

Observational study of corrected count increments after transfusion of platelets treated with riboflavin pathogen reduction technology in additive solutions

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BACKGROUND: Mirasol pathogen reduction technology (PRT) treatment inactivates bacteria, viruses, and parasites in plasma products and platelets (PLTs) suspended in plasma and PLT additive solutions (PAS). Few clinical studies exist documenting transfusions with PAS. This study objective was to evaluate the count increments of PRT-treated PAS-C and PAS-E buffy coat (BC) PLTs in routine use observational settings.

STUDY DESIGN AND METHODS: PLT pools of five or six BCs were collected, processed, and suspended in PAS-C or PAS-E, respectively. Products were exposed to ultraviolet light in the presence of riboflavin and then transfused into 19 patients with hematologic diseases. Patients were monitored for PLT corrected count increment (CCI) at 1 and 24 hours and for any adverse events in the 72 hours after transfusion. Sterility monitoring was performed with a microbial detection system (BacT/ALERT, bioMérieux).

RESULTS: The PAS-E products had significantly higher PLT concentrations and counts than the PAS-C products. The mean CCIs of per-protocol (PP) units at 1 and 24 hours were 11,900 (n = 27) and 5500 (n = 30), respectively. Seventy-eight percent of PP transfusions classify as successful with CCIs at 1 hour of higher than 7500, and 63% higher than 4500 at 24 hours. One patient was excluded from all analyses as she was refractory to Mirasol-treated PLT transfusions and follow-up untreated transfusion products. No adverse events were observed and no contaminated products were detected by BacT/ALERT.

CONCLUSION: PRT-treated BC PLTs in PAS-C or PAS-E demonstrate PLT transfusion success rates in hematology patients with thrombocytopenia that are comparable to previous studies examining PLTs stored in plasma.

As with any medical intervention, transfusion carries risks which factor significantly into therapeutic decisions.¹ While substantial progress has been made decreasing the risks of transfusion-transmitted infection, problems remain due to window period infections and to pathogens that are seasonal, geographically limited, or expanding their endemicity.² Blood donation screening, as formally recommended by the World Health Organization,³ can be a costly and time consuming burden, particularly in lower-income countries. Many challenges exist to effectively screen for infectious pathogens, including developing assays that are sensitive enough to detect early infections when pathogen numbers and antibody levels may be very low.^{4,5}

The Mirasol pathogen reduction technology (PRT) system (Terumo BCT, Lakewood, CO) uses riboflavin and ultraviolet (UV) light for the inactivation of pathogens in blood components. The addition of riboflavin and exposure to 285- to 365-nm UV light leads to riboflavin-mediated damage to nucleic acids.⁴ Mirasol PRT has

ABBREVIATIONS: BC(s) = buffy coat(s); MITT = modified intent to treat; PP = per protocol; PRT = pathogen reduction technology.

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shown promise in reducing bacterial, viral, and parasite loads in vitro and in contaminated blood products.^{4,6-9} A randomized controlled study of patients with thrombocytopenia demonstrated that patients receiving PRT platelets (PLTs) stored in plasma had lower corrected count increment (CCI) compared to patients receiving a traditional PLT product; however, the study was not powered to detect differences in bleeding between treatment and reference arms.¹⁰ The primary endpoints of the ongoing PREPAREs (Dutch Trial Registration NTR2106) and IPTAS (United States NIH Trial Registration NCT01642563) trials are assessing bleeding and currently over half of the total patients have been enrolled. No issues with the performance of Mirasol-treated PLTs have been identified by the data safety monitoring board. Applying PRT to PLTs stored in PLT additive solutions (PASs) has the added benefits of PAS as a suspension medium, including reduced transfusion-associated adverse events and potentially increased storage times.¹¹⁻¹³ The Mirasol system has been evaluated to ensure there are no significant biases in pathogen reduction performance, regardless of whether the pathogen reduction of the PLT product was carried out in plasma or in PAS.¹⁴ Reduction levels of human hepatitis A virus, infectious bovine rhinotracheitis virus, encephalomyocarditis virus, and several bacterial strains in plasma and in PAS were comparable. Basic in vitro assays published by independent groups have yielded variable results in PLT function of PRT-treated PLTs preserved in PAS or plasma.¹⁵⁻¹⁸

The objective of this study was to evaluate the count increment of PRT-treated PLTs stored in PAS-C or PAS-E in patients with hematologic diseases as measured by post-PRT product characteristics, 1- and 24-hour CCIs and transfusion-related adverse events. The study was designed as a prospective, observational, open-label, post-approval trial of two patient cohorts at two different sites (Hospital Clinico Universitario, Valladolid, Spain; and AZ Delta, Roeselare, Belgium).

