Purified Poloxamer 188 for Treatment of Acute Vaso-occlusive Crisis of Sickle Cell Disease A Randomized Controlled Trial

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Sickle cell disease (SCD) refers to homozygous sickle cell anemia (SS) as well as mixed heterozygous states, such as SC, SD, and S-β thalassemia. This entire group of genetic illnesses is characterized by a variety of vaso-occlusive complications, the most common of which is the acute painful episode, or vaso-occlusive crisis.

Context Sickle cell disease (SCD) can cause severe painful episodes that are often thought to be caused by vaso-occlusion. The current therapy for these uncomplicated painful episodes includes hydration, oxygen, and analgesics. Purified poloxamer 188 may increase tissue oxygenation and thereby reduce inflammation, pain, and the overall duration of such painful episodes in patients with SCD.

Objective To compare the duration of painful episodes in patients with SCD treated with purified poloxamer 188 to that of similar episodes experienced by patients who receive a placebo.

Design and Setting Randomized, double-blind, placebo-controlled, intention-to-treat trial conducted between March 1998 and October 1999 in 40 medical centers in the United States.

Participants Two hundred fifty-five patients with SCD (aged 9-53 years) who had a painful episode sufficiently severe to require hospitalization and narcotic analgesics.

Intervention Patients were randomly assigned to receive an intravenous infusion of purified poloxamer 188, 100 mg/kg for 1 hour followed by 30 mg/kg per hour for 47 hours (n=127), or a matching volume of saline placebo (n=128).

Main Outcome Measure Duration of the painful episode, from randomization to crisis resolution.

Results Mean (SD) duration of the painful episodes was 141 (42) hours in the placebo group compared with 133 (41) hours in those treated with purified poloxamer 188, a 9-hour reduction (P=.04). Subset analyses indicated an even more pronounced purified poloxamer 188 effect in children aged 15 years or younger (21 hours; P=.01) and in patients who were receiving hydroxyurea (16 hours; P=.02). Finally, the proportion of patients achieving crisis resolution was increased by purified poloxamer 188 (65/126 [52%] vs 45/123 [37%]; P=.02). Similar results were observed in children aged 15 years or younger (22/37 [60%] vs 10/36 [28%]; P=.009) and in patients who were also receiving hydroxyurea (12/26 [46%] vs 4/28 [14%]; P=.02).

Conclusions A decrease in the duration of painful episodes and an increase in the proportion of patients who achieved resolution of the symptoms were observed when the purified poloxamer 188–treated patients were compared with the patients receiving placebo. However, the difference between these groups was significant but relatively small. In subgroup analysis, a more significant effect on both parameters was observed in children and in patients who were receiving concomitant hydroxyurea. It is important to confirm both of these observations in further prospective trials.

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It has been estimated that approximately 90% of hospital admissions among patients with SCD are for treatment of acute pain. Current treatment of an uncomplicated painful

For editorial comment see p 2152.

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Table 1. Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aged 8 to 65 years</td>
<td>• Clinically significant bleeding</td>
</tr>
<tr>
<td>• Adequate liver function (alanine aminotransferase ≤2× upper limit of normal)</td>
<td>• Chronically bleeding hypothyroidisns</td>
</tr>
<tr>
<td>• Adequate renal function (serum creatinine ≤1.0 mg/dl [88.4 µmol/L] and ≤300 mg/dl of protein in spot urinalysis)</td>
<td>• Pregnancy or breastfeeding</td>
</tr>
<tr>
<td>• Documented sickle cell disease</td>
<td>• Inadequate venous access</td>
</tr>
<tr>
<td>• Sudden onset of acute pain involving ≥1 sites in case of vaso-occlusive crisis</td>
<td>• History of major surgery (≤2 wk prior)</td>
</tr>
<tr>
<td>• Severe pain requiring parenteral analgesics</td>
<td>• Episode of pain requiring hospitalization (≤2 wk prior)</td>
</tr>
<tr>
<td>• Consent to use reliable contraception while enrolled in the study and for 30 d thereafter</td>
<td>• Current hospitalization</td>
</tr>
<tr>
<td>• Provided written informed consent</td>
<td>• Participation in another investigational drug study</td>
</tr>
<tr>
<td></td>
<td>• Enrollment in a hypertransfusion program</td>
</tr>
<tr>
<td></td>
<td>• Recent cerebrovascular accident or seizure</td>
</tr>
<tr>
<td></td>
<td>• Other complications of sickle cell disease</td>
</tr>
<tr>
<td></td>
<td>• Not an appropriate candidate in the investigator’s judgment</td>
</tr>
</tbody>
</table>

