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Regular Article

CLINICAL TRIALS AND OBSERVATIONS

A randomized clinical trial of the efficacy and safety of rivipansel for sickle cell vaso-occlusive crisis

Carlton D. Dampier,[1-3] Marilyn Jo Telen,[4] Ted Wun,[5] R. Clark Brown,[1-3] Payal Desai,[6] Fuad El Rassi,[7,8] Beng Fuh,[9] Julie Kanter,[10] Yves Pastore,[11,12] Jennifer Rothman,[13] James G. Taylor VI,[14] David Readett,[15] Krupa M. Sivamurthy,[15] Brinda Tammara,[15] Li-Jung Tseng,[16] Jay Nelson Lozier,[17] Helen Thackray,[17] John L. Magnani,[17] and Kathryn L. Hassell,[18] on behalf of the RESET Investigators

[1]Department of Pediatrics, Emory University, Atlanta, GA; [2]Aflac Cancer and Blood Disorders Center, Atlanta, GA; [3]Children's Healthcare of Atlanta, Atlanta, GA; [4]Division of Hematology, Duke Comprehensive Sickle Cell Center, Duke University Medical Center, Durham, NC; [5]Division of Hematology Oncology, UC Davis School of Medicine, Sacramento, CA; [6]James Comprehensive Cancer Hospital & Solove Research Institute, The Ohio State University Wexner Medical Center, The Ohio State University, Columbus, OH; [7]Georgia Comprehensive Sickle Cell Center and Grady Health System, Atlanta, GA; [8]Department of Medicine, Emory University, Atlanta, GA; [9]East Carolina University Comprehensive Sickle Cell Center, Greenville, NC; [10]Department of Medicine, University of Alabama, Birmingham, AL; [11]CHU Sainte-Justine, Montreal, QC, Canada; [12]Department of Pediatrics, University of Montreal, Montreal, QC, Canada; [13]Division of Pediatric Hematology/Oncology, Duke University Medical Center, Durham, NC; [14]Center for Sickle Cell Disease, Howard University College of Medicine, Washington, DC; [15]Pfizer Inc, Collegeville, PA; [16]Pfizer Inc, New York, NY; [17]GlycoMimetics Inc, Rockville, MD; and [18]Division of Hematology, University of Colorado, Aurora, CO

KEY POINTS

- **Rivipansel was safe and well-tolerated in sickle cell patients hospitalized for VOC, but did not meet primary or secondary end points.**
- **Rivipansel use early in the course of VOC appeared to shorten length of hospital stay and duration of IV opioid use in post-hoc analyses.**

The efficacy and safety of rivipansel, a predominantly E-selectin antagonist, were studied in a phase 3, randomized, controlled trial for vaso-occlusive crisis (VOC) requiring hospitalization (RESET). A total of 345 subjects (204 adults and 141 children) were randomized and 320 were treated (162 with rivipansel, 158 with placebo) with an IV loading dose, followed by up to 14 additional 12-hourly maintenance doses of rivipansel or placebo, in addition to standard care. Rivipansel was similarly administered during subsequent VOCs in the Open-label Extension (OLE) study. In the full analysis population, the median time to readiness for discharge (TTRFD), the primary end point, was not different between rivipansel and placebo (−5.7 hours, *P* = .79; hazard ratio, 0.97), nor were differences seen in secondary end points of time to discharge (TTD), time to discontinuation of IV opioids (TTDIVO), and cumulative IV opioid use. Mean soluble E-selectin decreased 61% from baseline after the loading dose in the rivipansel group, while remaining unchanged in the placebo group. In a post hoc analysis, early rivipansel treatment within 26.4 hours of VOC pain onset (earliest quartile of time from VOC onset to treatment) reduced median TTRFD by 56.3 hours, reduced median TTD by 41.5 hours, and reduced median TTDIVO by 50.5 hours, compared with placebo (all *P* < .05). A similar subgroup analysis comparing OLE early-treatment with early-treatment RESET placebo showed a reduction in TTD of 23.1 hours (*P* = .062) and in TTDIVO of 30.1 hours (*P* = .087). Timing of rivipansel administration after pain onset may be critical to achieving accelerated resolution of acute VOC. Trial Registration: Clinicaltrials.gov, NCT02187003 (RESET), NCT02433158 (OLE).

Introduction

Sickle cell disease affects approximately 100 000 people in the United States and millions worldwide.[1-3] A β-globin gene mutation produces an abnormal hemoglobin (sickle hemoglobin [HbS]) that polymerizes when deoxygenated, leading to poorly deformable erythrocytes that contribute to microvascular occlusion.[4-6]

Vaso-occlusive crisis (VOC) is the most common manifestation of sickle cell disease. Severe pain during these episodes often requires IV opioid analgesics and hospital admission for pain relief. More than 50% of patients with sickle cell disease experience at least 1 VOC annually, and higher episode frequency is associated with early mortality in adults.[7,8] Adhesion of sickled erythrocytes to vascular endothelium has been implicated in the pathophysiology of vaso-occlusion, and leukocyte adhesion to activated endothelium may be a key step in initiating vaso-occlusive events.[5,6,9,10] Selectins (P-selectin, E-selectin, and L-selectin) are mediators of interactions between blood cells and the vascular endothelium, and selectin inhibition reduces vaso-occlusion in mouse models of sickle cell disease.[4,9,10]

Rivipansel (formerly GMI-1070), a predominantly E-selectin antagonist, given IV, targets selectin pathways and the pathophysiology of vaso-occlusion. In sickle cell mice, rivipansel administered after initiation of vaso-occlusion inhibited red blood cell, white blood cell, and endothelial cell interactions and improved blood flow and survival.[11] Results from early-phase trials, including observations of clinically meaningful reductions in time to resolution of VOC, time to hospital discharge, and use of IV opioids, supported conducting a phase 3 study.[3,12]

Methods

Study design

The phase 3, randomized, double-blind, placebo-controlled RESET study (NCT02187003), sponsored by Pfizer Inc, enrolled patients experiencing VOC requiring hospitalization for treatment with IV opioid analgesics. It was conducted in 62 sites in the United States and Canada between June 2015 and June 2019 (see the investigator list in the supplemental Material, available on the *Blood* website). Patients were randomized 1:1 to receive IV doses of rivipansel or placebo. Randomization was stratified by age (6-11, 12-17, and ≥18 years) and by genotype (category 1: HbSS, hemoglobin S-beta^0-thalassemia [HbSβ^0-thalassemia] and sickle cell hemoglobin D [HbSD]; category 2: HbSC, HbSβ$^+$-thalassemia, and HbS-variant). Patients, sponsor staff, site staff, and study personnel in direct contact with patients were blinded to treatment allocation. After treatment of a VOC episode in the RESET study, patients could receive open-label rivipansel for subsequent episodes in the Open-label Extension (OLE) study (NCT02433158). An Institutional Review Board or ethics committee at each site approved the study protocols, and written informed consent was obtained before enrollment. A parent or guardian provided permission for a child's participation, and children provided assent according to institutional guidelines. Safety oversight was provided by an independent data safety monitoring committee. Independent committees adjudicated potential cases of acute chest syndrome and cutaneous manifestations in response to phase 2 safety findings.[12]

Treatment

Study drug was initiated as early as possible after the decision to admit, but no later than 24 hours after the first dose of IV opioid administered during the hospital visit. For patients aged ≥12 years, weighing >40 kg, a 1680 mg IV loading dose of rivipansel was administered, followed by 840 mg IV maintenance doses every 12 hours. For patients aged 6 to 11 years, or those weighing ≤40 kg, a 40-mg/kg loading dose of rivipansel was administered (maximum 1680 mg), followed by maintenance doses of 20 mg/kg (maximum 840 mg) every 12 hours. Rivipansel was administered until patients met predefined readiness for discharge criteria or had received a total of 15 study drug doses, whichever occurred first. Pain management was provided according to institutional standards of care. Transfusions were permitted for treatment of sickle cell complications. In the OLE study, all patients were treated as in the active treatment arm of the RESET study.