MATERIALS AND METHODS

Device description: Mirasol system for PLTs

The Mirasol system for PLTs consists of an illuminator (Version 5.1.3), a disposable kit containing a sterile bag of riboflavin solution (500 $\mu\text{mol/L}$ in 0.9% NaCl solution), and an illumination and storage bag. The PLT product plus riboflavin is transferred to the illumination and storage bag and placed in the illuminator. The PLTs are illuminated for approximately 6 to 8 minutes, depending on the plasma volume in the PLT product.

Collection and processing of PLT products

Whole blood-derived PLT products were manufactured according to the standard procedures and

specifications of the respective institutions. Specifically, for the Valladolid study, PLTs from five buffy coats (BCs) were suspended in 280 mL of PAS-C (InterSol, Fenwal, Inc., a Fresenius-Kabi company, Lake Zurich, IL). For the Roeselare study, PLT concentrates obtained from six BCs were suspended in 300 mL of PAS-E (SSP+, MacoPharma, Tourcoing, France). These PASs have equivalent amounts of chloride, phosphate, and citrate. PAS-E differs from PAS-C by containing 8 mmol/L less sodium chloride and the addition of 5 mmol/L potassium and 1.5 mmol/L magnesium. PLT products were then transferred to the Mirasol illumination bag for treatment. The posttreatment weight of the product was measured and a sample was taken for a PLT count and to perform a sterility control with a bacterial detection system (BacT/ALERT, bioMérieux, Durham, NC). A positive swirl test was a criterion for release of the Mirasol-treated PLT products.¹⁹

Subject selection

Patients were identified from the hospitals' hematology services. Written informed consent had to be obtained from the subjects before any protocol-related procedure was performed. Inclusion criteria required that patients were expected to receive at least one PLT transfusion. The Valladolid study had no exclusion criteria. The Roeselare study excluded patients that had a documented history of immunologic refractoriness to PLT transfusions or were actively bleeding. In the Roeselare study, one enrolled patient was excluded from all analyses as she was refractory to Mirasol-treated PLT transfusions and follow-up untreated transfusion products.

Transfusions

The decision for PLT transfusion was made by the attending physician based on usual practice. During the study periods, subjects could receive as many PLT transfusions as required. Data on demographics, primary diagnosis, and history of PLT transfusions were recorded for each enrolled subject. Hematology laboratory testing (PLT count, hemoglobin [Hb], and hematocrit [Hct]) was performed on blood samples taken before transfusion, 30 to 75 minutes posttransfusion, and 18 to 36 hours posttransfusion. Bleeding events were not actively monitored during the study.

Statistical analysis

Descriptive statistics were used to summarize the subject demographics, transfusion history, PLT product, laboratory, and CCI data. CCI was calculated using the formulas:

$$\text{CCI} = \frac{(\text{Posttransfusion count}) - (\text{Pretransfusion count}) \left(\frac{\times 10^9}{\text{L}}\right)}{\text{PLT dose transfused} (\times 10^{11})} \times \text{BSA}. \quad (1)$$

$$\begin{aligned} \text{BSA (body surface area in m}^2\text{)} \\ = ([\text{Height (cm)} \times \text{Weight (kg)}]/3600)^{1/2}. \quad (2) \end{aligned}$$

Two PLT products transfused consecutively within 9 hours were considered as one transfusion product and only one CCI was calculated. The PLT count before transfusion of the first product was then used as pretransfusion count, the PLT count after transfusion of the second product was used as posttransfusion PLT count, and the PLT dose was the total number of PLTs in two products.

Comparisons of PLT variables and CCI data for the two study sites and PAS types (and thus, sites) were made using two-tailed t tests. Chi-squared tests were used for comparison of proportions. The significance criterion was a p value of less than 0.05.

Per-protocol analysis

Patient enrollment and data collection were closely observed, as were PLT products. Any deviation, including any product not handled according to the Mirasol systems instructions for use, was recorded. Data associated with these deviations are reported as modified intent to treat (MITT) and were removed for the per-protocol (PP) analyses. Thus, the PP population was defined as all transfusions involving units with properly handled PLT products and correctly collected data (i.e., CCI data obtained within the defined time ranges of 30 to 75 minutes or 18 to 36 hours posttransfusion).