Table 1. Inclusion and Exclusion Criteria

The study was a randomized, multicenter, double-blind, placebo-controlled phase 3 study designed to assess the efficacy of PP188 in reducing the duration of painful episodes in patients with SCD. Patients were randomized at a 1:1 ratio to receive either PP188 or placebo. Patients randomized to active therapy were given PP188 as a loading dose of 100 mg/kg for 1 hour followed by a maintenance dose of 30 mg/kg per hour for 47 hours. The selection of this dosage was based on a previous successful pilot study of PP188. Patients randomized to the placebo arm received a saline solution delivered at a volume and duration identical to that of the active drug. Parenteral analgesics were given intramuscularly or intravenously. Nonsteroidal anti-inflammatory drug use was not allowed during infusion of the study drug or for 12 hours following its discontinuation. Concurrent therapy with hydroxyurea was allowed. Parenteral analgesic use was limited to morphine, hydromorphone, and meperidine. Oral analgesic use was restricted to codeine, morphine, hydromorphone, oxycodone, acetaminophen, and appropriate combinations of each. One intravenous line was reserved exclusively for infusion of the study drug (ie, PP188 or placebo), and no other medications (eg, analgesics, antiemetics, antibiotics) were given through this line. Visual analog scale (VAS) pain assessments were obtained every 4 hours during treatment and through resolution of crisis or 5 days after infusion, whichever occurred first. This VAS scale (range, 0-100, with higher scores indicating more pain) has been used effectively and validated in SCD. Patient safety was also assessed throughout the study. Blood was collected from patients for pharmacokinetic assessments at baseline and 24, 48, 51, 54, and 60 hours after initiation of study drug infusion. Follow-up safety assessments...
were conducted between days 7 and 14 and days 28 and 35 after discontinuation of study drug infusion.

**Outcome Measures**

The primary end point of the study was duration of the painful episode. Secondary end points included proportion of patients achieving crisis resolution, time to discharge, VAS pain assessment area under the curve, and analgesic consumption (oral, parental, and total). Pharmacoeconomic data were also collected. The duration of each crisis was measured from randomization until all of the following had been simultaneously achieved: (1) pain relief (pain scores ≤ 40 maintained during 2 consecutive readings obtained 4 hours apart); (2) freedom from parental analgesic use (no parental analgesic use in preceding 12 hours); (3) ability to walk without difficulty (unless the patient was not able to walk for any reason other than acute vaso-occlusive crisis prior to onset of crisis); and (4) patient’s belief that the painful episode was over (defined as readiness for discharge with or without oral analgesic use). Specific covariates that were identified a priori included investigational site, age, sex, genotype, and concurrent use of hydroxyurea.

The study was powered to detect a 25% (26-hour) reduction in the duration of crisis with 80% power at \( \alpha = .05 \) based on a mean crisis duration for the control group of 103 hours and a pooled SD of 60 hours based on the earlier pilot study. In addition, the following clinical parameters were evaluated: duration and intensity of pain, total analgesic use, length of hospitalization, and pharmacoeconomic impact. Safety monitoring included assessment of adverse events, disease-related events, clinical laboratory test results, vital signs, and physical examinations. Finally, all aspects of the study were carefully monitored by an independent data and safety monitoring board composed of nationally recognized experts in the fields of SCD, nephrology, hepatology, and statistics.

**Statistical Analysis**

Using simple descriptive statistics, the groups were compared at baseline with respect to demographic and other clinical variables (Table 2 and Table 3). No substantial differences among the groups were identified for any of these parameters, and the modest differences observed were simply a consequence of the finite sizes of the 2 groups as well as the overall randomization process itself.

When duration of crisis was defined using the worst possible score algorithm, differences between treatments were analyzed using the Wilcoxon rank sum test. When duration of crisis was defined as a censored time-to-event variable, differences between treatments in the distribution of time to event were estimated using the Kaplan-Meier method and analyzed using the log-rank test. Differences between treatments in the reduction of pain intensity were tested using the Wilcoxon rank sum test. The proportion of patients achieving crisis resolution, the proportion of patients with adverse events, markedly abnormal laboratory values, and markedly abnormal vital sign measurements were evaluated using the Fisher exact test.