Participants

The study enrolled hospitalized patients who were ≥6 years of age with documented sickle cell disease and acute VOC. Men able to father children and women of childbearing potential agreed to use effective contraception from study entry to 28 days after the last dose of study drug. Patients were excluded for serious infection, clinical risk factors for or documented acute chest syndrome, atypical pain, estimated glomerular filtration rate of ≤60 mL/min/1.73 m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration equation for subjects ≥18 years of age or the Bedside Schwartz Equation for subjects aged <18 years, liver transaminase enzymes more than 3 times the upper limit of normal, platelet count <50 000/mm^3, current or anticipated use of transdermal analgesics, major surgery in the last 30 days, stroke or transient ischemic attack in the last 14 days, hospitalization or outpatient treatment with parenteral pain medications for uncomplicated VOC 2 to 14 days before study entry, or >5 VOC hospitalizations in the last 6 months.

Key outcome measures

The primary efficacy end point (time to readiness for discharge [TTRFD]) was the time from initiation of study drug to the time at which all readiness for discharge criteria were met: (1) IV opioids discontinued and only oral pain medication required, typically a combination of oral opioids and nonsteroidal anti-inflammatory drugs; (2) acute complications of VOC resolved to the extent that they could be managed as an outpatient; (3) IV hydration discontinued; (4) IV antibiotics discontinued; and (5) blood transfusions no longer required. Readiness for discharge was assessed at 4-hour intervals from 6:01 AM to 10:00 PM. If a patient was considered ready for discharge outside of these times, an ad hoc assessment was performed. Key secondary efficacy end points were time to hospital discharge (TTD), cumulative IV opioid use (CIVO, in morphine-equivalent units [MEU]/kg), and time to discontinuation of IV opioids (TTDIVO). Safety end points included incidence and severity of adverse events. Blood samples were drawn at prespecified intervals to assess biomarkers of interest. Self-reported time of vaso-occlusive pain onset was recorded at study entry. During the OLE safety study, TTD, CIVO, and TTDIVO (but not TTRFD) were assessed as exploratory efficacy end points.

Statistical analysis

Efficacy analyses were conducted on all randomized patients (full analysis population); all patients who received at least 1 dose of study drug (safety analysis population) were included in safety analyses. Median TTRFD, TTD, and TTDIVO were estimated using the Kaplan-Meier method. CIVO from the time of the loading dose to discharge and in the first 24 hours after the loading dose was analyzed using an analysis of covariance model, with treatment, age group, and genotype as factors. Sample size calculation was based on the assumptions that distribution of time to readiness for discharge was exponential and that median time to readiness for discharge was 156 and 106 hours for the placebo and rivipansel groups, respectively, based on phase 2 trial data.[12] The planned sample size of approximately 300 patients was calculated to provide 90% power to detect a between-group difference for the primary efficacy outcome measure, with a 2-sided alpha of 0.05. Between-group statistical comparisons for efficacy end points were based on a log-rank test and a Cox proportional-hazards model, stratified by age group and genotype. Subgroup analyses by age group, genotype, sex, and hydroxyurea use were undertaken for the primary efficacy end point and for the 3 key secondary efficacy end points.

A post hoc analysis was performed for the primary and key secondary efficacy end points in multiple subsets, defined by time from patient-reported onset of vaso-occlusive pain to initiation of study drug (≤18 hours, ≤24 hours, ≤26.4 hours, ≤30 hours, and ≤36 hours), using the same methods as for the full analysis population. Imputation of 12:00 noon was used for 85 participants with missing onset time but known onset date. To assess the potential impact of demographic/baseline characteristic variability within these subsets, multivariate analysis was performed, adjusting for age group, genotype, sex, and hydroxyurea use. To ensure adequate power for this multivariate analysis, it was undertaken on just 2 subsets: patients treated within 26.4 hours of onset of vaso-occlusive pain and patients treated more than 26.4 hours after onset of vaso-occlusive pain, the time corresponding to the upper boundary of the first quartile of the range of time from the reported onset of vaso-occlusive pain to initiation of study drug.

Following the suggestion of benefit of early treatment with rivipansel on TTRFD, TTD, and TTDIVO in the RESET study, we examined whether a similar effect could be demonstrated using exploratory efficacy data from the OLE study. Because of the smaller number of OLE patients treated, superiority of OLE early rivipansel treatment was tested by comparison of TTD, CIVO, and TTDIVO end points in OLE early rivipansel treatment patients with RESET early treatment placebo patients, with a prespecified 90% confidence interval (CI). Early rivipansel treatment OLE patients were also compared with RESET early rivipansel treatment patients to test for noninferiority with a 20% margin of noninferiority prespecified. Early treatment in OLE was defined as treatment within 26.4 hours of patient-reported onset of vaso-occlusive pain for adults and within 30 hours for pediatric patients, based on the RESET post hoc analysis. Because many OLE patients had multiple VOCs treated with rivipansel, only data from the first treated VOC episodes meeting early treatment criteria were analyzed. A statistical analysis plan was finalized by study personnel who had not seen the OLE data.

Results

Patients

A total of 345 patients were randomized (rivipansel, n = 173; placebo, n = 172) and included in the full RESET analysis population (Figure 1). Twenty-seven patients (15.6%) from the rivipansel group and 31 patients (18.0%) from the placebo

