Early Initiation of Treatment with Rivipansel for Acute Vaso-Occlusive Crisis in Sickle Cell Disease (SCD) Achieves Earlier Discontinuation of IV Opioids and Shorter Hospital Stay: RESET Clinical Trial Analysis.

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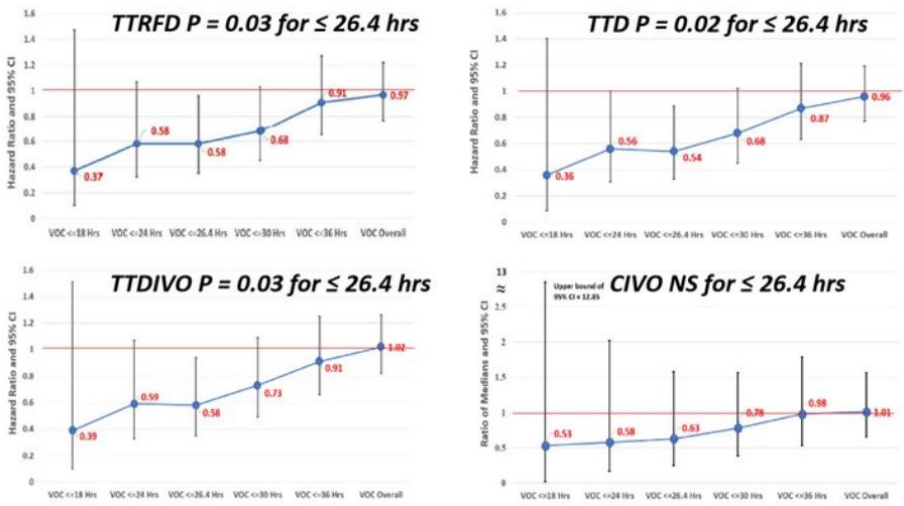
Background: Vaso-Occlusive Crises (VOCs) in SCD patients cause disabling pain, hospitalizations, missed school/work, end-organ damage, and early mortality. VOC still occurs despite prophylaxis.

E-selectin mediates leukocyte trapping, activation and aggregation and drives VOC (Morikis et al, *Blood* 2017). Rivipansel, a pan-selectin inhibitor with potent activity against E-selectin, prevents interaction between leukocytes and vascular endothelium (Morikis, *Blood* 2017) and increases blood flow by reducing cell-cell aggregates and vascular occlusion in SCD mice (Chang, *Blood* 2010).

Methods: The RESET trial (NCT02187003) was a phase 3, randomized, double-blind, controlled study of rivipansel for VOC requiring hospitalization. Three hundred forty-five patients (204 adults and 141 subjects 6-17 years old) were randomized to an intravenous rivipansel loading dose, followed by ≤14 additional doses Q 12 hr, or placebo, in addition to standard care. Overall, 162 were treated with rivipansel and 158 with placebo. The primary endpoint was time-to-readiness-for-discharge (TTRFD), and key secondary endpoints were time-to-discharge (TTD), time-to-discontinuation-of-IV-opioids (TTDIVO), and cumulative-IV-opioid-use (CIVO).

Results: Although RESET did not show significant outcome improvements for the total population, rivipansel treatment within 26.4 hr of pain onset (earliest quartile of duration of VOC until treatment) reduced median TTRFD by 56.3 hrs (from 122.0 to 65.7 hrs), reduced median TTD by 41.5 hrs (from 112.8 to 71.3 hrs), and reduced median TTDIVO by 50.5 hrs (from 104.0 to 53.5 hrs), vs. placebo.

Figure 1. Hazard Ratios for RESET Efficacy Endpoints by Duration of VOC before Treatment, Overall Population



Pediatric subjects (n=141) were 41% of patients treated in the RESET trial (71 in rivipansel arm, 70 in placebo arm). The observed benefit in pediatric subjects depended on VOC duration before treatment. Children 6-17 yrs old treated within 30 hrs of VOC onset experienced reduction in median TTRFD by 29.3 hrs (from 94.1 to 64.8 hrs), reduction in median TTD by 23.2 hrs (from 92.8 to 69.6 hrs), and reduction in median TTDIVO by 15.4 hrs (from 68.9 to 53.5 hrs). Early treatment led to more children ready for discharge by 24, 48, and 72 hrs, compared to placebo (Table 1). Efficacy endpoint hazard ratios favored early rivipansel treatment over placebo in the overall and pediatric populations (Table 2).

Table 1. RESET Study: Cumulative TTRFD at 24, 48, 72 hrs (Subjects 6-17 yrs of Age, Treated ≤30 hrs of VOC Onset)

	Rivipansel (N = 24)	**Placebo** (N = 23)
TTRFD ≤24 hrs	3/24 (13%)	2/23 (9%)
TTRFD ≤48 hrs	8/24 (33%)	5/23 (22%)
TTRFD ≤72 hrs	14/24 (58%)	9/23 (39%)

TTRFD = Time to Ready for Discharge

Table 2. RESET Study Hazard Ratios & 95% CIs, Key Endpoints

	TTRFD	**TTD**	**TTDIVO**
Early Treatment Overall Population	0.58 (0.35, 0.96) *P = 0.0347*	0.54 (0.33, 0.89) *P = 0.0154*	0.58 (0.35, 0.94) *P = 0.0274*
Early Treatment Ages 6-17 yrs	0.42 (0.20, 0.87) *P = 0.0193*	0.42 (0.21, 0.86) *P = 0.0169*	0.49 (0.24, 0.98) *P = 0.045*

TTRFD = Time to Ready for Discharge TTD = Time to Discharge
TTDIVO = Time to Discontinuation of IV Opioids

Conclusions: Early rivipansel conferred clinically meaningful benefit for subjects with SCD, shortening IV opioid use and hospital stay. This suggest that early treatment could change the VOC treatment paradigm from deferral of hospitalization to one of early intervention to shorten hospital stay and IV opioid requirement.