All inferential analyses that were performed and reported herein include testing of (1) a priori hypotheses regarding the primary end point (crisis duration); (2) exploratory analyses of other end points that were also identified a priori (eg, the various secondary efficacy end points and the subgroup analyses involving children aged ≤ 15 years and patients receiving concomitant hydroxyurea); and (3) the supportive post hoc test and analysis

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Table 2. Patient Demographic Characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Purified Poloxamer 188</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients receiving treatment</td>
<td>126 (100)</td>
<td>123 (100)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>52 (41)</td>
<td>50 (41)</td>
</tr>
<tr>
<td>Female</td>
<td>74 (59)</td>
<td>73 (59)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
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<tr>
<td>African American</td>
<td>123 (98)</td>
<td>121 (98)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>21.11 (9.05)</td>
<td>20.97 (8.99)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>58.29 (16.97)</td>
<td>58.66 (16.88)</td>
</tr>
<tr>
<td>Currently receiving hydroxyurea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26 (21)</td>
<td>28 (23)</td>
</tr>
<tr>
<td>No</td>
<td>100 (79)</td>
<td>95 (77)</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SS/SC</td>
<td>97 (77)</td>
<td>96 (79)</td>
</tr>
<tr>
<td>SS</td>
<td>18 (14)</td>
<td>17 (14)</td>
</tr>
<tr>
<td>SC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP+ thalassemia</td>
<td>11 (9)</td>
<td>9 (7)</td>
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*Data are No. (%) unless otherwise noted and reflect those who received study drug or placebo as allocated.

Table 3. Key Baseline Data*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Purified Poloxamer 188</th>
<th>Placebo</th>
<th>( P ) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from onset of crisis to randomization, d</td>
<td>2.25 (2.14)</td>
<td>1.87 (1.84)</td>
<td>.12</td>
</tr>
<tr>
<td>Time from admission to randomization, h</td>
<td>8.84 (5.69)</td>
<td>8.39 (5.02)</td>
<td>.51</td>
</tr>
<tr>
<td>Time from randomization to start of study drug infusion, h</td>
<td>2.22 (1.33)</td>
<td>2.29 (1.47)</td>
<td>.71</td>
</tr>
<tr>
<td>Length of study drug infusion, h</td>
<td>47.83 (6.12)</td>
<td>47.31 (6.71)</td>
<td>.52</td>
</tr>
<tr>
<td>No. of pain locations</td>
<td>3.75 (1.76)</td>
<td>3.76 (1.82)</td>
<td>.99</td>
</tr>
<tr>
<td>Baseline pain intensity (range, 0-100)</td>
<td>73.38 (17.78)</td>
<td>73.78 (20.84)</td>
<td>.67</td>
</tr>
</tbody>
</table>

*All data are mean (SD).
†Computed using 1-way analysis of variance.
Table 4. Proportion of Patients Achieving Crisis Resolution Within 168 Hours*

<table>
<thead>
<tr>
<th>Groups</th>
<th>Purified Poloxamer 188</th>
<th>Placebo</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All randomized patients (n = 255)</td>
<td>65/127 (51.2)</td>
<td>45/128</td>
<td>.01</td>
</tr>
<tr>
<td>All treated patients (n = 249)</td>
<td>65/126 (51.6)</td>
<td>45/123</td>
<td>.02</td>
</tr>
<tr>
<td>Patients concurrently receiving hydroxyurea (n = 54)</td>
<td>12/26 (46.2)</td>
<td>4/28 (14.3)</td>
<td>.02</td>
</tr>
<tr>
<td>Children ≤15 years old (n = 73)</td>
<td>23/37 (65.9)</td>
<td>10/36 (27.8)</td>
<td>.009</td>
</tr>
</tbody>
</table>

*All data are No. (%).
†Computed using the Fisher exact test.

Figure 1. Patient Enrollment

PP188 indicates purified poloxamer 188.

The primary end point of this study was the total duration (in hours) of each individual painful episode or crisis, measured from randomization to achievement of the criteria for crisis resolution. The duration of each episode was analyzed in 2 different ways. The first analysis, on which the study results are based, used the package number on that kit was given to the investigator and the site pharmacist. The package numbers had been randomly generated to prevent detection of a pattern that might indicate contents. Numbered kits containing eleven 100-mL vials were provided to each site. The vials in each kit were numbered using a double-panel tear-off label. After assignment of a kit number, the pharmacist prepared the infusion bottles and covered each with aluminum foil to minimize the possibility of treatment identification. These bottles were labeled 1, 2, or 3 for loading infusion, day 1 maintenance infusion, and day 2 maintenance infusion, respectively.