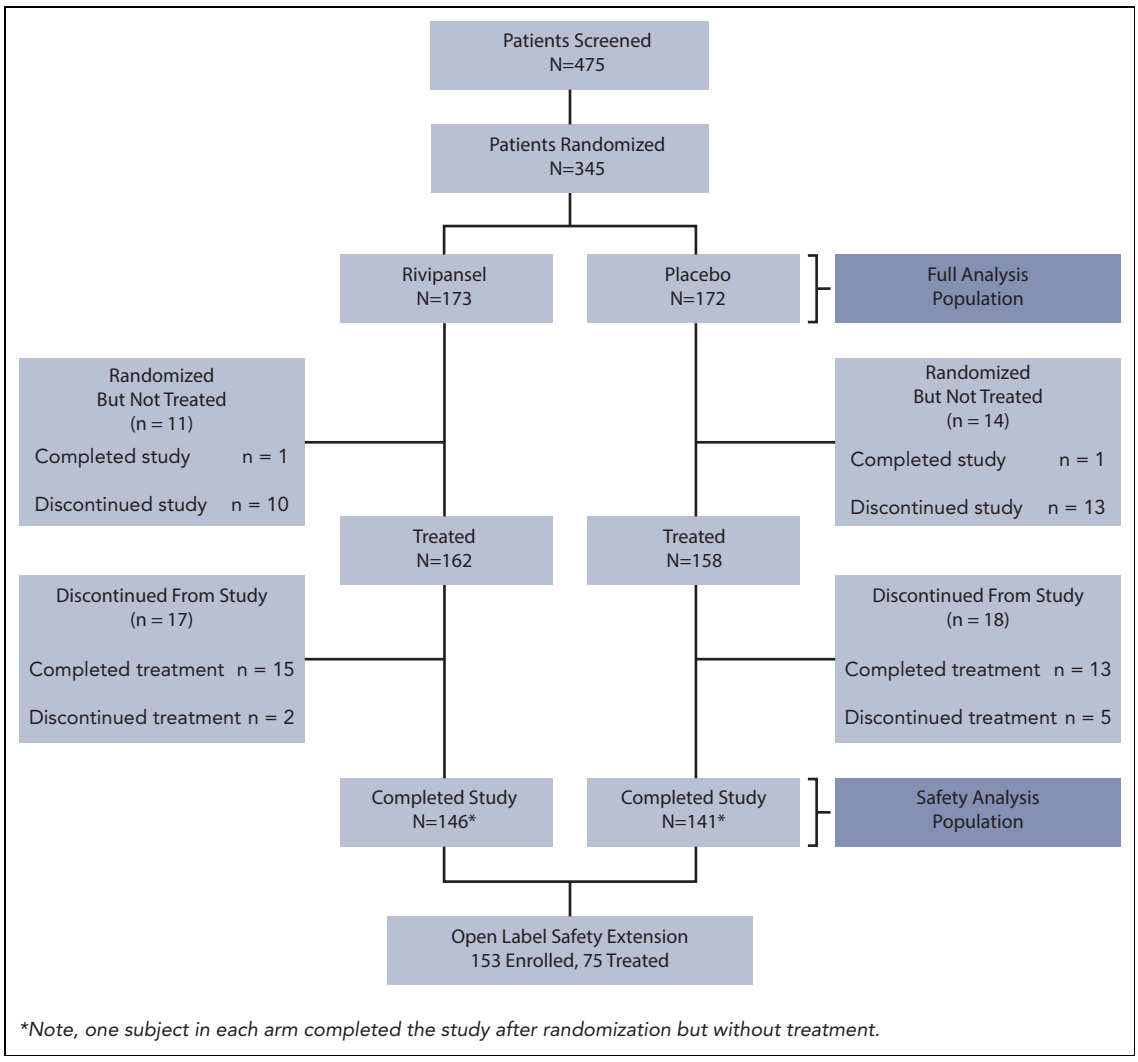

Figure 1. Patient disposition, RESET and OLE studies.

group discontinued the study, of whom 11 in the rivipansel group and 14 in the placebo group were randomized but not treated. Reasons for being randomized but not treated included patient self-withdrawal, logistic issues precluding initiation of dosing within the protocol-defined 24-hour window, and change in patient status so that patients no longer met all eligibility criteria. The most common reason for discontinuation in treated patients was being lost to follow-up postdischarge (14 in the rivipansel group; 10 in the placebo group). Demographics and baseline characteristics were well balanced between the groups except for sex (Table 1). Overall, mean age was 22 years, 94.5% of the patients were Black, and 66.1% were receiving treatment with hydroxyurea (63.5% of those aged 6-11 years, 75.3% of those aged 12-17 years, and 62.7% of those aged ≥18 years). Most patients (75.4%) did not report using daily analgesics at home when not having VOC.

In the OLE study, 153 patients were enrolled; of these, 43 (53.1%) had received placebo and 38 (46.9%) had received rivipansel in the RESET study. Mean age was 20 years (median age 18 years), 44.4% reported daily use of analgesics at home, and 53.1% were receiving hydroxyurea at baseline for the RESET study. Because of discontinuation of the OLE after results of the RESET study were available, only 75 patients (38 adults and 37 children) received rivipansel for at least 1 VOC episode.

Efficacy

Median (95% CI) TTRFD, the primary efficacy end point, was 87.8 (65.7-100.2) hours in the RESET rivipansel group and 93.5 (74.7-109.7) hours in the placebo group—a difference (rivipansel vs placebo) of −5.7 hours (P = .79; hazard ratio [HR], 0.97). Protocol-defined subgroup analyses by age group, genotype, sex, and hydroxyurea use did not identify any statistically significant or clinically meaningful between-group differences (Figure 2). For the secondary efficacy end points, the difference (rivipansel vs placebo) in median TTD was −3.9 hours (P = .72; HR, 0.96; 95% CI, 0.77-1.19), the difference in median CIVO use was −0.06 MEU/kg (P = .85, ratio of medians, 1.01; 95% CI, 0.65-1.57), and the difference in median TTDIVO was −1.25 hours (P = .86; HR, 1.02; 95% CI, 0.82-1.26) (Table 2). No significant differences were observed in any protocol-defined subgroup analyses.

Median TTD (90% CI) for early treatment subjects in the OLE study was 80.89 hours (67.07-90.33). Median TTDIVO (90% CI) was 63.87 hours (35.02-76.05), and median CIVO (Q1, Q3) was 1.83 MEU/kg (0.61, 5.15).

Table 1. Demographic and baseline characteristics of the RESET full analysis population

Characteristics	RESET rivipansel (n = 173)	RESET placebo (n = 172)	OLE rivipansel (n = 38)
Age, mean (SD), y	22.0 (10.6)	21.3 (10.2)	17.3 (6.6)
Aged 6-11 y (RESET: 26 rivipansel, 26 placebo; OLE: 6)	9.5 (1.8)	9.3 (1.7)	7.5 (1.4)
Aged 12-17 y (RESET: 45 rivipansel, 44 placebo; OLE: 15)	14.9 (1.8)	14.7 (1.8)	14.9 (2.0)
Aged ≥18 y (RESET: 102 rivipansel, 102 placebo; OLE: 17)	28.3 (9.3)	27.3 (9.1)	22.9 (4.5)
Male sex, no. of patients (%)	89 (51.4)	73 (42.4)	23 (60.5)
Race, no. of patients (%)			
White	0 (0.0)	6 (3.5)	0 (0.0)
Black	167 (96.5)	159 (92.4)	36 (94.7)
Other	6 (3.5)	7 (4.1)	2 (5.3)
Genotype, no. of patients (%)			
Category 1: HbSS, HbSβ^0-thalassemia, and HbSD	132 (76.3)	129 (75.0)	33 (86.8)
Category 2: HbSC, HbS β+-thalassemia, and HbS-variant other than HbSD	41 (23.7)	43 (25.0)	5 (13.2)
Hydroxyurea use — no. of patients (%)	117 (67.6)	111 (64.5)	30 (78.9)
Aged 6-11 y	16 (13.7)	17 (15.3)	5 (83.3)
Aged 12-17 y	36 (30.8)	31 (27.9)	12 (80.0)
Aged ≥18 y	65 (55.6)	63 (56.8)	13 (76.5)
Daily use of analgesic medications at home, no. of patients (%)	40 (23.1)	44 (25.6)*	6 (15.8)†
Aged 6-11 y	0 (0.0)	0 (0.0)	0 (0.0)
Aged 12-17 y	2 (5.0)	1 (2.3)*	0 (0.0)†
Aged ≥18 y	38 (95.0)	43 (97.7)	6 (100)

SD, standard deviation.

*One of the 44 patients in this cohort had missing data.

†One of the 38 patients in this cohort had missing data.

