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Efficacy and Safety of Rivipansel (GMI-1070) in the Treatment of Vaso-Occlusive Crisis in Hospitalized Patients With Sickle Cell Disease: Results From the RESET Phase 3 Study

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INTRODUCTION

- Vaso-occlusive crises (VOC), the most common acute manifestation of sickle cell disease (SCD), often cause severe pain requiring intravenous (IV) opioid analgesics and hospital admission[1,2]
- Pathophysiology of VOC includes adhesion of sickle cells and leukocytes to vascular endothelium[3-6]
  - Selectin adhesion molecules mediate interactions between blood cells and vascular endothelium; therefore, inhibition of selectins may target the pathophysiology of a VOC[5-7]
- Rivipansel (formerly GMI-1070), a novel investigational pan-selectin inhibitor, targets selectin pathways
  - Rivipansel administration after vaso-occlusion inhibited interactions of red and white blood cells and endothelial cells, and improved blood flow and survival in a murine model of SCD[8]
  - Results from phase 1 and 2 studies of rivipansel, including observations of clinically meaningful reductions in time to resolution of VOC, time to hospital discharge, and use of IV opioids, supported progression to a phase 3 study[9,10]
- Here, we report the results of a phase 3 study of rivipansel (RESET)

OBJECTIVE

- Evaluate the efficacy and safety of rivipansel for treatment of a single VOC episode in hospitalized children and adults with SCD

METHODS

Study Design and Interventions

- Randomized, double-blind, placebo-controlled, parallel-group study (NCT02187003) conducted at 62 sites in the United States and Canada from June 2015 to June 2019
- Participants were randomized (1:1), with stratification by age and genotype, to IV rivipansel or placebo
  - Initiated as early as possible after decision to admit, and no later than 24 hours after the first IV opioid dose during this hospital visit, and continued until VOC could be managed with oral analgesics only, or for maximum of 15 doses
- Rivipansel dosed based on age and weight
  - Aged ≥12 years + weight >40 kg: 1680-mg loading dose, then 840-mg IV maintenance doses every 12 ±2 hours
  - Aged 6–11 years or weight ≤40 kg: 40 mg/kg loading dose (maximum 1680 mg), then 20 mg/kg (maximum 840 mg) IV maintenance dose every 12 ±2 hours

Study Population

- Patients aged ≥6 years with SCD who were experiencing acute VOC requiring treatment with IV opioid analgesics and hospitalization were eligible for inclusion
- Exclusion criteria: serious infection, clinical risk factors for or documented acute chest syndrome, atypical pain, estimated glomerular filtration rate ≤60 mL/min/1.73 m^2, abnormal liver enzymes (alanine aminotransferase/serum glutamic-pyruvic transaminase >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, cerebrovascular accident 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 hospitalizations for VOC in the last 6 months

Key Outcomes

- Primary efficacy end point: time from study drug initiation to the time at which each of the following readiness-for-discharge criteria were met: (1) IV opioids discontinued and only oral pain medication required, (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
- Secondary efficacy end points: time to discharge, cumulative IV opioid consumption, and time to discontinuation of IV opioids
- Pharmacokinetic/pharmacodynamic end points: rivipansel concentration and soluble E-selectin
- Safety end points: incidence of adverse events and serious adverse events

Statistical Analyses

- Median times to readiness-for-discharge, hospital discharge, and discontinuation of opioids were estimated using the Kaplan-Meier method
- A rank analysis of covariance (ANCOVA) model was applied for cumulative IV opioid consumption data, with treatment, age group, and genotype as factors
- Treatment comparisons for time-to-event data were based on a log-rank test and Cox proportional hazards model, stratified by age group and genotype
- A post hoc analysis examined the relationship of efficacy to time between patient-reported onset of VOC pain and start of study drug (≤18 hours, ≤24 hours, ≤26.4 hours, ≤30 hours, and ≤36 hours), with imputation of noon for patients with missing onset time but known onset date (26.4 hours = first quartile)
  - Treatment comparison based on the same analysis model described above was conducted. Subgroup variability in baseline demographics of age group, genotype, sex, and hydroxyurea usage did not impact the results