RESULTS

Patient Population

Of the 255 patients enrolled, 127 were randomized to PP188 and 128 to placebo. Six of the patients who had been randomized (1 to PP188 and 5 to placebo) did not receive the study drug (FIGURE 1). The 2 treatment groups were similar in terms of sex, race, age, weight, number of pain locations, baseline VAS pain score, current use of hydroxyurea, and genotype distribution (Table 2). The groups were also comparable with regard to time from onset of pain to randomization, time from hospital presentation to randomization, time from randomization to start of infusion, and duration of infusion (Table 3).

Outcome Measures

The primary end point of this study was the total duration (in hours) of each individual painful episode or crisis, measured from randomization to achievement of the criteria for crisis resolution. The duration of each episode was analyzed in 2 different ways. The first analysis, on which the study results are based, assigned the worst possible outcome score for length of crisis (168 hours) to patients who did not achieve resolution of the crisis within 168 hours of randomization or for whom documentation of crisis resolution was not available. For patients who met the resolution...
criteria, the total duration was calculated as number of hours elapsed from randomization to crisis resolution. These data were evaluated primarily using the Wilcoxon rank sum test. The results are presented in Table 5. When all randomized patients (n=255) were assessed, the 9-hour difference was statistically significant (P=.04). However, when only the treated patients were evaluated (n=249), the results were no longer statistically significant (P=.07). In the subset evaluation of patients receiving concurrent hydroxyurea (n=54), a 16-hour decrease in duration of crisis was observed, which was significant (P=.02). In children, the observed 21-hour decrease in crisis duration reached even greater statistical significance (P=.01).

The second approach assigned a duration of crisis to patients who met the criteria for crisis resolution as hours from randomization to achievement of resolution. For patients who were discharged prior to 168 hours without crisis resolution, duration was calculated from randomization to hospital discharge. For patients discharged at more than 168 hours after randomization, duration of crisis was treated as a censored value. The data were analyzed in a time-to-event manner using the Kaplan-Meier log-rank method, and the results are presented in Figure 2. In this group, the differences failed to achieve statistical significance (P=.09). When the 2 subgroups were assessed by the latter method, the rate of crisis resolution in the patients receiving hydroxyurea was significant (P=.01), as were the responses for children (P=.007).

In PP188-treated patients, 65 (52%) of 126 achieved crisis resolution per the protocol definition compared with 45 (37%) of the 123 placebo-treated patients. This difference was statistically significant (P=.02). For patients receiving concurrent hydroxyurea, 12 (46.1%) of 26 treated with PP188 achieved crisis resolution. This was also significantly higher than the 4 (14.3%) of 12 placebo-treated patients (P=.02). Finally, the proportion of children who achieved crisis resolution was markedly higher in the PP188-treated group (22 [59.5%] of 37) than in those who received placebo (10 [27.8%] of 36; P=.009).

The secondary efficacy end points of time to discharge, pain, total analgesic use, and pharmacoeconomic costs were not statistically different between the 2 treatment groups (Table 6). The occurrences of secondary complications of SCD such as acute chest syndrome (PP188 group, 12/126 vs placebo group, 11/123; P=.82) and recurrent vaso-occlusive crisis (PP188 group, 32/126 vs placebo group, 36/123; P=.72) during the study period (33 days) were not significantly different between the groups. For both children and hydroxyurea-treated patients receiving PP188, the incidence of acute chest syndrome during hospitalization was somewhat lower (PP188 group, 3/37 and 0/26 vs placebo group, 6/36 and 3/28 for children and hydroxyurea-treated patients, respectively). However, these results were not statistically significant (P=.31 and .24, respectively).