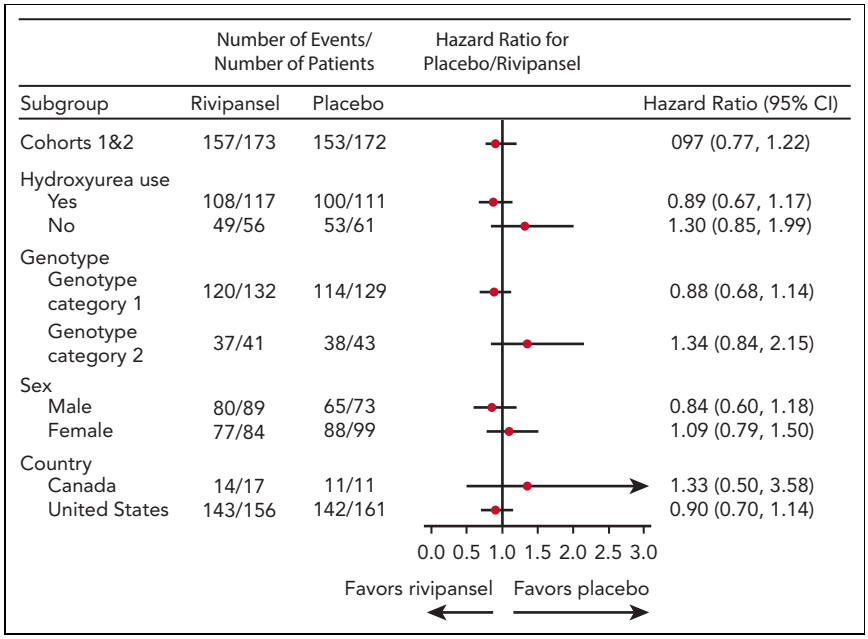

Figure 2. Effect of key demographic parameters on rivipansel treatment effect on TTRFD. Forest plot display of the effect of various demographic characteristics on primary efficacy end point for rivipansel and placebo arms of RESET trial. The HRs and 95% CIs are shown for TTRFD in each subgroup.

Pharmacokinetics and pharmacodynamics Pharmacokinetics of rivipansel were characterized using a 2-compartment model. Rivipansel exposures were consistent with prestudy modeling predictions and met target concentrations. The mean plasma concentrations of rivipansel at steady state were 46 µg/mL and 43 µg/mL for patients aged at least 12 years and patients aged 6 to 11 years, indicating comparability across age groups.

A 61% decrease ($P < .0001$) in mean plasma soluble (s)E-selectin from baseline was observed after the rivipansel loading dose (Figure 3). The decrease in mean plasma sP-selectin from baseline of 18% after the loading dose was not significant ($P = .1356$). There was no significant change in mean plasma sE-selectin or sP-selectin in the placebo group at any time point (Figure 3).

Safety

Among 162 RESET patients who received rivipansel, 143 (88.3%) reported adverse events; among 158 patients who received placebo, 130 (82.3%) reported adverse events. Treatment-related adverse events were uncommon and comparable across study arms. The most commonly reported treatment-emergent adverse events were sickle cell anemia with crisis, pyrexia, nausea, and constipation (Table 3), the majority of which were considered to be related to the current VOC, standard of care treatment, or underlying sickle cell disease. Serious adverse events occurred with similar frequency in the rivipansel and placebo groups, as did events of acute chest syndrome.

In 75 subjects who received at least 1 dose of rivipansel in the OLE study, treatment-related treatment emergent adverse events were also uncommon. As in RESET, the majority of treatment-emergent adverse events were considered to be related to the underlying VOC, standard of care treatment, or underlying sickle cell disease. The most commonly reported adverse events were sickle cell anemia with crisis, pyrexia, nausea, and constipation. No deaths were reported in patients who received rivipansel in either study.

Post hoc analyses

Although it was not a prespecified analysis in the RESET protocol, investigators had suggested that the duration of home treatment before arriving for hospital-based management might be an important variable for rivipansel efficacy. Thus, self-reported time of pain onset consistent with a VOC was prospectively obtained during enrollment similar to other clinical and demographic information. Post hoc analyses suggested a shorter time from patient-reported vaso-occlusive pain onset to study drug initiation was associated with a potential rivipansel

Table 2. Secondary efficacy end points

Outcome measure	Rivipansel (N = 173)	Placebo (N = 172)	*P* value	Hazard ratio
Time to discharge, median (95% CI), h	86.8 (71.3-98.7)	90.7 (72.1-108.6)	.72	0.96
Cumulative IV opioid use, median, morphine-equivalent units/kg	2.30	2.36	.85*	[Ratio of medians = 1.01]
Time to discontinuation of IV opioids, median (95% CI), h	67.2 (53.3-80.5)	68.5 (53.8-85.0)	.86	1.02

*Based on a rank analysis of covariance model.

Figure 3. sE-selectin overall population. sE-selectin levels (ng/mL) are shown before 40 mg/kg loading dose (T_0), 10 minutes postloading dose, 3 hours and 8 hours postloading dose, before first 20 mg/kg maintenance dose, 1 hour and 3 hours after first maintenance dose, before second 20 mg/kg maintenance dose, and 1 hour and 3 hours after second maintenance dose. All values are normalized to baseline sE-selectin value and plotted as percent of baseline value.

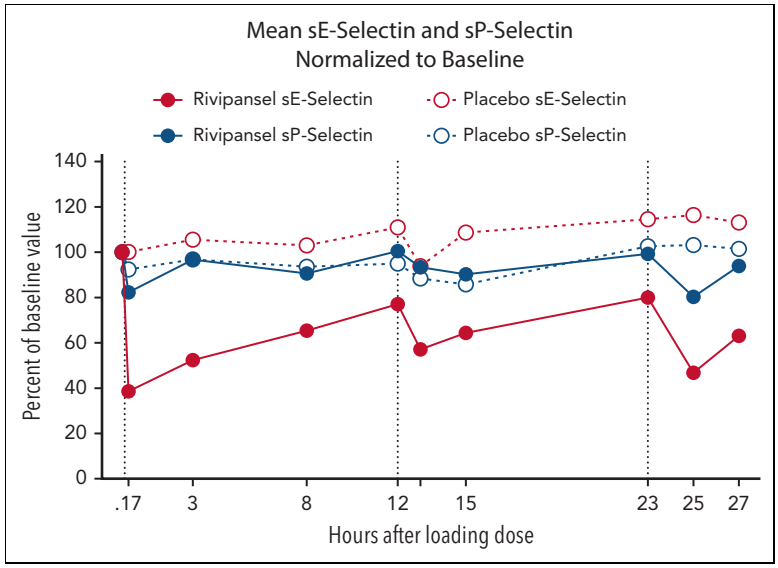

Table 3. Incidence of treatment-emergent adverse events occurring in at least 5% of patients in any study group

Event*	No. of patients (%)	
	Rivipansel (N = 162)	Placebo (N = 158)
Blood and lymphatic system disorders		
Anemia†	27 (16.7)	26 (16.5)
Sickle cell anemia with crisis‡	43 (26.5)	47 (29.7)
Gastrointestinal disorders		
Abdominal pain	9 (5.6)	6 (3.8)
Constipation	30 (18.5)	21 (13.3)
Nausea	26 (16.0)	27 (17.1)
Vomiting	17 (10.5)	16 (10.1)
General disorders and administration site conditions		
Chest pain	9 (5.6)	8 (5.1)
Pyrexia	29 (17.9)	33 (20.9)
Nervous system disorders		
Dizziness	9 (5.6)	4 (2.5)
Headache	19 (11.7)	30 (19.0)
Musculoskeletal and connective tissue disorders		
Pain in extremity	9 (5.6)	8 (5.1)
Onset during hospitalization	3 (1.9)	3 (1.9)
Onset after hospital discharge	6 (3.7)	5 (3.2)
Respiratory, thoracic, and mediastinal disorders		
Acute chest syndrome	9 (5.6)	10 (6.3)
Dyspnea	10 (6.2)	3 (1.9)
Hypoxia	9 (5.6)	8 (5.1)
Skin and subcutaneous tissue disorders		
Pruritus	24 (14.8)	17 (10.8)
Rash	9 (5.6)	6 (3.8)

*Adverse events reported from study day 1 to the 35-day postdischarge follow-up visit.