Safety data

From the time of study transfusion until 72 hours posttransfusion, the patients were monitored for any adverse events related to the PRT-treated PLT transfusion(s). No product-related adverse events were reported during the course of the study periods, and thus no safety data analysis was performed.

RESULTS

Study subjects and PLT product information

The study periods were 5 months and 3 weeks in Valladolid and Roeselare, respectively. A total of 77 Mirasol-treated products were transfused in 20 subjects (Table 1). One PLT-refractory patient who had received four transfusions was identified and removed from all subsequent analyses, as described. Nine times a subject received two product transfusions within a 9-hour period; thus a total of 64 transfusion events were included in the data analy-

sis. A majority (n = 13) of the patients received more than one transfusion during the study period, and 12 patients had a history of PLT transfusion before the study. Demographic characteristics and diagnoses of all patients are presented in Table 2.

Summary of Mirasol PLT product characteristics

Exclusion of PLT products for PP analysis

The PP analysis for the Valladolid study excluded a total of 21 transfused products for deviations. Seventeen of these units were handled contrary to the storage specifications provided in the manufacturer's instructions for use and were stored in an incubator containing fluorescent lamps that were continuously activated. One PLT unit was excluded for a PLT concentration below the specifications for storage, and 3 additional units were excluded because

TABLE 1. Disposition of enrolled subjects and Mirasol transfusions by study site

Disposition variable	Valladolid	Roeselare	Overall
Enrolled subjects	11	8	19*
Transfusions†	42	22	64
Products transfused	50	23	73
Mean number of transfusions per patient (range)	4 (1-9)	3 (1-6)	3 (1-9)
Patients who received more than one study transfusion	9	4	13
Number of transfusions with pretransfusion PLT count of $<20 \times 10^9/\text{L}$	27	18	45
Patients with history of previous PLT transfusions	4	8	12

* As discussed in the text, the four PLT products that were transfused to one PLT-refractory patient have been removed from these analyses.

† Nine times a subject received two PLT products within 9 hours. These transfusions were considered as one transfusion and only one CCI was calculated.

TABLE 2. Summary of population characteristics

Demographic characteristic (n = 19)	
Mean age (range)	67 (41-92)
Sex, number male/female	9/10
Body surface area (m ²), mean (range)	1.7 (1.4-2.0)
Diagnosis, number (Valladolid, Roeselare)	
Acute myeloid leukemia	8 (2, 6)
Non-Hodgkin's lymphoma	6 (5, 1)
Myelodysplastic syndrome	5 (4, 1)

pre- and posttransfusion patient PLT counts were obtained outside of the specified time ranges (30-75 min posttransfusion and 18-36 hr posttransfusion). The PP analysis for the Roeselare study excluded one transfusion because the pretransfusion PLT count was collected on the day before transfusion instead of the day of transfusion. These PLT unit exclusions are outlined in Fig. 1.

PLT product characteristics related to BC and PAS composition

Products composed of five pooled BCs in PAS-C had significantly lower PLT concentrations and PLT counts than those prepared from six pooled BCs in PAS-E ($p < 0.001$ for all between PAS type comparisons; Table 3). Of note, data generated by the Blood Service of the Belgian Red Cross-Flanders as a follow-up to the presented study at Roeselare compared five and six BC pools throughout storage in PAS-E. As shown in Fig. 2, PRT-treated products with high volume and PLT content (six BC pools) showed reduced PLT cell quality at the end of storage, compared to five BC pools.

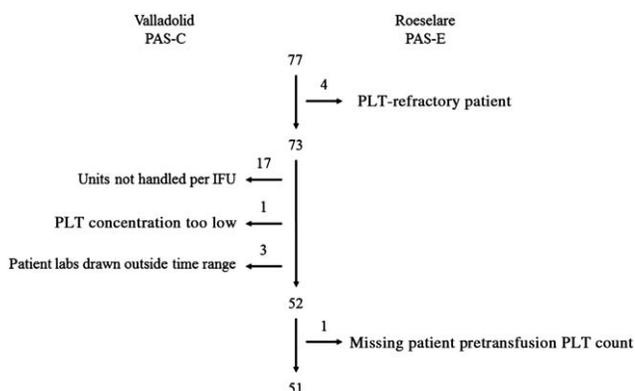


Fig. 1. Diagram outlining PLT unit exclusions, by site and PAS type. IFU = instructions for use.