Blood samples for PP188 pharmacokinetics were collected from 167 patients enrolled in the study. Of these, 81 patients were treated with PP188 and 86 received placebo. The number of blood samples that could be obtained was severely restricted by poor venous access. The mean (SD) PP188 concentration at steady state was 420 (420) μg/mL between 28 and 48 hours. These concentrations are within the expected therapeutic range for the rheological and antiadhesive effects of PP188.24,25

**Safety**

Of the 255 patients enrolled, 249 patients were actually treated. There were no differences between the 2 treatment groups in the overall incidence of adverse events, for adverse events defined as serious, or for adverse events involving any body system for the groups as a whole. There was no evidence of increased risk of bleeding during PP188 treatment. There was 1 death due to pulmonary fat embolism in a patient in the PP188 group; the patient had not received study drug infusion.

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**Table 5. Duration of Crisis**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Purified Poloxamer 188</th>
<th>Placebo</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All randomized patients (n = 255)</td>
<td>132.62 (41.38)</td>
<td>141.43 (41.90)</td>
<td>.04</td>
</tr>
<tr>
<td>All treated patients (n = 249)</td>
<td>132.34 (41.42)</td>
<td>140.35 (42.39)</td>
<td>.07</td>
</tr>
<tr>
<td>Patients concurrently receiving hydroxyurea (n = 54)</td>
<td>141.36 (37.04)</td>
<td>157.19 (27.58)</td>
<td>.02</td>
</tr>
<tr>
<td>Patients ≤15 years old (n = 73)</td>
<td>127.07 (42.47)</td>
<td>148.58 (36.71)</td>
<td>.01</td>
</tr>
</tbody>
</table>

*All data are mean (SD). Means include patients with imputed data.†Computed using the Wilcoxon rank sum test.

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**Figure 2. Kaplan-Meier Analysis of Proportion of Patients Remaining in Crisis Over Time**

- **A** All Treated Patients (n = 249)
- **B** Patients Receiving Concurrent Hydroxyurea (n = 54)
- **C** Children (≤15 Years Old) (n = 73)

PP188 indicates purified poloxamer 188.

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for 3 days prior to death. The underlying cause of death was judged by the investigator to be SCD and not study drug treatment.

Renal function was not influenced by PP188 treatment. However, the group randomized to PP188 did exhibit a modest but statistically significant increase in levels of alanine aminotransferase and direct bilirubin, each of which returned to its respective baseline level by the 35-day follow-up visit.

### COMMENT

Painful episodes are the most common medical complication of SCD. Patients experiencing such episodes frequently require hospitalization for adequate management. The course of these crises can be further complicated by life-threatening conditions such as acute chest syndrome. The 2 primary approaches to the management of sickle cell crisis are prevention and intervention. Hydroxyurea, the only preventive agent approved by the US Food and Drug Administration for this specific indication, has been shown to decrease the severity of SCD by reducing the frequency of acute painful episodes.\(^{28-31}\) Another modality, bone marrow transplantation, can cure SCD. However, transplantation is limited in SCD by a lack of HLA-matched donors and by a 9% mortality rate.\(^ {32,33} \)

Although hydroxyurea was found to be effective in reducing the frequency of painful episodes in adults with SCD, it is not useful as a treatment for patients who are experiencing an acute painful episode. During the past 25 years, a number of pharmacological agents (eg, cetiedil citrate, urea sodium, cyanate) have been evaluated as potential intervention strategies that might be capable of shortening or reducing the severity of painful episodes. However, each of these therapies was found to be either too toxic or only marginally effective.\(^ {34-37}\) In a more recent study, Griffin et al\(^ {38} \) observed that treatment with methylprednisolone significantly shortened the duration of acute painful episodes in children with SCD. However, the overall effectiveness of methylprednisolone was limited by a rebound in pain that occurred soon after the drug had been discontinued. It is important to emphasize that studies with preventive agents such as hydroxyurea involve end points that are relatively easy to quantify (eg, number of emergency department visits, number of hospitalizations). In contrast, all of the studies involving interventional agents, including this study, used end points, such as crisis duration, that inevitably rely on subjective pain severity assessments rather than on the much more easily quantifiable end points that are used in studies with preventive agents.

This report represents the first large-scale, rigorously controlled, multicenter, double-blind acute intervention study conducted in both children and adults with SCD. In this study, PP188 was found to be safe and well tolerated and demonstrated a modest treatment benefit in patients with SCD. The beneficial effects of PP188 were especially apparent in children and in those receiving concurrent hydroxyurea therapy. In these 2 subsets, PP188 reduced the overall duration of the crisis by 21 hours and 16 hours, respectively, and the proportion of patients achieving crisis resolution within 168 hours was increased by 30% and 32%, respectively.