†Anemia included preferred terms of anemia, hemoglobin decreased, and hematocrit decreased.

‡1 patient had an event reported during hospitalization and an event reported after discharge.

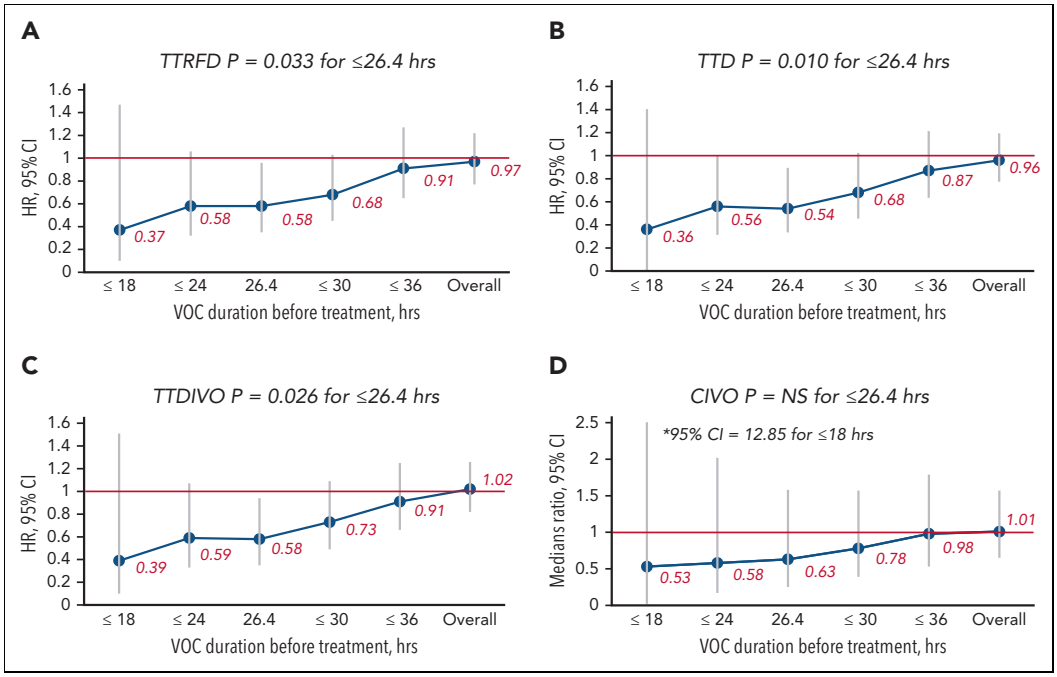

Figure 4. Post hoc analysis of clinical efficacy end points, overall population. HRs for TTRFD (A), the primary clinical efficacy end point, and key secondary efficacy end points TTD (B), TTDIVO (C), and CIVO (D) in RESET study. HRs with 95% CIs are shown for TTRFD, TTD, and TTDIVO end points for subjects with different duration of time from onset of VOC symptoms to first dose of rivipansel/placebo. The ratio of medians and 95% CIs are shown for CIVO end point for subjects with different duration of time from onset of VOC symptoms to first dose of rivipansel/placebo. HRs with upper CIs <1.0 are considered to be statistically significant. NS, not significant.

treatment benefit (Figure 4). Specifically, in the subgroup of patients with time from pain onset to initiation of study drug of 26.4 hours or less (the earliest quartile), rivipansel treatment reduced median TTRFD by 56.3 hours (from 122.0 to 65.7 hours, HR, 0.58, P = .033), reduced median TTD by 41.5 hours (from 112.8 to 71.3 hours, HR, 0.54, P = .010), and

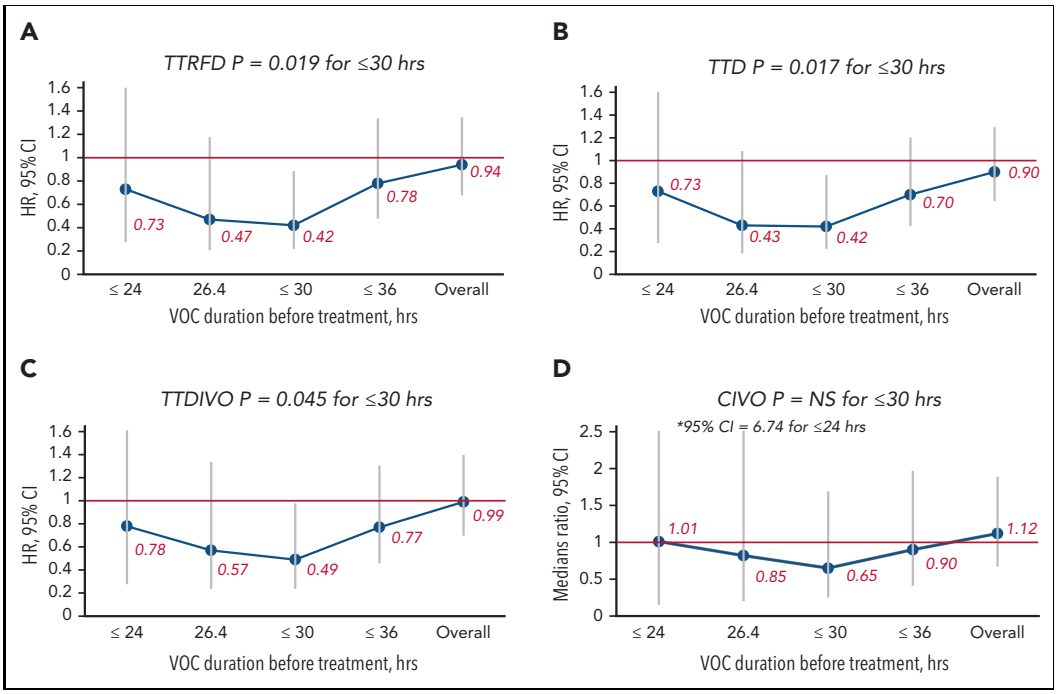

Figure 5. Post hoc analysis of clinical efficacy end points, pediatric population. HRs for TTRFD (A), primary clinical efficacy end point, and key secondary efficacy end points TTD (B), TTDIVO (C), and CIVO (D) in RESET study. HRs with 95% CIs are shown for TTRFD, TTD, and TTDIVO end points for subjects with different duration of time from onset of VOC symptoms to first dose of rivipansel/placebo. The ratio of medians and 95% CIs are shown for CIVO end point for subjects with different duration of time from onset of VOC symptoms to first dose of rivipansel/placebo. NS, not significant.