RESULTS

Study Population

- 345 patients (rivipansel, n=173; placebo, n=172) were randomized (full analysis population), and 320 (rivipansel, n=162; placebo, n=158) were treated (safety population)
- Demographics and baseline characteristics were well balanced between groups, except for sex (**Table 1**)

Table 1. Patient Demographics and Baseline Characteristics

Parameter	Rivipansel (n=173)	Placebo (n=172)
Age, mean (SD), years	22.0 (10.6)	21.3 (10.2)
6–11	9.5 (1.8)	9.3 (1.7)
12–17	14.9 (1.8)	14.7 (1.8)
≥18	28.3 (9.3)	27.3 (9.1)
Male, n (%)	89 (51.4)	73 (42.4)
Race, n (%)		
Black	167 (96.5)	159 (92.4)
White	0 (0.0)	6 (3.5)
Other	6 (3.5)	7 (4.1)
Genotype, n (%)		
Category 1: HbSS, HbSβ^0 thalassemia, and HbSD	132 (76.3)	129 (75.0)
Category 2: HbSC, HbSβ$^+$ thalassemia, and HbS variant other than HbSD	41 (23.7)	43 (25.0)
Hydroxyurea use, n (%)	117 (67.6)	111 (64.5)
Daily use of analgesic medications at home, n (%)[a]	40 (23.1)	44 (25.6)

[a]One patient in the placebo group had missing data.
HbS, sickle hemoglobin.

Efficacy

- Median time to readiness-for-discharge was 5.69 hours shorter in patients who received rivipansel than in patients who received placebo, but the difference was not statistically significant (hazard ratio=0.97, 95% CI: 0.77, 1.22; *P*=0.79) (**Table 2**)
- No statistically significant differences were found for time to discharge, cumulative IV opioid consumption, or time to discontinuation of IV opioids (**Table 2**)
- Analyses of the primary and secondary efficacy end points by age group, genotype, sex, and hydroxyurea use revealed no statistically significant and/or clinically meaningful efficacy signals (data not shown)

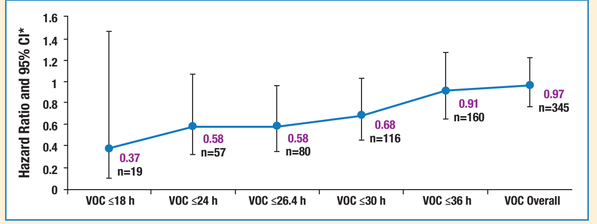
Table 2. Primary and Key Secondary Efficacy End Points

End Point	Rivipansel	Placebo	*P* Value	Hazard Ratio (95% CI)
Time to readiness-for-discharge from hospital, median, h (95% CI)	87.78 (65.68, 100.15)	93.47 (74.67, 109.73)	0.79	0.97 (0.77, 1.22)
Time to discharge, median, h (95% CI)	86.75 (71.25, 98.72)	90.67 (72.10, 108.62)	0.72	0.96 (0.77, 1.19)
Cumulative IV opioid consumption, median, morphine equivalent units/kg	2.30	2.36	0.85[a]	–
Time to discontinuation of IV opioids, median, h (95% CI)	67.20 (53.32, 80.53)	68.45 (53.75, 84.97)	0.86	1.02 (0.82, 1.26)

CI, confidence interval; IV, intravenous.
[a]*P* value based on a rank ANCOVA model.