The mean storage time at the moment of transfusion was 3.4 days and was shorter in Roeselare. Although the range extends from 1 to 8, only 1 unit was 8 days old with the remaining units not more than 5 days. The 8-day-stored unit was given in contrast to hospital policy because of urgent clinical need. None of the transfused units had a positive BacT/ALERT.

Analysis of clinical data

Pretransfusion and 1-hour-posttransfusion data

Table 4 shows the overall MITT and PP data set analyses. The 1- and 24-hour data were normally distributed, and two-tailed t tests were performed to compare sites. The sample size for each analysis is listed to account for missing data points. The pretransfusion patient PLT variables, Hb, and Hct were comparable between groups. Despite off-protocol transfusions in the MITT population, the CCIs at 1 hour were very similar between MITT and PP. The PP 1-hour CCIs were not different between patients receiving PAS-C or PAS-E stored PLTs, averaging 11,950 and 11,890, respectively. The British Committee for Standards in Haematology criteria for successful transfusion increment requires a 1-hour CCI of more than 7500; by these guidelines, 78% of all the Mirasol-treated PP PLTs were successful (again with no significant differences between PAS groups).²⁰

Twenty-four-hour-posttransfusion data with site and PAS type differences

PLT counts were minimally lower at 24 hours posttransfusion for the Valladolid PAS-C site, compared to the Roeselare PAS-E site. However, the 24-hour CCI and percentages of successful transfusion increments for the MITT PLT products in PAS-C were significantly lower than for the PAS-E units ($p = 0.01$ and $p < 0.01$, respectively). Interestingly, for the PP analysis, the 24-hour-posttransfusion CCIs were not different between

TABLE 3. Summary of Mirasol PLT product characteristics after illumination

Variable	Valladolid	Roeselare	Overall	p value
PAS used	PAS-C	PAS-E		
Number of BCs pooled	5	6		
All Mirasol-treated products used for study transfusion (n = 73)*				
PLT concentration ($\times 10^9/L$)	880 (120)	1100 (120)	950 (160)	< 0.001
PLT count ($\times 10^{11}/bag$)	3.40 (0.47)	4.27 (0.47)	3.67 (0.61)	< 0.001
Age of product at time of transfusion (days)	3.7 (1.5)	2.9 (1.5)	3.4 (1.5)†	0.016
Mirasol-treated products used for study transfusion and handled per instructions for use (n = 51)				
PLT concentration ($\times 10^9/L$)	870 (120)	1100 (130)	970 (170)	< 0.001
PLT content ($\times 10^{11}/bag$)	3.44 (0.48)	4.27 (0.47)	3.80 (0.63)	< 0.001
Age of product at time of transfusion (days)	3.3 (1.5)	2.9 (1.1)	3.1 (1.3)	0.39

* Values listed are mean (SD) unless otherwise noted.

† One PLT product was 8 days old at time of transfusion; all remaining transfused units were not more than 5 days.