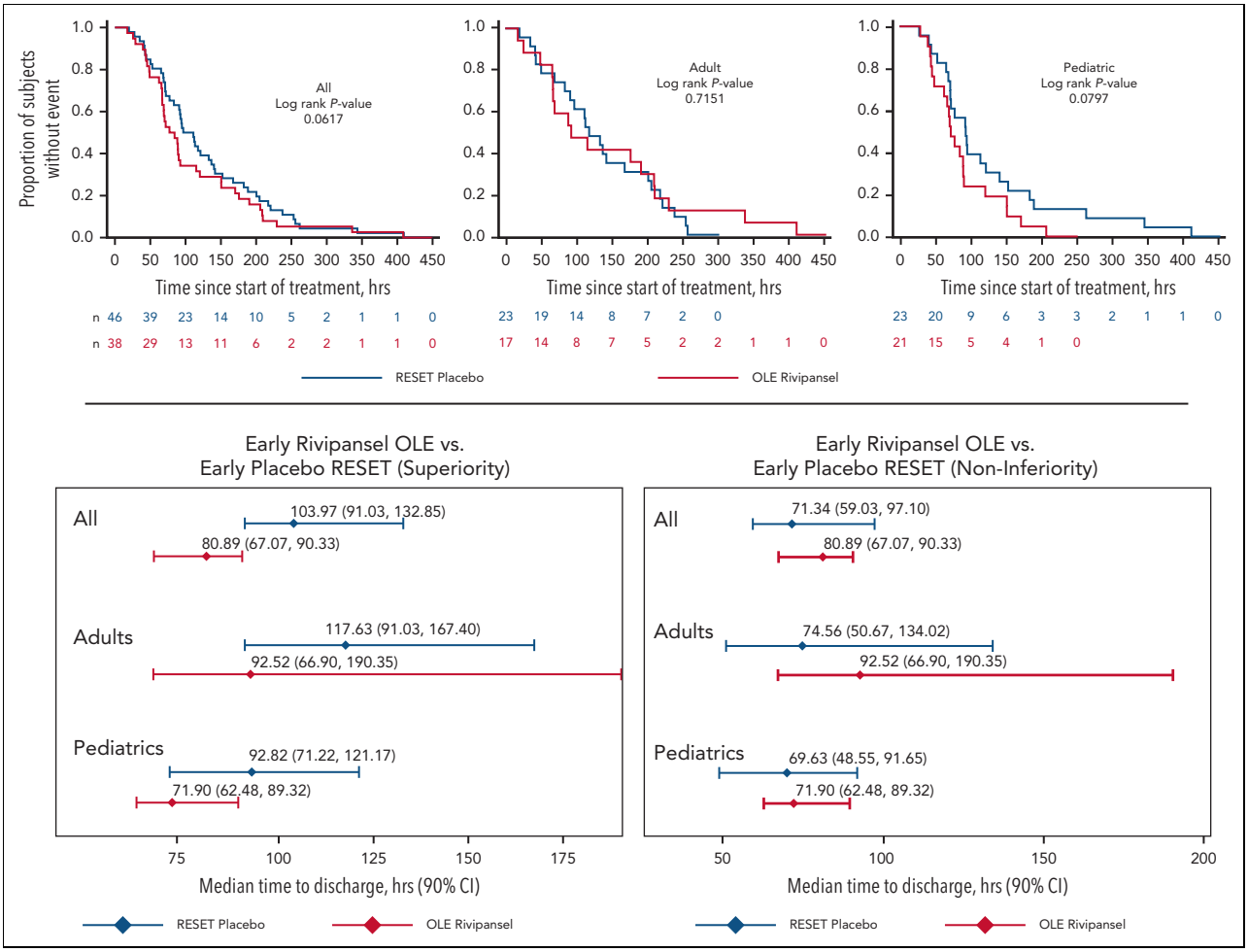

Figure 6. Time-to-discharge analysis: comparison of early rivipansel subjects in OLE with early placebo in RESET or early rivipansel in RESET. Kaplan-Meier plots are shown for superiority of early rivipansel TTD in OLE study to early placebo TTD in RESET for all subjects, adult subjects, or pediatric subjects (top row). Forest plots for TTD in all subjects, adult subjects, or pediatric subjects are shown below for superiority comparison of early rivipansel OLE subjects with early placebo RESET subjects (left) and noninferiority comparison of early rivipansel OLE subjects with early rivipansel RESET subjects (right). For each comparison, first early OLE treatments for each group are shown with the corresponding early placebo or rivipansel treatment patient in RESET: early treatment for adults is ≤26.4 hours from onset of VOC to start of treatment, and early treatment for pediatric patients is ≤30 hours from onset of VOC to start of treatment.

reduced median TTDIVO by 50.5 hours (from 104.0 to 53.5 hours, HR, 0.58, P = .026), compared with placebo. Although there was a decrease in CIVO in the rivipansel arm compared with the placebo arm (ratio of medians = 0.63), the wide CI precluded conclusions of significance. In 11 of 80 early treatment VOC episodes, the start time was imputed (8 in the rivipansel arm, 3 in the placebo arm). For all end points, there was a consistent trend for HRs to favor rivipansel treatment initiated for up to ~36 hours from onset of VOC pain (Figure 4). Subgroup variability in baseline demographics of age group, genotype, sex, and hydroxyurea use could not account for these results.

As in the overall population, a potential benefit with rivipansel in pediatric patients depended on reported duration of pain before treatment (Figure 5). Children 6 to 17 years of age treated with rivipansel within 30 hours of onset of VOC pain experienced reduction in median TTRFD of 29.3 hours (from 94.1 to 64.8 hours, HR, 0.42, P = .019), reduction in median TTD of 23.2 hours (from 92.8 to 69.6 hours, HR, 0.42, P = .017), and reduction in median TTDIVO of 15.4 hours (from 68.9 to 53.5 hours, HR, 0.49, P = .045) compared with placebo. CIVO was reduced in the pediatric population by early treatment with rivipansel (ratio of medians 0.65), but the difference was not statistically significant. As in the overall population, there was a consistent trend for all efficacy end points with HRs appearing to favor rivipansel treatment in children up to ~36 hours from VOC onset (Figure 5).

The first early rivipansel treatment (up to 26.4 hours from onset of VOC pain for adults or up to 30 hours for children) from 38 OLE patients (17 adults, 21 children) was compared with early placebo treatment in the RESET study. There was a reduction in TTD for OLE early rivipansel treatment patients compared with RESET early treatment placebo patients for the overall population (P = .062) and the pediatric population (P = .080), but not the adult population (P = .715) (Figure 6). Likewise, a comparison of first early rivipansel treatment patient episodes in the OLE study with early rivipansel treatment episodes in the RESET study suggested noninferiority of TTD for the overall and pediatric populations, but not the adult population, using the prespecified margin of ≤20% greater TTD in