It is important to emphasize that in an earlier phase 2 study, even greater benefits with PP188 had been observed.\(^ {19} \) This disparity may be explained at least in part by the assumptions used in our definition of crisis duration, the primary end point in this study. Specifically, we observed that fewer patients achieved crisis resolution within 168 hours than patients in the earlier pilot study had led us to anticipate.\(^ {19} \) The current study used a very stringent definition of crisis resolution, one that required repeated assessments of pain throughout the entire hospitalization, including the period following discontinuation of parental analgesics. In a number of instances, patients were discharged from the hospital before pain relief had been confirmed by a second pain assessment. In still other instances, study patients were discharged before the criteria for crisis resolution had been met. In either case, the analysis plan required that these patients be considered as treatment failures and that the worst-case duration of crisis (ie, 168 hours) be imputed for them.

Use of an extremely stringent definition of crisis resolution represented...
a very conservative approach to the analysis of the data. Because the propor-
tion of patients achieving crisis resolution within 168 hours was lower than anticipated, the ability of this study to detect differences in the length of crisis was correspondingly smaller than expected. The work reported here also differed from the earlier phase 2 study in that treatment assignment was made according to the stratified dynamic randomization method of Pocock and Simon. For these reasons, the statisti-
cal analysis methods used in this study were conservative. While less conserva-
tive methods might have shown sub-
stantially greater differences between the study populations, such an analy-
sis plan would have required taking into account the use of the randomization method.

Nevertheless, the decrease in the du-
ration of vaso-occlusive crisis and in-
crease in the proportion of patients able to achieve crisis resolution, particu-
larly in children, are very encourag-
ing. It is possible that children exhibit a better response to PP188 because they have less overall tissue and organ dam-
age due to previous crises and experi-
ence less chronic pain, thereby making more evident the rheologic and anti-
inflammatory effects of PP188. A beneficial effect was also observed in pa-
tients who received hydroxyurea along with PP188. This could be due to a co-
operative or even a synergistic effect be-
tween these 2 agents, one that might be a result of decreased adhesion of sickle
erythrocytes to the microvascular en-
thelium or to some other less well-
deﬁned mechanism. Future studies of
PP188 in sickle cell crisis would be use-
ful to conﬁrm the efﬁcacy observed in children and to determine the nature of the interaction between PP188 and hydroxyurea.

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ton, Mass. Dr Files is now with Children’s Healthcare of Atlanta, Atlanta, Ga. Dr Brown is an independent statistician in Colmar, Pa.

Financial Disclosure: Following completion of this trial, Dr Casella became a consultant to CytrRx Corp to help design a pediatric trial. For this effort, he received a fee of $3000. Dr Grindel is an ofﬁcer of CytrRx Corp, which funded this study, and holds signiﬁcant shares in the company.

Author Contributions: Dr Orringer had full access to all of the data in this study and takes full responsibil-
ity for the integrity of the data and the accuracy of the data analyses.

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Analysis and interpretation of data: Orringer, Ca-
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berg, Szwedlow, Ballas, Brown, Wojtowicz-Praga, Grindel.

Drafting of the manuscript: Orringer, Casella, Ataga, Files, Ballas, Wojtowicz-Praga, Grindel.

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Study supervision: Orringer, Ataga, Adams-Greaves, Wun, Abboud, Steinberg, Szwedlow, Ballas, Woj-
towicz-Praga.

Role of the Sponsor: CytrRx, the company that developed puriﬁed poloxamer 188 and funded this study, hired a contract research organization (Thera-
dex Corp, Princeton, NJ) to manage all aspects of the design and coordination of this study. Theradex ar-
d ranged a meeting with potential clinical investigators to help with the planning and design of the study. Based on the input received at this meeting, Ther-
dex drafted a protocol for the study. This document was then circulated for review by the investigators, each of whom had the opportunity to make correc-
tions and revise the proposed protocol. At the same time, an independent data and safety monitoring board (DSMB) was established. This 6-member panel in-
cluded experts in sickle cell anemia, biostatistics, and other relevant areas. The DSMB also reviewed and had signiﬁcant input into the protocol. Ultimately, an-
other meeting of the investigators was held at which the protocol was ﬁnalized. Theradex made the ne-
cessary corrections, prepared the ﬁnal version of the protocol, and submitted it to the Colman, Pa.

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