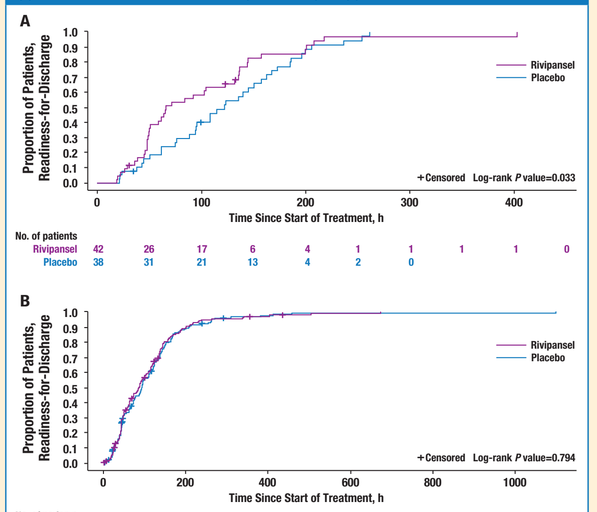
- In the post hoc analysis, a treatment effect favoring rivipansel was observed for patients with shorter time from VOC pain onset to start of study drug (**Figure 1**)
  - For patients with duration from VOC pain onset to start of study drug ≤26.4 hours (first quartile of range; **Figure 2A**), median time to readiness-for-discharge was 56.3 hours shorter with rivipansel (65.7 hours) than with placebo (122.0 hours; HR=0.58, 95% CI: 0.35, 0.96; *P*=0.033, without adjustment for multiplicity)
    - No between-treatment difference was seen for the assessment of patients across all durations from VOC pain onset to start of study drug (**Figure 2B**)

Figure 1. Time From First Study Drug to Readiness-for-Discharge From Hospital (Primary Efficacy End Point) by Time From VOC Onset to Start of Study Drug



*Hazard ratio calculated as time to readiness-for-discharge for placebo/rivipansel.
VOC, vaso-occlusive crisis.

Figure 2. Kaplan-Meier Curves for Time From Start of Study Drug to Readiness-for-Discharge From Hospital in (A) Patients With VOC Duration ≤26.4 Hours (First Quartile) and (B) All VOC Durations



VOC, vaso-occlusive crisis.

Pharmacokinetics/Pharmacodynamics

- Rivipansel exposure was similar across age groups and consistent with prestudy modeling predictions
  - Mean plasma concentration (C_{max}) at steady state was 46 µg/mL for patients aged ≥12 years, and 43 µg/mL for patients aged 6–11 years
- Soluble E-selectin was significantly decreased from baseline with rivipansel but not with placebo (maximum mean decrease 56% at loading dose C_{max}; 17%–44% decrease maintained with subsequent dosing)

Safety

- Adverse events were reported in 88.3% of rivipansel recipients and in 82.3% of the placebo group (**Table 3**)
  - Majority were considered related to sickle cell disease, the underlying VOC, or standard-of-care treatments
- Serious adverse events and events of acute chest syndrome occurred with similar frequency in the rivipansel and placebo groups
- One case of possible acute generalized exanthematous pustulosis was reported in a patient who received rivipansel, but this diagnosis was not confirmed by the Cutaneous Manifestations Adjudication Committee

Table 3. Incidence of Treatment-Emergent Adverse Events Occurring in ≥5% of Patients in Any Study Group

Event, n (%)[a]	Rivipansel (n=162)	Placebo (n=158)
Sickle cell anemia with crisis	43 (26.3)	47 (29.7)[b]
Onset during hospitalization	2 (1.2)	5 (3.2)
Onset after hospital discharge	41 (25.3)	43 (27.2)
Constipation	30 (18.5)	21 (13.3)
Pyrexia	29 (17.9)	33 (20.9)
Anemia[c]	27 (16.7)	26 (16.5)
Nausea	26 (16.0)	27 (17.1)
Pruritus	24 (14.8)	17 (10.8)
Headache	19 (11.7)	30 (19.0)
Vomiting	17 (10.5)	16 (10.8)
Acute chest syndrome	9 (5.6)	10 (6.3)
Dyspnea	10 (6.2)	3 (1.9)
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)
Rash	9 (5.6)	6 (3.8)
Chest pain	9 (5.6)	8 (5.1)
Hypoxia	9 (5.6)	8 (5.1)
Abdominal pain	9 (5.6)	6 (3.8)
Dizziness	9 (5.6)	4 (2.5)

[a]Adverse events reported from study day 1 through the 35-day post-discharge follow-up visit.
[b]1 patient had an event reported during hospitalization and an event reported after discharge.
[c]Anemia included preferred terms of anemia, hemoglobin decreased, and hematocrit decreased.