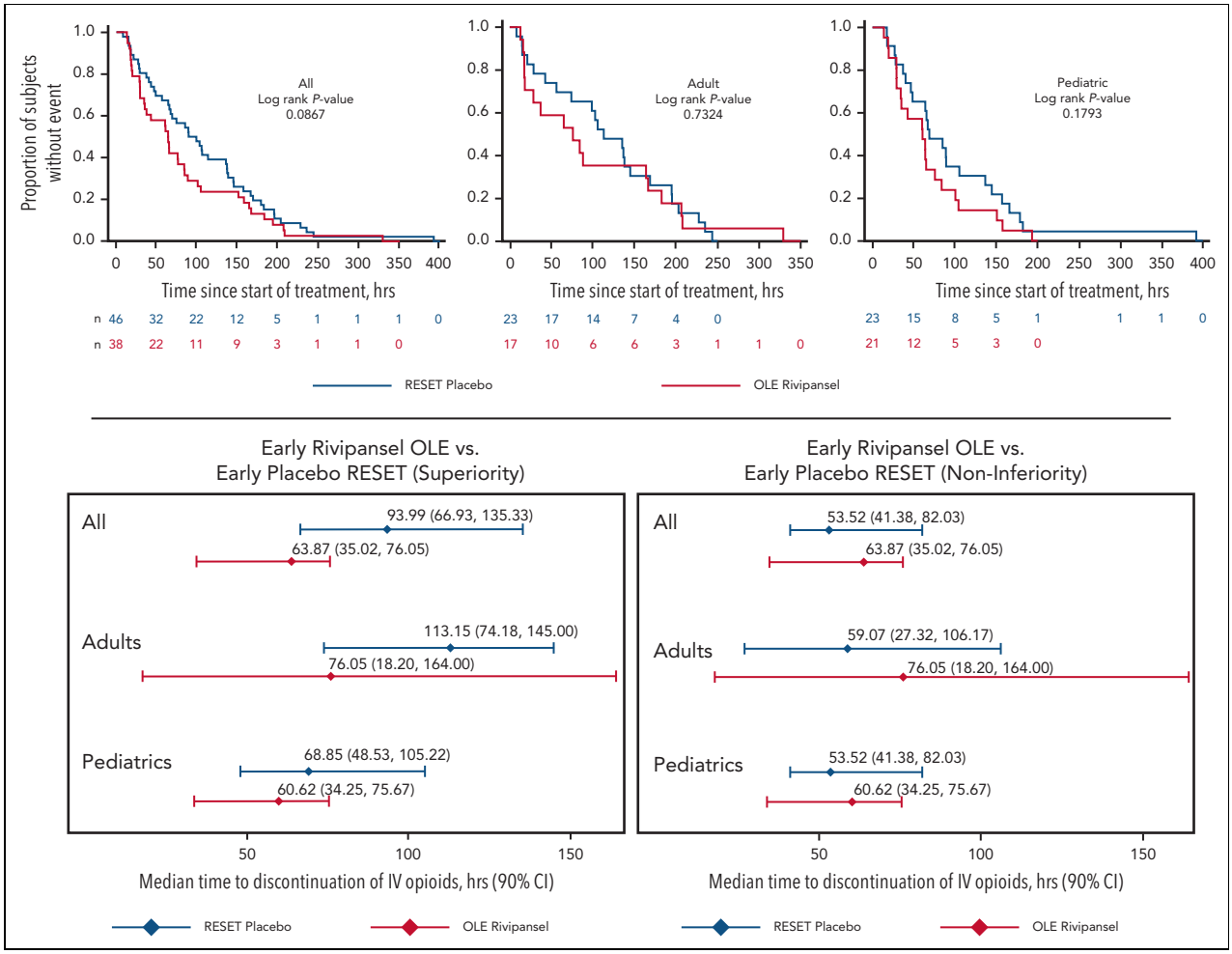

Figure 7. TTDIVO analysis: comparison of early rivipansel subjects in OLE with early placebo in RESET or early rivipansel in RESET. Kaplan-Meier plots are shown for superiority of early rivipansel TTDIVO in OLE study to early placebo TTDIVO in RESET for all subjects, adult subjects, or pediatric subjects (top row). Forest plots for TTDIVO in all subjects, adult subjects, or pediatric subjects are shown below for superiority comparison of early rivipansel OLE subjects with early placebo RESET subjects (left) and noninferiority comparison of early rivipansel OLE subjects with early rivipansel RESET subjects (right). For each comparison, first early OLE treatments for each group are shown with the corresponding early placebo treatments in RESET: early treatment for adults is ≤26.4 hours from onset of VOC to start of treatment, and early treatment for pediatric patients is ≤30 hours from onset of VOC to start of treatment.

OLE subjects (Figure 6). In the OLE study, the median TTD for first early treatment VOC events (80.9 hours, n = 38) was shorter (P = .012) than for first late treatment VOC events (94.5 hours, n = 54). In 5 of the 38 early treatment VOC episodes, the VOC start time was imputed.

There was a reduction in TTDIVO for OLE first early rivipansel treatment patients compared with RESET early treatment placebo patients for the overall (P = .087) but not the pediatric population (P = .179) or the adult population (P =.732) using a prespecified 90% CI (Figure 7). A comparison of first early rivipansel treatment patients in the OLE study with early rivipansel treatment patients in the RESET study suggested noninferiority of TTDIVO for the overall and pediatric populations but not the adult population, using the prespecified 20% margin of allowable increase in TTDIVO for this analysis (Figure 7). In the OLE study, the median TTDIVO for first early treatment episodes (63.9 hours, n = 38) was shorter (P = .014) than for first late treatment episodes (86.5 hours, n = 54).

Median CIVO (Table 4) for OLE first early rivipansel treatment episodes was decreased in the overall population (from 3.79 to 1.83 MEU/kg), in the adult population (from 4.99 to 3.45 MEU/kg), and in the pediatric population (from 2.54 to 1.48 MEU/kg) when compared with RESET early treatment placebo episodes. Only the pediatric CIVO reduction was significant at the 90% CI (P = .072).

Discussion

Since the early 1970s, a number of therapies have been tested in phase 2 or phase 3 clinical trials but failed to reduce the severity or duration of VOC that required hospitalization,[13] including IV poloxamer 188,[14] inhaled nitric oxide,[15] IV magnesium,[16] IV sevuparin,[17] and IV poloxamer 188 in a second pediatric study.[18] All studies were randomized, double-blind, and placebo-controlled, with initiation of treatment within a limited time window after hospitalization. Primary efficacy end points varied, but all were clinical outcome assessments related

Table 4. CIVO for first early rivipansel treatment in OLE phase of study and early placebo treatment in RESET study

Overall population		
	OLE early rivipansel (n = 38)	RESET early placebo (n = 46)
Median (Q1, Q3)	1.83 (0.61, 5.15)	3.79 (1.20, 9.06)
Difference in medians (90% CI)	−1.97 (−2.73 to 0.81)	
Ratio of medians (90% CI)	0.71 (0.37-1.34)	
P value*	.2311 (NS)	
Adult population		
	OLE early rivipansel (n = 17)	RESET early placebo (n = 23)
Median (Q1, Q3)	3.45 (1.21, 14.88)	4.99 (0.88, 9.49)
Difference in medians (90% CI)	−1.55 (−7.91 to 4.81)	
Ratio of medians (90% CI)	1.09 (0.39-3.04)	
P value*	.9039 (NS)	
Pediatric population (age 6-17 y)		
	OLE early rivipansel (n = 21)	RESET early placebo (n = 23)
Median (Q1, Q3)	1.58 (0.61, 2.25)	2.54 (1.20, 8.00)
Difference in medians (90% CI)	−0.96 (−2.93 to 1.01)	
Ratio of medians (90% CI)	0.48 (0.22-1.08)	
P value*	.0718	

NS, not significant.

*From analysis of covariance in rank-transformed values.

to cessation of parenteral opioids or discharge from the hospital. The RESET study likewise initiated treatment after hospital admission, and the primary efficacy end point (TTRFD), although slightly different than those used previously, was chosen to mirror the completion of hospital-based treatment for an acute VOC.

In this phase 3 study, rivipansel treatment was well tolerated but failed to show improvement compared with placebo for the primary and secondary efficacy end points. In contrast, the preceding phase 2 study had shown improvements in time to crisis resolution and cumulative parenteral opioid use.[12] Study differences included a lower mean age in the phase 3 study, reflecting eligibility down to age 6 years rather than 12 years, and a lower percentage of individuals using daily oral analgesics (26% vs 49%). Differences in the components of the primary efficacy end points between the studies precluded a direct comparison of time to crisis resolution. However, the secondary end point of CIVO use was substantially lower and TTDIVO was substantially shorter in the current phase 3 study, likely reflecting younger participant age and less frequent opioid tolerance or chronic pain. TTD in both studies was similar in those receiving rivipansel, but was markedly longer in those receiving placebo in the phase 2 study.