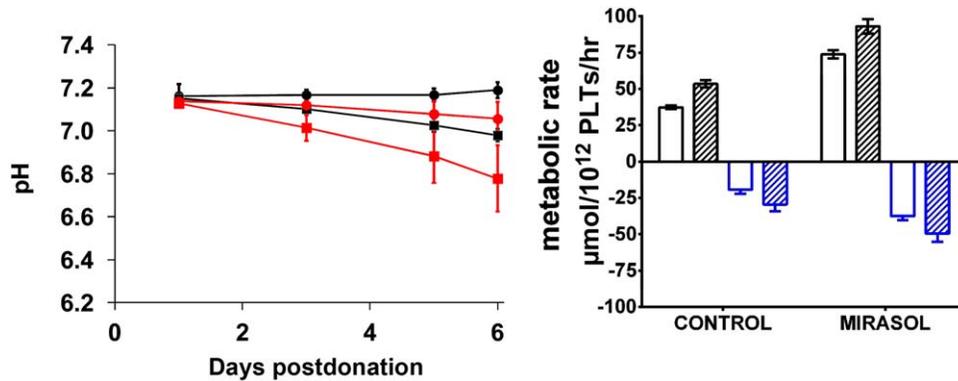


Fig. 2. PRT-treated product quality differs in function of volume and PLT content. Metabolic variables of PLT concentrates (n = 7) composed of five or six BCs stored in PAS-E were measured by blood gas analysis (RAPIDpoint 500, Siemens, Malvern, PA) in function of storage time and in function of Mirasol PRT treatment. (Left) The pH of products composed of 6BC (gray tracing) and of 5BC (black tracing). PRT-treated (■) versus untreated control (●) concentrates. (Right) The lactic acid production (black bars) and glucose consumption rates (gray bars) of PLT concentrates composed of 5BC (open bars) versus 6BC (shaded bars). All data are expressed as means with standard deviations as whiskers (n = 7). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 4. Summary of PP patient data analyses*

Variable	MITT			PP transfusions		
	Valladolid	Roeselare	Overall	Valladolid	Roeselare	Overall
PAS used	PAS-C	PAS-E		PAS-C	PAS-E	
Pretransfusion data (n)	40	22	62	23	21	44
Mean PLT count ($\times 10^9/L$)	16.6 (13.3)	15.0 (6.5)	16.0 (11.3)	16.8 (10.6)	14.2 (6.1)	15.6 (8.7)
Mean Hb (g/dL)	8.1 (1.9)	9.9 (1.2)	8.7 (1.9)	8.3 (1.7)	9.9 (1.2)	9.1 (1.7)
Mean Hct (%)	24.4 (5.4)	28.6 (3.3)	25.9 (5.1)	25.1 (4.9)	28.7 (3.4)	26.8 (4.6)
One-hour-posttransfusion data (n)	8	21	29	7	20	27
Mean CCI	10,630 (5,470)	11,765 (5,900)	11,500 (5,710)	11,950 (4,300)	11,890 (6,030)	11,900 (5,550)
Transfusion with CCI > 7500 (%)	75	76	76	86	75	78
Mean PLT count ($\times 10^9/L$)	39.6 (13.3)	44.1 (17.7)	42.9 (16.5)	43.0 (10.0)	44.1 (18.2)	43.8 (16.2)
Mean Hb (g/dL)	7.6 (1.3)	9.8 (1.2)	9.2 (1.6)	7.8 (1.3)	9.9 (1.2)	9.1 (1.7)
Mean Hct (%)	22.2 (3.0)	28.1 (3.5)	26.5 (4.2)	25.1 (4.9)	28.2 (3.5)	26.8 (4.1)
24-hour-posttransfusion data (n)	27	15	41†	15	15	30
Mean CCI	2,440 (5,470)	5,800 (2,800)‡	3,740 (4,960)	5,180 (4,960)	5,810 (2,800)	5,500 (3,970)
Transfusion with CCI > 4500 (%)	30	80§	48	47	80	63
Mean PLT count ($\times 10^9/L$)	22.7 (19.4)	30.2 (11.2)	25.2 (17.4)	29.4 (21.1)	30.2 (11.3)	29.8 (16.6)
Mean Hb (g/dL)	8.1 (1.6)	9.9 (1.2)	8.6 (1.6)	8.9 (1.0)	9.5 (1.2)	9.2 (1.1)
Mean Hct (%)	24.5 (4.6)	27.1 (3.2)	25.4 (4.4)	26.4 (2.8)	27.2 (3.2)	26.8 (3.0)

* Reported sample size, n, represents the number of available patient data points for each variable. Values listed are mean (SD) unless otherwise noted.

† For 24-hour MITT, all data n = 45 except CCI n = 41 because of missing pre- or posttransfusion PLT counts that precluded CCI calculation.

‡ Between-site comparison, p = 0.01.

§ Between-site comparison, p < 0.01.

|| Between-site comparison, p = 0.06.

the PAS types, yet the percentages of successful transfusion increments (>4500) were significantly different with 47 and 80%, at Valladolid and Roeselare, respectively (p = 0.06). Importantly, no patients in this study, including patients receiving transfusions of products treated outside the manufacturer's recommendation, experienced any adverse events related to PLT transfusions.