CONCLUSIONS

- For the overall study population, no significant or clinically meaningful efficacy signal was observed for rivipansel versus placebo
  - Lack of efficacy was not related to rivipansel exposure or lack of pharmacodynamic effect, defined by reduction in soluble E-selectin levels
- Post hoc analysis suggests that rivipansel administration early in the clinical course of a VOC may be associated with a treatment effect for rivipansel
  - This finding is worthy of further study
- The findings of this study will be important for the design of future clinical studies in patients with acute VOC

REFERENCES

1. Platt OS, et al. *N Engl J Med.* 1991;325(1):11-6. **2.** Payne J, et al. *Pediatr Blood Cancer.* 2018;65(12):e27420. **3.** Hoover R, et al. *Blood.* 1979;54(4):872-6. **4.** Hebbel RP, et al. *J Clin Invest.* 1980;65(1):154-60. **5.** Embury SH, et al. *Blood.* 2004;104(10):3378-85. **6.** Belcher JD, et al. *Am J Physiol Heart Circ Physiol.* 2005;288(6):H2715-25. **7.** Frenette PS, Atweh GF. *J Clin Invest.* 2007;117(4):850-8. **8.** Chang J, et al. *Blood.* 2010;116(10):1779-86. **9.** Wun T, et al. *PLoS One.* 2014;9(7):e101301. **10.** Telen MJ, et al. *Blood.* 2015;125(17):2656-64.

AUTHOR DISCLOSURES

CD Dampier has served as a consultant to Epizyme, Global Blood Therapeutics, Micelle BioPharma, Modus Therapeutics, Novartis, and Pfizer Inc.; has served on a board of directors or advisory committee for Micelle BioPharma, Novartis, and Pfizer Inc.; and has received research funding from the Katz Foundation, Merck, Micelle BioPharma, National Institutes of Health (NIH), Novartis, and Pfizer Inc. **MJ Telen** has received research funding from Forma Therapeutics and has served on clinical trial steering committees for Novartis and Pfizer Inc. **T Wun** has served on clinical trial steering committees for Janssen and Pfizer Inc. **RC Brown** has received research funding from Global Blood Therapeutics, Novartis, Pfizer Inc., and the University of Pittsburgh, and has served on a speakers' bureau for Potomac Pharmatech, an adjudication board for Ironwood Pharmaceuticals, and on a board of directors or advisory committee for Global Blood Therapeutics and Pfizer Inc. **F El Rassi** has received research funding from Novartis. **B Fuh** has served as a consultant for Bayer and Micelle BioPharma. **J Kanter** has served on a board of directors or advisory committees for Bluebird Bio, Editas Medicine, Global Blood Therapeutics, Imara, Inc., Modus Therapeutics, and Novartis, and has served on a speakers' bureau for Bluebird Bio and Novartis. **Y Pastore** has served as a consultant for Novartis, has served as a member of a board of directors or advisory committee for the Canadian Haemoglobinopathy Association, and has received honoraria and served on an advisory board for the RESET Operational Guidance Committee. **J Rothman** has served as a consultant for Agios Pharmaceuticals and has received honoraria and research funding from Agios Pharmaceuticals, Novartis, and Pfizer Inc. **JG Taylor, VI,** has served as a consultant for Global Blood Therapeutics and Pfizer Inc.; has received research funding from Cyclerion, NHLBI/NIH, NCTS/NIH, Pfizer Inc., and University of Pittsburgh; and has received honoraria or payment for travel and publication fees from Biogen, the Eastern Medicaid Pharmaceutical Administrators Association, and the NIH. **D Readett, KM Sivamurthy, B Tammara,** and **L-J Tseng** are employees of Pfizer Inc. and own stock/options in the company. **KL Hassell** has served on an advisory committee for the Steering Committee of the RESET Study and has received travel expenses from Pfizer Inc.

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