Although rivipansel did not reduce TTRFD or improve the key secondary efficacy end points (TTD, TTDIVO, and CIVO) in the overall study population, in a post hoc analysis we found effect sizes that suggested clinically meaningful improvements in TTRFD, TTD, and TTDIVO (if not CIVO) in the small number of patients treated within 26 to 30 hours of onset of VOC pain. Moreover, for all efficacy end points there was a consistent trend for lower HRs with shorter time from onset of VOC pain to initiation of treatment, and HRs favored rivipansel for all patients with treatment started within ~36 hours of VOC pain onset (Figures 4 and 5).

Rivipansel is a pan-selectin inhibitor; however, any clinical benefit is more likely due to E-selectin inhibition, based on the significant decrease in sE-selectin and the marginal decrease in sP-selectin after the loading dose (Figure 3). This is consistent with the observation that E-selectin is critical to neutrophil adhesion to vascular endothelium[19] and a critical driver of acute VOC in sickle cell disease.[20] Better outcomes might have been achieved in the RESET study with more substantial target engagement because the level of reduction in sE-selectin after the loading dose was not maintained during rivipansel maintenance treatment (Figure 3).

Study strengths and limitations

There are a number of strengths to this study, including its large sample size, inclusion of both adult and pediatric patients, and use of clinical outcomes assessments mirroring typical clinical practice. However, there are a number of important limitations to these additional analyses of the RESET and OLE studies. A potential benefit from early rivipansel treatment in the RESET study was suggested only in post hoc analyses of a subset of participants and would need to be confirmed in a larger adequately powered trial. Timing of pain onset relied on patient self-reports, which in some cases were incomplete and required imputations, and may have been subject to recall bias and individual differences in perception of pain onset. Because the OLE trial was focused on the safety of rivipansel, only secondary end points of TTD, TTDIVO, and CIVO use were available for analysis of efficacy. Likewise, the early termination of the OLE study due to the negative initial findings of the RESET study limited the sample size available for comparison of early rivipansel treatment in the (unblinded) OLE study population both for superiority to early treatment patients in the placebo arm of the RESET study and for noninferiority to early rivipansel treatment patients in the RESET study, and would need to be confirmed in a larger study.

The large patient safety database in the RESET/OLE studies described in this article, as well as in the phase 1 and phase 2 studies, indicates that rivipansel is well tolerated in healthy volunteer subjects and in patients with sickle cell disease experiencing VOC. No dose-limiting toxicities were reported for rivipansel in any of the clinical trials. However, GlycoMimetics has decided not to pursue further clinical development of rivipansel.

Conclusions

Our current understanding of VOC suggests vasoconstriction or vascular inflammation impedes microvascular blood flow and enhances multicellular adhesions.[21,22] Subsequent ischemic-reperfusion injury initiates an inflammatory response that activates nociceptors, causing pain. It is plausible that agents targeting adhesive processes need to be administered early in this cascade of events to be effective. Conversely, anti-adhesion agents given outside this early window may be ineffective, as seen in this trial. If the efficacy of this class of agents depends on early initiation of treatment, approaches relying on scheduled administration of long-acting agents, such as monoclonal antibodies, may be a useful approach as seen with the efficacy of crizanlizumab.[23] However, regularly scheduled administration of monoclonal antibodies may not be a practical or cost-effective treatment strategy for patients with less frequent pain episodes. Early treatment with anti-adhesive therapies in acute healthcare settings as suggested by this study may be difficult in many locations or for many families. Initiation of therapy within a few hours of pain onset at home, similar to current recommended management of acute migraine headaches, might be a more practical approach for treatment of acute VOC and could substantially reduce subsequent healthcare use and opioid use.

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Authorship

Contribution: C.D.D., M.J.T., T.W., K.L.H., and D.R. designed the study; C.D.D., M.J.T., T.W., R.C.B., P.D., F.E.R., B.F., J.K., Y.P., J.R., J.G.T., and K.L.H. participated in the study; all authors were responsible for the acquisition, analysis, or interpretation of data; C.D.D., D.R., and J.N.L. drafted the manuscript; K.M.S., B.T., and L.-J.T. performed statistical analysis; and all authors participated in critical review and revision of the manuscript, had final approval of the manuscript, had full access to the data, and take full responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict-of-interest disclosure: C.D.D. has received personal consulting fees from CLS Behring, Cyclerion, Epizyme, Fulcrum Therapeutics, Forma Therapeutics, GlycoMimetics Inc, Hilton Publishing Company, Micelle BioPharma, Modus Therapeutics, Novartis, and Pfizer Inc; received research grants from Merck, Micelle BioPharma, Novartis, and Pfizer Inc; and served on the steering committee for the current study for Pfizer Inc. M.J.T. has served on a steering committee for Pfizer Inc; served on a data monitoring committee for Novartis; received research grants/funding from Forma Therapeutics and Pfizer Inc.; and holds a patent (PCT/US2012/035837). T.W. has served as an advisor for GlycoMimetics, Inc; received research grants from Janssen, Inc, and Pfizer Inc; and served on steering committees for Janssen, Inc, and Pfizer Inc (for the current study). R.C.B. has received consulting fees from Global Blood Therapeutics, Imara, Novartis, and Novo Nordisk, and research grants from Global Blood Therapeutics, Imara, Novartis, Forma Therapeutics, and Pfizer. J.K. has served as an advisor for GlycoMimetics, Inc. P.D. has received research grants from Global Blood Therapeutics and Pfizer Inc., served on a speakers' bureau for Rockpointe, and served on an advisory board for Global Blood Therapeutics and Pfizer Inc. B.F. has received personal fees from Pfizer Inc. Y.P. has served as a consultant for Novartis and received personal fees from Pfizer Inc. J.R. has received research funding from Novartis, Agios Pharmaceuticals, Dova Pharmaceuticals, Sobi, and Bluebird bio; served on Advisory Boards for Novartis, Agios Pharmaceuticals, Pfizer, and Genentech; and has received personal fees from Pfizer Inc. J.G.T. has served as a consultant for Global Blood Therapeutics and Pfizer Inc; received paid travel or honoraria from Biogen, Cerus Corporation, and Eastern Medicaid Pharmaceutical Administrators Association; has had research contracts with and attended investigator meetings for Cyclerion and University of Pittsburgh; and received research grants from the NCATS (National Center for Advancing Translational Sciences), National Heart, Lung, and Blood Institute, National Institutes of Health, and Pfizer Inc. D.R., K.M.S., B.T., and L.-J.T. were employees of Pfizer Inc, during the RESET study and may own equity or stock options in the company. K.L.H. has received research grants from Pfizer Inc. J.N.L., J.L.M., and H.T. were employees of GlycoMimetics, Inc during the conduct of this study and may own equity or stock options in the company. The remaining author declares no competing financial interests.

A complete list of the members of the RESET Investigators appears in the supplemental Appendix.

ORCID profiles: C.D.D., 0000-0002-7738-2620; M.J.T., 0000-0003-3809-1780; T.W., 0000-0001-6383-7172; P.D., 0000-0003-1038-2500; F.E.R., 0000-0002-8583-0526; J.K., 0000-0001-7002-8891; J.R., 0000-0003-1582-2886; J.G.T. VI, 0000-0002-4421-1809.

Correspondence: Carlton D. Dampier, Aflac Cancer and Blood Disorders Center, 2015 Uppergate Dr NE, Room 464, Atlanta, GA 30322; email: cdampie@emory.edu.

Footnotes

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The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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