion patient platelet count of ~30 × 10^{9}/L. The model estimated platelet count increments from our data are consistent with those observed in the pivotal Phase 3 trial\(^{1}\) with PRPCs stored for up to 5 days, and with the PLADO study with variable dosing for 5-day-stored conventional PCs.\(^{40,44,45}\) Similarly, the data from Basel, Switzerland provides real-world data confirming a mean count increment with PRPCs of >10 × 10^{9}/L, even after 7 days of storage.\(^{22}\) Taken together with the extensive postmarket experience with PRPCs worldwide and
at sites that routinely store for up to 7 days, there is no indication of increased bleeding risk to patients with PRPCs stored for 7 days.

With effective inactivation of a range of bacterial strains and demonstrated sterility at outdate, many countries across Europe, Asia, and Latin America permit PRPC storage for up to 7 days before transfusion, facilitating improved platelet logistics, increased availability, and reduced wastage. The efficacy of 6-7-day-stored amotosalen–UVAuffy-coat derived platelets was demonstrated in a Phase 3 RCT that confirmed noninferiority of the 1-h corrected count increment (CCI) compared with conventional platelets. Post-transfusion bleeding, RBC use, and the median time to the next PC transfusion after the study PC were not different. These data were confirmed by postmarket hemovigilance data from the Basel, Switzerland that compared two 5-year periods (2006–2010 vs. 2011–2016), before and after universal PRPC implementation. In that study 2809 patients received a total of 22,570 PRPCs. With 7-day storage, 16.6% of transfused PRPCs were >5 days and wastage was reduced from 8.7% to 1.5%. PRPC storage duration had no effect on the proportion of index transfusions of 6-7-day PRPCs that required the transfusion of a second PC or of RBCs on the same or the next calendar day (as a surrogate marker for hemostasis).22 Transfusion of PRPCs >5 days compared with ≤5 days did not increase reported transfusion reactions. In a subset of patients receiving allogeneic stem cell transplants, the overall 100-day survival and treatment-related mortality were significantly improved after the implementation of PRPCs with extended storage to 7 days despite transplantation of older patients with higher EBMT risk scores.24 Mean CCI for PRPCs declined with increasing storage duration, although the correlation coefficient was weak ($r^2 = .005–.014$), suggesting that clinical factors were more important than PC characteristics when predicting CCI. Mean CCI for PRPCs stored for 5 days or less were 22.6% lower than for conventional PCs ($p < .001$). In the Swiss experience, where the minimum required platelet dose is 2.4 $\times 10^{11}$ platelets, the mean count increment for PRPCs was 16.5 $\times 10^9$/L on Day 2 and 10.2 $\times 10^9$/L on Day 7 of storage (derived from Infanti et al.), indicating an acceptable therapeutic response.

Further data supporting 7-day-stored PRPCs was reported from a study at Innsbruck Hospital, Innsbruck, Austria, showing no change in per patient platelet, plasma, or RBC use in hematology/oncology, cardiac surgery, pediatric, or neonatal patients in 23 months following the introduction of PRPCs stored for 7 days compared with conventional platelets in the prior 23-month period. In particular, no differences were noted in survival or time to discharge in patients undergoing massive transfusion protocols between the two time periods.

Overall, although in vitro characteristics do not always adequately predict in vivo platelet recovery and survival, these studies suggest 7-day amotosalen–UVA PRPCs retained sufficient in vitro functional characteristics consistent with in vivo viability for platelets stored in both 100% plasma and 65% PAS-3/35% plasma. The survival/recovery of PRPCs in 65% PAS-3/35% plasma and stored for 7 days are currently unknown. The benefits of pathogen reduction to reduce the risk of bacterial contamination combined with the potential to reduce platelet wastage and increase availability support a favorable benefit to risk profile for 7-day storage.

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**CONFLICT OF INTEREST**

Jamie R. Genthe, Subramanian Yegneswaran, Nina Mufti, Laurence Corash, Richard J. Benjamin, and Anna C. Erickson are employees of Cerus Corporation. Larry J. Dumont has received research support and consulting fees from Cerus Corporation. Other authors declare no conflict of interest.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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