DISCUSSION

Despite improved donor screening and testing, transfusion-transmitted infections remain a risk of receiving blood products. Pathogen inactivation offers potential method for lessening this risk, and clinical trials support its safety and applicability to large patient populations.^{10,21,22} Accordingly, pathogen-reduced PLTs are

routinely and safely used in Europe.^{23,24} Somewhat in parallel to the advent of PRT, the push to extend the shelf life of PLTs without compromising function or adding bacterial contamination risks has catalyzed the development of PAS. However, the majority of clinical data on Mirasol PRT-treated PLTs has been collected on units stored in plasma.^{10,25} Thus, the objective of this study was to examine the recovery and safety of PAS-stored PRT-treated PLTs in patients with hematologic diagnoses.

Herein, Mirasol-treated BC PLTs were suspended in either PAS-C or PAS-E solutions and transfused into patients at two different European hospital inpatient units. The main findings are threefold. First, PLTs stored in both PAS formulas had satisfactory 1-hour CCIs, and 78 and 63% of all PP transfused PLT units meeting criteria for successful PLT increments at both 1 and 24 hours post-transfusion, respectively. Second, PLT product characteristics differed significantly between the PAS-C- and PAS-E-stored units, likely related to the different number of BCs pooled for manufacture. However, these differences did not directly affect the CCIs, as those calculations correct for the PLT content of the transfused unit. Third, no transfusion-associated adverse events occurred during the study observation period. We stress the relevance of this last observation as 17 of the 50 transfused products were stored in an incubator containing fluorescent lamps that were continuously turned on during storage, yet no adverse events were observed after transfusion of these products. The manufacturer's instructions specify that treated products should be protected from prolonged exposure to strong ambient light sources.

The overall rates of successful transfusion increments in the current study population compare well to those reported in the larger randomized controlled MIRACLE trial of Mirasol-treated PLTs in plasma (1- and 24-hr CCIs of 78 and 63% vs. 71.3 and 58.9%, respectively).¹⁰ Mean overall 1-hour CCIs are also similar between this study's PAS PRT-treated units and the MIRACLE plasma PRT-treated units (11,900 and 11,725, respectively). Notable differences, however, are seen with the 24-hour data. While the overall 24-hour CCIs and successful transfusion rates are similar between this study and the MIRACLE trial, the breakdown by PAS type is discrepant. Specifically, only 47% of the transfusions had successful increments at 24 hours for the Valladolid PAS-C group compared to 80% for Roeselare PAS-E group. The explanation is likely multifactorial and may include differences in the patients' diagnoses and treatment status. For example, four of the 11 patients in Valladolid had myelodysplastic syndrome while only one of the seven patients in Roeselare carried this diagnosis. PLT refractoriness was an exclusion criterion, but myelodysplastic patients may have underlying hematopoietic failure and a history of alloimmunization from previous transfusions, which could affect their post-transfusion increments.²⁶

PAS composition may have contributed to the differences in successful 24-hour CCIs. More specifically, the addition of magnesium and potassium to PAS-E compared to PAS-C may have impacted the 24-hour time point. These additives have been shown previously to improve *in vitro* PLT function for PAS-E, but not necessarily *in vivo* PLT recovery and survival when transfused after 7 days.²⁷ Another possible explanation, which is also an important limitation to our study, is incomplete data. As shown in Table 4, the Valladolid PAS-C site has proportionately more missing data for the 1- and 24-hour CCI calculations than the Roeselare PAS-E site. The data were normally distributed; however, any nonrandom distribution to the missing points may skew the overall rate of successful transfusions.

This study design does not permit comparison of patient outcomes for PAS PRT-treated PLTs versus untreated units or PLTs in plasma, yet the data establishes an essential foundation for further clinical studies. Further, the absence of adverse events in the 72 hours after transfusion in this population with acute myeloid leukemia, non-Hodgkin's lymphoma, and myelodysplastic syndrome is strong support of the safety profile in this population at high risk for transfusion-associated events.²⁸ The data presented here are relevant as they study the CCI for PAS PRT-treated PLTs *in vivo*.^{11,22,29} The ongoing PRE-PAReS (Dutch Trial Registration NTR2106) and IPTAS (United States NIH Trial Registration NCT01642563) trials are studying PRT-treated PLTs in plasma and in PAS, respectively. The primary endpoints of the trials are differences in bleeding between treatment and reference arms. Currently, the PRE-PAReS trial has enrolled more than half of patients and no issues with the performance of riboflavin PRT-treated PLTs have been identified by the data safety monitoring board.

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CONFLICT OF INTEREST

SM is an employee of Terumo BCT; the other authors have disclosed no conflicts of interest.

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